STRESS-REACTIVITY

IN THE DUTCH HYPERTENSION AND OFFSPRING STUDY:

An epidemiological approach to

the psychophysiology of early hypertension

CIP-DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

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Stress reactivity in the Dutch Hypertension and Offspring Study: An epidemiological approach to the psychophysiology of early hypertension/ Adriana Cornelia de Visser. - [S.l. :s.n.]
Thesis Rotterdam. - With ref. - With summary in Dutch.
ISBN 90-9006579-2
Subject headings: stress hypertension epidemiology

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Stress-reactiviteit in 'the Dutch Hypertension and Offspring Study':
Een epidemiologische benadering
van de psychofysiologie van vroege hypertensie

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van rector magnificus
Prof. dr. P.W.C. Akkermans M. Lit.
en volgens besluit van het College van Dekanen.

De openbare verdediging zal plaatsvinden op
woensdag 5 januari om 11.45 uur

door
Adriana Cornelia de Visser
geboren te Rotterdam.

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Financial support by the Netherlands Heart Foundation and the Rotterdam Medical Research Foundation (ROMERES) for the publication of this thesis is gratefully acknowledged.

Seek simplicity and distrust it

Alfred North Whitehead

ACKNOWLEDGEMENT

This thesis is based on data collected in the Dutch Hypertension and Offspring Study. The design and conduct of the Dutch Hypertension and Offspring Study was supervised by a steering committee with the following members: prof. dr. D.E. Grobbee (chairman), prof. dr. P. van Brummelen, dr. L.J.P. van Doornen, prof. dr. A. Hofman, prof. dr. P.W. de Leeuw, dr. H.A.P. Pols, prof. dr. K.H. Rahn, prof. dr. M.A.D.H. Schalekamp, prof. dr. H.A.J. Struijker-Boudier, and prof. dr. Th. Thien. The Dutch Hypertension and Offspring Study was supported by the Netherlands Heart Foundation. The EPOZ study on which the selection of the subjects was based was supported by grants from the Netherlands Prevention Fund.

Manuscripts based on the study described in this thesis:

Chapter 2.2 Dianne C. de Visser, Paul G.H. Mulder, Lorenz J.P. van Doornen and Diederick E. Grobbee. Stress reactivity in subjects with a parental history of hypertension: a meta-analysis. (submitted)

Chapter 2.3 Dianne C. de Visser, Ingrid M.S. van Hooft, Lorenz J.P. van Doornen, Albert Hofman, Jacob F. Orlebeke and Diederick E. Grobbee. Cardiovascular response to mental stress in offspring of hypertensive parents: Dutch Hypertension and Offspring Study. (submitted)

Chapter 2.4 Dianne C. de Visser, Ingrid M.S. van Hooft, Lorenz J.P. van Doornen, Albert Hofman, Jacob F. Orlebeke and Diederick E. Grobbee. Cardiovascular response to physical stress in offspring of hypertensive parents: Dutch Hypertension and Offspring Study. (submitted)

Chapter 3.2 Dianne C. de Visser, Ingrid M.S. van Hooft, Lorenz J.P. van Doornen, Albert Hofman, Jacob F. Orlebeke and Diederick E. Grobbee. Body composition, fitness and habitual physical activity in offspring of hypertensive parents: Dutch Hypertension and Offspring Study. (submitted)

Chapter 3.3 Dianne C. de Visser, Annemarieke A. Vermeulen, Ingrid M.S. van Hooft, Lorenz J.P. van Doornen, Albert Hofman, Jacob F. Orlebeke and Diederick E. Grobbee. Personality traits and cardiovascular reactivity in offspring of hypertensive parents: Dutch Hypertension and Offspring Study. (submitted)

Chapter 4.2 Dianne C. de Visser, Ingrid M.S. van Hooft, Lorenz J.P. van Doornen, Albert Hofman, Jacob F. Orlebeke and Diederick E. Grobbee. Neural regulation of heart rate in offspring of hypertensive parents: Dutch Hypertension and Offspring Study. (submitted)

Chapter 4.3 Dianne C. de Visser, Ingrid M.S. van Hooft, Lorenz J.P. van Doornen, Albert Hofman, Jacob F. Orlebeke and Diederick E. Grobbee. Diminished baroreflex sensitivity in offspring of hypertensive parents: Dutch Hypertension and Offspring Study. (submitted)

Chapter 4.4 Dianne C. de Visser, Lorenz J.P. van Doornen, Johan de Vries and Diederick E. Grobbee. Assessment of baroreflex sensitivity using the Fin-a-pres measurements at hand and foot. (submitted)

LIST OF ABBREVIATIONS

BMI: Body Mass Index (kg/m^2).
CO: Cardiac Output (l).
HR: Heart Rate in beats per minute (bpm)
LVET: Left Ventricular Ejection Time (msec).
MAP: Mean Arterial Pressure (mmHg).
PEP: Pre-Ejection Period (msec).
RR: Respiration Rate in cycles per minute (cpm)
RSA: Respiratory Sinus Arrhythmia (msec).
SV: Stroke Volume (ml).
TPR: Total Peripheral Resistance ($dyne\text{-}sec/cm^5$)

CONTENTS

Chapter 1

INTRODUCTION

GENERAL INTRODUCTION

Blood pressure is constantly and carefully regulated to maintain perfusion of organs and tissues under different conditions. Since the beginning of this century, many mechanisms have been discovered which detect and maintain tissue blood flow and arterial pressure at levels that are optimal for survival during conditions ranging from sleep to exercise. The complexity and the number of the control systems results in a large number of opportunities for dysregulation, which may cause a temporary or sustained uncontrolled rise in blood pressure. Yet, in a majority of hypertensive subjects the cause is still unknown and hypertension is therefore called essential or primary.[1]

The pathogenesis of primary hypertension is generally accepted to be based on genetic as well as environmental factors and the interaction of genetic susceptibility with environmental factors.[2,3,4] Evidence for influences of environmental factors can be found in the relation of blood pressure with diet, obesity, fitness and behavioral stress.

Although in a general and unspecified way, stress is regarded by many as one of the most important environmentally determined factors related to the occurrence of hypertension in large groups of subjects.[3,5] Several arguments in favor of this view can be found. Blood pressure rises with age in the western world,[6] and hypertension shows the highest incidence and prevalence in these industrialized countries in which stress is an inevitable part of life notably when compared to unaccultivated societies.[7,8] Normotensive people who migrate from a so called low-stress area to a high-stress area more often develop hypertension in comparison to those who remain in low-stress areas.[5,9] In epidemiological studies, blood pressure levels obtained at work and blood pressure responses to stress have shown to be a good predictor for subsequent hypertension.[10,11,12] Evidence for a role of stress in the etiology of blood pressure elevation can also be found in 24-hour blood pressure recordings. Both in hypertensive and pre-hypertensive subjects, blood pressure was observed to be higher especially during the day as compared to normotensive controls.[13,14] Hypertensive subjects show an enhanced blood pressure response in particular to mental stress, which may indicate a role for behavioral factors in the etiology of hypertension.[1,15,16] In theory enhanced elevations of blood pressure under stressful circumstances in hypertensive subjects can result from several factors[3,14,17,18,19] (figure 1.1):

-the amount of stress subjects have to cope with in every day life

-perception of the stressor by the subject; this might be related to personality and behavioral characteristics which make a person more sensitive to stress

-neural or cardiovascular 'over-adaptation' to stress situations
-disturbances in neural feedback mechanisms
-structural changes in the cardiovascular system.

A simple direct influence of stress on blood pressure control is unlikely, because not all persons who have to cope with stress become hypertensive. It also seems unlikely that stress reactivity invariably has pathophysiological consequences for blood pressure regulation, since there are circumstances where reactivity clearly serves a useful adaptive function.

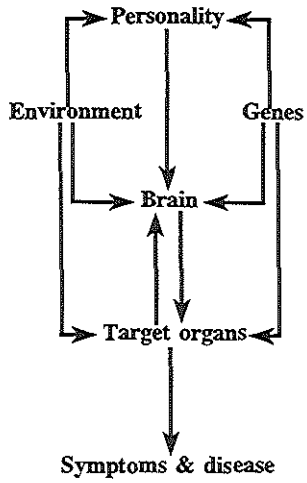

Figure 1.1: behavioral factors in the stress response

Several lines of evidence suggest that blood pressure reactivity to stress and the development of hypertension are related by way of neuro-humoral mechanisms.[20] The concept is intuitively attractive: stress induced increases in plasma epinephrine, which of sufficient magnitude could provide a physiological link between stressful environmental influences and the development of hypertension.[8] High levels of circulating catecholamines have been found in early hypertension,[21,22] and in children and young adults prone to hypertension.[23] Elevated muscle sympathetic nervous system activity has been demonstrated in borderline hypertensive subjects.[24] A conceptual framework for a neurogenic hypothesis of the pathophysiology of hypertension have been proposed, but

experimental support for this view leaves much to be desired.

One of the areas of research that focuses on neurogenic factors in the etiology of hypertension is psychophysiology. The central idea of psychophysiological research is that blood pressure hyperreactivity to mental stress, in particular, is indicative of a pathologic process. The proposition of a so-called psychodynamic factor and its possible relation with blood pressure regulating mechanisms is not new. In 1952 F. Alexander wrote in his book entitled ' Psychosomatic Medicine; its Principles and Applications':[25]

> *The complete answer to the etiology of hypertension does not lie in elucidation of the psychodynamic factors only. Many neurotic persons reveal an inhibition of aggressive impulses and the typical conflict between passive dependent and aggressive competitive tendencies similar to the nuclear conflict of the patient with hypertension and yet do not develop an elevation of blood pressure. If the psychological factor alone were responsible for this disease one would expect to find that every patient who chronically inhibits his aggressive impulses and does not utilize some neurotic symptoms for the release of such impulses will develop hypertension. Actually this is not the case. As has been stressed repeatedly, only in combination with still unknown, possibly inherited somatic factors can psychodynamic influences produce chronic disturbances of the vegetative functions; and so it is in patients with hypertension. On the other hand, the possibility that hypertension is related to the inheritance of an unstable vasomotor system does not minimize the etiologic significance of psychodynamic factors.*

This has resulted in a huge number of studies to unravel the role of behavioral factors in the etiology of hypertension. Several theories and a large number of new terms and concepts entered the scientific literature including 'hyperkinetic circulation', 'luxury perfusion', 'hyper-β-adrenergic circulation', 'emotional hyperreactivity', 'hot reactors' and 'labile hypertension', but no definitive answers were found to the question to what extent and by which mechanisms environmental stress is related to blood pressure elevation. Reasons for this may lay in the complexity of mechanisms involved, the large number of other variables which may influence blood pressure reactivity, and the use of only blood pressure and heart rate reactivity as rather crude measures to describe underlying pathological processes.

In addition, most studies on which the theory is based, have been executed in hypertensive subjects. Studies in hypertensive patients, frequently cannot provide answers on etiology because of an inability to distinguish etiological factors from physical adjustments secondary to elevated blood pressure.[19] The mechanisms that prevail in the initiation and maintenance of high blood pressure may be rather different.[26] To accept a behavioral basis in the pathogenesis of hypertension the behavioral factors must be

present before the development of high blood pressure.[27]

Selection of subjects in a pre-hypertensive state would be necessary, but is not easy because by definition the cause of primary hypertension is not know. The only unequivocal marker of hypertension is blood pressure levels itself, because of tracking of blood pressure through life.[28] At the same time, results from several studies on the pathogenesis of primary hypertension indicate that malfunction of regulatory mechanisms evolving into the hypertensive state may have their onset in the young.[29]

It is unlikely that the puzzle of the etiology of primary hypertension will be solved within one scientific discipline; a combined effort of expertise and knowledge of different disciplines is necessary. In epidemiology, occurrence of disease is studied in relation to possible determinants, i.e. risk factors. With respect to hypertension several factors have been shown to predict hypertension: high blood pressure levels, tachycardia, high relative weight and weight gain, parental history of hypertension, race and electrolyte intake.[2] Parental history of hypertension is one of the most powerful predictors probably partly because of shared genes, but also due to shared environment.[30,31,32,33,34,35,36,37] This notion provides a basis to select groups of normotensive subjects with contrasting risks to become hypertensive.[38]

The design of the Dutch Hypertension and Offspring Study is based on aggregation of blood pressure in families.[39] Subjects were selected for participation in the study when both systolic and diastolic blood pressure of their father as well as their mother was either in the upper or lower quartile of the age- and sex-specific blood pressure distribution, in order to create a maximal contrast in risk for hypertension across the participating groups of children. The objective of the Dutch Hypertension and Offspring Study was to study several intermediate phenotypes of blood pressure regulation as renal function, hemodynamic factors and neural activity to overcome the limitations of the distant phenotype blood pressure and to overcome the confounding effects of high blood pressure levels. Because several noninvasive ways to measure cardiovascular and neural characteristics have become available in the last decade, blood pressure regulating mechanisms could be studied in more detail at rest and during activity. This gives the opportunity to measure a large number of indices of cardiovascular regulating mechanisms in every single individual so as to gain insight into these mechanisms in a for the subject unobstructive way.

The objective of this thesis is to assess cardiovascular reactivity to different types of mental and physical stressors, in relation to risk for hypertension. For this purpose, cardiovascular and neural response patterns to different mental and physical stressors

were studied in subjects with contrasting risks for hypertension based on their parental history. The study was realized as part of the Dutch Hypertension and Offspring Study to provide information on possible early deviations in blood pressure in regulating mechanisms. A majority of the data were collected in one single experiment. The data will be presented in different chapters in which different aspects of blood pressure regulation or blood pressure influencing factors will be discussed. In the next chapter results on the reactivity of cardiovascular and neural indices to four different stressors are presented next to a meta-analysis on reactivity data presented in the last decade. Chapter three is dedicated to the influence of body composition and personality on blood pressure reactivity. Because of the importance of the activity of the sympathetic and parasympathetic nervous system in the potential effects of behavioral factors on blood pressure, neural activity and the baroreflex sensitivity has been given additional attention in the fourth chapter.

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Chapter 2

STRESS-REACTIVITY

Chapter 2.1

STRESS-REACTIVITY

INTRODUCTION

Psychophysiological research or cardiovascular responses strongly relies on the *reactivity paradigm*, by which responsiveness to stressors represents a temporally stable phenomenon. That is, a given individual's pattern of reactivity represents a stable characteristic for that individual.[1] This is of foremost importance in the examination of stress responses in pre-hypertensive subjects, as reactivity is supposed to be related to future hypertension. According to the *behavioral hypothesis*, hyperreactivity is characteristic of mental rather than of physical stress tasks because these tasks require an active coping response.[3] This is confirmed by a number of studies in which blood pressure reactivity was shown to be enhanced specially in response to certain types of mental stress in hypertensive subjects.[2,3] In stress reactivity two factors are of major importance: individual response specificity and stimulus response specificity.

In several studies, individual differences in blood pressure reactivity to stress between hypertensive and normotensive subjects have been shown to exist.[3] This, however, could not be confirmed in several studies in which normotensive subjects at risk for hypertension, as based on parental history, were studied.[3] These discrepancies most probably result from variability in factors that operate besides parental history of hypertension, such as gender,[4,5,6,7] age,[8] race,[1,7] body composition,[5] hormonal changes[5] and diet,[8] all of which could influence blood pressure reactivity. Some of these factors are reasonably stable within a subject, but others, notably hormonal characteristics and diet, might fluctuate over time. As a result, blood pressure reactivity may not be a characteristic as stable within a subject as desired.[1,9,10] Stress reactivity of variables such as cardiac output and total peripheral resistance have proven to be more stable over time.[11,12,13] Cardiac output and total peripheral resistance might also be better indicators of cardiovascular dysregulation. Blood pressure changes are largely determined by the interaction of cardiac output with peripheral resistance, and changes in these variables reflect blood pressure regulating mechanisms more closely.[14] A major source for differences in response pattern is formed by the relative contribution of cardiac output and total peripheral resistance to blood pressure reactivity and the influence of

central nervous system areas.[3,15] The individual response specificity, characterized by the relative contribution of cardiac output, has a higher impact on the response patterning than the stressors despite the different characteristics of stressors.[16]

The second type of specificity is stimulus specificity. Markedly different response patterns between mental and physical stress have been described as well as differences within these categories of stressors.[16,17,18,19] According to the behavioral hypothesis, hyperreactivity exists in response to certain types of mental stressors in hypertensive subjects.[2,3,20]

Because of the importance of measures such as cardiac output and total peripheral resistance and the specificity of responses to different types of stressors, stress reactivity to laboratory stressors rather than to real life stressors was examined in the Dutch Hypertension Offspring Study. Neural and circulatory blood pressure regulating mechanisms in early hypertensive subjects were studied by examining the stress responses to different stress tasks in offspring of hypertensive parents. Two mental and two physical stressors were selected, based on the expected stimulation of different hemodynamic mechanisms and the influence of central nervous system activity.

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Chapter 2.2

STRESS-REACTIVITY IN SUBJECTS WITH A PARENTAL HISTORY OF HYPERTENSION:

A META-ANALYSIS

INTRODUCTION

Sympatho-adrenergic hyperactivity has been implicated in the etiology of hypertension.[1,2] Despite substantial research, no definitive support for this hypothesis has been obtained, in part because no direct methods are available to measure sympathetic activation of the cardiovascular system in humans. Initially, evidence for sympathetic hyperactivity has been found in higher levels of plasma epinephrine and norepinephrine in hypertensive subjects,[3,4,5] and in hyperreactivity of blood pressure and catecholamines to mental stress in hypertensive or borderline hypertensive subjects.[6,7,8,9,10,11,12,13] The latter response measures are used as an indication of sympathetic overactivity because the results resemble cardiovascular circulatory patterns evoked by strong autonomic stimulation.[14,15] Theoretical support for the use of reactivity to stress and catecholamines as markers of abnormalities in blood pressure regulating mechanisms is furnished by Williams.[16] He referred to these measures as intermediate phenotypes in contrast to blood pressure levels at rest, which are called distant phenotypes.[16] Intermediate phenotypes are more closely related to the mechanism of blood pressure regulation and might thereby give a direct view on anomalies in blood pressure regulating mechanisms and eventually on genotype or environmental characteristics associated with these abnormalities.

In spite of an impressive number of studies there remains disagreement concerning the presence and principal site of distraction of the sympathetic nervous system. Two hypotheses concerning sympathetic overactivity prevail; the *ß-adrenergic hypothesis* and the *vascular hyperreactivity* hypothesis.[6,14]

Besides the limited use of presently available indices of sympathetic nervous system activity, studies on which these hypotheses are based have one major limitation; it is often impossible to discriminate between etiological factors and changes secondary to high blood pressure. In hypertension, and also in borderline hypertension, blood pressure already is elevated. The circulatory patterns and catecholamine levels in established hypertension could result from elevated blood pressure levels rather than the reverse. An approach to overcome this problem is to

study subjects before hypertension arises. There is substantial evidence that primary hypertension has its roots early in life.[17]

To study pre-hypertensive subjects, subjects at risk may be selected. 'Twin studies' have shown a genetic component in blood pressure levels at rest as well as during stress.[18,19,20] Because of shared genes and shared environment, blood pressure levels[21,22] and reactivity[23] track in families. Offspring of hypertensive parents is similarly of interest in studies on the etiology of hypertension because of their increased risk for hypertension. High blood pressure before the age of 55 occurs close to four times more often among persons with a strong positive family history of high blood pressure.[24] In view of this familial association, several investigators have compared the reactivity of heart rate and blood pressure to mental or physical stress of currently normotensive individuals, who have either hypertensive or normotensive parents.[25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]

In the last decade a large number of studies on sympathetic hyperreactivity has been published in which subjects participated with contrasting risk for hypertension, based on their parental history. In this article a meta-analysis will be presented in which studies published between 1979 and 1992 are included. The objective of this review is to assess hyperreactivity of blood pressure in pre-hypertensive subjects and to study the association of blood pressure reactivity with stress task characteristics and risk factors for hypertension. As the mechanisms by which high blood pressure tracks in families are still incompletely understood. Information about differences in cardiovascular reactivity in relation to variability of the factors mentioned might be valuable.

METHODS

Selection of the studies

To locate studies, we conducted MEDLINE searches for interactions of parental history of hypertension and stress and then culled additional articles using the bibliographies of the listed publications. Studies were traced and selected which matched the following descripted criteria:

-published in English between 1979 and 1992;

-inclusion of groups of subjects with a positive and a negative parental history of hypertension

-availability of data on stress reactivity during laboratory stress tasks of at least one of the variables heart rate, systolic or diastolic blood pressure.

Only studies published in 1979 or later were included, to obtain studies which were more uniform in the measurement techniques used. No 'twin studies' were included.

Reactivity

The main purpose of this meta-analysis was to assess to what extent a difference in reactivity between pre-hypertensive subjects and controls is present. Due to the presence of an effect of familial predisposition on blood pressure level that acts already early in life,[59] blood pressure levels in offspring of hypertensive parents may be relatively high even at a young age. When stress-task levels are used as measures of reactivity, differences in resting heart rate and blood pressure level can affect the results. In most articles, only baseline and task levels were presented, and no reactivity measures. For those studies, reactivity was calculated by subtracting baseline levels from task levels. If more than one stress task was used, 'mean stress reactivity' was calculated for heart rate, systolic and diastolic blood pressure separately, to avoid repeat inclusion of measurements in the same subjects.

Data analysis

A pooled meta-analysis was performed on the mean levels of systolic and diastolic blood pressure and heart rate and on reactivity of all three measurements for all studies together.[60]

In the formula SE_i denotes the standard error of the observed difference $\bar{d}_i$ between subjects with parental history of hypertension and subject without parental history in study i. A weight factors w_i is defined as

$$w_i = (1/SE_i^2) \ / \ \Sigma(1/SE_i^2)$$

so that $\Sigma w_i = 1$, i.e. the weight factors add up to 1 over all studies.

The mean differences $\bar{d}_i$ are assumed to be an estimator for one true common mean difference δ. This is called the homogeneity assumption across all studies as

$$\delta_{est} = \Sigma w_i \bar{d}_i$$

with estimated standard error

$$SE\ (\delta_{est}) = (\Sigma w_i^2 SE_i^2)^{½} = \{\Sigma\ (1/SE_i^2)\}^{-½}$$

A test for the homogeneity assumption (i.e. one common mean difference δ) is provided by chi-square statistic

$$\chi^2 = \Sigma\{(\bar{d}_i - \delta_{est})/SE_i\}^2$$

with degrees of freedom equal to the number of studies minus 1. Because information about the variability of a variable in the two groups of subjects with different parental

history is lacking in a large number of studies, the ad hoc assumption was made that these variances are the same in all studies and in the two groups, resulting in

$$SE_i = C(1/N_{0i} + 1/N_{1i})^{½}$$

Where C is some unknown constant, N_{0i} is the number of subjects with two normotensive parents and N_{1i} is the number of subjects with one or two hypertensive parents in study i. The weight factor w_i then reduces to

$$w_i = (1/N_{0i} + 1/N_{1i})^{-1} / \sum(1/N_{0i} + 1/N_{1i})^{-1}$$

so that the point estimate δ_{est} can still be calculated.

When estimates of the variances of a variable are available in, say, the first k studies i=1,....,k and missing only in a few remaining studies i > k, then we proceed as follows in an ad hoc way. In each study i ≤ k the pooled variance is calculated over both groups

$$S_i^2 = ((N_{0i}-1)S_{0i}^2 + (N_{1i}-1)S_{1i}^2) / (N_{0i} + N_{1i} -2)$$

and these variances are pooled over the first k studies:

$$SE_i^2 = \sum S^2(N_{0i} + N_{1i}) / \sum(N_{0i} + N_{1i}) - 2k$$

The pooled variance S^2 is used for calculation of the SE_i's of the mean difference between the two groups in studies i>k:

$$SE_i^2 = S^2(1/N_{0i} + 1/N_{1i})$$

This way of imputing standard errors in a few studies where information about the variability is missing, allows interval estimation and homogeneity testing regarding the common mean difference δ across all studies.

In conjunction with the overall meta-analysis on baseline and reactivity data, subgroup analyses were performed with studies grouped according to possible determinants of heterogeneity including:

-the use of mental or physical stress tasks,
-the type of mental stress task used,
-the gender of the subjects in the study,
-the age of the subjects.

In addition, an assessment was made of the extent to which corrections for confounding factors, like body composition, fitness and personality were made in the different studies.

The last determinant of heterogeneity reviewed is the selection method of the subjects because it determines the contrasts in risk between the two groups and, thereby, the likelihood to find differences. A positive parental history was defined as the presence of either a parent with clinical hypertension or a parent with a relatively high blood pressure (e.g. upper part of the blood pressure distribution of the

population). The following methods to select subjects with a parental history of hypertension and subjects without a parental history of hypertension were employed in the studies:

-selection based on a questionnaire filled in by the subjects,
-selection based on a questionnaire filled in by the parents,
-selection based on information given by the (family)physician,
-selection based on blood pressure measurements in the parents.

Additionally, selection could be based on hypertension in one or in both of the parents. Risk for hypertension in subjects almost doubles if both parents are hypertensive.[61] The studies were checked for the number of subjects with two hypertensive parents in the subjects with a positive parental history for hypertension.

RESULTS

General characteristics

In table 2.2.1 studies that matched the selection criteria and could be included are listed, with a short description of the subjects and the stress tasks used. The methods of subject selection are summarized in table 2.2.2. In most studies no correction for matching for risk factors was applied. Moreover, most authors did not provide data on possible dissimilarities in these factors between the groups. Homogeneity could only be tested for baseline levels due to unavailability of error measures on reactivity in the individual articles. Even at baseline, homogeneity was not significant for each of the variables, indicating large differences between studies.

Baseline levels

In table 2.2.3,baseline levels of heart rate and blood pressure are given. Average heart rate as well as systolic blood pressure and diastolic blood pressure were higher in subjects with a positive parental history of hypertension (difference in heart rate 1.42 bpm (95% CI 1.20 to 1.64) difference in systolic blood pressure 3.96 mmHg (95% CI 3.73 to 4.19) and difference in diastolic blood pressure 2.24 (95% CI 2.04 to 2.41)) (figure 2.2.1).

Selections were made to further evaluate the reasons for differences across studies (table 2.2.5). Differences in blood pressure at rest between the two offspring groups largely depended on the selection methods employed in the individual studies. When selection was based on blood pressure measurements of the parents by either the researchers or the (family) physicians, the contrast in systolic blood pressure at rest between subjects with a positive parental history of hypertension and those

without was larger, as compared to studies in which a questionnaire was used (figure 2.2.2 above). No such effect was observed for diastolic blood pressure (figure 2.2.2 below).

Analyses in subgroups were done for studies in which only males participated. This resulted in larger group differences for heart rate and systolic blood pressure, whereas the mean difference in diastolic blood pressure was smaller as compared to the overall meta-analysis (difference in heart rate 1.77 bpm (95% CI 1.42 to 2.12), difference in systolic blood pressure 4.38 mmHg (95% CI 4.02 to 4.74), difference in diastolic blood pressure 1.77 mmHg (95 % CI 1.49 to 2.05)). Analyses for females showed even larger group differences in systolic and diastolic blood pressure, but only six studies could be included. For unknown reasons, the remaining studies in which both male and female subjects participated showed only small differences in blood pressure between the two groups.

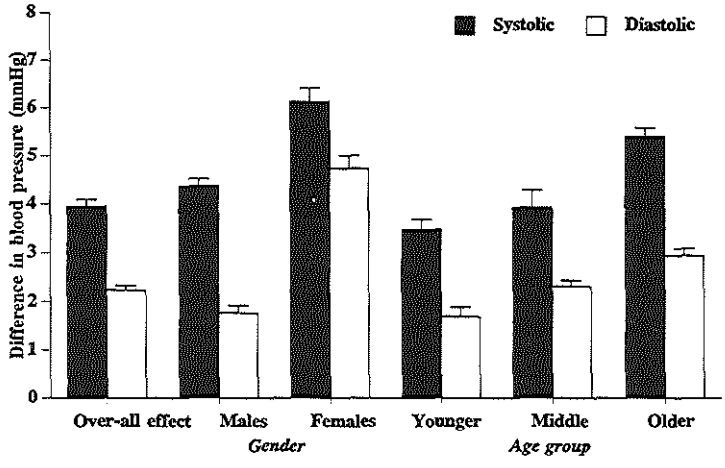

Figure 2.2.1:Differences in baseline, c.q. resting systolic and diastolic blood pressure between the two groups for all the studies together and in subsets of the studies according to gender and age

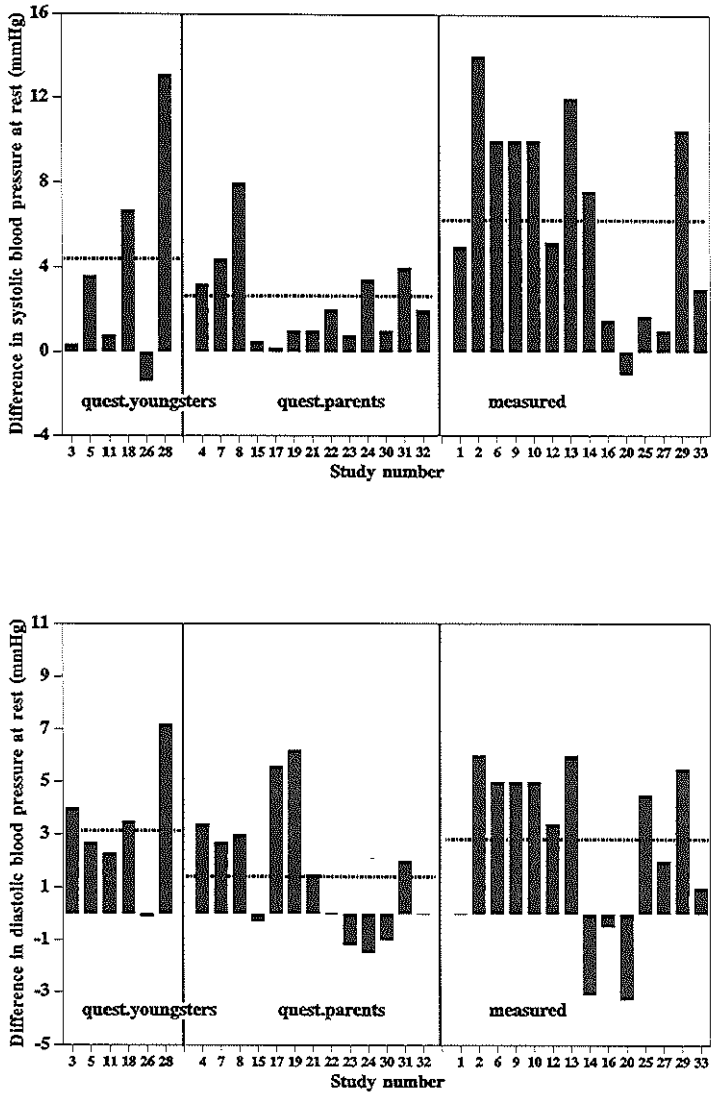

Figure 2.2.2:Differences in systolic (above) and diastolic (below) blood pressure at rest in studies grouped according to different selection methods used

Subsequently, studies were categorized according to mean age of the study population. If no mean age was given, the midpoint of the range of age was used. Students were assumed to be between the ages of 18 and 30 years. Pooled analyses on subjects aged between 18 and 30 years resulted in a more marked contrast between the groups in baseline diastolic blood pressure in comparison with subjects under the age of 18 (figure 2.2.1, table 2.2.5). Only 4 studies with subjects over the age of 30 could be included.

Reactivity

The results of the individual studies on heart rate and blood pressure reactivity to the stressors are shown in table 2.2.4. One mean value of heart rate, systolic and diastolic blood pressure reactivity pooled over all stress tasks for each study, was used in the meta-analysis to avoid repeated measurements within subjects. Because mental and physical stressors are fundamentally different, separate analyses were conducted for these stress tasks. Pooled estimates for reactivity on the mental stress tests revealed significant differences between the two groups; heart rate, systolic and diastolic blood pressure reactivity were higher in subjects with a positive parental history of hypertension (difference in heart rate 1.81 bpm (95% CI 1.78 to 1.83) difference in systolic blood pressure 1.34 mmHg (95% CI 1.31 to 1.37) difference in diastolic blood pressure 1.56 (95% CI 1.53 to 1.58))(figure 2.2.3, table 2.2.6). The group differences on the physical tasks were smaller for all variables.

Using the pooled data on male subjects only resulted in markedly higher contrast between the two groups of subjects for blood pressure and heart rate (table 2.2.6). The analyses on studies in which only females participated demonstrated a significantly reduced reactivity to mental stress in subjects with a positive parental history of hypertension, but again only a small number of studies could be included (figure 2.2.3; table 2.2.6). After categorising studies by age, subjects under the age of 18 with parental history of hypertension showed a relatively small response of systolic and diastolic blood pressure and heart rate as compared to the subjects aged 18 to 30 years (table 2.2.6, figure 2.2.3). Again, only few studies have been conducted in subjects above the age of 30.

A selection on type of stress task within the mental stress tasks was made to test whether or not different types of tasks could influence the group differences. The analyses showed that the mental arithmetic task induced a larger difference in response between the two groups of subjects on heart rate and a smaller response on systolic blood pressure in comparison to the analyses using all mental stress tasks together (table 2.2.6). No separate analyses for studies grouped by race could be made.

Table 2.2.1: General characteristics of studies on blood pressure and heart rate reactivity in subjects with and without a parental history of hypertension.

Ref	Year publ.	First author	Subjects with two normotensive parents (hp-)			Subjects with one/two hypertensive parent(s) (hp+)				
			Nr and gender	Age	Race	Nr and gender	Age	Race	Additional selection†	Type of stress task
1	1979	Falkner	14 males 11 females	14.8±0.4	10 white 5 black	14 males 19 females	14.4±0.3	10 white 8 black	??	mental arithmetic (10 min)
2	1981	Falkner	8 females	15.8±0.8	matched	7 females	16.0±0.9	matched	??	mental arithmetic (10 min)
3	1981	Jorgensen	14 males 16 females	students	??	13 males 15 females	students	??	??	stroop test (2 min) mental arithmetic (4 min) backwards digits (??)
4	1981	Lawler	24*	11-13	*	15*	11-13	*	??	reaction time task +tone avoidance (10 min) anagram task (10 min)
5	1981	Manuck	49 males	18.6	??	20 males	18.8	??	none	visual verbal task (4 min)
6	1981	Parfrey	16 males	19-22	??	17 males	19-22	??	7	isometric exercise (1 hour interm)
7	1982	Hastrup	78 males	19	**	25 males	19	**	??	reaction-time task (14 min)
8	1982	Manuck	18 males	18.1	??	18 males	19.4	??	2	visual-verbal task (3 min) mental arithmetic (3 min) isometric handgrip 30% (3 min)

continued....

Table 2.2.1(cont.)

Ref	Year publ.	First author	Subjects with two normotensive parents (hp-)			Subjects with one/two hypertensive parent(s) (hp+)				
			Nr and gender	Age	Race	Nr and gender	Age	Race	Additional selection†	Type of stress task
9	1982	Ohlsson	44 males 24 females	35±7.9 37±7.9	??	114 males 81 females	35±11.6 36±11.8	??	??	isometric handgrip 30% (5 min) binary choice generator (??) bicycle ergometer test (3*4min)
10	1982	Ohlsson	15 males	33±9.3	??	26 males	35±9.9	??	incidence hypertension at least 50% in 2 generations	isometric handgrip 30% (5 min) cold pressor (150 sec) binary choice generator (+7 min) bicycle ergometer test (3*4min)
11	1983	Holroyd	8/9 males	18-22	??	8/10 males	18-22	??	?? anger management	role play assessment (??)
12	1983	Hohn	29 males 36 females	10-17	42 black	41 males 35 females	10-17	20 black	??	treadmill walking (till max or 15 minutes)
13	1984	Svensson	9 males 8 females	12.5±1.3	??	15 males 8 females	12.8±1.8	??	1	broad band noise (10 min) videogame (4 min) bicycle ergometer task (80 Watt for 1 min)
14	1985	Horikashi	10 males 4 females	21.9	??	9 males 5 females	21.9	??	5	standing (10 min) mental arithmetic (3 min)
15	1985	Manuck	14/8 males	18.4	??	11/11 males	19.6	??	??	mental arithmetic (3 min)

continued....

Table 2.2.1(cont.)

Ref	Year publ.	First author	Subjects with two normotensive parents (hp-)			Subjects with one/two hypertensive parent(s) (hp+)				
			Nr and gender	Age	Race	Nr and gender	Age	Race	Additional selection†	Type of stress task
16	1986	Ditto	24 males	18.9±0.9	??	24 males	18.8±0.9	??	??	stroop test (4 min) mental arithmetic (4 min) isometric handgrip 20% (4 min)
17	1986	Ewart	26 males 13 females	14.9±0.9	25 black 13 white	19 males 19 females	15.0±1.2	21 black 18 white	??	video game (4 min)
18	1986	Jorgensen	29 males 32 females	students	??	32 males 29 females	students	??	?? several personality traits	mental arithmetic (4 min) backwards digits (4 min)
19	1987	Allen	15/23 males	17-29	??	6/16 males	17-29	??	?? type A-B	reading comprehension (2*5 min) backwards digits (15 trails) cold pressor (75 sec) isometric handgrip 30% (5 min)
20	1987	Anderson	8 males 5 females	13.7±0.4	??	6 males 6 females	14.8±0.6	??	??	mental arithmetic (9 min)
21	1987	Anderson	17 females	18-22	black	16 females	18-22	black	??	mental arithmetic (5 min)
22	1988	Ferrara	37 males 31 females	11	??	25 males 17 females	11		??	mental arithmetic (270 sec) isometric handgrip 60% (2 min)

continued....

Table 2.2.1(cont.)

Ref	Year publ.	First author	Subjects with two normotensive parents (hp-)			Subjects with one/two hypertensive parent(s) (hp+)				
			Nr and gender	Age	Race	Nr and gender	Age	Race	Additional selection†	Type of stress task
23	1988	McCann	137***	??	??	26***	??	??	??	serial subtraction (2*60 sec) mirror tracing (3 min) isometric handgrip 30% (2½ min)
24	1988	Molineux	20/20 males	14-16	??	12/12 males	14-16	??	??	bicycle ergometer task (4*??min)
25	1988	Polefrone	23 females	18.8/18.3	??	24 females	19.8/18.7	??	6	mental arithmetic (3 min) concept formation (3 min)
26	1988	Stoney	46 males 55 females	31-59	??	28 males 40 females	31-59	??	??	serial subtraction (2 min) mirror image tracing (3 min) isometric handgrip 30% (2½ min)
27	1989	Ditto	10 males	24	all white	10 males	24	all white	none	video games + mild shock (1 hour)
28	1989	Johnson	12 males	20	all black	12 males	20.2	all black	??	anagram task (10 min) mental arithmetic (5 min)
29	1990	Wilson	15 males	22±1.2	white	13/7 males	26±1.4 32±1.6	white	?? high resting blood pressure	bicycle ergometer test (4-6*3 min)
30	1991	Miller	24 males	23±4	22 white 1 black	24 males	23±6	22 white 1 black	??	video game + mild shock (1 hour)

continued....

Table 2.2.1(cont.)

Ref	Year publ.	First author	Subjects with two normotensive parents (hp-)			Subjects with one/two hypertensive parent(s) (hp+)				
			Nr and gender	Age	Race	Nr and gender	Age	Race	Additional selection†	Type of stress task
31	1991	Sausen	77 males	students	??	17 males	students	??	?? type A-B	serial subtraction (5 min) backwards digits (5 min) cold pressor (60 sec)
32	1992	Everson	61 males	??	****	44 males	??	****	7	serial subtraction (5 min) cold pressor (60-90 sec)
33	1992	Widgren	15 males	matched	??	16 males	31±6	??	two genera-tions	isometric handgrip 30% (3 min) adapted version of stroop test (20 min)

† number of subjects with two hypertensive parents, and factor on which additional selection is based
*in total population 19 males and 20 females; 13 black subjects (5 males and 8 females)
** 5 of the 103 participating subjects were black
*** in total 72 boys (14.6 years) and 99 girls (14.9 years)
**** in the study as a whole 105 males subjects participated of which 102 were Whites and 3 were Asian-Americans

Table 2.2.2: Selection method of the parents and adjustment for possible confounding variables

			Blood pressure status parents				Possible confounding factors considered in the study								
Ref.	Year publ.	First author	Quest off-spring	Quest parent	Quest phy-sician	Measu-red	Height	Weight	Body Mass Index	Skin fold	Diet	Fit-ness	Smok-ing	Perso-nality	Relaxa-tion
1	1979	Falkner				x									
2	1981	Falkner				x	x	x							
3	1981	Jorgensen	x												x
4	1981	Lawler		x					x					x	
5	1981	Manuck	x												
6	1981	Parfrey				x									
7	1982	Hastrup		x	*										
8	1982	Manuck	x	x											
9	1982	Ohlsson				x	x	x	x						
10	1982	Ohlsson				x	x	x			x		x		
11	1983	Holroyd	x											x	
12	1983	Hohn				x									
13	1984	Svensson				x	x	x							
14	1985	Horikashi	x		x			x							
15	1985	Manuck	x	x										x	
16	1986	Ditto		x	x		x	x						x	
17	1986	Ewart		x					x						
18	1986	Jorgensen	x											x	
19	1987	Allen	x	x			x	x							
20	1987	Anderson				x	x	x							

continued....

Table 2.2.2(cont.)

			Blood pressure status parents				Possible confounding factors considered in the study								
Ref.	Year publ.	First author	Quest off-spring	Quest parent	Quest phy-sician	Measu-red	Height	Weight	Body Mass Index	Skin fold	Diet	Fit-ness	Smok-ing	Perso-nality	Relaxa-tion
21	1987	Anderson	x	x											
22	1988	Ferrara		x				x							
23	1988	McCann		x										x	
24	1988	Molineux	x	x				x				x			
25	1988	Polefrone		x	x				x					x	
26	1988	Stoney	x				x	x							
27	1989	Ditto			x		x	x							
28	1989	Johnson	x				x	x						x	
28	1990	Wilson			%	%	x	x	x	x		x			
30	1991	Miller		x			x	x							
31	1991	Sausen	x	x										x	
32	1992	Everson	x	x			x	x							
33	1992	Widgren		x		x		x							

Table 2.2.3: Levels of blood pressure and heart rate at rest in offspring of hypertensive parents and offspring of normotensive parents*

Ref.	Year publ.	First author	Heart rate hp- (bpm)	Heart rate hp+ (bpm)	Systolic blood presssure hp- (mmHg)	Systolic blood pressure hp+ (mmHg)	Diastolic blood pressure hp- (mmHg)	Diastolic blood pressure hp+ (mmHg)
1	1979	Falkner	79.0±5.0	83.0±2.4	107.0±3.2	112.0±1.7	71.0±1.4	71.0±1.7
2	1981	Falkner	73±2.6	85±5.7	91±4.6	105±3.8	61±3.5	67±3.3
3	1981	Jorgensen	63.3	64.5	118.9/106.8	118.7/107.7	67	71
4	1981	Lawler	79.6±2.0	85.7±2.0	116.3±2.7	119.5±2.9	60.3±2.0	63.7±2.2
5	1981	Manuck	68.7±11.2	65.0±9.7	122.8±9.4	126.4±10.0	73.8±8.8	76.5±11.1
6	1981	Parfrey	67±1.4	66±1.8	112±2.1	119±2.7	71±1.7	76±1.9
7	1982	Hastrup	64.4	69.3	120.3	124.7	68.1	70.3
8	1982	Manuck	73	79	120	128	64	67
9	1982	Ohlsson	70±11.6/68±9.8	72±13.9/72±11.0	125±9.4/114±12.0	135±15.1/124±15.4	79±6.7/74±8.1	84±10.9/79±9.6
10	1982	Ohlsson	69±8.2	70±10.3	127±11.1	137±15.5	79±9.2	84±11.6
11	1983	Holroyd	73.5±15.0/ 62.7±8.7	77.9±8.0/ 78.5±9.9	122.6±14.2/ 113.3±14.1	116.4±12.2/ 121.1±11.2	69.3±10.3/ 64.9±7.6	69.5±9.4/ 69.3±10.3
12	1983	Hohn	74.9±10.3 69.2±9.7	73.7±9.0 71.9±11.2	104.3±10.5 103.5±9.0	106.7±10.2 111.4±9.7	69.5±9.8 71.6±9.9	70.4±7.4 77.4±7.9
13	1984	Svensson	63±11	68±11	112±6	124±10	65±6	71±7
14	1985	Horikashi	63.7±9.3	67.8±10.6	111.4±7.9	119.0±11.1	61.9±8.2	58.8±12.1
15	1985	Manuck	76.6/73.2	76.6/76.5	120.4/121.6	120.9/121.0	73.2/72.2	72.1/72.7
16	1986	Ditto			111.0	112.5	75.0	74.5
17	1986	Ewart	71.1±10.9	73.3±13.3	120.6±10.8	120.8±11.3	62.8±12.5	68.4±11.9
18	1986	Jorgensen	76.4/74.8/77.4	79.0/78.5	116.6/115.5/111.6	121.7/120.8	64.2/62.0/62.8	65.5/67.4
19	1987	Allen	58.4/61.3	62.3/65.0	121.7/122.2	122.9/122.9	72.5/71.8	78.7/76.3
20	1987	Anderson	80.9±2.3	74.5±2.9	114.7±3.3	113.6±2.0	74.4±2.7	71.1±1.6
21	1987	Anderson	70.8±2.0	64.6±2.4	112.3±1.5	113.3±1.3	63.2±1.4	64.7±1.5
22	1988	Ferrara	91±12	91±11	104±13	106±10	73±12	73±11

continued....

Table 2.2.3(cont.)

Ref.	Year publ.	First author	Heart rate hp- (bpm)	Heart rate hp+ (bpm)	Systolic blood presssure hp- (mmHg)	Systolic blood pressure hp+ (mmHg)	Diastolic blood pressure hp- (mmHg)	Diastolic blood pressure hp+ (mmHg)
23	1988	McCann	72.3	69.2	111.1	111.9	64.6	63.4
24	1988	Molineux	67.8±6.8/ 76.0±8.3	70.5±6.6/ 74.6±8.6	114.0±10.9/ 107.7±7.3	114.0±11.2/ 114.6±7.8	72.5±7.5/ 68.0±7.9	70.1±5.7/ 67.4±10.4
25	1988	Polefrone	72.8±10.0	72.3±13.1	117.2±4.7	118.9±6.2	72.9±5.5	77.4±6.5
26	1988	Stoney	70.3	69.1	117.6	116.2	75.5	75.4
27	1989	Ditto	72±4	70±2	126±4	127±3	63±2	65±3
28	1989	Johnson	69.0±9.1	73.5±14.3	117.9±13.9	131.0±13.1	69.4±13.4	76.6±15.6
29	1990	Wilson			118±2.0	130±1.8/127±2.8	72±2.0	78±1.7/77±3.3
30	1991	Miller	61±1	64±1	123±2	124±2	64±2	63±2
31	1991	Sausen	70±1.2	70±2.3	114±1.1	118±1.9	60±0.9	62±1.5
32	1992	Everson	63±1.1	65±1.8	121±1.0	123±1.3	68±1.0	68±1.1
33	1992	Widgren	63±5	62±9	122±10	125±11	68±4	69±8

* mean values ± measures of variability (SEM or SD) as presented in the articles

Table 2.2.4: Reactivity of heart rate and blood pressure to the stress tasks in offspring of hypertensive parents and in offspring of normotensive parents

Ref.	Year publ.	First author	Type stress task	Heart rate ph- (bpm)	Heart rate ph+ (bpm)	Systolic blood pressure ph- (mmHg)	Systolic blood pressure ph+ (mmHg)	Diastolic blood pressure ph- (mmHg)	Diastolic blood pressure ph+ (mmHg)
1	1979	Falkner	*mental arithmetic (10 min)	7.2±7.5	12.5±7.5	6.0±5.5	8.5±6.2	3.5±5.2	11.3±7.9
2	1981	Falkner	*mental arithmetic (10 min)	-1.3±0.5	-0.3±3.8	9.4±3.5	-2.3±2.7	7.7±2.7	1.4±2.9
3	1981	Jorgensen	*stroop test (2 min)	27.2	23.5	11.5/19.8	9.9/24.8	9.1	13.5
			*mental arithmetic (4 min)	27.3	22.7	10.8/17.0	7.5/22.7	10.7	14.7
			*backwards digits (??)	19.8	17.8	1.6/13.5	0.6/17.3	5.8	10.0
			*shock avoidance (??)	38.5	28.3	6.5/15.7	8.5/19.1	6.1	8.0
4	1981	Lawler	*reaction time task +tone avoidance (10 min)	6.9	1.7			9.9	9.8
			*anagram task (10 min)					10.8	6.5
5	1981	Manuck	*visual verbal task (4 min)	8.3	11.1	14.4	18.7	5.0	6.3
6	1981	Parfrey	*isometric exercise (1 hour interm)	22.3±2.8	24.9±3.0	19.6±2.0	23.9±4.0	15.1±3.1	16.6±1.6
7	1982	Hastrup	*reaction time task (2 min) **	25.2	35.1	23.3	30.8	5.8	6.0
8	1982	Manuck	*visual-verbal task (3 min)	5	9	2	6	8	14
			*mental arithmetic (3 min)	4	13	6	8	12	21
			*isometric handgrip 30% (3min)	8	8	12	16	14	24
9	1982	Ohlsson	*isometric handgrip 30% (5 min)	8/9	10/8	27/18	23/16	21/14	21/13
			*binary choice generator (??)	2/4	2/4	0/12	13/4	1/0	1/1
			*bicycle ergometer test (3*4min)	76/77	78/80	57/44	51/38	5/6	-2/9

continued....

Table 2.2.4(cont.)

Ref.	Year publ.	First author	Type stress task	Heart rate ph- (bpm)	Heart rate ph+ (bpm)	Systolic blood pressure ph- (mmHg)	Systolic blood pressure ph+ (mmHg)	Diastolic blood pressure ph- (mmHg)	Diastolic blood pressure ph+ (mmHg)
10	1982	Ohlsson	*isometric handgrip 30% (5 min)			45	40	11	18
			*cold pressor (150 sec)			44	33	14	8
			*binary choice generator (+ 7 min)			23	17	0	-2
			*bicycle ergometer test (3*4min)			103	95	15	11
11	1983	Holroyd	*role play assessment (??)						
			-neutral	10.9/6.4	11.0/4.0	4.8/-0.5	12.8/4.3	3.4/2.7	5.6/3.6
			-imitation	10.3/4.1	10.1/1.2	14.4/1.1	20.2/10.7	12.5/9.0	14.7/12.6
			-refusal	10.7/5.9	10.0/4.9	14.3/1.6	18.2/10.4	13.2/9.7	14.3/14.3
12	1983	Hohn	*treadmill walking (max 15 min)	115.9/118	114.5/119.4	55.5/71.9	81.5/62.2	19.0/16.4	16.8/16.4
13	1984	Svensson	*noise			0.8	1.4	4.9	4.0
			*videogame	17.7	5.5	1.7	2.8	11.0	4.4
			*bicycle ergometer test	64.4	68.5	18.3	20.2	-5.4	2.3
14	1985	Horikashi	*standing (10 min) *mental arithmetic (3 min)	13.1	19.4	10.0	15.0	17.0	17.0
15	1985	Manuck	*mental arithmetic (3 min)	-3.4	-0.1	1.2	0.1	1.0	0.6
16	1986	Ditto	*stroop test (4 min)			5.0	5.0	4.0	6.0
			*mental arithmetic (4 min)			7.0	4.0	5.0	4.0
			*isometric handgrip 20% (4 min)			9.5	6.5	9.5	9.5
17	1986	Ewart	*video game (4 min)	7.5	9.6	13.0	4.0	5.2	6.8

continued....

Table 2.2.4(cont.)

Ref.	Year publ.	First author	Type stress task	Heart rate ph- (bpm)	Heart rate ph+ (bpm)	Systolic blood pressure ph- (mmHg)	Systolic blood pressure ph+ (mmHg)	Diastolic blood pressure ph- (mmHg)	Diastolic blood pressure ph+ (mmHg)
18	1986	Jorgensen	*mental arithmetic (4 min) *backwards digits (4 min)†	10.4/10.2/ 5.0	10.0/12.4	11.6/9.4/1 1.4	12.3/16.5	3.6/5.6/1.0	6.0/9.1
19	1987	Allen	*reading comprehension (2*5 min) (reading period) *backwards digits (15 trails) *cold pressor (75 sec) *isometric handgrip 30% (5 min)	8.8/7.0 12.8/10.5 16.2/10.9 17.0/15.6	12.5/9.3 15.0/13.6 18.4/14.2 23.7/14.7	9.9/10.4 13.1/12.3 29.9/23.3 28.6/25.2	8.5/8.3 4.3/12.5 26.6/22.3 29.0/24.5	6.9/6.7 14.9/15.9 22.6/25.7 28.0/27.6	10.0/9.4 15.6/15.8 28.9/19.4 36.2/28.0
20	1987	Anderson	*mental arithmetic (9 min)	10.6	15.9	8.6	8.9	12.2	11.3
21	1987	Anderson	*mental arithmetic (5 min)	16.7	13.2	11.5	7.6	12.1	8.1
22	1988	Ferrara	*mental arithmetic (270 sec) *isometric handgrip 60% (2 min)	7 18	9 20	6 22	5 22	5 24	8 24
23	1988	McCann	*serial subtraction (2*60 sec) *mirror tracing (3 min) *isometric handgrip 30% (2½ min)	12.9 6.9 14.0	14.9 8.0 13.0	16.0 13.1 17.7	17.1 13.1 17.2	10.7 9.0 16.0	13.5 12.5 18.1
24	1988	Molineux	*bicycle ergometer test (4*4 min)			100 W 46.5 150 W 57.5	100 W 48.7 150 W 60.7		
25	1988	Polefrone	*mental arithmetic (3 min) *concept formation (3 min)	11.7 3.3	11.3 2.0	19.1 12.8	18.4 11.8	15.1 4.1	11.7 7.7

continued....

Table 2.2.4(cont.)

Ref.	Year publ.	First author	Type stress task	Heart rate ph- (bpm)	Heart rate ph+ (bpm)	Systolic blood pressure ph- (mmHg)	Systolic blood pressure ph+ (mmHg)	Diastolic blood pressure ph- (mmHg)	Diastolic blood pressure ph+ (mmHg)
26	1988	Stoney	*serial subtraction (2 min)			21.3/20.0	21.5/19.0	9.3	11.5
			*mirror image tracing (3 min)			20.4/17.9	24.9/15.9	11.4	10.7
			*isometric handgrip 30% (2½ min)			22.2/21.6	26.9/19.8	13.3	14.6
27	1989	Ditto	*video games + mild shock (1 hour)	12±5	19±5	5±3	16±5	9±2	12±3
				13±4	18±6	2±2	12±5	10±3	13±3
				8±4	17±5	0±2	10±4	9±2	14±3
				11±4	18±4	-2±2	11±5	9±2	17±3
28	1989	Johnson	*anagram task (10 min)	5.3	3.8	1.0	-0.6	1.4	4.6
			*mental arithmetic (5 min)	11.3	8.7	12.5	20.5	10.5	18.0
29	1990	Wilson	*bicycle ergometer test (4-6*3 min)			8	7/17	3	4/9
30	1991	Miller	*video game + mild shock (1 hour)	6	13	12.5	15	12	12
31	1991	Sausen	*serial subtraction (5 min)	10	16	11	16	11	13
			*backwards digits (5 min)	10	16	10	14	9	11
32	1992	Everson	*serial subtraction (5 min)	18	20	17	17	14	14
			*cold pressor (60-90 sec)	12	11	92	10	9	11
33	1992	Widgren	*isometric handgrip 30% (3 min)	16	20	16.7	30	9.5	21.5
			*stroop test (20 min)	13.1	14.9	9	16	7.7	13.6

† the two stress tasks have been used as one stress period
** no reactivity on cold pressor task, because there was no baseline given

Table 2.2.5: Results for systolic blood pressure, diastolic blood pressure and heart rate at rest

Variable	Homogeneity	N	Group difference	95% confidence interval of the difference
Rest				
Systolic blood pressure (mmHg)	904.6	41	3.96	(3.73,4.19)
Diastolic blood pressure (mmHg)	486.9	39	2.24	(2.07,2.41)
Heart rate (bpm)	565.8	36	1.42	(1.20,1.64)
Selection on gender				
Males				
Systolic blood pressure (mmHg)	431.2	24	4.38	(4.02,4.74)
Diastolic blood pressure (mmHg)	323.6	20	1.77	(1.49,2.05)
Heart rate (bpm)	256.1	20	1.77	(1.42,2.12)
Females				
Systolic blood pressure (mmHg)	130.5	6	6.13	(5.46,6.80)
Diastolic blood pressure (mmHg)	15.9	6	4.73	(4.20,5.25)
Heart rate (bpm)	121.9	6	1.88	(1.21,2.54)
Selection on age				
Subjects aged under 18				
Systolic blood pressure (mmHg)	245.0	12	3.48	(3.07,3.89)
Diastolic blood pressure (mmHg)	207.7	12	1.69	(1.39,2.00)
Heart rate (bpm)	214.6	12	1.15	(0.76,1.53)
Subjects aged 18-30				
Systolic blood pressure (mmHg)	376.9	26	3.93	(3.58,4.29)
Diastolic blood pressure (mmHg)	178.2	23	2.31	(2.04,2.59)
Heart rate (bpm)	300.4	20	1.82	(1.46,2.17)
Subjects aged over 30				
Systolic blood pressure (mmHg)	330.9	4	5.39	(5.02,5.76)
Diastolic blood pressure (mmHg)	87.4	4	2.93	(2.65,3.22)
Heart rate (bpm)	8.6	4	4.35	(4.07,4.63)

Table 2.2.6: Results for reactivity of systolic blood pressure, diastolic blood pressure and heart rate

Variable	N	Group difference	95% confidence interval of the difference
Mental stress			
Systolic blood pressure (mmHg)	33	1.34	(1.31,1.37)
Diastolic blood pressure (mmHg)	32	1.56	(1.53,1.58)
Heart rate (bpm)	29	1.81	(1.78,1.83)
Selection on gender			
Males			
Systolic blood pressure (mmHg)	22	3.07	(3.03,3.10)
Diastolic blood pressure (mmHg)	18	2.02	(1.99,2.06)
Heart rate (bpm)	16	3.35	(3.31,3.40)
Females			
Systolic blood pressure (mmHg)	6	-3.24	(-3.30,-3.17)
Diastolic blood pressure (mmHg)	4	-1.20	(-1.18,-1.22)
Heart rate (bpm)	4	-0.81	(-0.90,-0.71)
Selection on age			
Subjects aged under 18			
Systolic blood pressure (mmHg)	7	-1.85	(-1.90,-1.80)
Diastolic blood pressure (mmHg)	8	1.39	(1.34,1.44)
Heart rate (bpm)	8	0.65	(0.60,0.70)
Subjects aged 18-30			
Systolic blood pressure (mmHg)	23	1.84	(1.80,1.88)
Diastolic blood pressure (mmHg)	20	1.77	(1.73,1.81)
Heart rate (bpm)	19	2.84	(2.80,2.88)
Subjects aged over 30			
Systolic blood pressure (mmHg)	4	2.90	(2.85,2.95)
Diastolic blood pressure (mmHg)	4	1.26	(1.22,1.30)
Heart rate (bpm)	2	0.00	(-0.07,0.07)

continued...

Table 2.2.6(cont.)

Variable	N	Group Difference	95% confidence interval of the difference
Mental arithmetic			
Systolic blood pressure (mmHg)	16	0.24	(0.20,0.29)
Diastolic blood pressure (mmHg)	14	1.60	(1.56,1.64)
Heart rate (bpm)	15	2.23	(2.19,2.27)
Physical stress			
Systolic blood pressure (mmHg)	20	0.50	(0.47,0.53)
Diastolic blood pressure (mmHg)	17	1.14	(1.11,1.17)
Heart rate (bpm)	12	1.25	(1.21,1.28)

DISCUSSION

The objective of this meta-analysis was to asses the extent to which differences in blood pressure and heart rate reactivity during laboratory stress are present in subjects with contrasting parental history of hypertension and to evaluate the factors which may influence reactivity. To this aim, studies published in the last decade were reviewed. The data as summarized in the tables show a large heterogeneity in results. However, due to lack of specific data only indications could be given for causes of this heterogeneity. The results of the analyses have to be interpreted with care, because the studies appear not to represent one homogeneous data-base as meta-analysis requires.

Higher baseline levels of heart rate, systolic and diastolic blood pressure in subjects with a positive parental history of hypertension as compared to subjects of normotensive parents were observed for the studies taken together. The size of this difference depended on the selection method of the population, on gender, and on age of the subjects. Despite the poor reactivity data, the analyses indicated three subsequent sources of heterogeneity that have to be taken into account in interpreting parental history studies: type of stress task, gender and age of the subjects.

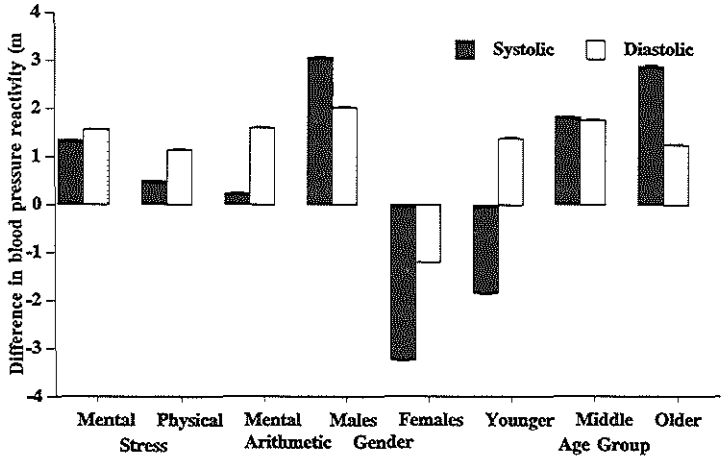

Figure 2.2.3:Differences in reactivity of systolic and diastolic blood pressure to stress between the two groups for all the studies together and in subsets of the data

Selection of participants

Studies in subjects with a different parental history of hypertension suffer from one elementary problem: not all subjects are pre-hypertensive and the likelihood of becoming hypertensive rests on the quality and criteria of selection. Most studies used a crude selection method based on questionnaires. Although a large proportion of false negative and false positive replies may be expected with such an approach, few investigators have sought to verify reported family histories (table 2.2.2). As shown in this meta-analysis, selection based on measured blood pressure results in more pronounced contrasts in systolic blood pressure as compared to selection by questionnaires. Additionally, researchers have argued that the family history approach, based on a single hypertensive parent, is neither sensitive nor specific enough as a predictor for future blood pressure levels to be used for this purpose.[61,62,63,64] Larger contrasts in blood pressure measured between parents result in larger differences in risk for hypertension in offspring.[61,63] Consequently, the number of real pre-hypertensive subjects in a group of offspring of hypertensive parents depends directly on the selection method. Secondly, as blood pressure tracks in families and

this phenomenon is present already early in life, it is most likely that children of hypertensive parents have higher blood pressure themselves as compared to children of normotensive parents.[63,65] Differences in baseline blood pressure are almost inevitable in studies in which subjects are selected on parental history of hypertension. Studies in which a difference in blood pressure is not observed should be questioned as to the validity of the selection procedures.

Besides these selection problems, indications have been found for a stronger relation of blood pressure between mother and child as compared to father and child.[66,67] With a positive parental history is based on hypertension in one of the parents, differences between studies might also be the result of differences in impact on blood pressure of maternal versus paternal hypertension.

Determinants of differences between studies

The studies considered in this meta-analysis differed with respect to several aspects besides selection. An impact of gender, age, type of stress task and race on reactivity have been stressed in literature[27,68,69,70] and for the first three evidence could be found in the present meta-analyses.

The large differences in age of the subjects is another problem. Older subject have a higher diastolic blood pressure at baseline and a markedly higher reactivity of systolic and diastolic blood pressure. Younger subjects are more likely to have younger parents, who might be pre-hypertensive themselves. On the other hand, the use of older subjects is undesirable. As subjects become older, the number of normotensive subjects with a positive parental history declines and the confounding effect of prevalent differences in blood pressure increases.

According to the psychophysiological literature, conditions inducing active, effortful behavioral responses provoke a hyperkinetic cardiovascular response in hypertensive subjects, mediated by the sympathetic nervous system.[71,72,73] Marked differences in cardiovascular response mechanisms between mental and physical stress have been demonstrated[74,75] and even between different types of mental stress.[76,77,78] This is most probably the result of interactions of blood pressure regulating mechanisms with different patterns of cardiovascular adaptation elicited by distinct types of stress tasks. Mental stress tasks with a large cognitive component produce a more pronounced cardiac activation, while a sensory intake task induces a relative increase in peripheral resistance.[75] Results from the analysis of data from mental arithmetic tasks showed a larger heart rate response in comparison with the overall analysis on mental stress tasks. Differences in reactivity to different types of physical stressors could not be tested due to the small number of studies in which

comparable types of physical stressors were used.

Problems and implications

Blood pressure responses to stress are generally studied as an index of malfunction of blood pressure regulating mechanisms. The absence of group differences in blood pressure reactivity in some studies does not necessary conflict with the view that sympathetic hyperreactivity exists. Short term fluctuation in blood pressure, lasting minutes, are the result of changes in cardiac output and peripheral resistance. The use of blood pressure and heart rate as measures of circulatory response instead of for example cardiac output and peripheral resistance may result in an underestimation of sympathetic activation, because changes in cardiac output and peripheral resistance can be compensated within the cardiovascular system. The 'hyper ß-adrenergic' and 'vascular hyperreactivity' hypotheses, referred to in the introduction, are supported both to some extent by reactivity of systolic blood pressure for the 'hyper ß-adrenergic' hypothesis, and diastolic blood pressure for the 'vascular hyperreactivity' hypothesis. Recently, it was proposed, that in pre-hypertensive subjects blood pressure responses are not higher, but are achieved by another mechanism.[75] If pre-hypertensive subjects raise their blood pressure by vasoconstriction rather than by an increase of cardiac output, this could be achieved with a normal increase of sympathetic nerve activity.[75,79]

Families not only share genes which may directly affect blood pressure regulating mechanisms. Factors as body composition, fitness, diet and personality characteristics also cluster in families and are related to reactivity.[26,80,81,82] To be able to interpret results of reactivity studies, control for these factors is important. Other factors, which have to be controlled because of their relation with both blood pressure levels and reactivity, are age, race and gender of the subjects.[83,84,85,86,87] A debatable feature of some of the studies is the use of additional selection criteria, based on suspected risk factors for cardiovascular disease, such as high blood pressure in the subjects themselves or personality traits. For some of these factors associations with cardiovascular reactivity are well established.[69,70,71,72] This additional selection might result in an overrepresentation of specific subgroups within the genetically predisposed groups of subjects in studies. In the present meta-analysis no correction could be made for this because of insufficient information in individual articles.

The large discrepancies in study design and the methodological limitations prohibit definitive general conclusions but are illustrative of the problems encountered in research on stress responses. To be able to detect differences in stress reactivity, studies should be conducted in carefully selected groups. A perfect selection in this

type of study seems hard to obtain, but better methods than those used in the studies presented here are available. It is possible to select subjects of which both parents have blood pressure in the upper or lower tails of a population based blood pressure distribution.[61,88] This implies that the risk differences between the offspring groups can be manipulated and made as large as possible, while the risk of misclassification between future normotensive and hypertensive subjects is as small as possible.[61,63] The stress tasks employed in a study must be carefully selected according to the cardiovascular adaptations they elicit, in view of the pathological process expected to be found in pre-hypertensive subjects. Finally, the measurement variables should be extended with more direct indicators of neural activation, stroke volume and total peripheral resistance to be able to assess differences in cardiovascular regulating mechanisms.

In conclusion, according to the studies reviewed, hyperresponsiveness of blood pressure on both mental and physical stress tasks in subjects with a parental history of hypertension most probably exists. Due to limitations in measurement techniques the mechanisms responsible for these enhanced responses are still largely concealed.

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Chapter 2.3

CARDIOVASCULAR RESPONSE TO MENTAL STRESS IN OFFSPRING OF HYPERTENSIVE PARENTS

INTRODUCTION

The etiology of primary hypertension is still subject to debate. Several mechanisms have been proposed to explain why blood pressure rises with age in some subjects and remains at normal levels in others. Hypertensive subjects show hyperreactivity of both heart rate and blood pressure to acute stress as compared to normotensive controls.[1,2,3,4,5,6,7] According to one of the theories, this hyperreactivity is attributed to an enhanced reactivity of the sympathetic nervous system and is supposed to precede the hypertensive state.[8,9,10] Hyperreactivity of hypertensives appears to manifest itself more during exposure to behavioral stressors.[11,12] During mental stress, reactivity is assumed to be the consequence of higher nervous system processes or of a specific perception of stimuli, which may be related to personality characteristics.[10] Either way, confrontation with mental stressors may result in hyperreactivity in subjects with hypertension.

Epidemiologic studies have indicated that high blood pressure clusters in families partly because of shared genes.[13,14,15,16] In a number of studies, offspring of hypertensive parents and normotensive parents have been compared with respect to their reactivity of blood pressure and heart rate to mental stressors with equivocal results.[17,18,19,20,21,22,23,24,25,26,27] A factor hampering the comparability of studies is the great diversity of tasks that have been used. A clear distinction between cardiovascular reactivity patterns resulting from behavioral tasks and from physical tasks is known, but has rarely been considered.[11,28,29] The known difference in response patterns to distinct types of mental stress are even more neglected. Tasks with a large cognitive component induce a more pronounced adrenergic cardiac activation, while execution of a sensory-motor task primary results in a heightening of the peripheral resistance.[11,29,30]

Sympathetic hyperreactivity can theoretically be the result of two different mechanisms.[2,11] Firstly, of an enhanced stimulation of the heart, as the hyper ß-adrenergic hypothesis claims.[31,32] Secondly, of an enhanced increase in total

peripheral resistance due to a strongervasoconstriction.[33] In most studies cardiovascular measurements have been limited to heart rate and blood pressure, which are used as indices of sympathetic activity. Restriction to these measures makes it hard to reveal information about basic blood pressure regulatory mechanisms involved.

In the present study two groups of offspring were compared with a different risk of developing hypertension, based on family history of hypertension. The selection of offspring was based on a rigorous screening of a large group of parents. The study was conducted to examine cardiovascular adaptations during two distinct types of behavioral tasks, a memory search task and a reaction-time task, in the two groups of subjects with a contrasting family history. By measuring cardiac output and total peripheral resistance along with indices of sympathetic and parasympathetic nervous system activity, differences in blood pressure regulating mechanisms between the two groups were evaluated. Because body composition as well as fitness cluster in families and they are suspect to influence cardiovascular reactivity,[34] these potential confounders were considered in this study, by including body mass index (BMI) and maximal aerobic power.

SUBJECTS AND METHODS

Subjects

The present study is part of the Dutch Hypertension and Offspring Study.[35] For this study subjects (mean age 22.6±0.7 years) were selected who have either two hypertensive parents or two normotensive parents. They were selected from a large epidemiological study in the Dutch town of Zoetermeer. In this study, from 1975 to 1978 all the residents from two districts of Zoetermeer, were invited to participate in a screening of blood pressure and other cardiovascular risk factors.[36]

Blood pressure was measured in 10,532 of 13,462 eligible residents (78 percent). This group included 1642 couples with children. A stringent selection procedure, described previously,[35] was applied to these couples to select families with a maximal contrast in familial predisposition to hypertension. Individual parents with both systolic and diastolic blood pressure in the upper (hypertensive) or lower (normotensive) quartile of the age- and sex-specific blood pressure distribution were selected. Those who were receiving anti-hypertensive medication were included in the hypertensive group. The Dutch Hypertension and Offspring study is a collaborative undertaking supervised by a steering committee representing five Dutch universities and clinical

research centres.

Three groups of couples were invited for remeasurement of blood pressure for this study after a period of more than ten years: couples of which both were normotensive, those with one normotensive and one hypertensive member, and those of which both had hypertension. At the time of remeasurement, the same criteria for hypertension and normotension were applied as at the initial screening. Of the 250 couples that were restudied (80 percent of those invited), 121 were still in the blood pressure category to which they had originally been assigned: 35 couples of which both members were normotensive, 35 with one hypertensive and one normotensive member, and 51 of which both members were hypertensive. These 121 couples had 291 healthy biologic children, aged 5 to 30 years, who were invited to take part in the Dutch Hypertension and Offspring Study. The blood pressure values and other characteristics of the parents and their children (subjects) at the time of enrollment have been described previously.[37]

56 of the subjects (36 male) with two hypertensive parents and 43 of the subjects (26 male) with two normotensive parents participated in the present study. At the time they participated, all subjects were free from serious medical problems and were not taking any medication which could influence the tests. They were asked to refrain from smoking, drinking alcohol and using caffeine containing products 24 hours before they visited the research centre.

The study protocol was approved by the ethical committee of the Erasmus University Medical School, and written informed consent was obtained from the subjects and their parents.

Physiological measures

Body weight and height were measured with the subjects wearing only light clothes and no shoes. The Body Mass Index (BMI) as an index of obesity was calculated as body weight divided by the square of the height. To calculate the maximal aerobic power the subjects performed a supramaximal exercise test on an electrically braked bicycle ergometer (Tunturi EL400). Subjects were asked to breath through a high velocity, low resistance mouthpiece with a minimal dead space that shunted all the expired air into a Oxycon (Mynhardt Ox-4). This device calculates the amount of oxygen used and measures the air volume the subjects exhale.

Stressors

In the study two active coping tasks were used. A memory search task which was modelled after the Sternberg memory search paradigm used by Schneider and Shiffrin.[38] The task has been shown to evoke relatively large increases in cardiac output and in adrenergic cardiac drive. Participants had to remember a set of three letters (the memory set), given to them before the task started.[30] Thereafter, sets of one to four letters (the test set) were presented on the monitor in which either none or one of the letters of the memory set was present. Subjects had to press the 'yes' or 'no' button for the presence or absence of one of the memorized letters. The number of points they could win depended directly on the speed of reaction.

The other task was a tone avoidance reaction-time task. This task has been shown to mainly evoke an increase in vascular resistance. Subjects were seated behind a response panel with four buttons, one in each corner of the panel. During the task a stimulus was presented very briefly (500 msec) in one of the four corners of a video screen. They had to respond as fast as possible to the stimulus by pressing the button at their response panel opposite to the corner in which the stimulus was presented. Two succeeding correct responses were rewarded with 10 points. Incorrect or slow responses were punished with a loud noise burst next to a reduction of 10 points after two mistakes. The tasks have been described in detail elsewhere.[30]

All subjects had the opportunity to practice the tasks during three minutes just before the real task was executed. Because of the differences between subjects in age and education, four different levels of difficulty were available for both of the tasks. For both tasks performance levels were adapted to the subject according to their performance in the last minute of the training period and during the task the performance level was adjusted to the performance of the subject each minute. This resulted in a performance level close to the maximum for all participants.

Cardiovascular measurements

Signal recording: ECG Ag-AgCl electrodes were placed on the sternum and at the lateral margin of the chest. ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Mega-ohm impedance. The impedance cardiogram (ICG)[39] was recorded with a Nihon Kohden Impedance Cardiograph utilising Ag-AgCl spot electrodes.[40] The current electrodes were placed behind the cervical vertebra C4 and behind the thoracic vertebra T9. The measuring electrodes were placed 4 cm above the clavicle on the front of the neck and over the sternum at the fourth rib.[40] Basal impedance during rest and at task levels was registered by one of the experimentators.

The first derivative of the impedance signal, $\delta Z/\delta t$, was recorded with a time constant of 0.3 sec, 1 Mega-Ohm impedance and a high frequency cut-off of 75 Hz. The respiration signal was recorded with a hollow tube around the chest at a level 7 cm above the umbilicus. Respiration was measured as a function of the change in length of the tube due to breathing.

ECG, $\delta Z/\delta t$ and the respiration trace were displayed on a Beckman polygraph and sampled continuously at 250 Hz using a Olivetti pc M250 in combination with a 12 bit AD-converter. Data were stored on a tape (Tecmar) for later off-line processing. Blood pressure was measured every second minute with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This device uses an oscillometric method that measures mean arterial blood pressure (MAP), and estimates systolic blood pressure and diastolic blood pressure.[41,42,43]

Signal processing: Of the original signals a mean ECG and mean ICG complex was computed for each period of one minute with reference to the ECG R-wave.[44] The average complexes of ECG and ICG were used to calculate the pre-ejection period (PEP), the left ventricular ejection time (LVET), and the $\delta Z/\delta t$. PEP was used as an index of ß-adrenergic activity on the heart [45] and was defined as the time in msec between the Q-wave in the ECG and the B-point in $\delta Z/\delta t$ signal. LVET was defined as the time that elapsed between the occurrence of the B- and Z-point in the ICG. In this study the ratio PEP/LVET was used as an index of ß-adrenergic activity to correct for the influence of possible differences in afterload on PEP. The $\Delta Z/\delta t_{max}$ is the maximal rate of change in impedance, defined as the difference between the maximal amplitude of the $\delta Z/\delta t$ and the amplitude of the $\delta Z/\delta t$ signal at the B-point. LVET and $\Delta Z/\delta t_{max}$ were used to calculate the stroke volume (SV) using the formula proposed by Kubicek,[46]

$$SV = \rho \times (L_0/Z_0)^2 \times \Delta Z/\delta t_{max} \times LVET$$

In which ρ is the resistance of the blood at 100 KHz, which is set at a constant value of 135 Ohm×cm. This was done, because in vivo experiments have shown this to be as adequate as estimations using the haematocrit value.[47] L_0 is the shortest distance between the two (measuring) electrodes. Z_0 is the basal thoracic impedance.

Heart rate (HR) was computed as the total number of interbeat intervals divided by the measuring time and expressed as beats per minute (bpm). Cardiac output (CO) was computed by multiplying the SV with the HR. Several authors have shown satisfactory correspondence between CO derived from impedance cardiography and CO assessed with other methods as dye-dilution technique,[48,49] thermodilution technique,[50] Fick method.[51,52] Mean values of blood pressure were calculated

from all the measured values every two minutes. Total peripheral resistance (TPR) was estimated from CO and MAP:

$$TPR = (MAP/CO) \times 80 \text{ in dyne-seconds/cm}^5$$

From the respiration signal together with the ECG signal the magnitude of respiratory sinus arrhythmia (RSA) was computed using the peak-to-trough method,[53] by subtracting the largest interbeat interval during the expiration period from the shortest interbeat interval during the inspiration period. Mean RSA in milliseconds was computed for every minute, by averaging the RSA values over all breaths within that minute. Respiration rate was computed as the mean total cycle length in a one minute period and expressed as cycles per minute (cpm).

Experimental protocol

After height and weight were measured, the measurement devices were attached to the subjects. Next the subjects were seated supine in a quiet temperature controlled (20° Celsius) and sound shielded room in which the light was dimmed. They faced a monitor on which the stimuli were presented. The physiological monitoring and the delivery of the stimuli were controlled from outside.

Following an adaptation period, baseline measurements were recorded for 10 minutes during which the subject remained resting quietly. Subsequently, the first task was explained to the subject and a 3 minute period was given for practising. Next, the first task was performed for 10 minutes followed by a recovery period of 5 minutes in which the subject sat quietly. The protocol was identical for both the tone avoidance reaction-time task and the memory search task. The order in which the tasks were presented to the subjects was randomized.

After a break of 25 minutes in which the subjects were asked to relax, the subjects were installed again and a new baseline was recorded for 10 minutes in order to assess the post-stress resting level.

Later on the same day maximal aerobic power was measured. Participants were seated on a bicycle ergometer for a supramaximal exercise test according to an adapted version of the protocol proposed by Åstrand.[54] The subjects started at a load of ½ Watt/kg bodyweight at a constant pedalling speed of 70 rpm. Children under the age of 14 started at a load of ¼ Watt/kg bodyweight. After three minutes the load was increased, based on the heart rate. This was repeated three times in succession till the load reached a level 10 % above the estimated maximal aerobic level in the last period. The test was stopped once oxygen consumption did not rise any further, or the subject gave up.

Data-analysis

Mean values were calculated for all variables measured at rest (10 minutes) and during the tasks (10 minutes), and for the first two minutes of the recovery period after each of the two tasks. Post stress resting levels were subtracted from levels measured during the tasks and the recovery periods in order to get reactivity measures for measures as heart rate and blood pressure. Reactivity to the tasks of RSA and variables in which stroke volume was used, were expressed as a relative change from post-stress level.

For comparisons between the two groups, means and standard errors of the mean (SEM) are given, with two sided p-value for the difference. Adjustments for the differences in age and the proportion of males across the two groups were made by multiple linear regression. Associations between variables for the group as a whole were adjusted for differences in group characteristics (with use of indicator variables for group) and for age, gender, BMI and fitness by multiple regression analysis when appropriate. The BMDP statistical software package was used for data analysis.

RESULTS

Table 2.3.1: Measurements during the post-stress resting period in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Systolic blood pressure (mmHg)	111.2±1.3	118.2±1.2	6.99±1.77	<0.01
Diastolic blood pressure (mmHg)	65.7±1.0	71.2±0.9	5.57±1.31	<0.01
Heart rate (bpm)	65.8±1.6	64.3±1.4	-1.53±2.11	0.47
PEP/LVET	0.4±0.0	0.4±0.0	0.01±0.02	0.47
RSA† (msec)	98.2±5.9	102.9±5.4	4.65±8.14	0.57
Respiration rate (cpm)	18.8±0.5	19.8±0.5	0.98±0.71	0.17

* mean values±SEM, differences between groups are adjusted for differences in age and gender
† adjusted for differences in respiration rate between the two groups

Table 2.3.1 gives the baseline values of physiological variables that were measured at rest. Although all subjects were still normotensive, blood pressure was significantly higher at rest in offspring of hypertensive parents (mean difference in systolic blood pressure (±SEM) 6.00±1.77 mmHg ($p<0.01$), and in diastolic blood pressure 5.57±1.31 mmHg, ($p<0.01$)). There was no difference between the two groups in maximal aerobic power or BMI. Similarly, no differences in performance on each of the two tasks between the two groups were observed, evaluated by mean reaction-time and end-score on the two tasks (table 2.3.2).

Table 2.3.2: Body composition, fitness and the performance on the two tasks in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Gender (male/female)	26/17	36/20		
Percentage of subjects under the age of 14 (%)	10.9	19.0		
Mean age (years)	21.5±1.1	23.4±0.9	1.97±1.42	0.17
Height (cm)	172.0±1.7	173.9±1.5	1.89±2.29	0.41
Weight (kg)	65.7±1.9	68.2±1.6	2.52±2.50	0.32
BMI (kg/m^2)	21.5±0.4	22.3±0.3	0.74±0.52	0.16
Relative VO_2max (ml/kg×min)	40.3±1.1	38.5±0.9	-1.78±1.44	0.22
Reaction-time task score	343.7±28.5	301.6±23.7	-41.6±37.3	0.27
Nr. faults	51.1±3.8	56.3±3.2	5.22±4.98	0.30
Nr. trials	207.5±1.3	208.4±1.1	0.83±1.69	0.62
Memory search task score	-219.7±40.5	-163.7±34.0	56.04±53.23	0.30
Mean reaction-time (msec)	1171.2±72.4	1243.8±60.8	72.56±95.17	0.53

*mean values±SEM, differences between groups are adjusted for differences in age and gender

Physiological reactivity.

In the first instance, data were analyzed in three age strata. Because the results in all strata were essentially the same, only the comparison of the two groups as a whole will be presented.

Memory search task: Table 2.3.3 gives the results of the measures of reactivity to the memory search task, which is supposed to induce a relative strong cardiac activation as compared to the reaction-time task. Subjects with hypertensive parents had a higher systolic blood pressure response to this task (difference in response: 2.99±1.51 mmHg, p=0.05). No differences were found in diastolic blood pressure or heart rate reactivity, nor in change of sympathetic or vagal activation of the heart, as indicated by PEP/LVET and RSA. Neither were there any differences in change of stroke volume, cardiac output and total peripheral resistance to this task.

Table 2.3.3: Reactivity to the memory search task in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Change in:				
Systolic blood pressure (mmHg)	4.8±1.1	7.7±1.0	2.99±1.51	0.05
Diastolic blood pressure (mmHg)	4.1±0.9	4.9±0.8	0.80±1.17	0.50
Heart rate (bpm)	7.9±0.9	7.6±0.8	-0.23±1.21	0.85
PEP/LVET ($\times 10^{-2}$)	-0.4±0.7	-0.7±0.6	-0.34±0.90	0.70
RSA† (%)	-34.6±3.4	-35.9±3.1	-1.30±4.59	0.78
Stroke volume (%)	-2.7±2.3	-6.4±1.9	-3.71±3.01	0.22
Cardiac output (%)	4.1±4.1	3.0±3.5	-1.11±5.41	0.84
Total peripheral resistance (%)	5.3±5.4	10.2±4.6	4.94±7.16	0.49
Respiration rate (cpm)	2.4±0.5	2.2±0.5	-0.18±0.70	0.78

* mean reactivity±SEM, differences between groups are adjusted for differences in age and gender (post-stress resting levels are taken as baseline)
† adjusted for differences in respiration rate between the two groups

Reaction-time task with tone avoidance: As expected the reaction-time task mainly showed a peripheral vasoconstrictive effect and only a small cardiac effect. As indicated in table 2.3.4 the rise in calculated total peripheral resistance was higher in subjects with hypertensive parents (difference: 16.23±7.12 %, p=0.03). This did not translate in a more pronounced rise in blood pressure, most probably, because of a larger decline of stroke volume in subjects with hypertensive parents (difference: 6.27±3.02 %, p=0.04). The differences in cardiovascular reactivity patterns between the two tasks is clearly depicted in the response of cardiac output and total peripheral resistance (figure 2.3.1).

Table 2.3.4: Reactivity to the reaction-time task in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Change in:				
Systolic blood pressure (mmHg)	6.3±1.2	8.0±1.1	1.72±1.63	0.29
Diastolic blood pressure (mmHg)	5.0±1.0	5.8±0.9	0.77±1.30	0.56
Heart rate (bpm)	7.5±1.0	8.3±0.8	0.79±1.31	0.55
PEP/LVET ($\times 10^{-2}$)	-0.2±0.7	-0.6±0.6	-0.42±0.94	0.65
RSA† (%)	-30.1±3.1	-30.5±2.8	-0.87±4.19	0.84
Stroke volume (%)	-5.2±2.4	-11.5±1.9	-6.27±3.02	0.04
Cardiac output (%)	1.6±3.9	-3.7±3.3	-5.34±5.08	0.30
Total peripheral resistance (%)	4.0±5.5	20.2±4.5	16.23±7.12	0.03
Respiration rate (cpm)	2.2±0.5	1.9±0.5.2	-0.36±0.72	0.62

* mean reactivity±SEM, differences between groups are adjusted for differences in age and gender (post-stress resting levels are taken as baseline)
† adjusted for differences in respiration rate between the two groups

To assess whether the difference in reactivity to each of the two stress tasks was confounded by the difference in blood pressure between the two groups, adjustments for baseline systolic blood pressure were made. The difference in reactivity of systolic blood pressure to the memory search task between the two groups, however, became larger (difference adjusted for rest level: 5.56±1.75, $p < 0.00$). Adjustment for differences in blood pressure between the two groups resulted in a slight reduction of the difference in reactivity of stroke volume and total peripheral resistance (difference in stroke volume adjusted for blood pressure: -5.67±3.24, $p = 0.08$; difference in total peripheral resistance after adjustment for blood pressure: 15.04±7.57, $p=0.05$).

In the recovery period after each of the two stressors all the physiological variables returned to baseline levels in the same way for both groups, with the exception of systolic blood pressure and PEP/LVET after the memory search task. The systolic blood pressure remained 2.87±1.33 mmHg ($p=0.06$) above the resting levels in the offspring of hypertensive parents 2 minutes after the task was finished. This, most probably, was the result of the higher systolic blood pressure during the memory search task, because the difference between the groups disappeared after adjustment for reactivity of systolic blood pressure during the task (difference 1.04±1.10 mmHg, $p=0.37$). The PEP/LVET ratio was marginally lower (-0.015±0.008, $p=0.06$) in offspring of hypertensive parents during the recovery period, suggesting a higher sympathetic drive to the heart. This appeared not to be the result of a higher sympathetic drive during the task, because after adjustment for PEP/LVET reactivity during the task the difference in the ratio did not disappear (difference: -0.013±0.007, $p=0.07$). For both tasks and the recovery periods there were no indications of any influence of performance level, BMI or fitness on the reactivity measures.

DISCUSSION

In this study two groups of adolescents and young adults at different risks for hypertension were compared in their reactivity to two mental stress tasks. The two tasks have been selected, because the associated stress elicit distinct cardiovascular response patterns. To be able to scrutinize mechanisms regulating blood pressure during these different mental stress tasks, indices of cardiac output, total peripheral resistance and vagal and sympathetic cardiac influences were measured.

The results indicate, that the systolic blood pressure response to a 'cardiac task' (the memory search task) is enhanced in offspring of hypertensive parents. Furthermore, in this group average systolic blood pressure levels are higher in the

recovery period following the task, most probable as a result of the higher systolic blood pressure level during the task. A larger increase in calculated total peripheral resistance in offspring of hypertensive parents was observed during a 'vascular task' (the tone avoidance reaction-time task). This is not accompanied by clear differences in blood pressure or heart rate, probably because of a concomitant decline in stroke volume.

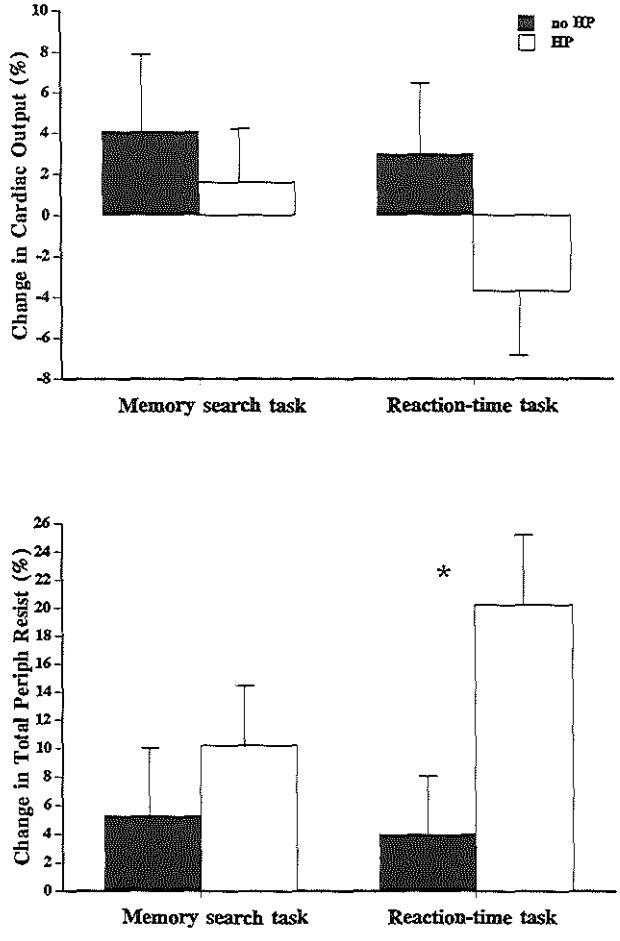

Figure 2.3.1:Reactivity of cardiac output and total peripheral resistance to the two mental stress tasks in offspring of two hypertensive parents (HP) and in offspring of two normotensive parents (no HP) (*: $p < 0.05$)

During the two tasks, no detectable differences in sympathetic or vagal drive to the heart were found. This is remarkable, in particular for the 'cardiac task', because confrontation with this kind of stressors, reportedly, results in a marked cardiac response. Earlier, this has been attributed to a higher sympathetic drive.[29,30] If sympathetic overactivation of the heart plays a role in the etiology of hypertension the 'cardiac task' is a condition in which this is expected to manifest itself. Yet in this study, only systolic blood pressure reactivity to this task was elevated in the high risk group, and the two groups did not differ in PEP/LVET or heart rate during either of the tasks.

The enhanced increase of the total peripheral resistance in offspring of hypertensive parents during the 'vascular task' could be an indication of an increased α-adrenergic responsiveness of peripheral vessels, resulting in vasoconstriction. In this respect it is worth noting, that we have observed an increased density of α_2-adrenoreceptors on platelets in the offspring of hypertensive parents (unpublished observations). This finding, and its relation to the present observations requires further attention.

The difference in systolic blood pressure in the recovery period after the 'cardiac task' is most probably not the result of differences in blood pressure regulating mechanisms, but a direct consequence of the higher blood pressure during the task. This prolonged elevation of the systolic blood pressure after a stress task, might cause additional strain on the cardiovascular system.

Subjects were selected as systolic and diastolic blood pressure of both of their parents were in either one of the most extreme quartiles of the blood pressure distribution. It has been shown, that larger contrasts in blood pressure measured between the parents result in larger differences in risk for hypertension in the offspring. Consequently, the number of real pre-hypertensive subjects in the group offspring of hypertensive parents depends directly on the selection method. Due to the extreme selection criteria in this study, large contrasts in risk for hypertension have been achieved. But as blood pressure runs in families and tracks within a subject, blood pressure is most likely already elevated at early age in offspring of hypertensive parents as compared to offspring of normotensive parents.[14,55,56,57,58] Although none of the subjects in our study had clear hypertension, it is conceivable that the difference in blood pressure between the groups may have caused the differences in cardiovascular reactivity rather than the reverse. This possibility is difficult to exclude, but one approach may be to adjust the observed differences for the difference in blood pressure between the groups. Adjustment for differences in systolic blood

pressure did not clearly affect the difference in response of systolic blood pressure to the 'cardiac task' or of stroke volume and total peripheral resistance to the 'vascular task'. It should be noted. however, that adjustment for blood pressure level may obscure true differences in characteristics related to the development of high blood pressure, as offspring with the highest blood pressure may be those with the highest risk for future hypertension.

Non-invasive measures are clearly advantageous in this study population. Impedance cardiography is easily performed and carries no risk or element of discomfort, as a result it can be used in larger groups of healthy subjects in a research centre. Accurate stroke volume and cardiac output measurements as compared to dye-dilution techniques as well as angiographic techniques have been demonstrated in adults as well as in children.[50,51,52] The results of impedance cardiography, however, may be affected by presence of heart failure, but this applies not to the subjects in this study. However, measurement errors of stroke volume might be somewhat large, as these measurements are an imperfect effort at best even by invasive techniques. Considering these limitations, it is even more striking that the results presented are so homogeneous.

The results presented here, provide arguments against sympathetic overactivation of the heart (the hyper-ß-adrenergic hypothesis) and are in favour of the hyper-vascular-reactivity theory. The results also fit the recently proposed idea, that blood pressure responses in subjects at risk for hypertension are primarily the result of peripheral vasoconstriction during stress, while in low-risk subjects blood pressure responses are largely due to an increased cardiac output.[59,60] This difference in hemodynamic pattern is considered to be the result of a more pronounced vascular activation pattern in pre-hypertensive subjects.

In most previous studies small, but statistically significant differences between offspring of normotensive and hypertensive parents in systolic or diastolic blood pressure response to mental stress were observed.[17,18,19,20,22,23,24,26,27] Comparison between these studies and the present work is difficult, because the already mentioned variety in relative contribution of vascular and cardiac components in reactivity to different types of mental stress. In general, tasks based on mental effort, like memory search tasks or mental arithmetic tasks, induce relatively strong ß-adrenergic cardiac impulses and vasodilatation. Greater increases in forearm blood flow during mental arithmetic in offspring of hypertensive parents have been demonstrated.[61] This could result in a higher systolic blood pressure in offspring of hypertensive parents. On the other hand, sensory intake tasks, such as reaction-time tasks, give a more pronounced

rise in peripheral resistance, which might result in a higher response of the diastolic blood pressure in offspring of hypertensive parents.[11,29,30]

Most studies only used blood pressure and heart rate as measures of hyperreactivity. In our study there were differences in systolic blood pressure response during the 'cardiac task'. Whereas there were indications of a more marked increase in peripheral resistance in offspring of hypertensive parents during the 'vascular task', there were no detectable differences in blood pressure reactivity. As blood pressure is the outcome of interactions of cardiac output and total peripheral resistance, evaluating blood pressure only gives no insight in mechanisms of cardiovascular adaptations to stress.

Comparing mean reactivity measures for whole stress periods, the duration of the tasks might be important. If hyperreactivity in pre-hypertensive subjects is the result of overactivation of the cardiovascular system in adaptation to the novelty of the stressor, it will only manifest itself in the first minutes of the task. Yet, analyses of cardiovascular reactivity data in which only the first two minutes of each of the two tasks were included show essentially similar results as analyses presented here for the whole task period.

In conclusion, our findings suggest that adolescents and young adults with a positive family history of hypertension have already elevated resting blood pressure levels and may also have an enhanced cardiovascular reactivity to mental stressors compared to subjects with normotensive parents. In spite of a higher systolic blood pressure response to a 'cardiac task', no indications were found for the presence of ß-adrenergic hyperreactivity of the heart during mental stress. The results of this study support the hypothesis that blood pressure responses in pre-hypertensive subjects are due rather to an enhanced vasoconstriction than to an increased cardiac output. Moreover, it is essential to take the type of mental stress task into consideration when interpreting the differences between groups with and without parental history of hypertension.

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Chapter 2.4

CARDIOVASCULAR RESPONSE TO PHYSICAL STRESS IN OFFSPRING OF HYPERTENSIVE PARENTS

INTRODUCTION

The use of stress tests to predict future hypertension is subject to debate. Mental stress tests, which are most often used, can discriminate between normotensive and hypertensive subjects as a group.[1,2,3,4] Physical stressors, without sizable concomitant psychological influences, have yielded conflicting results in discriminating between hypertensive and normotensive subjects.[5,6] However, they have been used successfully to predict future hypertension in longitudinal studies. In particular, the blood pressure response on a dynamic exercise test in (young) adults is reported to predict the development of hypertension within a period of three to six years.[7,8,9,10] Both kind of tests are claimed to trigger cardiovascular regulatory mechanisms, a disturbance of which might result in hypertension.

Basically two distinct categories of physical stressors are known. Static and dynamic muscle activity result in two different types of cardiovascular adaptations. During static exercise, as in the isometric handgrip task, blood pressure rises to supply additional blood flow through the active muscle necessary to satisfy the increased metabolic demands in the presence of the mechanical obstruction of muscle blood flow caused by the sustained contraction.[11] This can be accomplished by an increased cardiac output as well as by an elevated total peripheral resistance, due to vasoconstriction in inactive muscle groups. In contrast, dynamic exercise tasks as cycling or running lead to vasodilatation in large groups of active muscles.

The present study was conducted to examine reactivity to two different physical stressors in two groups of subjects with contrasting parental history of hypertension. An isometric handgrip task was used as a static exercise task and bicycle ergometry as dynamic exercise task. During the tests blood pressure and heart rate were measured. To study adaptations of the cardiovascular system, the cardiac output and the total peripheral resistance were assessed. Moreover, in order to investigate differences in cardiac drive, indices of sympathetic and parasympathetic activity on the heart were measured. Body composition as well as fitness cluster in families, and may both influence cardiovascular reactivity.[12] Potential mediating effects of differences in

body composition or fitness therefore were considered by including body mass index (BMI) and aerobic capacity in this study.

SUBJECTS AND METHODS

Subjects

The present study is part of the Dutch Hypertension and Offspring Study.[13] For this study adolescents and young adults (mean age 22.6±0.7 years) were invited who have either two hypertensive parents or two normotensive parents. They were selected from a large epidemiological study in Zoetermeer, the Netherlands. From 1975 to 1978 all residents from two districts of Zoetermeer were invited to participate in a study of blood pressure and other cardiovascular risk factors.[14] Blood pressure was measured in 10,532 of 13,462 eligible subjects (78 percent). This group included 1642 couples with children. A stringent selection procedure, described previously,[13] was applied to these couples to select families with a maximal contrast in predisposition to hypertension. Individual parents with both systolic and diastolic blood pressure in the upper (hypertensive) or lower (normotensive) quartile of the age- and sex-specific blood pressure distribution were selected. Those who were receiving anti-hypertensive medication were included in the hypertensive group. The Dutch Hypertension and Offspring study is a collaborative undertaking supervised by a steering committee drawn from five Dutch universities and clinical research centres.

Three groups of couples were invited for remeasurement of blood pressure for this study after a period of more than ten years: couples of which both were normotensive, those with one normotensive and one hypertensive parent, and those of which both had hypertension. At the time of remeasurement, the same criteria of hypertension and normotension were applied as at the initial screening. Of the 250 couples that were restudied (80 percent of those invited), 121 were still in the blood pressure category to which they had originally been assigned: 35 couples of which both members were normotensive, 35 with one hypertensive and one normotensive member, and 51 of which both members were hypertensive. These 121 couples had 291 healthy biologic children, all of whom were invited to take part in the Dutch Hypertension and Offspring Study. The blood pressure values and other characteristics of the parents and their children (subjects) at the time of enrolment have been described previously.[15]

56 of the subjects (36 male) with two hypertensive parents and 43 of the subjects (26 male) with two normotensive parents participated in the present study. At the

time they participated, all subjects were free from serious medical problems and were not taking any medication which could influence the tests. They were asked to refrain from smoking, drinking alcohol and the use of caffeine containing products 24 hours before they visited the research centre.

The study protocol was approved by the ethical committee of the Erasmus University Medical School, and written informed consent was obtained from the subjects and their parents.

Physiological measures

Body weight and height were measured with the subjects wearing only light clothes and no shoes. The Body Mass Index (BMI) as an index of obesity was calculated as body weight divided by the square of the height. To calculate the maximal aerobic capacity the subjects performed a supramaximal exercise test on an electrically braked bicycle ergometer (Tunturi EL400). Subjects were asked to breath through a high velocity, low resistance mouthpiece with a minimal dead space that shunted all the expired air into an Oxycon (Mynhardt Ox-4). This device calculates the amount of oxygen used and measures the air volume the subjects exhale.

Stressors

In the study two physical stressors were used. The first stressor was an isometric handgrip task.[11,16,17] The subjects had to squeeze a handle as hard as possible three times. The highest value they achieved was defined as their maximal power. The stressor consisted of keeping the handle squeezed at 22 % of the maximal power for five minutes. At this force, blood flow has been described to increase steadily during the activity,[16] so that cardiovascular adaptation mechanisms can be studied.

The second task was a dynamic exercise test on a bicycle ergometer.[11] After resting on the bicycle ergometer for three minutes, in which the anticipation reaction was measured, the subjects started to cycle at a load of ½ Watt/kg body weight at a constant pedalling speed of 70 rpm. Children under the age of 14 started at a load of ¼ Watt/kg. After each three minutes the load was imposed with ½ or ¼ Watt/kg body weight respectively.

Cardiovascular measurements

Signal recording: ECG Ag-AgCl electrodes were placed on the sternum and at the lateral margin of the chest. An ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Mega-ohm impedance. The impedance cardiogram (ICG)[18]

was recorded with a Nihon Kohden Impedance Cardiograph utilising Ag-AgCl spot electrodes.[19] The current electrodes were placed behind the cervical vertebra C4 and behind the thoracic vertebra T9. The measuring electrodes were placed 4 cm above the clavicle on the front of the neck and over the sternum at the location of the fourth rib.[19] Basal impedance during rest and at task levels was registered by one of the investigators. The first derivative of the impedance signal, $\delta Z/\delta t$, was recorded with a time constant of 0.3 sec, 1 Mega-Ohm impedance and a high frequency cut-off of 75 Hz. The respiration signal was recorded with a hollow tube around the chest at a level of 7 cm above the umbilicus. Respiration was measured as a function of the change in length of the tube due to breathing.

ECG, $\delta Z/\delta t$ and the respiration trace were displayed on a Beckman polygraph and sampled continuously at 250 Hz using a Olivetti pc M250 in combination with a 12 bit AD-converter. Data were stored on a tape (Tecmar) for later off-line processing.

Blood pressure was measured every second minute with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This device uses an oscillometric method that measures mean arterial blood pressure (MAP), and estimates systolic blood pressure and diastolic blood pressure.[20,21,22]

Signal processing: Of the original signals a mean ECG and mean ICG complex was computed for each period of one minute with reference to the ECG R-wave.[23] The average complexes of ECG and ICG were used to calculate the pre-ejection period (PEP), the left ventricular ejection time (LVET), and the $\delta Z/\delta t$. PEP was used as an index of ß-adrenergic activity on the heart [24] and was defined as the time in msec between the Q-wave in ECG and the B-point in $\delta Z/\delta t$ signal. LVET was defined as the time that elapsed between the occurrence of the B- and Z-point in the ICG. In this study the ratio PEP/LVET was used as an index of ß-adrenergic activity to overcome inaccurateness on PEP. The $\Delta Z/\delta t_{max}$ is the maximal rate of change in impedance, defined as the difference between the maximal amplitude of the $\delta Z/\delta t$ and the amplitude of the $\delta Z/\delta t$ signal at the B-point. LVET and $\Delta Z/\delta t_{max}$ were used to calculate the stroke volume (SV) using a formula proposed by Kubicek,[25]

$$SV = \rho \times (L_0/Z_0)^2 \times \Delta Z/\delta t_{max} \times LVET$$

in which ρ is the resistance of the blood at 100 KHz, which is set at a constant value of 135 Ohm×cm. This was done, because in vivo experiments have shown this to be as adequate as estimations using the haematocrit value.[26] L_0 is the shortest distance between the two (measuring) electrodes. Z_0 is the basal thoracic impedance.

Heart rate (HR) was computed as the total number of interbeat intervals divided

by the measuring time and expressed as beats per minute (bpm). Cardiac output (CO) was computed by multiplying the SV with the HR. Several authors have shown satisfactory correspondence between CO derived from impedance cardiography and CO assessed with other methods as the dye-dilution technique[27,28] thermodilution technique,[29] Fick method,[30,31] Mean values of blood pressure were calculated from all the measured values every two minutes. Total peripheral resistance (TPR) was estimated from CO and MAP:

$$TPR=(MAP/CO)\times 80 \quad \text{in dyne-seconds/cm}^5$$

From the respiration signal together with the ECG signal the magnitude of respiratory sinus arrhythmia (RSA) was computed using the peak-to-trough method,[32] by subtracting the largest interval during the expiration period from the shortest interval during the inspiration period. Mean RSA in milliseconds was computed for every minute, by averaging the RSA values over all breaths within that minute. Respiration rate was computed as the mean total cycle length in a one minute period and expressed as cycles per minute (cpm).

Experimental protocol

After height and weight were measured, the measurement devices were attached to the subjects. Next the subjects were seated supine in a quiet temperature controlled (20° Celsius) and sound shielded room in which the light was dimmed.

Following a relaxation period, baseline measures were recorded for 10 minutes during which the subject remained resting quietly. Then the maximal handgrip power was determined and 5 minutes later the handgrip task was executed. Subsequently the dynamic exercise test was carried out on the bicycle ergometer. This test was extended with two more periods of three minutes to measure the maximal aerobic capacity according to the protocol proposed by Åstrand.[11] For which, load was imposed based on heart rate, every three minutes, till it reached a level 10 % above the estimated maximal aerobic level in the last period. The test was stopped once oxygen consumption did not rise any further, or if the subject gave up.

Data-analysis

Mean values were calculated for all variables measured at rest (10 minutes), during the isometric handgrip task (5 minutes) and during the dynamic exercise task (three periods of 3 minutes). Resting levels were subtracted from levels measured during the tasks in order to get reactivity measures for heart rate and blood pressure. All reactivity scores to the tasks, for RSA and variables in which stroke volume was

used, were expressed as a relative change from resting levels.

For the comparisons between the two groups, means and standard errors of the mean (SEM) are given, with two sided p-value for the difference. Adjustments for differences in age and the proportion of males across the two groups were made with use of a multiple linear regression model. Associations between variables across the groups combined, were adjusted for differences in group characteristics (with use of indicator variables for group status) and for age, sexe, BMI and fitness by multiple regression analysis when appropriate. The BMDP statistical software package was used for data analysis.

RESULTS

Table 2.3.1 gives the baseline values of the physiological variables that were measured. Although the participants were still normotensive, blood pressure was higher at rest in offspring of hypertensive parents (difference in systolic blood pressure 6.99± (SEM) 1.77 mmHg, $p<0.01$, and in diastolic blood pressure 5.57±1.31 mmHg, $p<0.01$). There was no difference in relative aerobic capacity, BMI (table 2.3.2) or performance level on the isometric handgrip task between the two groups (table 2.4.1).

In the first instance data were analyzed in three age strata. Because the results in all strata were essentially the same, only the comparison of the two groups as a whole will be presented. In response to the isometric handgrip task both systolic and diastolic blood pressure were raised with the same magnitude in the two groups (table 2.4.1). The increase in heart rate was less pronounced in offspring of hypertensive parents (difference in heart rate response: -2.51±1.21 bpm, $p=0.04$), which resulted in a larger decline of the cardiac output in those subjects (difference: -8.95±4.55 %, $p=0.05$) (figure 2.4.1). The reactivity of the calculated total peripheral resistance during the task tended to be higher in the offspring of hypertensive parents (13.20±6.83 %, $p=0.06$) (figure 2.4.1). There were no differences in neural activation to the heart as measured indirectly by PEP/LVET and RSA (table 2.4.2).

To assess whether the difference in reactivity of the cardiac output and total peripheral resistance was confounded by the difference in blood pressure between the two groups, adjustments for baseline systolic blood pressure were made. The difference in change in cardiac output between the two groups, however, remained statistically significant (difference adjusted for blood pressure: -10.51±4.71 %, $p=0.03$). Adjustment for differences in blood pressure between the two groups resulted in a

slight reduction of the difference in reactivity of peripheral resistance (11.92±7.16 % , p=0.10). Analyses adjusted for differences in BMI or fitness did not reveal new insights.

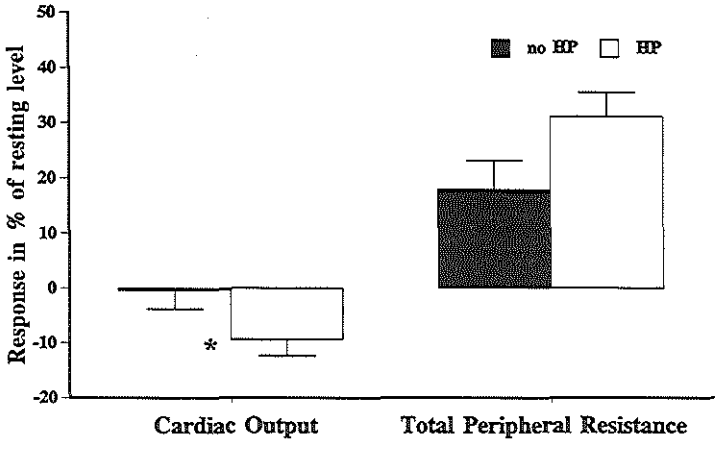

Figure 2.4.1:Reactivity of cardiac output and total peripheral resistance to the isometric handgrip task in offspring of two hypertensive parents (HP) and in offspring of two normotensive parents (no HP) (*: p=0.05)

Table 2.4.2 shows the reactivity measures during anticipation and two stages of cycling. As expected a substantial rise in cardiac output was found in both groups (over 60 % during the second cycling period). The increase of the stroke volume was smaller in offspring of hypertensive parents during each of the two cycling periods (difference in the first cycling period -11.49±5.42 %, p=0.04, and in the second cycling period -10.31±6.13 %, p=0.10) (figure 2.4.2). This resulted in a reduced elevation of the cardiac output in subjects with hypertensive parents as compared to subjects with normotensive parents (difference in the first cycling period -25.53±13.94 %, p=0.07, and in the second cycling period -16.77±17.09 %, p=0.33). The differences in adaptation of stroke volume between the two groups was not related to differences in systolic blood pressure.

Table 2.4.1: Reactivity to an isometric handgrip task in offspring of normotensive parents and offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Relative force (kg)	7.6±0.4	7.5±0.3	-0.10±0.46	0.83
Change in:				
Systolic blood pressure (mmHg)	9.3±1.2	10.1±1.1	0.78±1.65	0.64
Diastolic blood pressure (mmHg)	7.7±1.2	9.6±1.1	1.84±1.61	0.26
Heart rate (bpm)	5.0±0.9	2.5±0.8	-2.51±1.21	0.04
PEP/LVET ($\times 10^{-2}$)	-0.3±0.6	-0.4±0.6	0.66±0.85	0.44
RSA† (%)	-9.7±4.9	-3.8±4.7	5.87±6.89	0.40
Stroke volume (%)	-7.1±2.1	-10.2±1.8	-3.09±2.77	0.27
Cardiac output (%)	-0.4±3.4	-9.4±3.0	-8.95±4.55	0.05
Total peripheral resistance (%)	18.0±5.2	31.2±4.4	13.20±6.83	0.06
Respiration rate (cpm)	0.7±0.5	-0.3±0.4	-0.99±0.61	0.11

* mean reactivity values, adjusted for differences in age and gender
† adjusted for differences in respiration rate reactivity between the two group

No differences in reactivity between the two groups were found in the other variables both during anticipation and the two cycling periods. Due to technical limitations it was not possible to measure blood pressure reliably during cycling on the bicycle ergometer with a non-invasive method. Consequently only results from blood pressure measurements in the anticipation towards the test are presented in the table 2.4.2.

Table 2.4.2: Reactivity to a bicycle ergometer test in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Anticipation period				
Change in:				
Systolic blood pressure (mmHg)	2.0±2.6	3.8±2.2	1.73±3.42	0.61
Diastolic blood pressure (mmHg)	5.4±1.6	5.1±1.4	-0.37±2.14	0.86
Heart rate (bpm)	7.8±0.9	7.7±0.8	-0.12±1.24	0.92
PEP/LVET ($\times 10^{-2}$)	2.5±1.2	3.0±1.1	0.52±1.65	0.75
RSA† (%)	17.0±6.7	10.4±6.0	-6.63±9.05	0.47
Stroke volume (%)	0.4±3.4	-5.1±2.7	-5.46±4.33	0.21
Cardiac output (%)	16.3±6.8	9.3±5.8	-7.06±8.95	0.43
Respiration rate (cpm)	-2.3±0.6	-2.7±0.5	0.40±0.82	0.63
First cycling period				
Change in:				
Heart rate (bpm)	24.1±1.1	24.6±1.0	0.48±1.47	0.74
PEP/LVET ($\times 10^{-2}$)	-4.3±1.5	-5.2±1.3	-0.92±2.01	0.65
RSA† (%)	-35.5±6.2	-31.9±5.1	3.57±8.20	0.67
Stroke volume (%)	3.3±4.2	-8.2±3.4	-11.49±5.42	0.04
Cardiac output (%)	50.3±10.4	24.8±9.0	-25.53±13.94	0.07
Respiration rate (cpm)	0.8±0.7	2.0±0.6	1.19±0.98	0.23
Second cycling period				
Change in:				
Heart rate (bpm)	38.7±1.6	39.4±1.3	0.68±2.06	0.74
PEP/LVET	-7.6±1.7	-7.7±1.4	-0.13±2.22	0.95
RSA† (%)	-40.2±7.5	-45.1±6.3	-4.94±9.95	0.62
Stroke volume (%)	12.5±4.7	2.2±3.9	-10.31±6.13	0.10
Cardiac output (%)	82.8±13.4	66.0±10.5	-16.77±17.09	0.33
Respiration rate (cpm)	2.4±0.9	1.9±0.7	-0.53±1.10	0.63

* mean reactivity values, adjusted for age and gender
† adjusted for differences in reactivity of respiration rate between the two groups

DISCUSSION

The objective of this study was to examine short term adaptations of blood pressure regulatory mechanisms in subjects of hypertensive parents. Cardiovascular as well as neural indices were measured during two different types of physical stress in offspring of hypertensive parents and in offspring of normotensive parents.

The results of this study indicate an augmented response of total peripheral resistance to static exercise in offspring of hypertensive parents. This does not result in an enhanced blood pressure response most probably due to a larger decline of the cardiac output during the isometric handgrip task in subjects of hypertensive parents. During the dynamic exercise task the increase of stroke volume was reduced in offspring of hypertensive parents as compared to offspring of normotensive parents. The two groups did not differ significantly in sympathetic activation, measured by PEP/LVET, or vagal activation of the heart, measured by RSA.

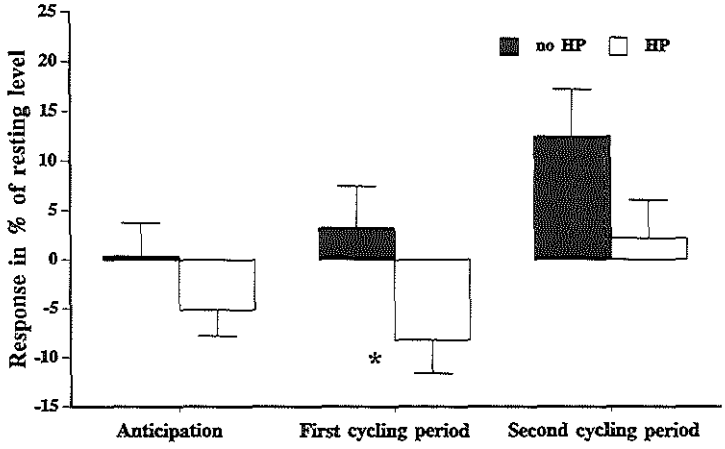

Figure 2.4.2:Reactivity of stroke volume to the dynamic exercise test in offspring of two hypertensive parents (HP) and in offspring of two normotensive parents (no HP) (*: $p < 0.05$)

The stronger response of the total peripheral resistance during static exercise may be explained by some other characteristics of the study groups. Total peripheral resistance largely depends on vasoconstriction. At least three mechanisms are known by which an enhanced vasoconstriction could explain a stronger response of the peripheral resistance in offspring of hypertensive parents. Besides structural changes of the blood vessels, as vascular hypertrophy[33] or reduced compliance of the arteries,[34,35] specific mechanisms of vascular smooth muscle, as defects in the calcium regulatory system,[36] might induce stronger vasoconstriction in pre-hypertensive subjects. Differences in calcium metabolism have been found between the two groups of subjects.[37] Finally vasoconstriction is also highly influenced by α and ß-adrenergic receptor density. Earlier studies in this group of subjects have shown a higher α-adrenergic receptor density on platelets in offspring of hypertensive parents (unpublished results).

The major result of the dynamic exercise test was a reduced increase of the cardiac output in offspring of hypertensive parents, due to an attenuated increase of the stroke volume. An explanation may be found in previously reported findings on the left ventricular dimension measured in the same groups.[38] The estimated left ventricular mass and the mass index was respectively 12.3 g and 8.7 g/m^2 greater in the offspring of hypertensive parents compared to offspring of normotensive parents. The same results have been found in borderline hypertensive subjects by Lund-Johansen.[39] According to this author, due to higher total peripheral resistance in early hypertension, the heart has to work against a higher blood pressure. This may result in a compensational growth of wall thickness of the left ventricle. The structural changes, consequently, result in a depressed response of the stroke volume during dynamic exercise.

From other studies, hyperreactivity of blood pressure to dynamic exercise was expected.[17,18] This could not be confirmed in this study. The non-invasive blood pressure measurements during cycling were not reliable, consequently those measures have not been presented. It is possible that there were differences in reactivity of blood pressure or peripheral resistance during cycling rather than in anticipation to the test. On the other hand, one might question the reliability of non-invasive blood pressure measurements in previous studies. Henschel[40] as well as Karlefors[41] showed that during physical activity the differences in mean arterial pressure between invasive and noninvasive measurements may amount to at least 10 mmHg.

Subjects were selected when systolic and diastolic blood pressure of both of their parents were in either one of the most extreme quartiles of the blood pressure

distribution. It has been shown, that larger contrasts in blood pressure measured in the parents result in larger differences in risk for hypertension in the offspring. Consequently, the number of real pre-hypertensive subjects in the group offspring of hypertensive parents depends directly on the selection method. Due to the extreme selection criteria in this study, large contrasts in risk for hypertension have been achieved. As blood pressure runs in families and tracks within a subject, blood pressure is most likely already elevated at early age in offspring of hypertensive parents as compared to offspring of normotensive parents.[42,43,44,45,46] None of the subjects in our study had clear hypertension, but it is conceivable that the difference in blood pressure between the groups may have caused the differences in cardiovascular reactivity rather than the reverse. Although this possibility is difficult to exclude, one approach may be to adjust the observed differences for the difference in blood pressure between the groups. Adjustment for differences in systolic blood pressure did not clearly affect the differences in response of cardiac output or total peripheral resistance to the isometric handgrip task. It should be noted, however, that adjustment for blood pressure level may obscure true differences in characteristics related to the development of high blood pressure, as offspring with the highest blood pressure may be those with the highest risk for future hypertension.

Non-invasive measures are clearly advantageous in this study population. Impedance cardiography is easily performed and carries no risk or element of discomfort, as a result it can be used in larger groups of healthy subjects in a research centre. Stroke volume and cardiac output measured by impedance cardiography has shown to provide valid results as compared to dye-dilution techniques as well as angiographic techniques in adults and children. The results of impedance cardiography, however, may be affected by presence of heart failure, but this applies not to the subjects in this study. However, measurement errors of stroke volume might be somewhat large, as these measurements are an imperfect effort at best even by invasive techniques.[29,30,31] Considering these limitations, it is even more striking that the results presented are so homogeneous.

In this study the enhanced increase in total peripheral resistance during static exercise did not result in an enhanced blood pressure response. In an earlier study higher blood pressure reactivity has been found, but this study was restricted to subjects with both a parental history of hypertension and high blood pressure.[47] When we compared offspring in our study population with both relative high blood pressure (systolic blood pressure $\geq$ 120 mmHg) and a positive parental history (n=27) to offspring with a negative parental history, the findings were essentially the same as

those presented; a significantly higher increase in total peripheral resistance but no difference in reactivity of blood pressure.

In conclusion, subjects with a parental history of hypertension have an enhanced response of total peripheral resistance during static exercise. It is probably because of a concomitant larger decrease of the cardiac output, that blood pressure reactivity is not increased. During dynamic exercise the physiologic increase of the stroke volume was limited in offspring of hypertensive parents.

The results presented here confirm the theory, that blood pressure responses during physical stress are achieved through different hemodynamic mechanisms in pre-hypertensive subjects as compared to normotensives. It is conceivable that such deviations in blood pressure regulation play a role in the etiology of hypertension.

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Chapter 3

FACTORS RELATED TO STRESS RESPONSES WHICH AGGREGATE IN FAMILIES

Chapter 3.1

FACTORS RELATED TO STRESS RESPONSES WHICH AGGREGATE IN FAMILIES

INTRODUCTION

In the previous chapter stress-reactivity was examined in subjects with contrasting risks for hypertension based on differences in parental blood pressure. This selection was inspired by the clustering of blood pressure in families.[1,2] A encumbrance of the selection method used is the possible clustering of other determinants of blood pressure in families.[3] Since families share environments as well as genes, the explanation of familial aggregation is not simply genetic. There is certainly a genetic component, but it is not known whether this is specially related to neural or circulatory blood pressure regulating mechanisms.

Genes could also be related to the tendency of for example anthropometric characteristics, fitness and personality to aggregate in families. All these factors have also shown to be related to blood pressure elevation[1,4,5,6,7,8,9,10] and are at least suspected to be related to blood pressure reactivity.[3] Hyperreactivity to mental stress in primary hypertensive subjects is assumed to be influenced by one's emotional disposition or personality traits.[11] At the same time indications have been found for a role of the sympathetic nervous system in the relation between obesity and hypertension, especially central fat patterning is suspected to be involved in this relation.[12,13]

Knowledge about these characteristics is of importance for the interpretation of the data on stress reactivity in the Dutch Hypertension and Offspring Study.

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Chapter 3.2

ANTHROPOMETRIC MEASURES, FITNESS AND HABITUAL PHYSICAL ACTIVITY IN OFFSPRING OF HYPERTENSIVE PARENTS

INTRODUCTION

The prevalence of obesity is relatively high among hypertensive subjects. Whether or not obesity is causally related to hypertension and the mechanism involved is, however, still unknown.[1,2,3] Evidence for a causal relation between obesity and blood pressure has been found in a reduction of blood pressure in obese hypertensive adults after weight reduction.[3,4,5]

Results from several studies have suggested an important role for obesity in childhood and adolescence in the development of high blood pressure.[6,7,8] Higher levels of blood pressure in childhood tend to be maintained throughout life.[9,10] Also, as childhood weight patterns tend to track into adulthood, markedly overweight children often become overweight adults.[13] An excess body weight gain appears to be highly predictive for elevation of systolic blood pressure levels in adults[11,12] and adolescents.[13] In particular, those who have a parental history of hypertension and high relative body weights are likely to develop hypertension later in life.[7]

Most studies have used the body mass index (BMI) as an index of obesity. This measure, however, does not take skeletal weight into account. Moreover, normal weighted individuals may be metabolically obese. Skinfolds thickness probably provides a better index for fatness, and fat distribution is more closely related to blood pressure levels than the total amount of fat.[7] The amount of central fat (upper body obesity) is associated with blood pressure levels[14] and with risk to become hypertensive in adult women.[15] It has been shown in middle aged Americans, that central fat measured by subscapular skinfolds predicts the development of hypertension even after adjustment for overall obesity or peripheral fat.[6]

Obesity results both from genetic factors and (over)-eating patterns, but there may also be other factors that concurrently influence fat distribution and blood pressure. A common denominator of blood pressure and fat distribution, for instance, may be physical fitness because exercise training affects fatness, fitness and blood pressure.[16,17,18,19]

Parental history of hypertension can be used as an indicator of risk for development of high blood pressure.[20] In an attempt to unravel the mechanisms, involved in familiar risk of high blood pressure, we studied whether there were differences in anthropometric measures, fitness and the amount of habitual physical activity between groups of subjects who differ in risk to become hypertensive.

SUBJECTS AND METHODS

Subjects

The present study is an extension of the Dutch Hypertension and Offspring Study.[21] For this study subjects were invited (mean age 22.6±0.7 years) who have either two hypertensive parents or two normotensive parents. They were selected from a large epidemiological study in Zoetermeer, the Netherlands. From 1975 to 1978 all the residents of two districts were invited to participate in a study of blood pressure and other cardiovascular risk factors.[22] Blood pressure was measured in 10,532 of 13,462 eligible residents (78%). This group included 1642 couples with children. A stringent selection procedure, as described previously,[21] was applied to these couples to select groups of parents whose offspring would have a maximal contrast in familial predisposition to hypertension. Individual parents with both systolic and diastolic blood pressure in the upper (hypertensive) or lower (normotensive) quartile of the age- and blood pressure distribution were selected. Those who were receiving anti-hypertensive medication were included in the hypertensive group. The Dutch Hypertension and Offspring Study is a collaborative study supervised by a steering committee drawn from five Dutch universities and clinical research centres.

Three groups of couples were invited for remeasurement of blood pressure for the present study after a period of more than ten years: couples of which both members were normotensive, those with one normotensive and one hypertensive parent, and those of which both members had hypertension. At the time of remeasurement, the same criteria of hypertension and normotension were applied as at the initial screening. Of the 250 couples that were restudied (80 percent of those invited), 121 were still in the blood pressure category to which they had originally been assigned: 35 couples of which both members were normotensive, 35 with one hypertensive and one normotensive member, and 51 of which both members were hypertensive. These 121 couples had 291 healthy biologic children, all of whom were invited to take part in this study. Of these subjects, who ranged form 7 to 32 years of age, 154 participated. The blood pressure values and other characteristics of the

parents and their children (subjects) at the time of invitation have been published previously.[23] 56 subjects (36 male) with two hypertensive parents and 43 (26 male) subjects with two normotensive parents participated in the present study. At the time they participated, all adolescents and young adults were free from serious medical problems and were not taking any medication that could influence the tests.

The study protocol was approved by the ethical committee of the Erasmus University, and written informed consent was obtained from the subjects and their parents.

Methods

Body weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) were measured with the subjects wearing only light clothes and no shoes. Two skinfolds (mid-triceps and subscapular) were measured as anthropometric indices. Both skinfolds were measures twice with a skinfolds thickness measurement device (Ponderal). The mean value of the two measurements was used as index of the skinfolds thickness. As an index of fat-distribution the ratio subscapular skinfolds to triceps skinfolds was calculated. The Body Mass Index (BMI) was calculated as body weight (kg) divided by the square of the height (meters). To estimate daily physical activity, a questionnaire modified after Taylor was used.[24] Questions were added referring to activities at school or work and the questionnaire was adapted to the Dutch population. Activities above 60% of the estimated maximal aerobic power have shown to produce cardiovascular training effects.[18] As indication for daily physical activity, the time spent on activities at a estimated level of minimal 60% of the maximal aerobic power was calculated from the questionnaire by the algorithm Taylor described. Test-retest reliability of this questionnaire was high (Pearson's $r = 0.99$) in subjects who reported their physical activities twice in a period of three months.

Maximal aerobic power was measured as an indicator of fitness. Subjects performed a supramaximal exercise test on an electrically braked bicycle ergometer (Tunturi EL400). They were asked to breath through a high velocity, low resistance mouthpiece with a minimal dead space that shunted all the expired air into an Oxycon (Mynhardt Ox-4). This device calculates the amount of oxygen the subjects use and measures the volume of air the subjects exhale. Subject started cycling at a load of ½ Watt/kg bodyweight at a constant pedalling speed of 70 rpm. Children under the age of 14 started at a load of ¼ Watt/kg bodyweight. After three minutes the load was increased based on heart rate levels. This was repeated three times in succession till the load reached a level 10% above the estimated maximal aerobic level. The test was

stopped if oxygen consumption did not rise any further, or the subject gave up.

Cardiovascular measurements

Blood pressure was measured every two minutes with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This device uses an oscillometric method to measure the mean arterial pressure, and calculates systolic blood pressure and diastolic blood pressure.[25,26]

ECG Ag-AgCl electrodes were placed at the sternum and at the 7th intercostal space near the axillaryline. The reference electrode was placed at the right side of the abdomen. Heart rate was computed as the total number of interbeat intervals derived from the ECG divided by the total measurement period and expressed as beats per minute (bpm).

Procedure

When the subjects arrived at the research centre, height, weight and the two skinfolds were measured. All subjects were asked to fill out the questionnaire modified after Taylor, by which daily activity and sport participation were measured in order to get an impression of the amount of physical work they performed over the last 6 months. After this the measurement equipment was attached to the subject. The subjects were seated in a quiet, temperature controlled (20° Celsius) and sound shielded room in which the light was dimmed. The physiological monitoring was controlled from outside the room.

After an adaptation period, baseline measures were recorded for 10 minutes during which the subject remained resting quietly. Subsequently, the subject performed a supramaximal exercise test according to an adapted version of the protocol of Åstrand on a bicycle ergometer.[18]

Data analysis

Descriptive data for the two groups are presented as means and standard errors of the mean (SEM). For comparisons between groups, means and standard errors of the mean are given, with the 95 % confidence interval (95 % CI) for the differences. Adjustments for differences in age and proportion of males across the two groups were made with use of a multiple linear regression model. Associations between variables across groups were adjusted for group characteristics (with use of indicator variable for group status) and for age and sex by multiple linear regression analysis. The BMDP statistical software package was used for data analysis.

RESULTS

Table 3.2.1 gives the mean values for blood pressure, heart rate, anthropometric measures and fitness corrected for differences in age and gender. Blood pressure of subjects with hypertensive parents was significantly higher (difference in systolic blood pressure: 6.99 mmHg, 95 % CI: 3.52, 10.46 and difference in diastolic blood pressure: 5.57 mmHg, 95% CI: 3.00, 8.14). The offspring of hypertensive parents was also somewhat older and this group comprised slightly more males.

Table 3.2.1: Anthropometric measures and measures of fitness and physical activity in offspring of two normotensive parents and offspring of two hypertensive parents*

	Offspring of two normotensive parents (A)	Offspring of two hypertensive parents (B)	Difference between B and A	95 % confidence interval of the difference
Gender (male/female)	26/17	36/20		
Mean age (years)	21.5±1.1	23.5±0.9	1.97	(-0.81, 4.75)
Systolic blood pressure (mmHg)	111.2±1.3	118.2±1.2	6.99	(3.52, 10.46)
Diastolic blood pressure (mmHg)	65.7±1.0	71.2±0.9	5.57	(3.00, 8.14)
Heart rate (bpm)	65.8±1.6	64.3±1.4	-1.53	(-5.60, 2.61)
Weight (kg)	65.7±1.9	68.2±1.6	2.52	(-2.38, 7.42)
Height (cm)	172.0±1.7	173.9±1.5	1.89	(-2.60, 6.38)
BMI (kg/m^2)	21.6±0.4	22.3±0.3	0.74	(-0.39, 1.78)
Subscapular skinfold (mm)	9.2±0.8	11.8±0.7	2.58	(0.62, 4.54)
Triceps skinfold (mm)	11.7±0.7	12.8±0.6	1.06	(-0.82, 3.98)
Ratio subscapular to triceps	0.9±0.1	1.0±0.1	0.16	(0.01, 0.31)
Relative VO_2max (ml/kg×min)	40.3±1.1	38.5±0.9	-1.78	(-4.60, 1.04)
Activity scale (×100,000 min/year)	0.6±0.1	0.6±0.1	0.01	(-0.01, 0.02)

* mean values±SEM, differences between the groups adjusted for differences in age and gender

In the first instance the data were analyzed in three age strata. Because the results in all strata were essentially the same, only the comparison of the two groups as a whole will be presented. After adjustment for differences in age and gender, subscapular skinfolds remained significantly higher in offspring of hypertensive parents

(difference: 2.58 mm, 95 % CI: 0.62, 4.54), while no significant difference in BMI was present (difference in BMI: 0.74 kg/m^2, 95 % CI: -0.39, 1.78). The subscapular skinfolds thickness remained higher in offspring of hypertensive parents after further adjustment for triceps skinfolds and BMI, indicating a difference in body fat distribution with an excess central fat in those adolescents and young adults. The same conclusion can be drawn from the higher ratio of subscapular skinfolds to triceps skinfolds (difference: 0.16, 95 % CI: 0.01, 0.31). No differences between the two groups were found in the measures of fitness or habitual physical activity.

Because the offspring of hypertensive parents already had a higher blood pressure, the differences in anthropometric measures might theoretically be the result of the differences in blood pressure, or an unknown factor closely associated with blood pressure. As a means of trying to exclude this hypothetical effect of blood pressure levels on body fat distribution, the anthropometric measures were adjusted for concomitant differences in systolic blood pressure. For both BMI and subscapular skinfolds the differences between the two groups slightly reduced. The subscapular skinfolds thickness, however, remained significantly higher in offspring of hypertensive parents (difference: 2.32 mm, 95 % CI 0.18, 4.46 after adjustment for systolic blood pressure, table 3.2.2).

Table 3.2.2: Anthropometric measures and measures of fitness and physical activity in offspring of two normotensive parents and in offspring of two hypertensive parents, adjusted for systolic blood pressure*

	Offspring of two normotensive parents (A)	Offspring of two hypertensive parents (B)	Difference between B and A	95 % confidence interval of the difference
Weight (kg)	68.0±1.8	66.5±1.5	-1.56	(-6.40, 3.28)
Height (cm)	174.0±1.7	172.4±1.4	-1.58	(-6.90, 2.93)
BMI (kg/m^2)	21.9±0.4	22.0±0.3	0.13	(-0.95, 1.21)
Subscapular skinfold (mm)	9.3±0.8	11.7±0.7	2.32	(0.18, 4.46)
Triceps skinfold (mm)	11.9±0.8	12.7±0.6	0.77	(-1.25, 2.79)
Ratio subscapular to triceps	0.8±0.1	1.1±0.1	0.15	(-0.01, 0.31)
Relative VO_2 (ml/kg×min)	40.4±1.1	38.4±1.0	-2.07	(-5.13, 0.99)
Activity scale (×1000 min/year)	0.6±0.1	0.6±0.1	-0.02	(-0.02, 0.02)

*mean values±SEM, differences between the groups adjusted for differences in age and gender

There were no direct associations between maximal aerobic power or habitual physical activity and blood pressure. In table 3.2.3a and 3.2.3b the continuous relations between maximal aerobic power, habitual physical activity and anthropometric measures for offspring of normotensive and offspring of hypertensive parents are given respectively. A clear inverse relation was found between maximal aerobic power as measure of fitness and subscapular skinfolds as a measure of central fat (b=-0.40 ml/kg×min/mm, 95 % CI: -0.56, -0.24), and between maximal aerobic power and triceps skinfolds as a measure of peripheral fat (b=-0.26 ml/kg×min/mm, 95 % CI: -0.42, -0.10) in adolescents and young adults with two hypertensive parents. The relation between central fat and fitness could not be confirmed in offspring of normotensive parents. This might be the result of the smaller skinfolds in this group. The relations between fitness and BMI or peripheral fat, however, were similar in the two groups. There was no relation between measures of central fat and peripheral fat or BMI and the amount of habitual physical activity the subject reported in either groups of offspring.

Table 3.2.3a: Relation between fitness, physical activity and anthropometric measures in offspring of two normotensive parents*

	Relative VO_2 (ml/kg×min)	95 % confidence interval	Activity scale (×100,000 min/year)	95 % confidence interval
Subscapular skinfolds (mm)	-0.02±0.12	(-0.25, 0.21)	-0.24±0.13	(-0.51, 0.03)
Triceps skinfolds (mm)	-0.22±0.12	(-0.45, -0.01)	-0.26±0.12	(-0.50, -0.02)
BMI (kg/m_2)	-0.18±0.10	(-0.38, 0.02)	-0.12±0.09	(-0.29, 0.06)
Activity scale (×100,000 min/year)	2.89±1.19	(0.57, 5.21)		

* results are coefficients of linear regression with 95 % confidence interval, adjusted for differences in gender.

Table 3.2.3b: Relation between fitness, physical activity and anthropometric measures in offspring two hypertensive parents*

	Relative VO_2 (ml/kg×min)	95 % confidence interval	Activity scale (×100,000 min/year)	95 % confidence interval
Subscapular skinfolds (mm)	-0.40±0.08	(-0.56, -0.24)	-0.18±0.20	(-0.57, 0.21)
Triceps skinfolds (mm)	-0.26±0.08	(-0.42, -0.10)	-0.10±0.17	(-0.44, 0.23)
BMI (kg/m_2)	-0.12±0.05	(-0.22, 0.02)	-0.05±0.11	(-0.26, 0.16)
Activity scale (×100,000 min/year)	2.46±0.96	(0.59, 4.33)		

* results are coefficients of linear regression with 95 % confidence interval, adjusted for differences in gender.

DISCUSSION

In this study subjects with contrasting risk for hypertension, according to their parental history of hypertension, were compared with respect to anthropometric measures, fitness and habitual physical activity. Offspring of hypertensive parents had more central fat, defined as subscapular skinfolds. This finding was independent from overall obesity measured as BMI. They also had higher levels of systolic and diastolic blood pressure, but an association between parental history of hypertension and central fat was found independently of actual blood pressure levels. Levels of habitual physical activity and maximal aerobic power did not differ between the two groups of adolescents and young adults. No indications were found for a direct relation between maximal aerobic power or habitual physical activity and blood pressure, most probably as a result of the lack of variation between subjects in aerobic power and physical activity. However, a relation between central and peripheral fat and fitness, as observed in the group as a whole confirms findings in previous studies and, may indicate an indirect influence on blood pressure.

The skinfolds measures used in this study were slightly skewed. Log transformed data gave marginally smaller p-values, but essentially the same results. For reasons of comprehensibility the non-transformed data were used in the tables. Relative body weight and presence of obesity are most often evaluated using the BMI. In our study, however, BMI did not differ between the two groups, although there was a clear

difference in central fat. One reason may be that the study population was relatively young and differences in BMI may become manifest only after maturation, with advancing age. Yet, analyses in which only subjects above the age of 18 were included, showed essentially similar results as those presented in this article. Only 5 out of 99 of the subjects were frankly obese (BMI>27), and three of them had hypertensive parents.

In this study aerobic fitness and habitual physical activity have both been measured, because of the conceptual differences between these two measures. Although habitual physical activity and relative aerobic power were significantly related, ($0.02\pm0.01 \times 100{,}000$ min/year/ml/kg×min $p<0.00$), an individuals' level of aerobic fitness is only partly determined by his or her physical activity. Twin studies have estimated that about 40% of the interindividual variance in aerobic fitness is of genetic origin,[27] a recent study even quoted a figure as high as 71%[28]

Although aerobic fitness has more intensively been studied, habitual physical activity is far more interesting from the perspective of prevention. Habitual physical activity level is difficult to measure. There are many different types of questionnaires in use, measuring physical activity over periods of a week to several years.[29] Their intercorrelation is only moderate, most probably because of low recall reliability. In this study a questionnaire was used to be able to correct for major differences between the two groups. Only vigorous activities as running, were recalled to trace extremely active subjects.

It is generally accepted that blood pressure levels are the result of the interaction of both environmental and constitutional factors.[30,31,32] In particular, anthropometric measures are most likely influenced by both environmental and genetic factors. From our study, it is not possible to make a distinction between genetic influences and effects of for instance diet on anthropometric measures. Although beyond the scope of this article several mechanisms have been proposed to link anthropometric measures to high blood pressure. Two mechanisms linking hypertension to obesity both involve the inhibition of insulin assimilation in the liver due to the release of free fatty acids from central deposits in the trunk. One potential mechanism involves the action of insulin in increasing renal reabsorption of sodium, alternatively insulin and carbohydrate metabolism may influence the sympathetic nervous system activity.[33,34,35,36,37] Also, a direct link between eating and hypertension by way of the sympathetic nervous system has been proposed.[38]

Although none of the subjects had clear hypertension, it is conceivable that the difference in blood pressure between the groups may have caused the differences in

anthropometric measures rather than the reverse. Although this possibility is difficult to exclude, one approach may be to adjust the observed differences for the difference in blood pressure between the groups. Adjustment for differences in systolic blood pressure did not clearly affect the differences in central fat. It should be noted however, that adjustment for blood pressure level may obscure true differences in characteristics related to the development of high blood pressure, as offspring with the highest blood pressure may be those at the highest risk of future hypertension.

Central fat has been claimed to be the most important indicator cardiovascular risk associated with obesity.[7] At the same time central fat may influence several mechanisms which might affect blood pressure levels, such as the activity of the sympathetic nervous system and renal function.[9] Although the subscapular skinfolds probably is the best indicator of central fat,[7] several authors have used the waist circumference as an approximate measure. The waist circumference strongly correlates with the subscapular skinfolds as a measure of fat patterning and several studies in adults have shown strong relations between waist circumference and blood pressure.[7,15,39]

In conclusion, our findings suggest that adolescents and young adults at risk of hypertension, as indicated by parental history, have more central fat than subjects of two normotensive parents. The relation between central fat and parental history appears to be independent of actual blood pressure levels. Bodyfat distribution and in particular an increase in central fat may play a part in the etiology of primary hypertension. The extent to which these factors determine future blood pressure, however, needs to be assessed in future studies.

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Chapter 3.3

PERSONALITY TRAITS AND CARDIOVASCULAR REACTIVITY IN OFFSPRING OF HYPERTENSIVE PARENTS

INTRODUCTION

Personality characteristics are suspect to play a role in the etiology of hypertension.[1,2,3] Cross-cultural differences in incidence of hypertension and hyperreactivity of blood pressure or heart rate to mental stress in hypertensive and borderline hypertensive subjects are proposed to support this view.[1] At least two factors are important to substantiate an influence of personality characteristics in the etiology of hypertension.[1] Firstly, hypertensive and normotensive subjects have to differ in personality characteristics. Secondly, an enhanced reactivity specially to mental stress should be demonstrated, because of the supposed influence of personality characteristics through sympathetic nervous system activity.[1]

Several personality characteristics have been suggested to be associated with hypertension[3,4] and could affect the results of reactivity studies. High blood pressure has been associated with type A behaviour:[5,6,7] a multifaceted personality construct comprising hard-drivingness, ambition, competitiveness, hostility, impatience and hyperalertness. Type A behaviour is also associated with hyperreactivity to certain stressors.[8,9,10,11,12,13,14] It appears to be more prevalent in untreated, mildly hypertensive individuals than in matched normotensive subjects[15] and in one study treatment of Type A behaviour resulted in a reduction of 'Type A score' along with a decrease in blood pressure reactivity.[16] Blood pressure levels have also been related to single faceted personality characteristics like neuroticism,[15,17] hostility and anger management,[18,19] or inhibited aggression.[17] At the same time, relations between enhanced sympathetic arousal and personality characteristics like 'denial and unwillingness to admit to neurotic feelings' or aggressiveness,[20] locus of control,[21,22] hostility,[17,23,24] and anxiety[17,25,26] have been suggested.

Different patterns in cardiovascular response to mental stress can be evoked either by task characteristics or by interactions between the task and certain characteristics of participants, such as personality characteristics.[26] It is generally accepted that sympathetic influences on the cardiovascular system are most

pronounced when subjects are engaged in active coping tasks and the degree of engagement in such tasks can be associated with personality characteristics as well as task characteristics.[27] The sympathetic nervous system has already been described as the major effector of cardiovascular reactivity and a possible site of malfunction in regulation, which might lead to sustained hypertension.[28]

In accepting a behavioral contribution to the pathogenesis of hypertension, the psychosomatic influences must be present well before the development of high blood pressure. Differences in personality characteristics and hyperreactivity to mental stress in already hypertensive subjects cannot be used as critical arguments since marked differences in blood pressure or even treatment may theoretically confound the association. In an attempt to overcome this problem, personality characteristics as well as blood pressure reactivity have been tested in offspring of hypertensive parents.[6,14,17,18,19] They form a non-hypertensive group with a relatively high probability to develop high blood pressure later. Results of these studies are, however, inconclusive. Only minor indications have been found for a relation between parental history of hypertension and personality characteristics or for a relation between personality characteristics and hyperreactivity. One reason might be the imperfect selection of the subjects in the studies, frequently based on family health questionnaires. Another reason might be the use of only heart rate and blood pressure as indices of cardiovascular hyperreactivity, as these measures may be too crude to detect minor circulatory changes. Another line of evidence for a relation between personality characteristics and hypertension, has been found in tracking in families of blood pressure[29] together with certain personality characteristics such as Type A behaviour patterns.[30]

In the present study two groups of adolescents and young adults with a contrasting risk for hypertension, based on parental blood pressure were compared. Recently, non-invasive methods to study neural activity at rest and during stress have come available. Pre-ejection time can serve as an index for sympathetic activation of the heart and respiratory sinus arrhythmia as an index for vagal inhibition of the heart. In the Dutch Hypertension and Offspring Study,[31] this provides an opportunity for an explorative study on the interrelations between parental history of hypertension, personality characteristics and stress reactivity to find indications for the influence of behavioral demands in the etiology of hypertension.

SUBJECTS AND METHODS

Subjects

The present study is an extension of the Dutch Hypertension and Offspring Study.[31] For this part of the study subjects (mean age 24.1±0.6) were selected who have either two hypertensive parents or two normotensive parents. They were selected from a large epidemiological study in a small Dutch town of Zoetermeer. In this study, from 1975 to 1978 all residents from two districts of Zoetermeer, were invited to participate in a study of blood pressure and other cardiovascular risk factors.[32] Blood pressure was measured in 10,532 of the 13,462 eligible residents (78 percent). This group included 1642 couples with children. A stringent selection procedure, described previously,[31] was applied to these couples to select families with a maximal contrast in predisposition to hypertension. Individual parents with both systolic and diastolic blood pressure in the upper ('hypertensive') or lower ('normotensive') quartile of the age- and sex-specific blood pressure distribution were selected. Those who were receiving anti-hypertensive medication were included in the hypertensive group. The Dutch Hypertension and Offspring Study is a collaborative undertaking supervised by a steering committee drawn from five Dutch universities and clinical research centres.

Three groups of couples were invited for remeasurement of blood pressure for this study after a period of more than ten years: couples of which both members were normotensive, those with one normotensive and one hypertensive member, and those of which both had hypertension. At the time of remeasurement, the same criteria of hypertension and normotension were applied as at the initial screening. Of the 250 couples that were restudied (80 percent of those invited), 121 were still in the blood pressure category to which they had originally been assigned: 35 couples of which both members were normotensive, 35 with one hypertensive and one normotensive member, and 51 of which both members were hypertensive. These 121 couples had 291 healthy biologic children, who were invited to take part in the study. The blood pressure values and other characteristics of the parents and their children at the time of enrolment have been described elsewhere.[33]

To fill out the questionnaires the subjects had to be over 15 years of age. 37 adolescents and young adults with two hypertensive parents and 24 with two normotensive parents fitted the criteria and were willing to fill out the questionnaires. At the time they participated, all subjects were free from serious medical problems and were not taking any medication which could influence the tests. They were asked

to refrain from smoking, drinking alcohol and using caffeine containing products 24 hours before they visited the research centre. The study protocol was approved by the ethic committee of the Erasmus University Medical School, and written informed consent was obtained from the subjects and their parents.

Measurements of psychological characteristics

All questionnaires used had been translated and adapted for use in a Dutch population.[34] The choice of psychological characteristics was based on the previous demonstration of a relationship between the variable and hypertension or between the variable and psychophysiological reactivity. Personality characteristics were assessed with the ABV, a Dutch questionnaire similar to the Eysinck Personality Questionnaire.[35] This questionnaire measures neurotic lability and introversion versus extraversion. In addition the subjects filled out the Jenkins Activity Survey (JAS) for type A behaviour.[36] Individual differences in coping style were assessed with the Utrecht Coping List.[37,38] This list has subscales for seven styles of habitual coping with stressful situations: active problem solving, palliative coping, problem avoidance, depressive responding, comforting cognitions, social support seeking, and expressing emotions. Since cardiovascular reactivity is particularly prominent in anger provoking situations, coping with such situations was measured specifically with a scale based on the Spielberger Anger Expression Scale.[39] The questionnaire yields scores for controlling anger-in, controlling anger-out, anger-in and anger-out. Anxiety was measured with the Spielberger Inventory for Trait Anxiety.[40] The questionnaires with their subscales are listed in table 3.3.1.

Stressor

As active coping task a memory search task was used, because this task has previously shown to differentiate between the two groups in systolic blood pressure reactivity.[41] The stressor was modelled after the Sternberg memory search paradigm used by Schneider and Shiffrin.[42] Participants had to remember a set of three letters (memory set), given to them before the task started. Thereafter sets of one to four letters (test set) were presented on the monitor in which none or one of the memory set would be present. Subjects had to press the 'yes' or 'no' button for the presence or absence of one of the memorized letters. To stress the subjects to speed and accuracy, they could win a number of points that depended directly on the correct reaction-time. The task has been shown to evoke relatively large increase in cardiac output.

All subjects had the opportunity to practice the task during three minutes just

before the real task had to be executed. Because of the large interindividual differences in age and education four different versions of the task with increasing difficulties were available. The level of difficulty was adapted to the subject according to their performance in the last minute of the training period and during the task the difficulty was adjusted to the performance of the subject each minute. This resulted in a performance level close to the maximum for all participants.

Table 3.3.1:Characteristics of the psychological questionnaires used in this study

Psychological variable	Psychodiagnostic test
Type A behaviour pattern	**Jenkins Activity Survey**[37]
Coping behaviour	**Utrecht Coping List**[38,39]
	-scale A: to attack and solve a problem
	-scale P: palliative reaction pattern
	-scale V: to avoid, to await
	-scale S: to search social support
	-scale D: depressive reaction pattern
	-scale E: to express emotions, anger
	-scale G: to have reassuring and comforting thoughts
Anger in / anger out	**Anger Expression List**[40]
	-scale AI: anger in feelings
	-scale AO: anger out feelings
	-scale CAI: control anger in
	-scale CAO: control anger out
Trait anxiety	**Zelf-beoordelingsvragenlijst-DY-2**[41](Dutch adapted version of Spielberger State-Trait Anxiety Inventory)
Neuroticism	**ABV**[36](Dutch Personality List similar to the Eysenck Personality Inventory)
	-scale N: neurotic lability, as far as manifested in psychoneurotic complaints
	-scale NS: neurotic lability, as far as manifested in functional physical complaints
	-scale E: introversion versus extraversion

Cardiovascular measurements

Signal recording: ECG Ag-AgCl electrodes were placed on the sternum and at the lateral margin of the chest. The ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Mega-ohm impedance. An impedance cardiogram (ICG)[43] was recorded with a Nihon Kohden Impedance Cardiograph utilising Ag-AgCl spot electrodes.[44] The current electrodes were placed behind the cervical vertebra C4 and behind the thorax vertebra T9. The measuring electrodes were placed 4 cm above the clavicle on the front of the neck and over the sternum at the fourth rib.[44] Basal impedance during rest and at task levels was registered by one of the experimentators. The first derivative of the impedance signal, $\delta Z/\delta t$, was recorded with a time constant of 0.3 sec, 1 Mega-Ohm impedance and a high frequency cut-off of 75 Hz.

The respiration signal was recorded with a hollow tube around the chest at a level 7 cm above the umbilicus. Respiration was measured as a function of the change in length of the tube due to breathing. ECG, $\delta Z/\delta t$ and the respiration trace were displayed on a Beckman polygraph and sampled continuously at 250 Hz using an Olivetti personal computer M250 in combination with a 12 bit AD-converter. Data were stored on a tape (Tecmar) for subsequent off-line processing.

Blood pressure was measured every other minute with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This device uses an oscillometric method that measures mean arterial blood pressure, and calculates systolic blood pressure and diastolic blood pressure.[45,46,47]

Signal processing: Of the original signals an average ECG and ICG complex was computed for each period of one minute with reference to the ECG R-wave.[48] The average complexes of ECG and ICG were used to calculate the pre-ejection period (PEP), the left ventricular ejection time (LVET). PEP was used as an index of ß-adrenergic drive to the heart,[49] and was defined as the time in msec between the Q-wave onset in the ECG and the B-point in $\delta Z/\delta t$ signal. LVET was defined as the time that elapsed between the occurrence of the B- and Z-point in the ICG. In this study the ratio PEP/LVET was used as index of sympathetic activity to the heart to overcome inaccurateness in PEP due to differences between the two groups in afterload. Heart rate was computed as the total number of interbeat intervals, calculated from the ECG signal, divided by the duration of the measurement period and expressed as beats per minute (bpm). Mean blood pressure was calculated from all the measured values every two minutes. From the respiration signal combined with the ECG signal the magnitude of respiratory sinus arrhythmia (RSA) was computed using the peak-to-trough method.[50] It calculates the RSA by subtracting the largest

interbeat interval during the expiration period from the shortest interbeat interval during the inspiration period. Mean RSA in milliseconds was computed for every minute, by averaging the RSA values over all breaths within that minute. Respiration rate was computed as the mean total cycle length in a one minute period and expressed as cycles per minute (cpm).

Experimental protocol

Subjects were seated supine in a quiet temperature controlled (20° Celsius) and sound shielded room in which the light was dimmed. They faced a monitor on which the stimuli were presented. The physiological monitoring and the delivery of the stimuli were controlled from outside.

After an adaptation period, baseline levels were recorded for 10 minutes during which the subject remained resting quietly. Subsequently, the memory search task was explained to the subject and a 3 minute period was given for practising. Next, the task was performed for 10 minutes. After a break of 25 minutes in which subjects were asked to relax, they were installed again and a new baseline was recorded for 10 minutes in order to assess the post-stress resting level. Finally, the subjects were asked to fill out the psychological questionnaires at home and to send them back.

Data-analysis

Mean values were calculated for descriptive data and the cardiovascular and neural indices measured at rest (10 minutes) and during the memory search task (10 minutes). Post stress resting levels were subtracted from levels measured during the task in order to get reactivity measures. For all of the personality variables, median values were calculated for each of the two groups of subjects. For the comparisons of the cardiovascular measures between the two groups, means and standard errors of the mean (SEM) are given, with two sided p-values for the difference. Adjustments for the differences in age and gender among the two groups were made with use of a multiple linear regression model. Because the results of some of the questionnaire were skewed, these data were analyzed non-parametricly. The Mann-Whitney-U test was used to examine the presence of differences in psychological variables between the two groups. Since it is likely that personality characteristics as assessed by different questionnaires are correlated, the data were entered in a factor analysis. In order to examine the correlations between the scores on the calculated factors and the physiological variables for the offspring of hypertensive parents, Kendall's tau (τ) was calculated. The BMDP statistical software package was used for data analysis.

RESULTS

Table 3.3.2 gives the baseline values of the cardiovascular and neural indices which were measured. Although all subjects were still normotensive, both systolic and diastolic blood pressure was higher at rest in subjects with hypertensive parents (difference in systolic blood pressure 4.26±1.96 mmHg, $p<0.03$ and in diastolic blood pressure 5.14±1.60 mmHg, $p<0.01$). Reactivity of systolic blood pressure to the mental load task in subjects with hypertensive parents was enhanced (difference in reactivity: 5.02±2.59, $p=0.06$) (table 3.3.3). No differences were observed in performance on the task between the two groups, as evaluated by mean reaction-time and end-score on the task. None of the psychological variables differed significantly between the two groups (table 3.3.4).

Table 3.3.2: Results from measurements during the resting period in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Gender (male/female)	13/11	22/15		
Mean age (years)	24.7±1.1	24.8±1.1	0.08±1.38	0.96
Systolic blood pressure (mmHg)	115.0±1.5	119.3±1.2	4.26±1.96	0.03
Diastolic blood pressure (mmHg)	67.4±1.2	72.5±1.0	5.14±1.60	<0.01
Heart rate (bpm)	63.4±2.2	63.9±1.8	0.53±2.84	0.85
PEP/LVET ($\times 10^{-1}$)	4.2±0.2	4.2±0.2	0.06±0.28	0.83
RSA† (msec)	88.0±10.2	100.6±8.3	12.6±13.1	0.34
Respiration rate (cpm)	18.4±0.7	19.6±0.5	1.17±0.84	0.17

* mean values±SEM, adjusted for differences in age and gender between the groups
† adjusted for differences in respiration rate between the two groups

The factor analysis comprising five factors explained 75 % of the total variance. The analysis revealed one factor that can be labelled as 'neurotic lability', 'anxiety' and 'depression', one factor as 'type A behaviour', 'expression of emotions' and 'search for social support', one factor as 'control of anger direction' and 'palliative reaction patterns', one factor as 'extraversion' and one factor 'avoidance behaviour'. Table 3.3.5

presents the labels for each factor, together with the weight of the associated questionnaires on that factor. The offspring of normotensive and hypertensive parents did not differ on the factor-scores for any of the factors.

Table 3.3.3: Reactivity to the mental load task in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Memory search task score	-219.7±40.5	-163.7±34.0	56.04±53.23	0.30
Mean reaction-time (msec)	1171.2±72.4	1243.8±60.8	72.56±95.17	0.53
Change in:				
Systolic blood pressure (mmHg)	3.0±2.0	8.0±1.6	5.02±2.59	0.06
Diastolic blood pressure (mmHg)	2.9±1.2	3.9±1.0	1.07±1.54	0.49
Heart rate (bpm)	8.4±1.2	7.8±1.0	-0.54±1.54	0.73
PEP/LVET ($\times 10^{-2}$)	1.0±1.0	-1.0±1.0	-1.91±1.00	0.38
RSA† (%)	-30.0±8.3	-29.8±6.8	0.17±10.7	0.99

* mean values±SEM, adjusted for differences in age and gender between the groups
† adjusted for differences in respiration rate between the two groups

Psychological characteristics and physiological measures

It can be assumed that offspring of hypertensive parents were most variable in their predisposition to become hypertensive. Since the two groups differed significantly in blood pressure levels, they were not pooled for the computation of the correlation between factors and physiological variables. Assuming that a predisposition to become hypertensive is associated with particular personality characteristics, the high-risk group was used for the computation of correlations between physiological variables and personality factor-scores.

A few weak inverse correlations were found between psychological factors and cardiovascular variables for offspring of hypertensive parents. There was an inverse correlation between heart rate at rest and factor 3 ($\tau=-0.43$, $p<0.01$). An inverse correlation was also found between PEP/LVET at rest and factor 5 ($\tau=-0.44$, $p<0.01$). RSA at rest and factor 3 showed a positive correlation ($\tau=0.41, p=0.01$).

A weak negative correlation was observed between the systolic blood pressure reactivity and factor 1 (τ=-0.28, p=0.05). Heart rate reactivity showed negative correlations with factor 2 (τ=-0.35, p=0.02) and factor 5 (τ=-0.41, p=0.01).

Table 3.3.4: Measures of personality characteristics in offspring of normotensive and in offspring of hypertensive parents*

	offspring of two normotensive parents	offspring of two hypertensive parents	p-value
Type A behaviour pattern	12.0 (5-22)	11.5 (3-21)	0.76
To express emotions, anger	57.0 (3-9)	57.0 (4-11)	0.79
Palliative reaction pattern	18.5 (11-29)	18.0 (13-23)	0.44
To have comforting thoughts	13.0 (10-18)	13.0 (7-17)	0.25
To avoid, to await	17.5 (10-25)	16.0 (11-23)	0.31
To attack and solve a problem	20.0 (11-26)	18.0 (11-25)	0.28
Depression reaction pattern	12.0 (7-18)	11.0 (8-23)	0.98
To search for social support	13.0 (8-21)	12.0 (7-24)	0.90
Anger in	36.0 (20-46)	35.0 (19-56)	0.89
Anger out	32.0 (18-45)	28.0 (17-62)	0.15
Control anger in	43.5 (28-60)	41.0 (25-59)	0.31
Control anger out	37.0 (24-48)	38.0 (21-51)	0.86
Trait anxiety	35.0 (22-50)	35.0 (24-67)	0.91
Introversion versus extraversion	57.0 (23-85)	57.0 (17-86)	0.20
Neurotic lability (psychoneurotic complaints)	44.0 (17-115)	46.5 (11-115)	0.95
Neurotic lability (physical complaints)	17.0 (12-31)	17.5 (12-40)	0.60

*values are median scores with ranges

DISCUSSION

To study the relation between personality characteristics and blood pressure levels or reactivity in pre-hypertensive subjects, two groups of adolescents and young adults were compared with respect to personality characteristics and stress reactivity.

These two groups of subjects were at different risks for hypertension due to their parental blood pressure. No evidence was found for differences in personality characteristics between these groups. Offspring of hypertensive parents already had a higher systolic as well as diastolic blood pressure at rest and their reactivity of systolic blood pressure to mental stress tended to be higher. Only a few relatively weak correlations were found between psychological characteristics and cardiovascular variables at rest in offspring of hypertensive parents. No major correlations were found between psychological variables and reactivity to the mental stress task in the same group.

Table 3.3.5: The personality factors with the weight of associated questionnaires on that factor

Factor	Questionnaire	Correlation
Factor 1	Neurotic lability (psychoneurotic complaints)	0.98
	Neurotic lability (physical complaints)	0.88
	Trait anxiety	0.80
	Depressive reaction pattern	0.76
Factor 2	Anger out	0.86
	To express emotions, anger	0.86
	Type A behaviour pattern	0.54
	To search for social support	0.40
Factor 3	Control anger out	0.86
	Control anger in	0.68
	Anger in	0.61
	Palliative reaction pattern	0.48
	To attack and solve a problem	0.34
Factor 4	Introversion versus extraversion	0.89
	To have comforting thoughts	-0.35
Factor 5	To avoid, to await	0.91

The absence of a clear relation between parental history of hypertension and personality characteristics is in accordance with part but not all of the literature.

[51,52] On the other hand, a number of studies related parental history of hypertension with Type A personality,[6] neurotic lability or aggression,[53] or anxiety and aggression.[19,53] Some studies reported higher sympathetic activity indicated by enhanced reactivity of heart rate ($p < 0.05$)[6,18,19,52,53] or systolic blood pressure reactivity ($p < 0.05$).[18,50,52,53] It has been shown that the type of stress task is of major importance for the cardiovascular reaction pattern.[54,55] A mental load task, such as the memory search task, induces a more pronounced cardiac activation, in contrast to the intake-rejection tasks which induce a relatively high response of the peripheral resistance. This, together with the use of heart rate and blood pressure as indices of sympathetic activity and the methodological limitations of selection methods used in previous studies, makes it hard to find conclusive evidence for a behavioral contribution to the pathogenesis of hypertension. In our study the participants were recruited based on blood pressure levels of both of their parents in a very stringent way, and PEP and RSA were added as indices of neural activation of the heart.

One factor which could potentially influence the outcome of the psychological scores relates to sensitivity of the questionnaires themselves. In this study the Dutch version of the JAS was used for practical reasons, while the structured interview type A score reportedly predicts better for differences in reactivity.[56] Also, not all questionnaires used have so far satisfactory been validated, this particularly applies to the Utrecht Coping List. Finally, the questionnaires for personality characteristics may not be sensitive enough to detect differences between groups with small numbers of subjects as presented here. In the epidemiological study in Zoetermeer from which participants for the present study were drawn, another list; the 'Dutch Personality Questionnaire' was used.[57] For the population as a whole (n=10,532) the subscales 'inadequacy', 'social inadequacy' and 'dominance' revealed small but significant relations with systolic and diastolic blood pressure (unpublished results). These scales are correlated with the three subscales of the ABV used in this study. However, when only the parents of the subjects participating in this study were compared on these scales, no significant differences in personality characteristics between the two groups were found, while large differences were present in blood pressure levels.

The findings of this study and of others, indicate that personality characteristics are unlikely to play an important role in the development of hypertension. As a result, differences found in cardiovascular reactivity to mental stress in offspring of hypertensive and normotensive parents are most probably the result of differences in adaptations of the neural or cardiovascular system rather than of differences in personality characteristics.[41] Further research should clarify to what extent a high

blood pressure could secondarily lead to personality changes, for example through an effect of hypertension on neuropsychological functions[58] or interpersonal relationships.[59]

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Chapter 4

NEURAL ACTIVATION OF THE HEART

Chapter 4.1

NEURAL ACTIVATION OF THE HEART

INTRODUCTION

Neural activation of the heart

It has been suggested that hypertension results from abnormalities in neural control of the circulation. Arguments in favour of this view can for example be found in a higher heart rate observed in some borderline hypertensive subjects.[1,2] Heart rate and cardiac output are neurogenically mediated and several reports have indicated that the sympathetic tone may be increased and the vagal tone reduced in pre-hypertensive subjects.[3] The increase in heart rate and cardiac output may reflect a hyper-ß-adrenergic state, because the abnormality resembles that induced by isoproterenol infusion.[4] Despite circumstantial evidence relating neural activity to hypertension, it is hard to find conclusive data. The next chapters present results of an approach to study indices of neurogenic activation to the heart in subjects at risk for hypertension by way of spectral analysis.

Two different aspects of neural activation have been studied. In the first chapter emphasis is on the neural activation to the heart by indices of sympathetic and parasympathetic activity. The baroreflex, which is one of the most important short term blood pressure regulating mechanisms, is object of research in the following chapter. Sympathetic and vagal activation are generally known concepts, but the baroreflex is less well-known, and a more detailed introduction is appropriate.

The level of blood pressure is the result of an equilibrium between cardiac output and peripheral resistance. Short term adjustments of heart rate to changes in blood pressure level (within seconds) are regulated by the baroreflex. The baroreflex has been defined as the loop between blood pressure levels, registered by the baroreceptors, and the interbeat-intervals (fig 4.1.1). The baroreceptors give a signal to the central nervous system and by way of sympathetic or vagal activity the interbeat-intervals are lengthened or shortened. To prevent high blood pressure, immediate and adequate correction of higher levels of blood pressure is of great importance. In this respect, two parameters of the baroreflex need to be considered. First, the average level of blood pressure the body tries to maintain. Second, the

sensitivity of the baroreflex, this is the extent of adaptation in heart rate within one cardiac cycle after a disturbance of the blood pressure.

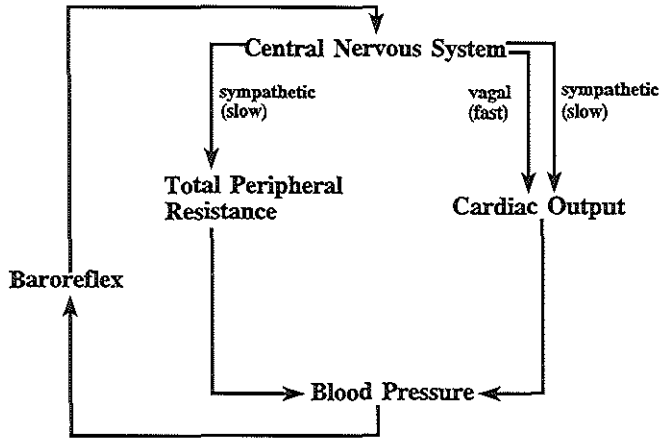

Figure 4.1.1: Scheme of baroreflex feedbackloop

Recently in literature new theories concerning the modification of these two parameters and their possible role in etiology of hypertension have been put forward. It is generally accepted that the setpoint of the baroreflex is tuned up as a result of a chronic rise in blood pressure.[5] Therefore, it is unlikely that longterm changes in setpoint play a role in the etiology of hypertension. For a long time the same reasoning was applied to baroreflex sensitivity,[1] until studies in rats showed a reduced baroreflex sensitivity in pre-hypertensive animals.[6,7] Consequently, it is most interesting to study the relation between hypertension and baroreflex sensitivity in pre-hypertensive subjects.

Baroreflex sensitivity is not a stable phenomenon, and changes in sensitivity have been documented throughout the day.[8,9,10,11,12] The sensitivity is at its highest level during sleep and declines rapidly during mental or physical activity. Baroreflex sensitivity may therefore play a role in the medium-term regulation of blood pressure during the day. Theoretically, baroreflex sensitivity, as a short term blood pressure regulating mechanism as well as the medium-term regulation by changes in baroreflex

sensitivity itself, might play a role in the initiation and maintenance of high blood pressure. Medium term regulation and the short term changes in baroreflex sensitivity which have been found can be the result of a feedback mechanisms activated by a pressor response (high blood pressure levels), for example due to physical activity. Another possibility is that blood pressure rises because the baroreflex sensitivity is reduced by inhibition from higher levels of the central nervous system. This, might occur during mental stress as the baroreflex sensitivity is supposed to be modulated by supramedullary influences as part of the central nervous system adjustments.[10]

Until recently, intra-venous administration of α-adrenergic agents such as phenylephrine have been used to study the baroreflex.[13] The only non-invasive ways of studying the baroreflex were the Valsalva manoeuvre or the neck chamber technique,[14] techniques which are hard to use during stress testing. Another major obstacle for research in larger healthy populations was the need for intra-arterial blood pressure measurements, which are necessary to obtain continuous blood pressure signals. The availability of the Fin-a-pres blood pressure measurement system together with spectral analysis gives researchers the opportunity to study the baroreflex reliably, in a for the subject unobtrusive way even during stress tests.[11,15,16]

Measuring neural activity by way of spectral analysis

Fluctuations in interbeat-interval have shown not to be completely random.[17,18] They are influenced by cardiovascular regulating mechanisms. In power spectra three 'spikes' can be observed (fig 4.2.1). These spikes are located at more or less the same spot in all subjects, across different situations[16]. One spike, located round 0.1 Hz is the reflection of influences of blood pressure regulating mechanisms. Both sympathetic and parasympathetic influences have shown to be present at this frequency.[19,20] The second spike can be found around 0.25 Hz. This spike depends on respiratory activity and appears to be predominantly determined by vagal activity.[18] This spike can move through the spectrum following changes in frequency of respiration. Extremely low breathing frequencies (round 10 cpm) make this spike shift to approximately 0.1 Hz. A third spike is present between 0.04 and 0.08 Hz. and is, among other factors, the result of influences of the renin-angiotensin system. This particular spike, however, is hard to measure because of the influences of the DC-component in the spectrum at the same location.[16,17] The relation between spikes in the spectra and neural blood pressure regulating mechanisms has been evaluated predominantly in studies in which autonomic nervous system blocking agents were used.[16,17,18]

In spectra made during different kinds of activity, the relative influence of different neural blood pressure regulating mechanisms can be evaluated. Figure 4.2.1 shows spectra made at rest and during stress. The differences in sympathetic and vagal activity during these different conditions are reflected in the shape and magnitude of the spikes in the spectra.

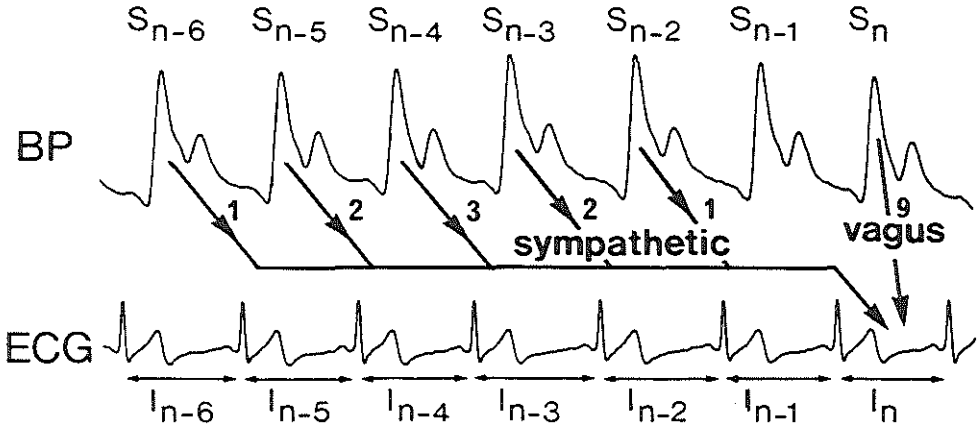

Figure 4.1.2: **The gain of the baroreflex (figure adapted from de Boer 1985)[21]**
Blood-pressure registration and electrocardiogram, indicating the control of cycle length by the vagus nerves and the sympathetic nerves. The interval length I_n is affected by the systolic values S_n and S_{n-2} to S_{n-6}. The vagal effect of S_{n-1} has already died out, and its sympathetic effect is not yet effective.

Measuring baroreflex sensitivity by way of spectral analyses

Variability in cardiac interbeat-intervals have a certain delay relative to systolic blood pressure fluctuations. In a comparison of spectra based on these two signals, the modulus or gain function specifies the ratio between changes in interbeat interval time (msec) and changes in systolic blood pressure (msec/mmHg) in a specified frequency band in the cross spectra of the two signals.[11] Generally, the modulus is measured in

the 0.1 Hz band, because there are no influences of respiration in this band. The spike is influenced by both the sympathetic and the parasympathetic activity. The response time of the parasympathetic nervous system is much shorter than that of the sympathetic nervous system (fig 4.1.2). Therefore, only the parasympathetic nervous system reacts rapidly enough to mediate high frequency fluctuations in heart rate corresponding to the mid- and high-frequency peaks of the spectrum, and the results found in cross spectra can be interpreted as results of vagal activity to the heart.

Spectral analysis together with Fin-a-pres blood pressure recordings gave us the opportunity to measure neural activation to the heart as well as the baroreflex sensitivity in young subjects non-invasively and unobstructively during different periods of rest and stress. In the next chapters the results of these studies will be described.

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Chapter 4.2

NEURAL REGULATION OF HEART RATE IN OFFSPRING OF HYPERTENSIVE PARENTS

INTRODUCTION

Alterations in neural activity have been implicated in the pathogenesis of primary hypertension.[1,2,3] In particular, an enhanced activity of the sympathetic nervous system has been put forward as one of the potential causes of primary hypertension.[2,3] Yet, the relative importance of sympathetic nervous system activity in the etiology of high blood pressure, and the pathway mediating such a role remains largely unexplained. One way of assessing the activity of the sympathetic nervous system in hypertensives is by monitoring reactivity of blood pressure or circulating catecholamines to stressors in hypertensive or borderline hypertensive subjects.[3,4] This approach is, however, rather indirect and global. A certain rise in blood pressure can be the result of enhanced cardiac activity as well as of stronger vasoconstriction. It is difficult to explain the mechanisms in detail from blood pressure rises alone. Moreover, the measurement of catecholamines in urine and in blood samples gives rather crude results.[1,5] Such measures may be useful to provide an overall picture of sympathetic activity, but do not monitor selectively sympathetic activation to the heart. For this purpose, more specific and sensitive methods are needed.

Power spectra may be used to analyze the frequency component of fluctuations in heart rate. In heart rate variability at least three frequencies can be distinguished.[6] One centred at the respiratory frequency, the so-called high-frequency peak (0.15-0.35 Hz). The second identifiable spectral peak, the mid-frequency peak, occurs typically between 0.07 and 0.14 Hz and appears to be related to blood pressure regulation. The third peak of the spectrum occurs typically at a central frequency from 0.02 to 0.06 Hz. This peak is claimed to be related to thermoregulatory fluctuations and renin-angiotensin system. More specifically, indications have been found for a representation of neural activation of the heart in the three peaks.[7,8,9] The parasympathetic system affects heart rate fluctuations above 0.1 Hz, as a result the high-frequency peak is only mediated by vagal activity.[8] The mid-frequency peak round 0.1 Hz appears to be influenced by both the sympathetic and the parasympathetic nervous system.[7,8,9] Enhanced sympathetic drive to the heart, as obtained by an orthostatic stimulus[9] as

band. Adrenergic blockade leads to a decrease of the mid-frequency component of the spectrum.[9]

In hypertension research the balance between sympathetic and parasympathetic activity is of particular importance. Activation of the heart can be accomplished by both a withdrawal of vagal stimulation or an enhanced stimulation by the sympathetic nerve. Both a lower vagal activity[11] as well as higher sympathetic activation,[3] of the heart have been described in hypertensive subjects. Although the mid-frequency peak has to be interpreted with care, the ratio mid-to-high frequency band has shown to provide a convenient index of the interaction (balance) between sympathetic and vagal cardiac drive.[9]

The aim of the present study was to assess sympathetic and parasympathetic impact on cardiac activity by means of power spectrum analysis of heart rate variability under conditions of mental and physical load in adolescents and young adults at risk of hypertension. Body composition as well as fitness cluster in families and are suspect to influence stress responses.[12] Therefore, body mass index (BMI) and aerobic power were simultaneously considered in the present study.

SUBJECTS AND METHODS

Subjects

The present study is an extension of the Dutch Hypertension and Offspring Study.[13] For this part of the study subjects (mean age 22.6±0.7 years) were selected who have either two hypertensive parents or two normotensive parents. The parents were selected from a large epidemiological study in Zoetermeer, the Netherlands. From 1975 to 1978 all residents from two districts of Zoetermeer, were invited to participate in a study of blood pressure and other cardiovascular risk factors.[14] Blood pressure was measured in 10,532 of the 13,462 eligible residents (78 percent). This group included 1642 couples with children. A stringent selection procedure, described previously,[13] was applied to these couples to select families with a maximal contrast in predisposition to hypertension. Individual parents with both systolic and diastolic blood pressure in the upper (hypertensive) or lower (normotensive) quartile of the age- and sex-specific blood pressure distribution were selected. Those who were receiving antihypertensive medication were included in the hypertensive group. The Dutch Hypertension and Offspring Study is a collaborative undertaking supervised by a steering committee representing five Dutch universities and clinical research centres.

Three groups of couples were invited for remeasurement of blood pressure for

the study after a period of more than ten years: couples of which both were normotensive, those with one normotensive and one hypertensive member, and those of which both had hypertension. At the time of remeasurement, the same criteria of hypertension and normotension were applied as at the initial screening. Of the 250 couples that were restudied (80 percent of those invited), 121 were still in the blood pressure category to which they had originally been assigned: 35 couples of which both members were normotensive, 35 with one hypertensive and one normotensive member, and 51 of which both members were hypertensive. These 121 couples had 291 healthy biologic children, who were invited to take part in the Dutch Hypertension and Offspring Study. The blood pressure values and other characteristics of the parents and their children at the time of enrolment have been described elsewhere.[15] 56 of the subjects (36 male) with two hypertensive parents and 43 of the subjects (26 male) with two normotensive parents participated in the present study. At the time they participated, all subjects were free from serious medical problems and were not taking any medication which could influence the tests. They were asked to refrain from smoking, drinking alcohol and using caffeine containing products 24 hours before they visited the research centre. The study protocol was approved by the ethical committee of the Erasmus University Medical School, and written informed consent was obtained from the subjects and their parents.

Physiological measures

Body weight and height were measured with the subjects wearing light clothes and no shoes. The Body Mass Index (BMI) as an index of obesity was calculated as body weight divided by the square of the height. To calculate the maximal aerobic power the subjects performed a supramaximal exercise test on an electrically braked bicycle ergometer (Tunturi EL400). Subjects were asked to breath through a high velocity, resistance mouthpiece with a minimal dead space that shunted all the expired air into an Oxycon (Mynhardt Ox-4). This device calculates the amount of oxygen used and measures the air volume the subjects exhale.

Stressors

As an active coping task the memory search task, modelled after the Sternberg memory search paradigm was used.[16] The task has been shown to evoke relatively large increases in cardiac output as compared to intake-rejection tasks.[17] This category of active coping tasks are most likely to induce differences in neural activation of the heart between the two groups.[18,19]

Participants had to remember a set of three letters (memory set), given to them before the task started. Thereafter sets of one to four letters were presented on the monitor in which none or one of the letters would be present (test set). Subjects had to press the 'yes' or 'no' button for the presence or absence of one of the letters of the memory set. The number of points they could win depended directly on the speed of reaction.[19]

All subjects got the opportunity to practice the task during three minutes just before the real task was executed. Because of the differences between subjects in age and education four different versions of the task with increasing degree of difficulty were available. The performance level was adapted to the subject according to performance in the last minute of the training period and during the task the individual performance level was adjusted to the performance of the subject each minute. This resulted in a performance level close to the maximum for all participants.

The second stressor was an isometric handgrip task.[20] During this task the muscle blood flow is inhibited by mechanical obstruction caused by sustained contraction of the muscle. Blood pressure rises to supply additional blood flow through the active muscle necessary to satisfy the increased metabolic demands. This can be accomplished by an increased cardiac output or an elevated total peripheral resistance, due to vasoconstriction in inactive muscle groups. The subjects had to squeeze a handle as hard as possible three times. The highest value they achieved was taken as their maximal power. During the task they had to keep the handle squeezed at 22% of this maximal power for five minutes.

Cardiovascular measurements

Signal recording: ECG Ag-AgCl electrodes were placed on the sternum and at the lateral margin of the chest. ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Mega-ohm impedance. The respiration signal was recorded with a hollow tube around the chest at a level 7 cm above the umbilicus. Respiration was measured as a function of the change in length of the tube due to breathing. The ECG and the respiration trace were displayed on a Beckman polygraph and sampled continuously at 250 Hz using an Olivetti personal computer M250 in combination with a 12 bit AD-converter. This frequency is very close to the one used in other studies,[21] and is adequate as long as the whole ECG is sampled and interbeat intervals are determined off-line. Data were stored on a tape (Tecmar) for later off-line processing. For accurate blood pressure measurement, blood pressure was measured every second

minute with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This devise uses an oscillometric method that measures mean arterial blood pressure, and calculates systolic blood pressure and diastolic blood pressure.[22,23]

Signal processing and spectral analysis: Interbeat intervals were calculated for each measuring period by scanning of the ECG signal at a trigger level at 20 % of the maximal amplitude of the Q-R interval with a correction procedure based on an interpolation algorithm. Because the interpolation algorithm did not correct all errors due to triggering of T-waves, the signal was additionally inspected for interbeat intervals shorter than 500 msec. Necessary corrections were made by hand. The number of corrections never exceeded 0.5 % of the total number of interbeat intervals. Spectral analyses were performed on the interbeat intervals with the CARSPAN program (version 1.2). The first 60 seconds of each rest or stress condition was not used because of expected stability problems.[24,25] Stability of the signal was assured by verifying that the difference between the spectral components calculated in two successive equally sized, interbeat interval series, which together constituted the rest or stressor condition, was less than 5% for all subjects together.[9] To be able to use the output of the program for interindividual comparisons the squared modulation index was calculated.[23,24] This means that all signal-fluctuations are considered as relative variations with respect to the mean value over the measuring period of the rest and stress conditions respectively.

The energy under three spectral bands was used (figure 4.2.1). The high-frequency band (0.15-0.35 Hz) which is linked to vagal activity. Although less well documented, as a working hypothesis, the mid-frequency band was used as a marker of sympathetic activity.[9,10,26] The ratio between the mid-frequency and the high-frequency peak was used as an index for sympatho-vagal balance.[9] The last peak which was analyzed was the 0.02-0.06 Hz peak, because of its relation with the function of the renin-angiotensin system and thermoregulation.[9]

Heart rate was computed as the total number of interbeat intervals divided by the measuring period and expressed as beats per minute (bpm). Respiration rate was computed as the mean total cycle length in a one minute period and expressed as cycles per minute (cpm).

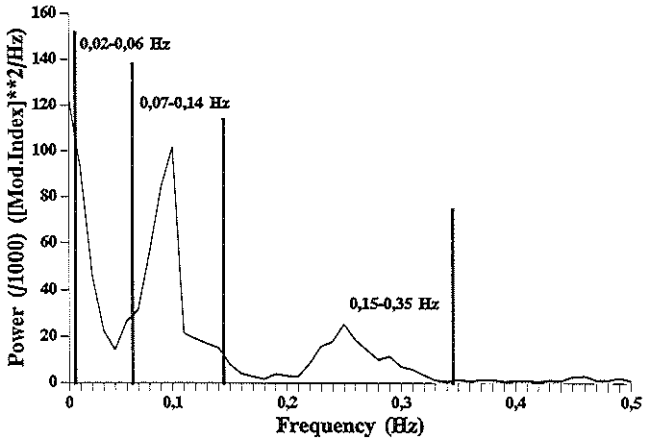

Figure 4.2.1:Power spectrum of interbeat intervals with the bands of interest

Experimental protocol

After height and weight were measured, the measurement equipment was adjusted to the subjects. Next the subjects were seated supine in a quiet temperature controlled (20° Celsius) and sound shielded room in which the light was dimmed. They faced a monitor on which the stimuli were presented. The physiological monitoring and the delivery of the stimuli were controlled from outside.

After an adaptation period, baseline measurements were recorded for 10 minutes during which the subject remained resting quietly. Subsequently, the memory search task was explained to the subject and a three minute period was given for practising. Then the task was performed for 10 minutes. After a break of 25 minutes in which the subjects were asked to relax, they were installed again and a new baseline was recorded for 10 minutes. This resting period was taken for baseline values in the analyses. Next the maximal handgrip power was determined and the handgrip task was executed for 5 minutes.

Later on the same day maximal aerobic power was measured. Participants were seated on a bicycle ergometer for a supramaximal exercise test according to an adapted version of the protocol of Åstrand.[27] They started at a load of ½ Watt/kg bodyweight at a constant pedalling speed of 70 rpm. Children under the age of 14 started at a load of ¼ Watt/kg bodyweight. After three minutes the load was increased, based on the heart rate. This was repeated three times in succession till the load reached a level 10 % above the estimated maximal aerobic level in the last

period. The test was stopped once oxygen consumption did not rise any further, or if the subject gave up.

Data-analysis

Mean values were calculated for all measured variables at rest (10 minutes), during the mental load task (10 minutes) and the isometric handgrip task (5 minutes). Because the distribution of the three spectral peaks was skewed, logarithmically transformed data were used in the statistical analyses. For comparisons between the two groups, untransformed means and standard errors of the means (SEM) are presented, with two sided p-values for the difference. Adjustments for the differences in age and gender across the two groups were made with use of linear regression. Associations between variables were adjusted for differences in group characteristics (using indicator variables for group), for age, gender, BMI and fitness by multiple linear regression analysis when appropriate. The BMDP statistical software package was used for data analysis.

RESULTS

Table 4.2.1 gives the results for the resting period as reported previously.[17] Although all subjects were still normotensive, blood pressure was higher in offspring of hypertensive parents (difference in systolic blood pressure (±SEM) 6.99±1.77 mmHg, $p<0.01$, and in diastolic blood pressure 5.57±1.31 mmHg, $p<0.01$). There was no difference in BMI or aerobic power between the two groups. Similarly no differences in performance on each of the two tasks between the two groups was observed. The results of the spectral analysis showed no differences in power at rest between the two groups in either one of the peaks (table 4.2.2).

Three subjects were removed from the final analyses because of large differences in power between the first and the second part of a measurement period. Table 4.2.3 gives the results of the spectral analysis during the two stressors; the memory search task and the handgrip task. The shift in neural activation of the heart from rest to stress in one subject is depicted in figure 4.2.2. During the memory search task the energy in all three bands of the spectrum declined as expected, but no differences were found in neural activity between the two groups. The blood pressure persisted at significant higher levels in response to the memory search task in subjects with hypertensive parents as compared to subjects with normotensive parents (table 4.2.4).

In response to the isometric handgrip tasks the power in the high-frequency band

declined in offspring of normotensive parents as expected, but remained at a high level in offspring of hypertensive parents (difference in high-frequency band between the two groups: 553.3±250.9 milli-modulation index^2, $p=0.05$). Most probably as a result, the difference in sympathetic-vagal balance relatively reduced in subjects of hypertensive parents (difference: -0.09±0.03, $p<0.01$). To assess whether the differences in the high-frequency band or the ratio mid-to-high frequency band were confounded by differences in blood pressure between the two groups, the results were adjusted for systolic blood pressure. After adjustment, the difference between the two groups remained the same (difference in high-frequency band: 565.5±235.0 milli-modulation index^2, $p=0.03$ and difference in ratio: -0.10±0.03, $p=0.01$).

Heart rate tended to be lower in adolescents and young adults with hypertensive parents during isometric exercise (difference -4.64±2.40 bpm, $p=0.06$; table 4.2.4). To test whether or not differences in heart rate between the two groups during the isometric handgrip task were related to differences in vagal activity as depicted by the power in the high frequency band, heart rate was analyzed with adjustment for differences in the high frequency band and ratio mid-to-high frequency. The difference in heart rate between the two groups disappeared after adjusting for high-frequency band or ratio mid-to-high frequency band (after adjusting for the high-frequency band difference in heart rate: -2.54±2.29 bpm, $p=0.27$ and after adjusting for the ratio difference in heart rate: -2.87±2.57 bpm, $p=0.27$). No direct associations were observed between the measures of neural activity at rest or during stress, and respiration rate, BMI or fitness. There were also no indications for either task of any influence of performance level.

Table 4.2.1: Body composition, fitness and the performance on the memory search task and the isometric handgrip task in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Gender (male/female)	26/17	36/20		
Mean age (years)	21.5±1.1	23.4±0.9	1.97±1.42	0.17
Height (cm)	172.0±1.7	173.9±1.5	1.89±2.29	0.41
Weight (kg)	65.7±1.9	68.2±1.6	2.52±2.50	0.32

Table 4.2.1(cont.)

	Offspring of two normotensive parents (A)	Offspring of two hypertensive parents (B)	difference between B and A	p-value
Relative VO_2 (ml/kg×min)	40.3±1.1	38.5±0.9	-1.78±1.44	0.22
Systolic blood pressure (mmHg)	111.2±1.3	118.2±1.2	6.99±1.77	<0.01
Diastolic blood pressure (mmHg)	65.7±1.0	71.2±0.9	5.57±1.31	<0.01
Heart rate (bpm)	65.8±1.6	64.3±1.4	-1.53±2.11	0.47
Respiration rate (cpm)	18.8±0.5	19.8±0.5	0.98±0.71	0.17
Isometric handgrip relative force (kg)	7.6±0.4	7.5±0.3	-0.10±0.46	0.83
Memory search task score	-219.7±40.5	-163.7±34.0	56.04±53.23	0.30
Mean reaction-time (msec)	1171.2±72.4	1243.8±60.8	72.56±95.17	0.53

*mean values±SEM, adjusted for differences in age and gender between the groups

Table 4.2.2: Results spectral analysis on interbeat intervals measured at rest in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value†
Low-Frequency band (milli-modulation index^2)	643.9±116.2	982.4±112.7	38.5±161.8	0.83
Mid-Frequency band (milli-modulation index^2)	943.9±117.4	1012.3±115.0	68.4±164.3	0.77
High-Frequency (milli-modulation index^2)	953.4±123.4	1212.0±120.9	258.6±172.8	0.42
Ratio Mid-to-High Frequency band	1.01±0.02	0.99±0.01	-0.03±0.03	0.34

*mean values±SEM

†results of statistical testing apply to data analyzed on a log transformed scale, adapted for differences between the groups in age and gender

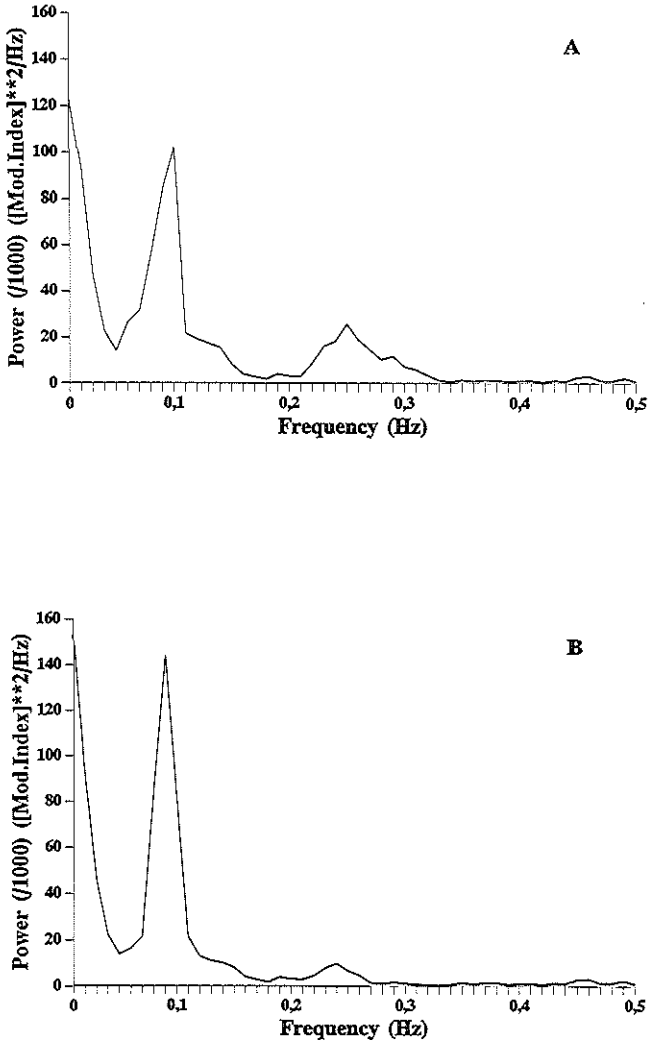

Figure 4.2.2:An example of two power spectra of data collected at rest (A) and during mental stress (B) in one of the subjects. Fluctuations are expressed as a fraction of the mean power

Table 4.2.3: Results spectral analysis on interbeat intervals measured in response to the two stressors in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value†
Memory search task				
Low-Frequency band (milli-modulation index^2)	372.4±120.9	372.4±115.0	0.00±166.8	0.99
Mid-Frequency band (milli-modulation index^2)	437.0±123.3	566.8±126.2	129.8±169.4	0.33
High-Frequency band (milli-modulation index^2)	464.1±131.0	566.8±120.9	102.7±178.3	0.57
Ratio Mid-to-High Frequency band	1.00±0.03	1.02±0.02	0.02±0.03	0.62
Handgrip task				
Low-Frequency band (milli-modulation index^2)	804.3±116.2	897.8±112.7	93.5±161.9	0.57
Mid-Frequency band (milli-modulation index^2)	1022.5±119.8	1074.9±116.2	52.4±166.9	0.84
High-Frequency band (milli-modulation index^2)	772.8±153.4	1326.1±198.5	553.3±250.9	0.05
Ratio Mid-to-High Frequency band	1.06±0.02	0.98±0.01	-0.09±0.03	<0.01

*mean values±SEM, adjusted for differences in age and gender between the groups
†results of statistical testing apply to data analyzed on a log transformed scale

Table 4.2.4: Heart rate and blood pressure levels in response to the two stressors in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	p-value
Memory search task				
Systolic blood pressure (mmHg)	113.5±1.9	125.1±1.4	11.56±2.39	<0.01
Diastolic blood pressure (mmHg)	69.1±1.3	75.9±1.0	6.79±1.64	<0.01
Heart rate (bpm)	73.1±2.6	72.6±1.9	-0.42±0.32	0.90
Handgrip task				
Systolic blood pressure (mmHg)	121.6±2.4	126.8±2.0	5.10±3.15	0.11
Diastolic blood pressure (mmHg)	74.3±1.7	79.0±1.4	4.71±2.17	0.04
Heart rate (bpm)	70.4±1.9	65.8±1.5	-4.64±2.40	0.06

*mean values±SEM, adjusted for differences in age and gender between the groups

DISCUSSION

Hypertension, at least in certain individuals, has been suggested to result from neural disregulation.[1,2,3] In this study neural activation was evaluated by way of spectral analysis in subjects with different risk for hypertension due to their parental history. No difference in neural activation at rest between the two groups of adolescents and young adults could be demonstrated using spectral analysis on variability of interbeat intervals. Rather, the findings suggest a more pronounced vagal activation of the heart in response to static exercise in offspring of hypertensive parents as compared to offspring of normotensive parents. As no difference was found in mid-frequency band, this is an indication of a reduced sympatho-vagal balance.

It is possible, that the relative increase in vagal activity as indicated by more power in the high-frequency band during static exercise, is secondary to processes elsewhere. In a separate project, we have observed an increased density of α_2-adrenoreceptors on platelets in offspring of hypertensive parents (unpublished results). During mental stress as well as during static exercise the same adolescents and young adults showed a tendency to react with a relatively strong rise in peripheral

resistance.[28] The differences in vagal activity found in this study may reflect a protection of the body to a further rise of blood pressure as a result of an increased peripheral resistance, although such an explanation remains speculative.

Vagal activity is known to be related to respiration rate.[6,8,29,30] Spectral analyses in which the high-frequency band was calculated as a respiratory-linked peak (mean respiration frequency ± 0.03 Hz)[31] showed essential the same results as in the high-frequency band defined 0.15-0.35 Hz, presented here. Therefore, differences in respiration rate between subjects most likely do not explain the differences between the two groups in response to static exercise.

The selection method used in this study resulted in large contrasts in risk for hypertension between the two groups adolescents and young adults. As blood pressure clusters in families, differences in blood pressure levels of the parents can be used to predict risk to become hypertensive in their offspring.[32,33] Similarly, blood pressure tracks within subjects and future hypertensives most likely have relatively high blood pressure, already, at a young age. A high contrast in risk to become hypertensive between groups of offspring almost certainly induces differences in blood pressure level at rest. Although none of the subjects had clear hypertension at the time of the study, it is conceivable that the difference in blood pressure between the groups may have caused the differences in neural activity rather than the reverse. This possibility is difficult to exclude, but one approach may be to adjust the observed differences for the difference in blood pressure between the groups. Adjustment for differences in systolic blood pressure did not clearly affect the differences in vagal tone or sympatho-vagal balance during static exercise. It should be noted however, that adjustment for blood pressure level may obscure true differences in characteristics related to the development of high blood pressure, as offspring at the highest blood pressure may be those at the highest risk of future hypertension.

No difference between the two groups in heart rate was found at rest and during mental stress. A tendency towards a lower heart rate in adolescents and young adults with hypertensive parents was found during static exercise, which could be explained by an enhanced vagal activity to the heart, as also indicated by more power in the high frequency band in subjects at risk.

In this study specific bands of the power spectrum are used as an indication for neural activity. Although well documented, it remains an indirect method to measure neural activation of the heart. Especially the peak at 0.1 Hz which is used as an indication for sympathetic activity must be interpreted with care, because of the vagal influences at this frequency.

Direct measures of neural activity to the heart in pre-hypertensive subjects are still not available, but spectral analysis is gradually accepted as a valid noninvasive and unobstructive way to study neural activity to the heart under varying conditions. This makes it possible to study large groups of subjects in a further attempt to unravel the role of neural activity in the etiology of hypertension. The results of our study indicate that sustained vagal activity of the activity of the heart during static exercise rather than enhanced sympathetic drive may characterise the early phase of primary hypertension.

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Chapter 4.3

DIMINISHED BAROREFLEX SENSITIVITY IN OFFSPRING OF HYPERTENSIVE PARENTS

INTRODUCTION

One of the most important short term blood pressure regulatory mechanisms is the baroreflex. It is generally accepted that the sensitivity of the baroreflex declines with age and is remarkably lower in subjects with high blood pressure.[1,2,3,4] For long it has been assumed that a suppression of baroreflex sensitivity may result from chronically increased blood pressure.[5] However, recent evidence suggests that baroreflex sensitivity is in part determined by genetic factors[6] and that it may be suppressed at rest in normotensive individuals with hypertensive parents.[7,8,9] It is possible, therefore, that the baroreflex is involved in the etiology of hypertension.

Although the baroreflex is known for its reactivity to, and modification of, acute changes in blood pressure it also plays a role in circadian control of pressure throughout the day. The sensitivity of the baroreflex decreases during physical work and mental stress and peaks during sleep.[10,11,12,13,14] Recently, it has become possible to measure blood pressure continuously in a noninvasive way[15,16] and spectral analysis of heart rate and blood pressure provides a reliable index of the baroreflex sensitivity.[14,17] Using these methods, it is possible to estimate the baroreflex sensitivity reliably and noninvasively in healthy subjects.

The present study was carried out to clarify the role of the baroreflex in the control of blood pressure under varying conditions, including two stress periods, in subjects at risk for hypertension. Three conditions have been chosen because of the differences in blood pressure regulation they reflect. Using the family history approach, the present study was conducted as part of the Dutch Hypertension and Offspring Study in 56 subjects with two hypertensive parents and 43 subjects with no hypertensive parents.

SUBJECTS AND METHODS

Subjects

The study is an extension of the Dutch Hypertension and Offspring Study.[18,19] For this study adolescents and young adults (mean age 22.6±0.7 years) with either two hypertensive parents or two normotensive parents were included. They were selected from a large epidemiological study that was conducted from 1975 to 1978 in all residents from two districts of the Dutch town Zoetermeer, who participated in a study of blood pressure and other cardiovascular risk factors.[20] Blood pressure was measured in 10,532 of the 13,462 eligible residents (78 percent). This group included 1642 couples with children. A stringent selection procedure, described previously,[17] was applied to these couples to select families with a maximal contrast in predisposition to hypertension. Individual parents with both systolic and diastolic blood pressure in the upper or lower quartile of the age- and sex-specific blood pressure distribution were selected (figure 4.3.1). Those who were receiving anti-hypertensive medication were included in the hypertensive group. The Dutch Hypertension and Offspring Study is a collaborative undertaking supervised by a steering committee drawn from five Dutch universities and clinical research centers.

Three groups of couples were invited for remeasurement of blood pressure for this study after a period of more than ten years: couples of which both were normotensive, those with one normotensive and one hypertensive member, and those of which both had hypertension. At the time of remeasurement, the same criteria for hypertension and normotension were applied as at the initial screening. Of the 250 couples that were examined (80 percent of those invited), 121 were still in the blood pressure category to which they had originally been assigned: 35 couples of which both members were normotensive, 35 with one hypertensive and one normotensive member, and 51 of which both members were hypertensive. These 121 couples had 291 healthy biologic children, who were invited to take part in the study. The blood pressure values and other characteristics of the parents and their children at the time of enrollment have been reported previously.[18]

56 subjects (36 male) with two hypertensive parents (high blood pressure family) and 43 subjects (26 male) with two normotensive parents (low blood pressure family) participated in the present study. At the time they participated, all subjects were free from serious medical problems and were not taking any medication which could influence the tests. They were asked to refrain from smoking, drinking alcohol and using caffeine containing products 24 hours before their visited to the research center.

The study protocol was approved by the ethical committee of Erasmus University Medical School, and written informed consent was obtained from the subjects and their parents.

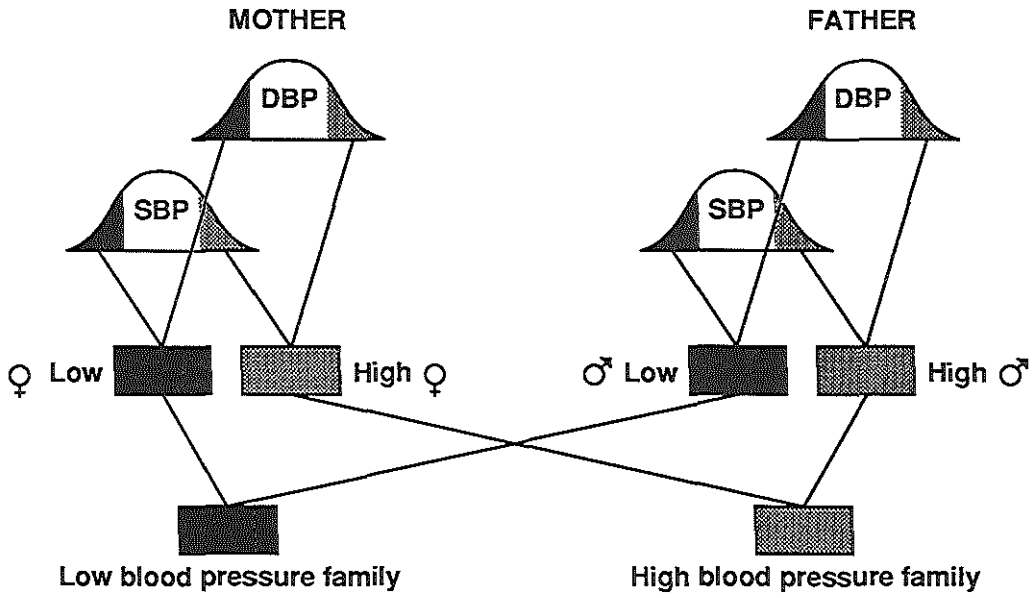

Figure 4.3.1:Schematic representation of the selection of parents in the upper (high blood pressure family) or lower (low blood pressure family) quartile of the age- and sex-specific blood pressure distribution

Physiological measurements

Body weight and height were measured with the subjects wearing light clothes and no shoes. The Body Mass Index (BMI) as an index of obesity was calculated as body weight divided by the square of the height. To calculate the maximal aerobic

power the subjects performed a supramaximal exercise test on an electrically braked bicycle ergometer (Tunturi EL400). Subjects were asked to breath through a high velocity, low resistance mouthpiece with a minimal dead space that shunted all the expired air into an Oxycon (Mynhardt Ox-4). This device calculates the amount of oxygen used and measures the air volume the subjects exhale.

Stressors

As an active coping task a memory search task was used,[21] modelled after the Sternberg memory search paradigm used by Schneider and Shiffrin.[22] Participants had to remember a set of three letters (the memory set), given to them before the task started. Thereafter, sets of one to four letters were presented on the monitor in which none or one of the letters would be present (test set). Subjects had to press the 'yes' or 'no' button for the presence or absence of one of the letters of the memory set. The number of points they could win depended directly on the speed of reaction. All subjects got the opportunity to practice the task. The performance level was adapted to the subjects performance in the training period and during the task the performance level was adjusted to the performance of the subject each minute. This resulted in a performance level close to the maximum for all participants.

The second stressor was an isometric handgrip task.[23] The subjects had to squeeze a handle as hard as possible three times. The highest value they achieved was taken as their maximal power. During the task they had to keep the handle squeezed at 22% of this maximal power for five minutes.

Cardiovascular measurements

Signal recording: ECG Ag-AgCl electrodes were placed on the sternum and at the lateral margin of the chest. ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Mega-ohm impedance. Blood pressure was measured continuously by a Fin-a-pres (Ohmeda 2300 Fin-a-pres).[24] The ECG and the continuous blood pressure signal were displayed on a Beckman polygraph and the ECG was sampled continuously at 250 Hz using a personal computer (Olivetti M250) in combination with a 12 bit AD-converter. Data were stored on a tape (Tecmar) for subsequently off-line processing. To obtain accurate blood pressure levels blood pressure was measured every second minute with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This devise uses an oscillometric method that measures mean arterial blood pressure, and calculates systolic blood pressure and diastolic blood pressure.[25,26,27]

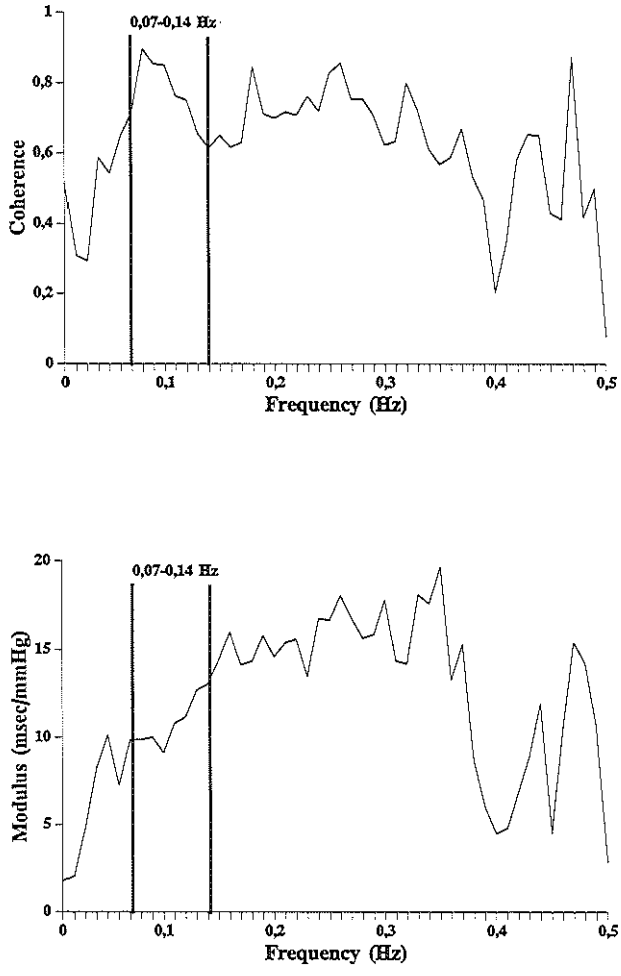

Figure 4.3.2:Coherence spectrum of heart rate and systolic blood pressure (above) and modulus spectrum (below) with the 0.07-0.14Hz band

Signal processing: Interbeat intervals were calculated for each measuring period by scanning the ECG signal at a trigger level at 20 % of the maximal amplitude of the Q-R interval with a correction procedure based on an interpolation algorithm. Because the interpolation algorithm did not correct all errors due to triggering of T-waves the signal was additionally inspected for interbeat intervals shorter than 500

msec. Necessary corrections were done manually. Systolic blood pressure was determined from the continues blood pressure signal with correction for artefacts if necessary. Spectral analyses were performed on the interbeat interval and continuous blood pressure signals with the CARSPAN program (version 1.2).[14,28] The modulus in the mid-frequency band (0.07-0.14 Hz) of the two signals provides an appropriate index of the baroreflex sensitivity.[14] To obtain a reliable estimate of the baroreflex sensitivity, the modulus was calculated if the coherence between the interbeat intervals and the systolic blood pressure was above 0.5 (figure 4.3.2). The first 60 seconds of each rest or stress condition were not used because of expected stability problems.[14,29] Stability of the signal was assessed by verifying that the difference between the spectral components calculated in two successive equal sized, interbeat interval series, which together constituting the rest or stressor condition, was less than 5 % for all subjects together.[30] Heart rate was computed as the total number of interbeat intervals divided by the duration of the measurement period and expressed as beats per minute (bpm).

Experimental protocol

After height and weight were measured, the measurement equipment was adjusted to the subjects. Next the subjects were seated in a quiet temperature controlled (20° Celsius) and sound shielded room in which the light was dimmed. They faced a monitor on which the stimuli were presented. The physiological monitoring and the delivery of the stimuli were controlled from outside the room.

After an adaptation period, baseline measurements were recorded for 10 minutes during which the subject remained resting quietly. Subsequently, the memory search task was explained to the subject and a 3 minute period was given for practicing. Then the task was performed for 10 minutes. After a break of 25 minutes in which the subjects were asked to relax, the subjects were installed again and a new baseline was recorded for 10 minutes. This baseline was used as reference in the analyses. Next the maximal handgrip power was determined and the handgrip task was executed for 5 minutes.

Later on the same day maximal aerobic power was measured. Participants were seated on a bicycle ergometer for a supramaximal exercise test according to an adapted version of the protocol of Åstrand.[31] The subjects started at a load of ½ Watt/kg bodyweight at a constant pedalling speed of 70 rpm. Children under the age of 14 started at a load of ¼ Watt/kg bodyweight. After each three minutes the load was increased, based on the heart rate. This was repeated for three times subsequently

until the load reached a level 10% above the estimated maximal aerobic level in the last period. The test was stopped once oxygen consumption did not rise any further, or if the subject gave up.

Data-analysis

Mean values were calculated for all variables measured at rest (10 minutes), during the memory search task (10 minutes) and during the isometric handgrip task (5 minutes). For comparisons between the two groups, means and standard errors of the means (SEM) are given, with a 95 % confidence interval (95 % CI) for the differences. Adjustments for the differences in age and the proportion of males across the two groups were made with use of a multiple linear regression model. Associations between variables were adjusted for differences in group characteristics (with use of indicator variables for group) and for age, gender, BMI or fitness by using multiple linear regression analysis when appropriate. The BMDP statistical software package was used for data analysis.

RESULTS

Table 4.2.1 gives the results of baseline measurements. Although the participants were still normotensive, blood pressure was higher at rest in offspring of hypertensive parents (difference in systolic blood pressure 6.99 mmHg, 95 % CI 3.52, 10.46 and in diastolic blood pressure 5.57 mmHg, 95 % CI 3.00, 8.14). There were no differences in body composition, measured by BMI, or fitness, measured in relative VO_2, between the two groups. Similarly, no differences in performance on each of the two tasks between the two groups were observed.

In 80 out of 99 subjects reliable data, suitable for statistical analysis could be obtained. Missing data resulted from measurements problems during one or more of the experimental conditions. The sensitivity of the baroreflex measured as the modulus of the mid-frequency band was depressed in subjects of hypertensive parents (difference: -4.81 msec/mmHg, 95 % CI -9.51, -0.11; table 4.3.1). To assess whether the difference in baroreflex sensitivity was confounded by the difference in blood pressure between the two groups, the results were adjusted for systolic blood pressure. After adjustment, the difference in baroreflex sensitivity, as measured in the modulus of the mid-frequency band was essentially unaffected (difference: -5.11 msec/mmHg, 95 % CI -10.51, 0.29).

The sensitivity of the baroreflex declined during the memory search task in both

groups, but no difference in reactivity between the two groups was found. The difference in baroreflex sensitivity between the two groups became smaller (difference: -2.95 msec/mmHg, 95 % CI -6.85, 0.95; table 4.3.1). At the same time offspring of hypertensive parents had a higher systolic blood pressure response to this task (difference: 2.99 mmHg, 95 % CI 0.03, 5.95). No differences were found in diastolic blood pressure or heart rate reactivity.

Table 4.3.1: Baroreflex sensitivity at rest and during the two stressors in offspring of normotensive parents and in offspring of hypertensive parents*

	offspring of two normotensive parents (A)	offspring of two hypertensive parents (B)	difference between B and A	95 % confidence interval of the difference
At rest (msec/mmHg)	20.9±1.8	16.1±1.6	-4.81	(-9.53, -0.09)
During active coping (msec/mmHg)	16.3±1.7	13.4±1.1	-2.95	(-6.85, 0.95)
Change to active coping	-4.4±2.2	-2.9±1.5	1.51	(-3.64, 6.67)
During handgrip (msec/mmHg)	15.5±1.8	15.0±1.5	-0.49	(-5.06, 4.08)
Change to handgrip task	-3.3±1.7	-2.8±1.4	0.52	(-3.77, 4.81)

*mean values±SEM, adjusted for differences in age and gender

For the baroreflex sensitivity estimated by the modulus in the mid-frequency band the same reactivity pattern was found during the isometric handgrip task. The decline in baroreflex sensitivity was somewhat larger in subjects with normotensive parents, but no significant difference in response between the two groups was found. Here the difference in baroreflex sensitivity between the two groups disappeared completely during the task (difference: -0.49 msec/mmHg, 95 % CI -5.06, 4.08; table 4.3.1). No difference between the two groups was found in reactivity of both systolic and diastolic blood pressure. The increase in heart rate during this task was smaller in offspring of hypertensive parents (difference: -2.51 bpm, 95 % CI -4.88, -0.14).

Although group differences in baroreflex sensitivity found at rest disappeared during both of the stress tasks, no significant differences in reactivity of the baroreflex could be demonstrated. This might be the result of large individual differences in

response to the stress tasks. There were no indications for both tasks of any influence of performance level, BMI or fitness on the reactivity measures.

DISCUSSION

The present study was conducted in order to study the sensitivity of the baroreflex in the early phase of primary hypertension at a stage before frank elevation of blood pressure has developed. Baroreflex sensitivity was measured at rest and during stress in subjects with contrasting risk for hypertension, due to their parental history. The results indicate that subjects with hypertensive parents have a lower sensitivity of the baroreflex at rest. This phenomenon appeared not to be related to actual blood pressure levels, which gives further support to the view that the defect is primary rather than secondary. Baroreflex sensitivity was reduced during mental and physical stress in comparison with the resting period, but no difference in magnitude of response between the two groups was found.

The results in the resting period are in agreement with other studies in which the baroreflex sensitivity in hypertensives or adolescents and young adults at risk for hypertension was studied.[7,8,9,32] The level of baroreflex sensitivity found in this study is highly comparable to studies using other research methods.[2,4,10] Baroreflex sensitivity is known to decline during stress,[10,11,12,13,14] but we are not aware of studies in which offspring of hypertensive parents has been studied during mental or physical stress.

A higher activity of cerebral defence centra has been proposed to play a role in the etiology of the disorder,[33] and this would lead to a central inhibition of the baroreflex. During mental stress the baroreflex is supposed to be modulated by these supramedullary influences as part of the central nervous system adjustments.[34] A decline in the baroreflex sensitivity was found in this study during the mental stress task. Under conditions like this blood pressure is more free to rise, because the baroreflex is less able to correct variations in blood pressure levels by inhibition of the heart rate. Systolic blood pressure did rise in subjects with hypertensive parents in particular, as indicated by a higher systolic blood pressure reactivity in this group in earlier part of the Dutch Hypertension and Offspring Study.[35] During the static exercise task no inhibition of the baroreflex from central mechanisms is assumed. This kind of task gives primarily a blood pressor response because of an increase in the total peripheral resistance.[36,37] The sensitivity of the baroreflex itself declines most probably as a result of the higher blood pressure levels. Baroreceptor resetting is known to occur following acute mechanically induced changes in arterial blood

pressure.[38] In this study the reaction of the baroreflex during the static exercise task was also highly similar in the two groups.

The selection method used in this study resulted in large contrasts in risk for hypertension between the two groups adolescents and young adults. As blood pressure clusters in families, differences in blood pressure levels of the parents can be used to predict risk to become hypertensive in their offspring.[39,40] Similarly blood pressure tracks within subjects and future hypertensives most likely have relative high blood pressure at a young age.[39,40] High contrasts in risk to become hypertensive between groups offspring almost certain induces differences in blood pressure levels at rest. Although none of the subjects had clear hypertension, it is conceivable that the difference in blood pressure between the groups may have caused the difference in baroreflex sensitivity rather than the reverse. Although this possibility is difficult to exclude, one approach may be to adjust for the observed differences in systolic blood pressure between the groups in the analysis. Adjustment for differences in systolic blood pressure did not clearly affect the differences in baroreflex sensitivity at rest. It should be noted however, that adjustment for blood pressure level may obscure true differences in characteristics related to the development of high blood pressure, as offspring with the highest blood pressure may be those at highest risk of future hypertension. Additional research is necessary to further explore the potential causative role of a diminished baroreflex sensitivity in the etiology of high blood pressure.

In conclusion, our findings suggest that pre-hypertensive subjects have a reduced baroreflex sensitivity at rest. No indications were found for a deviation in short term adaptations of baroreflex sensitivity during mental or physical stress.

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Chapter 4.4

ASSESSMENT OF BAROREFLEX SENSITIVITY USING THE FIN-A-PRES AT HAND AND FOOT

INTRODUCTION

Spectral analysis of blood pressure measured by the Fin-a-pres continuous blood pressure measurement device provides the possibility to assess blood pressure variability and the baroreflex sensitivity in a non-invasive and for the subjects unobstructive way.[1] This opens doors to study the baroreflex in large populations of healthy subjects under varying conditions, without the need for intra-arterial measurements. Studying adaptations of baroreflex sensitivity under different conditions can be of great importance to shed light on the physiology of medium-term blood pressure regulation throughout the day and the potential role of baroreflex malfunction in the etiology of hypertension.

At the same time new problems appear. The Fin-a-pres was developed to measure blood pressure continuously at a finger.[2] Under certain test-conditions the participants may have to use both hands to perform a task and in those circumstances the Fin-a-pres cannot be used in its usual way. In addition, it is hard to measure absolute blood pressure levels reliably with the Fin-a-pres under these conditions, because of the effects of the position of the finger relative to the heart.[3] Therefore, it is sometimes inevitable to measure absolute blood pressure with a regular cuff method. In principle, the Fin-a-pres can also be used at a toe, and this would leave both hands free. All reliability studies we are aware of have been executed using finger measurements.[4,5] It is conceivable, however, that variability of the blood pressure determined at a toe can be amplified by influence of hydrostatic pressure or reflections of the peripheral arterial system or can be damped by influences of skin-thickness and the toenail.

Spectral analysis on systolic blood pressure and interbeat intervals together can be used to estimate baroreflex sensitivity.[6,7] In an earlier study, it has been shown that variability of blood pressure derived by a Fin-a-pres at a finger very closely resembles that derived by intra-arterial measurements.[1] In the present study, the

reliability of assessment of baroreflex sensitivity measured at the foot was determined by comparing Fin-a-pres measures at a finger and a toe both at rest and during mental stress.

SUBJECTS AND METHODS

In this study 20 students (10 male; mean age 27.3±1.0) participated. At the time they participated, all subjects were free from serious medical problems and were not taking any medication which could influence the results of the tests. Before they visited the laboratory they were informed about the purpose of the study and all gave informed consent.

Body weight and height were measured with the subjects wearing light clothes and no shoes. The Body Mass Index (BMI) as an index of obesity was calculated as body weight divided by the square of the height.

Table 4.4.1: General characteristics of the participating subjects*

	males	females
Number of subjects	10	10
Age (years)	28.1±1.5	26.5±1.3
Height (cm)	184.6±2.7	166.6±2.6
Weight (kg)	74.6±4.2	69.1±4.0
BMI (kg/m^2)	21.8±0.9	24.7±0.9

* mean values ± SD

An active coping task, modelled after the Sternberg memory search paradigm, was used.[8] Participants had to remember a set of three letters (the memory set), given to them before the task started. Thereafter, sets of one to four letters (the test set) were presented on the monitor in which none or one of the letters of the memory set would be present. Subjects had to press the 'yes' or 'no' button for the presence or absence of one of the memorized letters. The number of points they could win depended directly on the speed of reaction. A detailed description is given elsewhere.[9] All subjects got the opportunity to practice the task during three minutes

just before the real task had to be executed.

For signal recording ECG Ag-AgCl electrodes were placed on the sternum and at the lateral margin of the chest. The ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Mega-ohm impedance. Blood pressure was measured continuously by two Fin-a-pres devices; the Ohmeda 2300 at the first toe and Fin-a-pres model 4 from TNO, Biomedical Instruments at the second finger. The ECG and the continuous blood pressure signals were displayed on a Beckman polygraph and the ECG was sampled continuously at 250 Hz using a Olivetti personal computer M250 in combination with a 12 bit AD-converter. This frequency is close to the one used in other studies,[10] and seems adequate as long as the whole ECG is sampled, and interbeat intervals were determined off-line. Data were stored on a tape (Tecmar) for later off-line processing.

Simultaneous with the above measurements, blood pressure was measured every second minute with a Dinamap Vital Signs Monitor (Critikon model 845 XT). This device uses an oscillometric method that measures mean arterial blood pressure, and calculates systolic blood pressure and diastolic blood pressure.[11,12]

Interbeat intervals were calculated for each measuring period by scanning of the ECG signal at a trigger level at 20 % of the maximal amplitude of the Q-R interval with a correction procedure based on an interpolation algorithm. Because the interpolation algorithm did not correct all errors due to triggering of T-waves, the signal was additionally inspected for interbeat intervals shorter than 500 msec. Necessary corrections were made manually, the number of corrections never exceeded 0.5 % of the total number of interbeat intervals. Systolic blood pressure was determined from the continues blood pressure signals derived from hand and foot with correction for artefacts if necessary.

The power measures presented in this study are calculated for the systolic blood pressure signals, rather than for the interbeat intervals, to be able to compare the signals derived from finger and toe.

Spectral analyses were performed on the interbeat intervals and the systolic blood pressure with the CARSPAN program (version 1.2). The modulus of the mid-frequency band (0.07-0.14 Hz) of the two signals provides an appropriate index of the baroreflex sensitivity.[5] To get a reliable estimate of the baroreflex sensitivity, the modulus was calculated if the coherence between the interbeat interval and the systolic blood pressure was above 0.5. The first 60 seconds of both the rest and the stress condition were not used because of expected stability problems.[13] Stability of the signal was assured by verifying that a difference of less than 5 % for all subjects

together was present between the spectral components calculated in two successive equally sized, interbeat interval series, which together constituted the rest or stressor condition. Baroreflex sensitivity was determined for the two blood pressure signals of hand and foot separately. Heart rate was computed as the total number of interbeat intervals divided by the duration of the measuring period and expressed as beats per minute (bpm).

After height and weight were measured, the measurement equipment was adjusted to the subjects. Next, the subjects were seated supine in a quiet, temperature controlled (20° Celsius), and sound shielded room in which the light was dimmed. They faced a monitor on which the stimuli were presented. The physiological monitoring and the delivery of the stimuli were controlled from outside the room.

Baseline measurements were recorded for ten minutes during which the subject remained resting quietly. Subsequently, the memory search task was explained to the subject and a three minute period was given for practising. Then the task was performed for ten minutes.

Mean values of blood pressure and heart rate were calculated at rest (10 minutes) and during the memory search task (10 minutes). For each of the measures derived from the finger and toe, means and standard deviations of the means (SD) are given for males and females separately. The reliability was examined by calculation of a regression coefficient (with a 95 % confidence interval) from hand on foot measurements, both with and without an intercept. The BMDP statistical software package was used for data analysis.

RESULTS

Table 4.4.1 gives the general characteristic of the participating males and females separately. In table 4.42 and 4.4.3 the levels of the circulatory parameters which were measured are shown. No differences between men and women were found. In the further analyses all subjects were considered together. The results presented in table 4.4.4 show the relations between measures of power, coherence and modulus determined of blood pressure measured at hand and foot. Total power as well as the power in the mid-frequency band was higher when based on blood pressure measurements derived from the foot. This affects the values of the modulus in the mid-frequency band, which tend to underestimate the levels of the baroreflex sensitivity. Nevertheless the regression analysis indicates an acceptable comparability between modulus calculated from continuous blood pressure measures at hand and

foot. The results improved with the intercept put to zero, while the SEM of the regression coefficient declined slightly.

Table 4.4.2: Measures at rest in men and women*

	males	females
Systolic blood pressure (mmHg)	121.6±4.1	121.6±3.9
Diastolic blood pressure (mmHg)	72.1±2.8	69.8±2.7
Heart rate (bpm)	63.6±3.5	65.6±3.3
Modulus finger (msec/mmHg)	12.03±4.91	12.49±1.63
Coherence finger	0.75±0.14	0.74±0.10
Modulus toe (msec/mmHg)	7.30±2.20	8.58±2.37
Coherence toe	0.71±0.09	0.72±0.15

* mean values ± SD

Table 4.4.3: Measures during active coping in men and women*

	males	females
Systolic blood pressure (mmHg)	130.9±4.0	125.6±3.8
Diastolic blood pressure (mmHg)	78.6±2.8	78.6±2.6
Heart rate (bpm)	68.5±2.7	74.0±2.5
Modulus finger (msec/mmHg)	11.73±1.73	12.13±2.93
Coherence finger	0.75±0.10	0.68±0.08
Change modulus finger (msec/mmHg)	-1.36±2.85	-0.70±2.16
Modulus toe (msec/mmHg)	7.59±0.28	9.68±1.28
Coherence toe	0.70±0.12	0.62±0.09
Change modulus toe (msec/mmHg)	-2.09±4.13	-2.10±2.96

* mean values ± SD

Table 4.4.4: Relations between variables derived from spectral analyses on systolic blood pressure measured at hand and foot*

	Inter-cept	Regression coefficient†	95 % confidence interval	Regression coefficient‡	95 % confidence interval
rest					
Total power	-292.0	1.08	(0.95, 1.21)	1.04	(0.96, 1.12)
Power (0.09-0.14Hz)	42.9	1.04	(0.89, 1.19)	1.05	(0.95, 1.15)
Modulus	-0.25	0.80	(0.39, 1.21)	0.79	(0.32, 1.26)
Coherence	0.07	0.86	(0.49, 1.23)	0.96	(0.91, 1.01)
Active coping					
Total power	-197.6	1.17	(1.02, 1.32)	1.14	(1.02, 1.26)
Power (0.09-0.14Hz)	-58.8	1.11	(1.01, 1.20)	1.07	(1.01, 1.13)
Modulus	-0.04	0.82	(0.09, 1.55)	0.78	(0.61, 0.96)
Coherence	0.33	0.47	(-0.20, 1.13)	0.92	(0.84, 1.00)
Change in modulus	0.45	0.49	(-0.16, 1.14)	0.58	(0.27, 0.89)

* regression coefficient, with 95 % confidence interval

† regression coefficient determined with the variable measured at the hand as dependent variable.

‡ regression coefficient determined with the variable measured at the hand as dependent variable, while intercept was forced to zero

DISCUSSION

This study was conducted to evaluate the reliability of baroreflex sensitivity determined from continuous blood pressure measurements at the foot by way of Fin-a-pres. Power spectra and cross-spectra were calculated from interbeat intervals and continuous blood pressure signals determined at hand and foot. Although the modulus in the mid-frequency band of the cross spectra of interbeat intervals and systolic blood pressure is strongly and significantly related to the one determined at the hand, the baroreflex sensitivity determined at the foot is lower when measured at the toe. This is most probably the effect of a higher variability in the blood pressure signal. This can be caused by amplification of the signal due to reflections of the peripheral arterial system or enlarged hydrostatic pressures in the foot. The close association between the two measures does, however, suggest that two measurements may both

successfully be used to evaluate baroreflex sensitivity under stressful conditions.

Baroreflex sensitivities determined of measures taken from the hand were also somewhat lower compared to other studies.[14,15] This might be the result of the absence of a relaxation period before the baseline measurements were taken. As a result the resting period could be influenced by the stress of being in a laboratory situation. The minor differences in baroreflex sensitivity between rest and stress period are also an indication in this direction. This probably has no consequences for most of the results presented here, because the two blood pressure signals were registered simultaneously. The regression coefficient of the change in modulation might, however, be influenced by small differences in modulus between the two conditions in combination with an accumulation of measurement errors.

In conclusion, from our findings it appears that continuous blood pressure measurements at a toe are suitable for determination of power spectra of systolic blood pressure signals. Although somewhat depressed, the modulus of systolic blood pressure to interbeat interval in continuous blood pressure measured at the toe may be as useful as measures derived from the finger as a basis for spectral analysis to evaluate of baroreflex sensitivity.

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Chapter 5

GENERAL DISCUSSION

A reasonable probability is the only certainty.
E.W. Howe

INTRODUCTION

The main aim of this thesis was to study stress reactivity in early hypertension in order to examine the role of blood pressure regulatory mechanisms and behavioral factors in the etiology of hypertension. As part of the Dutch Hypertension and Offspring Study, stress reactivity to different types of mental and physical stress was assessed in two groups of adolescents and young adults with contrasting risks for hypertension. Two approaches were chosen. The first approach related hyperreactivity to so-called behavioral factors. According to the theory, hyperreactivity occurs only in response to mental stress during which the central nervous system plays a crucial role.[1,2,3] The second approach focused on irregularities in the blood pressure regulatory mechanisms. Finally, the results of this study will contribute to the overall assessment of the pathophysiology of early primary hypertension which is the objective of the Dutch Hypertension and Offspring Study.

The nervous system is taken as one of the most important candidates for disturbances. There are three theories concerning deviations in blood pressure regulation that may lead to hypertension.

According to the hyper-ß-adrenergic hypothesis, hypertension is the result of cardiac activity that exceeds the metabolic need of the system.[4,5,6,7,8] This hypothesis is similar to the so-called 'hyperdynamic circulation' or 'hyperkinetic circulation' hypotheses. Support for this hypothesis has been found in tachycardia at rest and in response to stress in borderline hypertensives and in subjects with a family history of hypertension.[9,10,11,12,13] The tachycardia and its accompanying increase in cardiac output is thought to be the result of neurogenic influences, namely of enhanced sympathetic activation of the heart and an enhanced inhibition of the heart by parasympathetic nervous system.[4,14,15,16] Theoretically, the hyperkinetic circulation may result in two distinct patterns of adaptation. One is a reflection of autoregulation, which implies a functional myogenic increase in vascular resistance to prevent overperfusion of the organs.[17,18] The second mechanism consists of structural changes in the vascular system like hypertrophy or atherosclerosis in response to high

blood pressure levels.[19]

According to the hypervascular reactivity hypothesis, hypertension is the result of increases in peripheral resistance, probably as a result of an enhanced functional activation of the arterioles or structural vascular changes.[20] The blood pressure response to stress would be the result of enlarged vasoconstriction and not of an enhanced cardiac activity.

According to a more recent hypothesis, hypertension is the result of an altered neural activation.[21,22] Sympathetic activation of the cardiovascular system in hypertensive subjects is more directed to the vascular system and less to the heart in comparison to normotensive subjects.

These theories are based mainly on studies in which blood pressure and heart rate were measured in hypertensive and borderline hypertensive subjects at rest and during stress.[1,4,5,8,9,10] The research strategy of these studies is limited by the inability to distinguish etiological factors from secondary physiological adjustments to an elevated blood pressure.

In the Dutch Hypertension and Offspring Study previous methodological problems have been approached by,

-the stringent selection of normotensive subjects with contrasting risk for hypertension, based on their parental history

-the incorporation of measures of intermediate phenotypes of blood pressure regulating systems at rest as well as during several different types of stressors.

CHARACTERISTICS OF BLOOD PRESSURE REGULATING MECHANISMS IN THE DUTCH HYPERTENSION AND OFFSPRING STUDY

Baseline

In previous publications of the Dutch Hypertension and Offspring Study most of the baseline measures have been presented.[23] A synopsis of the results is given in table 5.1. Although none of the subjects was markedly hypertensive at the time of baseline examination, on the average offspring of hypertensive parents already had a higher blood pressure at rest. Nevertheless, there were no indications for a hyperdynamic circulation or luxury perfusion at rest, as evaluated by measures of cardiac output and arteriovenous oxygen difference[20]. In contrast, heart rate tended to be lower in offspring of two hypertensive parents at their first visit to the research center (table 5.1) In addition, the two groups did not differ in total peripheral resistance or catecholamine levels (measured in plasma), the latter being an indicator of overall

sympathetic activity.

Table 5.1: Baseline characteristics of participants in the Dutch Hypertension and Offspring Study†

	Offspring of two normotensive parents (A)	Offspring of two hypertensive parents (B)
Systolic blood pressure (mmHg)*	118±1.2	125±1.0
Diastolic blood pressure (mmHg)*	71±1.2	78±1.0
Heart rate (bpm)	72.5±1.8	68.0±1.4
Stroke volume (ml)	44.6±2.0	45.1±1.8
Cardiac output (l/min)	3.09±0.12	3.05±0.11
Arteriovenous oxygen difference (ml/l)	79±5	87±5
Total peripheral resistance (mmHg/l/min/m^2)	45.1±1.9	48.2±1.7
Epinephrine (pg/ml)	30.0±4.3	21.2±1.6
Norepinephrine (pg/ml)	253±13.3	233±11.3

† mean values±SEM, corrected for differences in age, height, weight and gender between the two groups[19,20]
* difference between the two groups is significant at $p < 0.05$

Reactivity to stress

Reactivity to mental and physical stress tasks has been examined. The stress tasks were selected on their expected effect on different aspects of blood pressure regulatory mechanisms. In particular, blood pressure responses to mental stress tasks are considered to be enhanced in hypertensive and pre-hypertensive subjects due to behavioral factors.[2,3] During different types of mental stress tasks a rise of blood pressure is thought to be evoked by several cardiovascular adaptation mechanisms.

Figure 5.1 presents a scheme of the pathways potentially involved in the acute rise of blood pressure during stress.

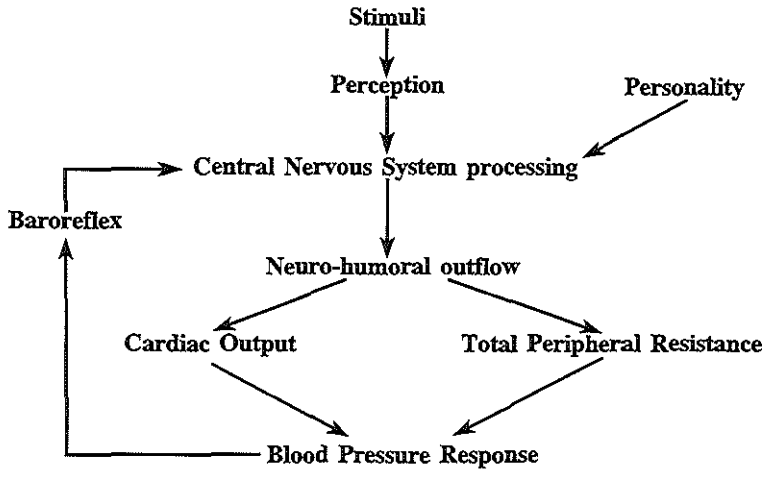

Figure 5.1: Scheme of pathways potentially involved in an acute rise in blood pressure under stressful conditions

In this study two mental stressors were chosen which differed in their relative activation of the heart. During the mental load task no indications were found for hyperreactivity of heart rate, stroke volume and cardiac output in offspring of hypertensive parents. If anything, the response pattern suggested a less pronounced cardiac reactivity in offspring of hypertensive parents than in offspring of normotensive parents. The enhanced blood pressure response could be interpreted as a reflection of either a higher cardiac-directed sympathetic reactivity of the cardiovascular system or structural factors in the cardiovascular system. During the reaction time task and during the static exercise task, indications were found for a stronger response of total peripheral resistance in subjects with hypertensive parents. The more marked rise in peripheral resistance in offspring of hypertensive parents suggests a more pronounced vascular responsivity. No differences between the two groups were found in reactivity of indices of sympathetic activation (PEP/LVET) or inhibition of the heart by vagal activation (RSA) of the heart in any of the tasks. The

pattern of response to the reaction-time task did not differ from that to the static exercise task. This argues against the notion that hypertension is the result of deviations in the central nervous system regulation of stress responses. The results presented are in accordance with the similarity found in personality traits of two groups.

Because of the mediating role of the sympathetic and parasympathetic nervous system in the effects of behavioral factors on blood pressure, indices of neural activation and baroreflex sensitivity were measured by way of spectral analysis at rest and during the mental load task and the static exercise task. At rest as well as during the mental load task, no differences in neural regulation between the two groups were found. A higher vagal activation of the heart was found in offspring of hypertensive parents during the static exercise task, most probably as a result of the larger response of total peripheral resistance. Since the isometric handgrip test at 22 % of the maximal force allows a limited blood flow through the active muscles, the rise in total peripheral resistance is most probably the result of a lack in vasodilatation in response to ischemia. The relatively low heart rate resulting in a larger decrease in cardiac output was in accordance with the initiation of a higher vagal activity in offspring of hypertensive parents. Together with these neural indices, the baroreflex sensitivity was studied at rest and during mental load test and static exercise test. The subjects at risk for hypertension showed a decreased baroreflex sensitivity at rest as compared to offspring of normotensive parents. No indications were found for a deviation in short term adaptation of baroreflex sensitivity during stress. The reduced sensitivity at rest was not related to actual blood pressure levels and can be the result of differences in central nervous system processing as well as a reduced activation of the baroreceptor due to e.g. vascular wall stiffness.

The last stressor was a dynamic exercise test, during which the feedback mechanisms of the cardiovascular system were tested under more 'usual' circumstances. In response to this test the physiological increase of the stroke volume was blunted in offspring of hypertensive parents, which can be a reflection of a reduced compliance.[24] This might be related to the higher left ventricular wall thickness that has been reported in the same group of subjects.[20]

In addition to the personality characteristics and cardiovascular reactivity, obesity, fitness and habitual physical activity were studied because of their possible relation to blood pressure reactivity. No differences in body mass index between the two groups could be demonstrated, but subjects with hypertensive parents had more central fat. In theory, central fat can influence blood pressure regulation through the

sympathetic nervous system or an enlargement of blood volume.[25,26,27,28] No differences were found in fitness or habitual physical activity between the two groups.

IMPLICATIONS OF THE RESULTS

The results of the stress reactivity tests in the Dutch Hypertension and Offspring Study do not provide evidence for a specific role of behavioral factors in the etiology of hypertension, because no differential response pattern to mental stress could be demonstrated across the offspring groups. This is further supported by the absence of differences in personality characteristics. Compared to the reaction-time task, the static exercise stress task had an analogous impact on the cardiovascular system. These types of stress tasks may induce a rise in total peripheral resistance, independent of an emotional component or influence of higher cognitive functions. This does not imply that emotional stress cannot induce elevated blood pressure. In the industrialized countries a large number of people have to cope with severe (mental) stress every day. Repeated static exercise, however, might have the same impact on the cardiovascular system as mental stress.

The results of this study support the hypothesis that blood pressure responses in subjects with a parental history of hypertension are characterized by an enhanced vasoconstriction rather than an increased cardiac output. This favors the hypervascular reactivity hypothesis, although no clear evidence for a neural basis for this hyperreactivity could have been found. The measurements at baseline as well as the response patterns to the stress tasks did not support the hyperkinetic circulation theory because no differences between the two groups of subjects were found in cardiac output at rest or during any of the mental stressors. Similarly, no indications were found for a role of luxury perfusion or cardiac hyperactivation in early primary hypertension.

In conclusion, no evidence was found for a specific role of behavioral factors on cardiovascular regulation during stress in offspring of hypertensive parents as compared to offspring of normotensive parents. The feedback to increased pressure from peripheral tissue however may be disturbed in subjects at risk for hypertension. The highly similar responses to the reaction-time task and to static exercise as well as the reduced baroreflex at rest may be regarded as pointing in that direction.

HETEROGENEITY IN ETIOLOGY OF HYPERTENSION

Hypertension is an multifactorial disease and the nature of deviations in blood pressure regulatory mechanisms that lead to hypertension may vary from subject to subject or from family to family. A large number of different mechanisms are involved in blood pressure regulation (figure 5.2).[29] In the previous chapters, neural activation and behavioral aspects have been highlighted. The differences in response pattern between the two groups of adolescents and young adults are not necessarily only the result of neural dysregulation. In the Dutch Hypertension and Offspring Study, the only measure of neural activation, that differentiated between the two groups was the ratio of α/β receptor density on peripheral blood cells. Differences between the two groups in reactivity of the total peripheral resistance declines slightly after adjustment of reactivity for adrenoreceptor ratio (difference in total peripheral resistance: 11.2±8.8 %, p=0.20).

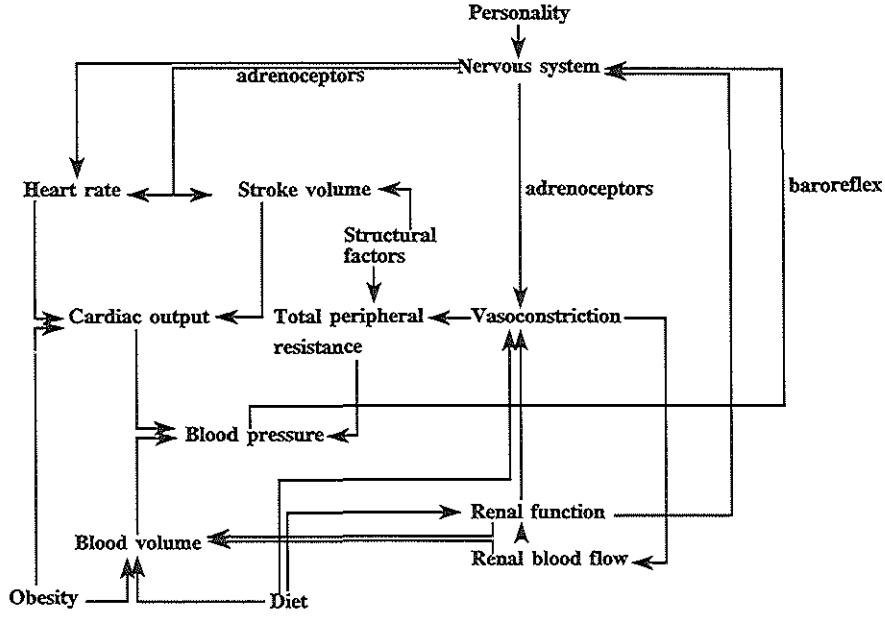

Figure 5.2: Scheme with the selected factors involved in blood pressure regulation[29]

Theoretically, other physiological models can also explain the results. Williams described several pathophysiological characteristics, e.g. intermediate phenotypes, and some of these may be of importance in explaining the deviations in stress reactivity described in the offspring of hypertensive parents.[30]

Salt sensitivity and central fat

In the Dutch Hypertension and Offspring Study a number of dietary factors has been studied. The amount of energy consumed and the body fat pattern may influence fat disposition. Central fat has been mentioned as a factor of importance because of its potential relation to sympathetic nervous system activity and blood volume.[25,26,27]

A second dietary factor studied in the Dutch Hypertension and Offspring Study is salt consumption. Salt intake has been associated with both blood pressure levels and hyperreactivity of blood pressure to stress, although the data are inconsistent.[31,32,33,34,35] Hyperreactivity is supposed to be the consequence of either an enlarged blood volume or higher vascular resistance (reactivity).[28,29] Sodium as well as potassium excretion aggregate in families.[36] An enhanced response of blood pressure may be related to salt sensitivity, which may in part be genetically determined.[37] A relative high or normal salt consumption can lead to hyperreactivity of blood pressure in subjects at risk.[38] Stress can also lead to sodium retention in subjects prone to hypertension.[39]

The third dietary factor is calcium consumption. Although no differences in calcium intake between the groups were found in the Dutch Hypertension and Offspring Study, calcium metabolism appeared to be altered in the offspring of hypertensive parents.[40] This may influence the blood pressure response to stress, because calcium may be involved in vasoconstriction and -dilatation mechanisms[41] and might therefore affect total peripheral resistance. No difference, however, in excretion of either of these electrolytes between the two groups was found (table 5.2). To test whether of not potassium, sodium or calcium excretion is related to stress reactivity, systolic blood pressure response to the mental load stressor was analyzed with adjustment of 24 hour urine levels of these electrolytes and for dietary intake of calcium. After adjustment of blood pressure reactivity for 24-hour urine level of each of the electrolytes and for dietary intake of calcium, the difference in systolic blood pressure response to the mental load stress task between the two groups did not decline. This provides a crude indication that the influence of electrolytes on blood pressure regulation with respect to reactivity to stress is limited. Further study is

necessary to evaluate the potential differences between the two groups in salt sensitivity and sodium retention in response to stress.

Table 5.2: Electrolytes in offspring of two normotensive parents and in offspring of two hypertensive parents[35]*

	Offspring of two normotensive parents (A)	Offspring of two hypertensive parents (B)
Urinary Sodium (mmol/24 hr)	128±56	134±60
Urinary potassium (mmol/24 hr)	58±20	61±22
Urinary calcium (mmol/24 hr)	3.10±0.24	3.48±0.21
Dietary calcium (mg/day)	1,644±92	1,434±77

*** mean values ± SEM, adjusted for differences in age, height, body weight and gender**

Structural factors

A second possible intermediate phenotype is hypertrophy of e.g. the arterial wall or the cardiac left ventricular wall. Structural changes of the vascular wall can be the result of a persistent rise in blood pressure, but may also be primary[42] and can induce (acute) increases in blood pressure. A higher wall-to-lumen ratio can be caused by vasocontriction or an enlarged wall thickness, which might be related to structural changes in the vascular wall. The enhanced response of total peripheral resistance found in this study might be the result of primary vascular hypertrophy. Recently, results have been reported that support the presence of structural vascular abnormalities early in the development of primary hypertension.[43,44,45,46,47] Subjects at risk of hypertension also appear to have a reduced vascular compliance.[48,49,50,51]

Primary or secondary structural changes may also be present in the heart. Indices of left ventricular hypertrophy were assessed in the Dutch Hypertension and Offspring Study and showed a subnormal adaptation of stroke volume during the dynamic exercise test and an enlarged thickness of left ventricular wall on echocardiography.[23] Left ventricular hypertrophy in subjects with hypertensive parents may result from secondary adaptations to the already higher blood pressure levels in this group,

although adjustment for blood pressure and a comparison in different blood pressure strata did not influence the group difference in left ventricular wall thickness.[23] Reactivity of stroke volume to dynamic exercise, similarly, was also not related to actual blood pressure levels.

Hypertrophy has been demonstrated to be an independent risk factor for cardiovascular disease besides hypertension.[38,52,53] Several studies provide evidence in favor or against primary structural changes in cardiac tissue. Lund-Johansen showed a subnormal cardiac output and a slightly increased arteriovenous oxygen difference in subjects with early essential hypertension during muscular exercise.[18] Studies on the pump function of the left ventricle by the more sophisticated blood-pool isotropy method have suggested that a decreased filling rate may be the first functional abnormality in the left ventricle in moderate hypertension.[18] It is most likely that this reflects increased stiffness of the left ventricular wall, probably due to early structural changes in the left ventricle.[18] More recent studies in normotensive subjects at risk of hypertension showed an enlarged left ventricle wall thickness compared to subjects with normotensive parents, although not always independent of differences in blood pressure between the two groups.[54,55,56] To test whether or not the reduced stroke volume response to dynamic exercise was related to structural changes in cardiac tissue in offspring of hypertensive parents, the change in stroke volume was analyzed with adjustment for left ventricular wall thickness. The analysis showed a strong decline in difference of the response of the stroke volume to the first cycling period after adjustment for left ventricular wall thickness (difference in stroke volume adjusted for left ventricular wall thickness: -4.0±7.2 %, $p=0.58$). This finding suggests that left ventricular wall thickness may indeed be important in explaining the relatively reduced stroke volume response on exercise in offspring of hypertensive parents.

Baroreflex sensitivity

A disturbances in baroreflex function in known to play an important role in the maintenance of an already elevated blood pressure in primary hypertension. The results of the cross-spectral analysis suggested another role that might be involved in the etiology of hypertension. The baroreflex sensitivity was found to be reduced in offspring of hypertensive parents. This seems to be a primary factor because no relation with differences in actual blood pressure levels could be found. This reduction is marginally related to total peripheral resistance (difference in baroreflex sensitivity after adjustment for total peripheral resistance: -7.3±4.0, $p=0.08$). In theory,

baroreflex sensitivity can be reduced due inadequate function of the reflex arch itself or due to central inhibition or diminished input at the receptor site possibly due to vascular wall stiffness. Changes in baroreflex sensitivity did not differ between the two groups in response to mental and physical stress. As a result no indications have been found which favor specific central or peripheral disturbances in this neural regulating mechanism.

Renal function

The last intermediate phenotype to be discussed in the relation to the findings presented in this thesis is the renal function. In the Dutch Hypertension and Offspring Study, renal blood flow was lower in offspring of hypertensive parents (difference in renal blood flow: 198±61 ml per 1.73 m^2 of body surface area, p=0.002).[57] Renal function may influence blood pressure reactivity in a number of ways. Reduced renal function can influence stress response, for example by way of retention of electrolytes which could affect total peripheral resistance through enhancement of vasoconstriction. Reduced renal blood flow might also be related to stress reactivity through an increased blood volume. At the other hand, renal blood flow might be reduced by renal vasoconstriction due to functional or structural vascular changes.

To assess whether or not renal blood flow is related to stress reactivity, the responses of total peripheral resistance and systolic blood pressure to the mental load task were reanalyzed with adjustment for renal blood flow. No effect could be determined for adjustment of renal blood flow on systolic blood pressure reactivity (difference: 5.25±2.56 mmHg, p= 0.04). Although not significant, the difference between the two groups became larger after adjustment for renal blood flow in the analysis of reactivity of total peripheral resistance (difference: 11.19±9.77 %, p=0.26).

FAMILY HISTORY: GENES OR ENVIRONMENT?

Estimates of the magnitude of genetic factors in the development of high blood pressure may be obtained from family studies in which both parents and children, in particular twins, participate.[58,59,60,61,62] Continuous and unimodal distribution of blood pressure in the general population, as well as in the offspring of hypertensive parents suggests that the inheritance of blood pressure variation is multifactorial, thereby complicating the search for blood pressure determining genes.[63] Additionally, hypertension appears to be the result of an interaction of genes and environmental factors.[64] It is inevitable to study phenotypes first because, due to the multifactorial

origin of hypertension, many genes may influence phenotypes at different places to different degrees and with varying importance in different individuals. Moreover, the effects of environmental factors are probably dependent on genetic susceptibility. An accepted strategy to study hypertension is to define certain intermediate phenotypes and search for the environmental factors and the genotypes that fit with these phenotypes afterwards.[30] The Dutch Hypertension and Offspring Study was designed to examine intermediate phenotypes in early hypertension and data were collected in the offspring only. Intermediate phenotypes reveal more information in comparison to distant phenotypes like blood pressure because they are more closely related to the blood pressure regulating mechanisms.[30]

The analyses performed so far are informative on the relative importance of different possible pathophysiological mechanisms, e.g. phenotypes, that are involved in the etiology of hypertension but can not be used to estimate the relative frequency of pathological mechanisms to occur in early hypertensive subjects. To shed some light on the issue of relative impact of certain mechanisms or intermediate phenotypes a statistical approach, however, could be taken. Blood pressure tracks within subjects and differences in blood pressure between subjects at a young age are most probably the result of early influence of the same intermediate phenotype that predisposes a subject to hypertension at higher age. Blood pressure differences between the two groups can be analyzed with an index of an intermediate phenotype in the regression equation in addition to gender and age. The disappearance of a difference in blood pressure between the two groups provides an indication of the impact of this intermediate phenotype on blood pressure levels at a young age. Analyses have been performed with correction for total peripheral resistance, baroreflex and renal blood flow. The results did not favor one 'intermediate phenotype' above the other.

THE RESEARCH METHOD

A drawback of reactivity studies in which hypertensive subjects participate is the inability to separate etiological factors from changes secondary to high blood pressure levels. Consequently, differences in reactivity between normotensive and hypertensive subjects can similarly be the result of differences in blood pressure. In studies with normotensive offspring of hypertensive parents this is assumed to be a less important factor. However, although all the participating subjects in this study were normotensive, (none of them had a blood pressure above the 140/90 mmHg) the high risk group had already higher average blood pressure levels and the overall

distributions of blood pressure levels in the offspring of hypertensive parents was shifted to the right (in figure 5.3 the cumulative distribution of systolic blood pressure is given). The most obvious explanation is that blood pressure aggregates in families and tracks within persons.[65,66,67,68] This results in increasing blood pressure differences with age that may already be present to some degree at the first days of life. The results of the meta-analysis presented in chapter two indicate that the differences in blood pressure in the present study are most probably the result of the stringent selection criteria applied. A potentially valid way to handle this problem is statistical correction. All differences between the two groups of subjects were therefore corrected for baseline systolic blood pressure differences, before they were interpreted as differences. This adjustment, however, also has a drawback that offspring with the highest blood pressure may be those with the highest risk for future hypertension and thus adjustment may imply adjustment for the very factor of interest.

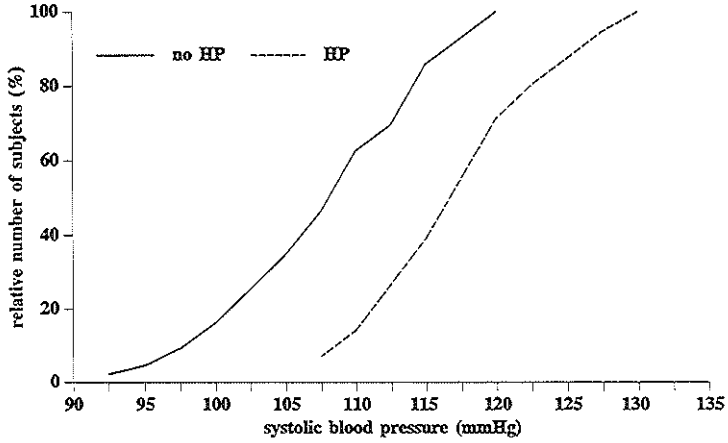

Figure 5.3: Cumulative distribution of systolic blood pressure at rest in the two groups of adolescents and young adults (adjusted for age and gender) (HP: subject with two hypertensive parents; no HP: subject with two normotensive parents)

Families have been included in the study if both parents were in either the upper or lower quartile of the blood pressure distribution at two moments separated by ten years. This method resulted in small groups of subjects with a highly contrasting risk to become hypertensive. The contrast in risk is probably higher than that in most of the other studies summarized in the meta-analysis presented in chapter 2.

The selection was done to create two groups of an acceptable number of subjects and with a contrast in risk as large as possible. This, however, also resulted in heterogeneity for other characteristics across and within the groups. Both male and female subjects in a rather large age-range were accepted in the study. The expression of heritability with respect to blood pressure might depend on age and gender. It is even possible that different phenotypes are gender specific or are sex-hormone related. In principle, males and females should be analyzed separately. In general and for reasons of sample size, this was not done but in the analyses of the major differences between the two groups differential effects across gender were checked and adjustments for gender were made in the total results.

Subjects in the age range of 5 to 30 years were asked to participate. Consequently, only approximately 20 % of the subjects with two normotensive parents and 10 % of subjects with two hypertensive parents were under the age of 14. Although all analyses were adjusted for age differences, growth and development in these subjects might influence the results. The major results were checked for age effects by analyses of the data in age strata.

Selection was not limited to one child per family in the study; 53 subjects of 35 normotensive families and 69 subjects of 51 hypertensive families participated. Siblings were accepted because they were assumed not to be genetic identical. Due heterogeneity in etiological factors of hypertension, in the groups with two hypertensive parents several different etiological factors might be present within families. This assumption was checked by analyses in which only the first child for each family was included and analysis in which adjustments were made for multiple family members. No major differences in results were found.

In spite of the stringent selection method, the study has certain limitations. In studies on the etiology of hypertension direct evidence is hard to obtain. Even with the knowledge and measurement arsenal of today, it is not possible to study one specific intermediate phenotype, e.g. mechanism, in isolation in humans in vivo. Additionally, in this study only non-invasive measures of cardiovascular and neural activation could be used. The major reasons were: not to influence the reactivity by

invasive measurements and the allowance for a measurement of these indices in healthy normotensive subjects in a research center. All the measures used in this study have been validated in several other studies. The similarity of our results with those of invasive studies in borderline hypertensive subjects by for example Lund-Johansen and others indicate that the limitations in measurement techniques do not pose a major problem on the conclusion.[5,6,7,8]

CONCLUSION

No indications were found for a specific effect of behavioral factors in the etiology of hypertension. Evidence for disturbances in physiological regulatory mechanisms can be found in the reduced sensitivity of the baroreflex observed in the offspring of hypertensive parents together with a similar response pattern to the reaction-time task and static physical stress. Of the various mechanisms studied, total peripheral resistance, renal function and possibly the baroreflex itself seem to be the major sites of dysregulation rather than an hyperactivation of the heart as predicted by the hyper-ß-adrenergic hypothesis.

Sympathetic hyperactivity has repeatedly been put forward as one of the mechanisms by which hypertension might be induced. No indications for an enhanced sympathetic activation of the heart have been found in the Dutch Hypertension and Offspring Study. An augmented response of the total peripheral resistance to sympathetic activation appears more likely. The more marked inhibition of the heart by an increase of vagal activity, observed in this study, seems to be a response secondary to the amplified rise of the total peripheral resistance.

Blood pressure remains a major risk factor for cardiovascular disease in westernized societies and increasingly so in other countries. Early detection of future hypertension may lead to timely intervention, which may prevent hypertension and its cardiovascular sequelae. The characteristics of early hypertensive subjects and those at risk for the development of high blood pressure make it possible to speculate about intervention. Subjects at risk for hypertension might benefit more from certain changes in diet, lifestyle and even be eligible for pharmacological intervention. Control of central fat in early hypertensive subjects needs specific attention. The reactivity of the total peripheral resistance can theoretically be linked to receptor density, calcium metabolism or structural changes of the vessels.

The present study adds only modestly to our understanding of the causes of high

blood pressure and means of prevention and treatment. Yet, the family history approach adopted in this study, when applied carefully and with adequate selection of subjects, may continue to show fruitful results not only for the study of hypertension but also in other chronic conditions that have their roots early in life.

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Chapter 6

SUMMARY

INTRODUCTION

The results presented in this thesis were obtained within the framework of the Dutch Hypertension and Offspring Study. This study was designed to examine early determinants of primary hypertension in adolescents and young adults with contrasting risks for hypertensive. Subjects were selected when both systolic and diastolic blood pressure of their father as well as their mother was either in the upper or in the lower quartile of the age and gender specific blood pressure distribution.

The major topic of this thesis was to evaluate the role of behavioral factors in the etiology of hypertension and more in particular the cardiovascular response to physical and mental stress. It has been proposed that cardiovascular hyperreactivity in hypertension is the result of enhanced, behaviorally induced, neural-humoral activation. This enhanced activation stems from central nervous system structures, and might be related to personality characteristics. Results from previous studies have supported the presence of hyperreactivity of blood pressure in hypertensive subjects. Three hypotheses have been put forward regarding malfunctions in the blood pressure regulatory mechanisms, which might lead to hypertension. The hyper-ß-adrenergic hypothesis suggests that hypertension is the result of an exaggerated cardiac activation. According to the hypervascular-reactivity hypothesis, hypertension is the result of an increased peripheral resistance, probably due to an enhanced sympathetic stimulation of arterioles or to vascular structural changes. More recently an alternative hypothesis was formulated, proposing that hypertension is the result of an altered balance in neural activation. Sympathetic activation of the cardiovascular system is more directed to the vascular system and less to the heart in hypertensive as compared to normotensive subjects.

Blood pressure is a distant phenotype reflecting the net result of several blood pressure regulatory mechanisms. In subjects with a similarly elevated blood pressure level markedly different mechanisms may have been involved in the elevation. Short term changes in blood pressure are the net result of an interaction of cardiac output and peripheral resistance together with the neural activation of the cardiovascular system. These variables might be better, i.e. more direct, indices of the activity of these blood

pressure regulatory mechanisms than blood pressure itself. Recently developed techniques make it possible to non-invasively register indicators of these variables at rest and during stress.

Several different types of mental as well as physical stress have been proposed to induce distinctive cardiovascular response patterns. In the studies presented in this thesis, four stressors were chosen, which are considered to differ in relative impact of several cardiovascular and neural mechanisms on blood pressure. Two mental stress tasks were chosen; a mental load task, that induces a relatively strong activation of the heart and a tone avoidance reaction-time task, which primarily induces peripheral vasoconstriction. The isometric handgrip task also induces a rise in total peripheral resistance due to vasoconstriction. The fourth task was a dynamic exercise task on a bicycle ergometer. During this task the cardiovascular response pattern can be measured under more 'natural' circumstances.

Cardiovascular stress responses were studied by measuring the short term adaptations of systolic and diastolic blood pressure, heart rate, cardiac output and total peripheral resistance besides indices of sympathetic activation (PEP/LVET and 0.1 Hz component of the spectral analysis) and vagal inhibition (RSA and 0.25 Hz component of the spectral analysis) of the heart and baroreflex sensitivity.

RESULTS

Three factors which are known to cluster in families and which are related to hypertension were evaluated in combination with the cardiovascular stress responses; body composition, fitness, habitual physical activity and personality characteristics. Offspring of hypertensive parents had more central fat, as indicated by a higher subscapular skinfold. Central fat has been related to higher sympathetic activity as well as with an enlarged blood volume. No differences between the two groups were found in aerobic power and habitual physical activity. Differences in response to mental stress between hypertensive and normotensive subjects have previously been assigned to differences in personality characteristics. In the present study, however, no differences in personality characteristics such as type A personality, anger, anxiety, depression and coping style between the two groups of offspring could be demonstrated.

The participating subjects at risk for hypertension had a higher systolic and diastolic blood pressure at rest compared to subjects of normotensive parents. This is most probably the results of tracking of blood pressure in early hypertensive subjects and

the expression of the strict selection procedure followed in the Dutch Hypertension and Offspring Study. The proposed presence of an enhanced sympathetic activation at rest in pre-hypertensive subjects could not be corroborated in this study. None of the indices for sympathetic cardiac activation differed significantly between the two groups.

STRESS REACTIVITY

Systolic blood pressure response was more pronounced during the cardiac mental stress task in subjects at risk of hypertension. During the vascular mental stressor an enhanced response of the total peripheral resistance could be documented in offspring of hypertensive parents as compared to offspring of normotensive parents. Nevertheless, this did not result in a larger blood pressure response in the high risk group, most probably due to a concomitant decrease of cardiac output. Subjects with two hypertensive parents tended to respond to both mental stress tasks with a more pronounced response in total peripheral resistance as compared to subjects with two normotensive parents. No indications were found for stronger neural-cardiac reactivity to mental stress.

During the isometric handgrip task, the increase in total peripheral resistance was larger in offspring of hypertensive parents as compared to offspring of normotensive parents. This did not result in an enlarged response of blood pressure, most probably because of the enhanced decline of cardiac output. The physiological increase in stroke volume was blunted during the bicycle ergometer test. Blood pressure could not reliably be measured during this task. As a result, no index of total peripheral resistance could be calculated for this stressor. Again no evidence could be found for an enhanced cardiac activation during the two physical stressors in subjects at risk for hypertension.

NEURAL ACTIVITY

Notwithstanding the absence of sympathetic hyperactivity in subjects at risk for hypertension either at rest or in response to stress, differences in neural-cardiac activity were observed between the two groups. Results of spectral analysis suggested that inhibition of the heart by vagal activity is larger in offspring of hypertensive parents during the isometric handgrip task. The question remains whether this is a primary phenomenon as it could well reflect a response to the higher total peripheral resistance present in this group. The diminished modulus of the cross-spectra between heart rate and systolic blood pressure indicates a reduced baroreflex sensitivity in adolescents and

young adults at risk. No evidence could be found for differences in baroreflex sensitivity in response to mental or physical stress.

The differences found between the two groups most likely were not dictated by existing differences in resting blood pressure or body composition as adjustment in the analyses for these factors did not influence the results.

CONCLUSION AND DISCUSSION

The Dutch Hypertension and Offspring Study provides the opportunity to study a large number of factors that might play a role in the etiology of hypertension in the same groups of well selected young individuals. The results contribute to the knowledge about the adaptations of the cardiovascular system during stress in the early phase of hypertension. In spite of the notion that not all subjects at risk are really pre-hypertensive, clear differences in certain characteristics between the two groups could be demonstrated while certain differences proposed previously based on findings in hypertensive subjects could not be substantiated.

Sympathetic hyperreactivity and neural disregulation have claimed to be involved in the etiology of hypertension. Within the Dutch Hypertension and Offspring Study several indices of neural regulation were studied at rest and during exposure to different kinds of stressors. No indications could be found for sympathetic hyperreactivity of the heart. The results, therefore, do not support the so-called hyper-ß-adrenergic activation hypothesis.

Adolescents and young adults at risk of hypertension expressed a more pronounced vasoconstrictive response pattern to stress as compared to the control group. Previously in the Dutch Hypertension and Offspring Study a higher ratio α/ß adrenergic receptor density on platelets has been documented in the same subjects. Although indirectly, this could in theory be related to the higher response of total peripheral resistance to stress. This enhanced response of the total peripheral resistance appears to be compensated by a reduced cardiac output, to avoid an enhanced response of the blood pressure.

Evidence was obtained to support the presence of amplified vagal activity leading to inhibition of the activity of the heart in offspring of hypertensive parents, in particular during static exercise. This, however, is not likely to be a primary factor in the etiology of hypertension. It most probable reflects an attempt to compensate for an enhanced rise in total peripheral resistance. Baroreflex sensitivity was reduced in offspring of

hypertensive parents as compared to offspring of normotensive parents. Although such a reduced sensitivity has been described previously in hypertensive individuals, the present findings suggest that this may predate high blood pressure and is potentially involved in its etiology in certain individuals.

Blood pressure remains a major risk factor for cardiovascular disease in westernized societies. Early detection of future hypertension may lead to timely intervention, which may prevent hypertension and its cardiovascular sequelae. The characteristics of early hypertensive subjects and those at risk for the development of high blood pressure make it possible to speculate about intervention. Subjects at risk of hypertension might benefit more from certain changes in diet, lifestyle and even be eligible for pharmacological intervention. The relation of hypertension to body composition requires further research. Control of central fat in early hypertensive subjects needs more attention. The reactivity of the total peripheral resistance can theoretically be linked to receptor density, calcium metabolism and structural vascular changes.

The present study adds only modestly to our understanding of the causes of high blood pressure and means of prevention and treatment. Yet, the family history approach adopted in this study, when applied carefully and with adequate selection of subjects, may continue to show fruitful results not only for the study of hypertension but also in other chronic conditions that have their roots early in life.

Chapter 7

SAMENVATTING

Hoge bloeddruk, hypertensie, is een belangrijke risicofactor voor het krijgen van hart- en vaatziekten. Wat de oorzaak is van de bloeddrukstijging by een groot deel van de mensen met hoge bloeddruk is niet bekend. Bij het verlagen van bloeddruk, met als doel het risico op hart en vaatziekten te verminderen, kan men dus nog niet de oorzaken van hoge bloeddruk behandelen. Tot op heden is naar deze oorzaken veel onderzoek gedaan onder mensen waarbij al een verhoogde bloeddruk was vastgesteld. Een probleem van dergelijke onderzoeken is echter juist dat de deelnemers al een hoge bloeddruk hebben. Een aantal organen, bijvoorbeeld de nieren, die betrokken zouden kunnen zijn bij het ontwikkelen van hoge bloeddruk kunnen in hun werking ook beïnvloed worden door die verhoogde bloeddruk. Onderzoek bij mensen met een 'gewone bloeddruk' maar waarvan bekend is dat ze in de toekomst hoge bloeddruk zouden kunnen ontwikkelen, is dan een goed alternatief. Op dit moment kunnen we nog niet met zekerheid zeggen welke mensen met een gewone bloeddruk ooit hoge bloeddruk zullen ontwikkelen. Wel weten we dat in sommige families vaker hoge bloeddruk voorkomt dan in andere families. We kunnen daarom op grond van bloeddruk van ouders de kans inschatten dat iemand hoge bloeddruk zal krijgen.

In de wetenschappelijke literatuur worden verschillende mechanismen genoemd die van belang zijn in het reguleren van de bloeddruk en die anders zouden werken bij mensen met hoge bloeddruk. Een aantal van die mechanismen werken onderling nauw samen en kunnen het beste tegelijkertijd onderzocht worden. In dit onderzoek is daarom een aantal belangrijke factoren samen bestudeerd. Hoge bloeddruk wordt regelmatig toegeschreven aan een sterkere activatie van hart en bloedvaten of een andere manier van aanpassing van hart en bloedvaten tijdens bijvoorbeeld stress. Door de reacties van de activiteit van het hart en bloeddruk te meten tijdens verschillende vormen van stress kunnen aanpassingen van drie mechanismen worden onderzocht. Er is een aantal theorieën die beschrijven waardoor die bloeddrukstijging sterker zou kunnen zijn. De eerste theorie stelt dat dit vooral komt door een verhoogde activatie van het hart, terwijl de tweede zegt dat een sterkere vernauwing van de bloedvaten de voornaamste factor is. Met name een verhoogde activatie door

het sympatische deel van het autonoom zenuwstelsel is volgens de eerste theorie regelmatig een veroorzaker van hoge bloeddruk. Deze theorieën zijn echter voor een belangrijk deel gebaseerd op onderzoek bij mensen die al een hoge bloeddruk hadden. Een bijkomend probleem is dat in nogal wat onderzoek alleen bloeddruk en hartfrequentie gemeten is en daarmee geen nader inzicht wordt verkregen in de wijze waarop verhoogde reacties van de bloeddruk op stress tot stand komen.

In onderzoek is gevonden dat de hoge bloeddruk meer voorkomt bij mensen die te dik zijn, een slecht conditie hebben, weinig sporten, depressief, zenuwachtig of 'gestressed' zijn. Verhoogde reacties van bloeddruk tijdens stress hangen echter mogelijk ook samen met bijvoorbeeld de hoeveelheid vetweefsel, de lichamelijke conditie of de persoonlijkheid. Als mensen onderling verschillen in deze factoren kan niet zonder meer geconcludeerd worden dat eventuele verschillen in bloeddrukreactie op stress het gevolg zijn van een sterkere activatie van hart en bloedvaten.

Het huidige onderzoek is uitgevoerd in het kader van het project 'Voorspellende factoren van essentiële hypertensie', dat mogelijk is gemaakt door financiële steun van de Nederlandse Hartstichting. Het doel van het project was een groot aantal factoren te bestuderen waarvan in de wetenschappelijke literatuur naar voren is gebracht dat ze samenhangen met hoge bloeddruk. De gegevens zijn verzameld bij jongeren die verschillen in kans op het krijgen van hoge bloeddruk. Aan dit deel van het project nam groep jongeren deel waarvan beide ouders een relatief hoge bloeddruk hadden of voor hoge bloeddruk behandeld zijn en een groep jongeren waarvan beide ouders lage bloeddruk hadden. De ouders zijn geselecteerd uit de mensen die deelgenomen hebben aan een van de onderzoeksprojecten van de Erasmus Universiteit in Zoetermeer. Jongeren zijn uitgenodigd om deel te nemen aan het onderzoek als de bloeddruk van hun ouders twee keer, met een tussenperiode van 10 jaar, relatief hoog dan wel laag was in vergelijking met andere mensen uit Zoetermeer. Het heet dan dat de bloeddruk van beide ouders zich stabiel in een van de twee extremen van de, voor leeftijd en geslacht gecorrigeerde, bloeddrukverdeling van de onderzoekspopulatie bevindt.

In het onderzoek zijn de reactie van hart, bloedvaten en zenuwstelsel op verschillende vormen van stress bekeken. Uit de literatuur was reeds bekend dat mensen met hoge bloeddruk een sterkere stijging van de bloeddruk vertonen als ze aan verschillende vormen van stress worden blootgesteld. Een stijging van de bloeddruk door stress is heel gewoon en zelfs gewenst. Stressreacties zijn in principe niets meer dan een voorbereiding van het lichaam op vluchten of vechten. Eeuwen lang was dat bijzonder nuttig. Mensen die bedreigd werden door bijvoorbeeld een

beer, of een leeuw konden twee dingen doen; proberen het beest te doden of heel hard weglopen. De schrikreactie (stressreactie) die ontstond op het moment dat ze het dier waarnamen had tot doel het lichaam voor te bereiden op de vlucht. In de moderne wereld is deze reactie meestal niet zo adequaat, want weglopen voor een boze chef of schoolmeester wordt over het algemeen niet als normaal beschouwd. De voorbereiding op de actie leidt niet tot een actie en een overmatige 'voorbereiding', een hogere bloeddrukreactie wordt als ongezond beschouwd.

De ontwikkeling van nieuwe meetmethoden en het gebruik van computers maken het mogelijk de reacties van het lichaam nauwkeurig te volgen tijdens verschillende vormen van stress. In dit onderzoek is gekozen voor vier verschillende vormen van stress, twee computerspelletjes (een letter-zoek-spel en een reactietijdtest), een handknijptaak en een fietstest op een fietsergometer. Tijdens deze taken steeg de bloeddruk. De bloeddrukstijgingen tijdens de verschillende vormen van stress kwamen op verschillende manieren tot stand: het zij door een extra activatie van het hart dan wel door een extra samenknijpen, de contractie, van de bloedvaten of een combinatie van beide.

Vóór de deelnemers de computerspelletjes speelden werden eerst zogenaamde rustmetingen uitgevoerd. Onder andere werd de hartslag en de bloeddruk bepaald terwijl de deelnemers rustig in een stoel zaten. Uit die metingen bleek dat de groep jongeren, waarvan de ouders hoge bloeddruk hadden, zelf gemiddeld ook een iets hogere bloeddruk hadden al was er geen sprake van echte hypertensie. Er werden geen verschillen gevonden in de frequentie van de hartslag of activiteit van het zenuwstelsel.

Tijdens het letter-zoek-spel bleek dat de bloeddruk sterker steeg bij deelnemers waarvan de ouders hoge bloeddruk hadden. Gedurende de reactietijdtest bleken de bloedvaten sterker samen te knijpen bij deze jongeren, maar de bloeddruk steeg niet meer. Het lichaam was blijkbaar in staat om deze sterkere reactie van de bloedvaten te compenseren. Zodat er (nog) geen bloeddrukverschil ontstond. Over het geheel genomen werd de reactie tijdens beide taken gekenmerkt door een sterker samenknijpen van de bloedvaten, terwijl geen verschillen tussen de groepen gevonden werd in activatie van het hart door het zenuwstelsel. Dezelfde verschillen tussen de groepen werden gevonden tijdens de handknijptaak. Bij deelnemers waarvan de ouders hoge bloeddruk hadden was de contractie van de bloedvaten sterker. Hier is de bloeddrukstijging die daar een gevolg van is in principe nuttig voor de doorbloeding van de hand en arm die voor het samenknijpen van het apparaat zorgen zodat deze goed van zuurstof en voedingsstoffen worden voorzien. Tijdens de fietstest

bleek dat de jongeren van ouders met hoge bloeddruk niet minder fit zijn in vergelijking met jongeren van ouders met lage bloeddruk. Wel verliep de aanpassing aan het fietsen van de slagvolume van het hart een beetje trager. Iets dat bij mensen met een hoge bloeddruk al eerder is aangetoond.

Van het deel van het zenuwstelsel dat hart en bloedvaten activeert, het sympatische deel, is regelmatig gesteld dat het een rol speelt in het ontstaan van hoge bloeddruk. In dit onderzoek is dan ook nauwkeurig naar dit deel van het zenuwstelsel gekeken. Het bleek dat er geen verschillen in activiteit te vinden waren tussen de groepen zowel in rust als tijdens de stresstaken. Wel bleek tijdens dezelfde metingen, dat snelle bloeddrukveranderingen minder goed gecorrigeerd konden worden.

Bij de deelnemende jongeren werd het vetpercentage in het lichaam, hun conditie en het aantal uren dat ze aan sport of zwaar lichamelijke arbeid deelnamen bepaald en werd hen gevraagd een aantal vragenlijsten in te vullen om bepaalde persoonlijkheidsgegevens te onderzoeken, zoals de manier van het uiten van woede, angst en depressiviteit. Er werden tussen de twee groepen deelnemers geen verschillen gevonden in de scores op de vragenlijsten of de conditietest. Wel bleek dat de jongeren, waarvan de ouders hoge bloeddruk hadden, wat meer vetweefsel in de buik hadden, ook al waren ze gemiddeld niet dikker. Uit ander onderzoek is bekend dat mensen die vet vooral opslaan in de buik, het bierbuikje of het 'appel'model, vaker hoge bloeddruk hebben en een grotere kans op hart en vaatziekten. De manier waarop vet wordt opgeslagen lijkt erfelijk bepaald te zijn.

Uit het onderzoek is gebleken, dat mensen waarbij hoge bloeddruk in de familie voorkomt zelf ook een hogere bloeddruk hebben op jongere leeftijd. De bloeddrukniveaus zijn echter nog niet zo hoog dat er al sprake is van hypertensie en we weten dat slechts een deel van de groep echt hoge bloeddruk zal ontwikkelen. De jongeren vertonen geen verhoogde reactie van de bloeddruk tijdens stress, maar de bloeddrukstijging komt op een andere manier tot stand. De bloeddrukstijging wordt in sterkere mate bepaald door het samenknijpen van de bloedvaten. Tevens werken de mechanismen die snelle veranderingen in de bloeddruk moeten werken iets trager. De oorzaak hiervoor kan in de bloedvaten liggen, aangezien sensoren die de bloeddrukveranderingen moeten constateren afhankelijk zijn van de rekbaarheid van de bloedvatwanden. Zekerheid hierover hebben we nog niet en daarvoor is verder onderzoek nodig.

De plaats waar mensen overtollig vet in het lichaam opslaan is erfelijk bepaald en het feit dat mensen, waarvan de ouders hoge bloeddruk hebben, relatief meer vet in hun buik dragen kan in theorie leiden tot een andere activatie van hart en

bloedvaten via een terugkoppeling in het zenuwstelsel. Ook andere mechanismen kunnen hierbij echter een rol spelen. In het onderzoek zijn geen aanwijzingen gevonden voor verschillen in eetgewoonten (hoeveelheid calorieën in de voeding, zoutinname enz) sportdeelname of persoonlijkheid tussen de groepen deelnemers waarvan de ouders hoge of lage bloeddruk hebben.

Stress leidt niet direct tot hogere bloeddrukreacties, maar de bloeddrukreacties zijn meer het gevolg van vernauwing van de bloedvaten bij jongeren waarvan de ouders hoge bloeddruk hebben. Bovendien verlopen de correcties van bloeddrukstijgingen trager. Als gevolg hiervan zou langdurige stress bij kunnen dragen tot het ontstaan van hoge bloeddruk. Die stress hoeft daarbij niet noodzakelijk 'mentaal' van aard te zijn. Ook vormen van lichamelijke activiteit zoals tijdens de handknijptaak roepen vergelijkbare reacties van hart en bloedvaten op. Dit zou bijvoorbeeld het geval kunnen zijn bij veelvuldige en langdurige krachttraining.

Het onderzoek heeft laten zien dat nieuwe gegevens over de oorzaken van hoge bloeddruk kunnen worden verkregen door personen te bestuderen voordat ze hoge bloeddruk krijgen. Metingen van ouders en onderzoek bij hun kinderen biedt een manier om dergelijke hoog risicogroepen te vinden. In de vroege fase van de ontwikkeling van hoge bloeddruk zijn de te bestuderen mechanismen nog niet, of minder, door de hoge bloeddruk zelf beïnvloed. Naast onderzoek naar het ontstaan van hoge bloeddruk zou een dergelijke aanpak ook gebruikt kunnen worden bij onderzoek naar andere chronische aandoeningen die geleidelijk tijdens het leven ontstaan.

EEN WOORD VAN DANK

Na vele bladzijden tekst is een woord van dank op zijn plaats aan de vele mensen die een steentje hebben bijgedragen in het ontstaan van dit proefschrift. Ik ben niet in staat allen de eer toe te dichten, die hen toekomt. De mensen die steeds, soms bij nacht en ontij, klaar stonden met noodzakelijk advies of bereid waren een moment van afleiding te bezorgen. Zij weten als geen ander, dat ze op die momenten onmisbaar waren. Hen allen proberen te noemen, zou velen van hen te kort doen. Toch zijn er een paar die genoemd moeten worden.

Om te beginnen de respondenten en hun ouders. Hun enthousiasme heeft ertoe geleid, dat we konden beschikken over de o.a. voor dit proefschrift noodzakelijke gegevens. Een winter met veel koude en een soms dichtgevroren onderzoeksbus was voor hen geen belemmering deel te nemen aan het project. Essentieel was de steun van de medewerkers van de werkplaats van de Faculteit Psychologie van de Vrije Universiteit. Zij hebben ervoor gezorgd, dat de metingen in de bus verricht konden worden en in geval van calamiteiten vonden ze steeds weer het juiste bejaardenhuis om de problemen in de bus op te lossen.

Het project kon binnen een redelijke tijd afgerond worden, omdat de jongeren al geselecteerd waren en de infrastructuur binnen het project er al lag. Ingrid van Hooft was verantwoordelijk voor dat karwei en zonder haar hulp was het niet gelukt. Het 'binnenhalen van de dataset' was mogelijk door de administratie en steun van Hilda Kornman.

De vakgroep Psychonomie van de Vrije Universiteit onder de leiding van Ko Orlebeke ben ik dank verschuldigd voor de gastvrijheid gedurende de eerste twee jaren van het project. Hierdoor was het mogelijk de data te verzamelen en te bewerken. Lorenz van Doornen was heel belangrijk bij de opzet van het hiervoor beschreven deel van DHOS. De laatste twee jaren zijn de vele epi's mij tot steun geweest. Rick Grobbee is het gelukt DHOS in leven te houden. Alle snelle bewerkingen van manuscripten tot leesbare teksten moeten vele avonden en weekeinden hebben opgeslokt. Hij was steeds in staat een 'passend fysiologisch mechanisme' bij schijnbaar onoplosbare vragen te vinden. Bert Hofman bracht het idee van de studie, nog voor mijn academische vorming was begonnen. Hij verloor nooit het overzicht, als de twijfel bij anderen al lang was toegeslagen.

CURRICULUM VITAE

Adriana Cornelia de Visser was born on November 2, 1962 in Rotterdam, The Netherlands. She passed her secondary school exam in 1982 at the 'Christelijke Scholengemeenschap Henegouwerplein' in Rotterdam. Subsequently, she studied Human Movement Science at the Free University in Amsterdam. In 1989 she obtained her doctoral degree in both Workphysiology and Psychology in relation with human movement. In the last two years of her study she participated in a research project on stress reactivity in relation with aerobic fitness. In 1990 she started as research assistant at the Department of Epidemiology and Biostatistics of the Erasmus University Rotterdam (head: prof. dr. A. Hofman). To carry out her work in the Dutch Hypertension and Offspring Study she was based both at the Department of Epidemiology and Biostatistics of the Erasmus University Rotterdam and the department of Physiological Psychology at the Free University Amsterdam (head: prof. dr. J.F. Orlebeke).