Blood pressure and catecholamine reactivity to adrenergic stimulation in essential hypertension

J.W.M. Lenders

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Een wetenschappelijke proeve op het gebied van de Geneeskunde
en Tandheelkunde

door

JACOBUS WILHELMUS MARIA LENDERS

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te Blerick

Promotores: Prof. Dr A. van 't Laar
                Prof. Dr R.A. Binkhorst

Co-referent: Dr Th. Thien

CONTENTS

CHAPTER 1

INTRODUCTION

INTRODUCTION

It has been recognized for a long time that blood pressure variability
is strongly affected by environmental stimuli. In particular, it has
been suggested that patients with essential hypertension reveal an ab-
normal haemodynamic reactivity to various stressful conditions as
occurring in daily life (1). However, it still remains a matter of
debate whether this functional derangement is predominantly an expres-
sion of a cardiovascular system structurally altered by the elevated
blood pressure itself (2) or whether it reflects an abnormal inter-
mediating role of the autonomic nervous system (3). It is beyond any
doubt that structural vascular factors are important determinants of
haemodynamic reactivity since vascular responses to all vasocon-
strictor stimuli are amplified. Although there is strong evidence for
an excessive central sympathetic activity in essential hypertension
(4) and probably also for a diminished parasympathetic activity in
early hypertension (5), the relative importance of these findings to
the pathogenesis of hypertension remains open for debate. In addition,
excessive central sympathetic neural activity does not preclude a role
for peripheral mechanisms involved in vascular reactivity. There is
still inconclusive evidence for an enhanced vascular alpha-adrenocep-
tor sensitivity (4,6) and it remains uncertain whether impaired baro-
receptor reflexes play a causal role.
Despite the rapidly accumulating knowledge in this field, there are
still many unsettled and controversial issues concerning the pathoge-
netic role of the autonomic nervous system in essential hypertension.
Except for the well-known confusing effect of the heterogeneity of the
hypertensive population and the complex interrelations between the
cardiovascular and the autonomic nervous system, methodological diffi-
culties with regard to a reliable assessment of sympathetic nervous
(re)activity have not yet been resolved. The interpretation of the
effects of adrenergic stimulation in essential hypertension is hamper-
ed by the recent evidence that different adrenergic stimuli elicit a
differential sympathetic discharge to peripheral organs (2). In spite
of the recent availability of sensitive and specific laboratory
methods for the measurement of plasma catecholamines, several metho-
dological pitfalls in the assessment of sympathoadrenal activity may
confound unequivocal conclusions. So, the type of adrenergic stimulus,

a venous or arterial sampling of catecholamines, the size of the study sample, the choice of the control groups, the influence of age, sex and race, the defining of the inclusion blood pressure, the performance of the laboratory assay for the determination of catecholamines, the sodium intake; all these factors should be taken into account when haemodynamic and sympathoadrenal reactivity are studied. In particular, the validity of venous plasma catecholamine samples for measurement of sympathoadrenal activity has been seriously questioned in a recent review (6). However, arterial sampling or kinetic studies for regional catecholamine metabolism are not feasible in large groups of patients.

Haemodynamic and plasma catecholamine reactivity have been studied during different types of adrenergic stimulation in patients with essential hypertension (1,7-9). However, different stress tests have been carried out in varying and sometimes small groups of patients and the normotensive controls were sometimes ill-defined.

The main part of the study, presented in this thesis, consists of a complete study protocol of 7 standardized tests that was carried out in one and the same group of mildly hypertensives and in a control group of normotensives. The tests used in this study were: a handgrip isometric exercise test, a mental arithmetic test, a head-up tilt test, a graded submaximal bicycle exercise test and a cold pressor test. A noradrenaline and adrenaline infusion completed the protocol.

OUTLINE OF THE INVESTIGATIONS

In chapter 2, the hypertensive and normotensive groups of the main study are described and the study protocol and the procedures of the used tests are presented in detail.

The reproducibility of the haemodynamic and plasma catecholamine responses to some tests is reported in chapter 3. The subjects involved in this study did not participate in the main study.

Chapter 4 presents the baseline circulatory variables and the baseline plasma catecholamine levels of all participants in the main study and in chapter 5 to 11 the results of the 7 tests are described.

To investigate the role of circulating adrenaline, some adrenergic stress tests were carried out in a group of adrenalectomised females (chapter 12).

Finally, in 8 hypertensive subjects the entire study protocol of the main study, was repeated after 6 months treatment with the β_1-selective β-adrenoceptor blocker atenolol (chapter 13).

The following specific questions will be addressed:

1) Do patients with essential hypertension have higher basal plasma catecholamine levels than a normotensive control group of comparable age/sex stratification?

2) What is the reproducibility of the haemodynamic and plasma cate-cholamine responses of frequently employed adrenergic stress tests like mental arithmetic, handgrip exercise, head-up tilt and cold pressor test?

3) Do patients with essential hypertension exhibit an increased haemo-dynamic responsiveness to exercise (isometric and isotonic), mental arithmetic, head-up tilt and a cold pressor test?

4) Do patients with essential hypertension have an enhanced vascular sensitivity for exogenous administered catecholamines?

5) Do adrenalectomised subjects, who are devoid of circulating adrena-line, exhibit normal haemodynamic and plasma noradrenaline responses during adrenergic stimulation?

6) What is the effect of long-term betablockade on the haemodynamic and plasma catecholamine responses during adrenergic stimulation?

7) Is it possible to predict the chronic hypotensive effect of a beta-blocker on basis of the basal plasma catecholamine levels or on the haemodynamic and/or plasma catecholamine responses during adrenergic stimulation as assessed before treatment?

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SUBJECTS AND METHODS

SUBJECTS

Seventy patients with essential hypertension (range 20-55 years) par-
ticipated in the study on a voluntary basis after informed consent.
After withdrawal of antihypertensive therapy for at least 3 months, a
diagnosis of hypertension was made if the mean of the blood pressure
(BP) values of 3 outpatient visits was higher than 140 and/or 90 mmHg
(1). These BPs were measured in the outpatient clinic after at least 5
minutes of supine rest and each value was the mean of 2 BP readings.
The mean BP ($\pm$SD) for the whole group was 146$\pm$9/91$\pm$8 mmHg and the mean
of three heart rate (HR) ($\pm$SD) values was 77$\pm$11 b/min. Secondary
hypertension was excluded according to the standard clinical criteria
and patients with signs of target organ damage like electrocardio-
graphic left ventricular hypertrophy (2) or a creatinine clearance of
less than 100 ml/minute were excluded from the study. Patients with
any other disorder than hypertension or a body weight higher than the
ideal body weight + 10% were also excluded from the study (3). Body
mass index (Quetelet's index) was calculated by dividing body weight
by height square.

Forty-one healthy normotensive subjects served as a control group.
These volunteers were recruited by means of a newspaper announcement
and were not familiar with the investigative procedures. All subjects
had a normal physical examination, normal values for plasma electro-
lytes, serum creatinine, transaminases and had a normal ECG. BP was
measured three times at one occasion and normotension was defined when
the BP values were below 140/90 mmHg.

As shown in table 2-1, there were no differences between the two
groups with regard to age, weight, height and Quetelet's index. Except
for a higher blood pressure, the hypertensive subjects had a signifi-
cantly higher heart rate. Both groups had a similar sex distribution.
Furthermore, to account for the effect of age, each group was divided
in three subgroups stratified by age: 20-29, 30-39 and 40-55 years.

Table 2-1.

Characteristics of the normotensive (NT) and hypertensive (HT) sub-
jects (mean±SD).

	NT	HT
n	41	70
Male/female	22/19	40/30
n: age class		
20-29 years	15	22
30-39 years	13	23
40-55 years	13	25
Age (years)	34.8 ± 9.5	35.2 ± 9.9
Weight (kg)	68.9 ± 7.4	71.4 ± 11.2
Height (cm)	174.9 ± 7.1	172.3 ± 8.8
Quetelet's index (kg/m^2)	22.5 ± 1.8	24.0 ± 2.6
Blood pressure		
supine systolic (mmHg)	118 ± 11	146 ± 9
supine diastolic (mmHg)	72 ± 7	91 ± 8
Heart rate (beats/min)	64 ± 10 *	77 ± 11
24 hour sodium excretion	12.1 ± 5.3	11.4 ± 4.9
(mmol/mmol creatinine)	(n=16)	(n=31)

* $p < 0.05$

STUDY DESIGN

All subjects underwent 7 different tests in the same sequence: hand-
grip exercise (HG), mental arithmetic (MA), head-up tilt (T), bicycle
exercise (BYC), noradrenaline infusion (NA), adrenaline infusion (A)
and a cold pressor test (CPT). These tests were carried out on two
separate days and all experiments were done in the morning at 9.00
o'clock to exclude the effect of diurnal variability of haemodynamics
and plasma catecholamines. All tests were carried out in the supine
position, except for the dynamic exercise test. On a separate day
prior to the experiments, the goal of the study was explained to the
subjects and they were made familiar with the investigational proce-
dures. The subjects were asked to refrain from caffeine containing
products and smoking after midnight before the experiment. An ad libi-
tum breakfast was allowed and 16 normotensive and 31 hypertensive sub-
jects collected 24-hour urine on the day prior to the first experi-
mental day to estimate sodium intake. All experiments were performed
by the same investigator with the assistance of a trained nurse.
During the experiments special care was taken to avoid conversation
with the subjects as much as possible.
On arriving at the laboratory (with a constant room temperature of
$21.5\pm1.1°C$)(SD) on the first experimental day, the subjects were asked
to empty their bladder. The clothes consisted of light sportswear and
a blanket was used to prevent cooling down during lying quietly. In
the non-dominant arm an indwelling catheter was inserted in an ante-
cubital vein to take blood samples for plasma catecholamines and blood
lactate (4). The line was kept open with NaCl 0.9% (10 ml/hr). Before
drawing a plasma sample, the first two milliliters of blood were dis-
carded. For the catecholamine infusion tests a second indwelling
catheter was inserted in an antecubital vein of the other arm. Thirty
minutes prior to the infusion of the catecholamines, an infusion with
NaCl 0.9% (10 ml/hr) was commenced. A blood pressure cuff of the
Arteriosonde 1225 (semiautomatic blood pressure monitor) and a mercury
strain gauge venous occlusion plethysmograph (for forearm blood flow
registration) (FBF) (5) were attached to the non-dominant arm. The
forearm was supported 10 cm above heart level. The mean of three flow
curves represents one FBF value. HR was recorded with a continuous
electrocardiogram and the HR was calculated from the last 10 RR inter-

vals in a stated minute. After a supine rest period of at least 20 minutes the first test was started. Between tests always a rest period of 30 minutes was inserted.

Determination of plasma catecholamines

Each blood sample (5 ml) was collected in a prechilled tube on melting ice and was immediately centrifuged at +4 °C. The plasma was stored at -20 °C and all samples were analysed within 6 weeks from collection by a COMT-based (catechol-0-methyltransferase) radioenzymatic assay with thin-layer chromatography (6). The interassay precision of the assay could be improved considerably by dissolving and diluting the internal standard catecholamines in plasma instead of in aqueous solution (7). The interassay coefficient of variation for plasma epinephrine is 9% and for norepinephrine 7.5%. The lower limit of detection is 0.05 nmol/l for both catecholamines.

TEST PROCEDURES

Handgrip exercise

Handgrip isometric exercise (HG) was performed with a calibrated strain gauge handgrip dynamometer as previously described (8). The subject squeezed with the dominant hand with a force of 30% of the maximal voluntary strenght (MVC) during 3 minutes. The individual's MVC was determined on a separate day prior to the real test and was defined as the mean of three successive trials of maximal strength. The subject was instructed not to hold his breath during squeezing and
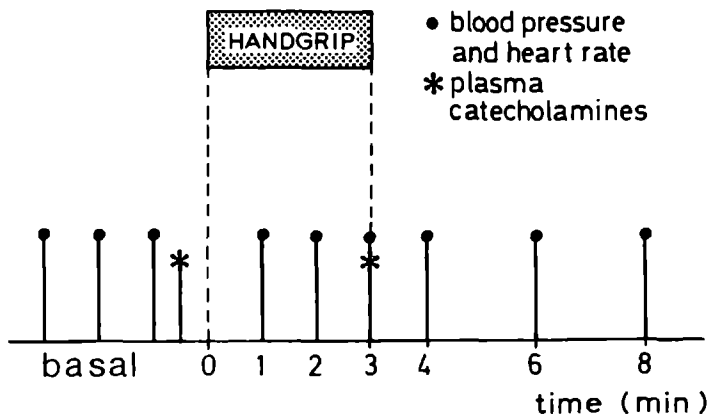
Figure 2-1

The protocol of the handgrip exercise.

the used force was recorded continuously to enable the subject to
adhere to the prescribed force. The protocol of the haemodynamic and
humoral measurements is depicted in figure 2-1.

Mental arithmetic

Mental arithmetic (MA) was carried out by subtracting continuously the
number 17 from a four-digit number as quickly as possible for 5 min-
utes while a metronome was spurring the subject (9). The subjects had
to perform the calculations aloud and were corrected for mistakes. BP,
HR, FBF and plasma catecholamines were measured according to figure
2-2.
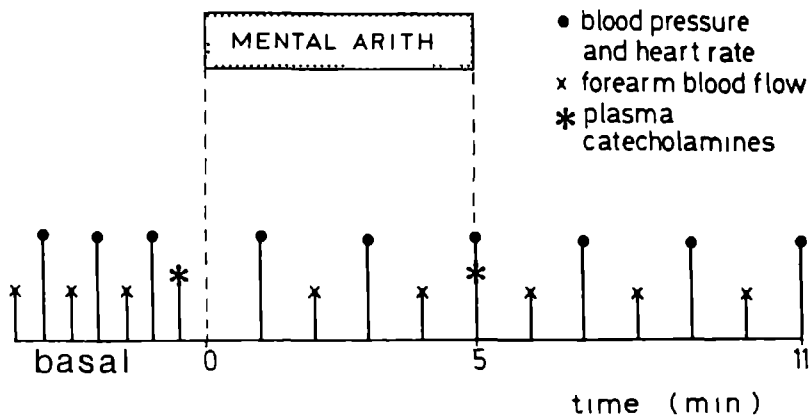
Figure 2-2
The test protocol of the mental arithmetic test.

Head-up tilt

During the head-up tilt test (T) the subjects were passively tilted
head-up to 45 degrees on an electric tilt table with foot support in
15 seconds. The subjects remained in this position for 10 minutes. BP
and HR were measured three times before and after and six times during
the T test. Before and during the last 10 seconds of the T test, blood
samples for plasma catecholamines were drawn (figure 2-3).
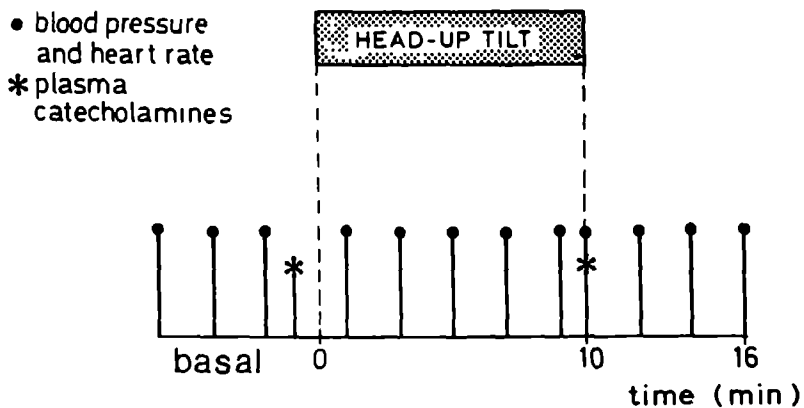
Figure 2-3

The test protocol of the head-up tilt test.

Bicycle exercise

A standardized isotonic exercise test (BYC) was carried out in the up-
right position with a Lode electric bicycle ergometer (Lode's Instru-
ments B.V., Groningen, The Netherlands). The used pedal rate was 60
rpm in all tests and the height of the bicycle saddle and handle bar
were standardized for each subject. BP and HR were recorded with an
automated exercise blood pressure monitor (Critikon 1165). This non-
invasive device reliably measures exercise blood pressure by ECG-
assisted auscultation (10,11).

To circumvent a maximal exercise test in the hypertensive patients, a
submaximal exercise pretest was carried out in each subject on a sepa-
rate day to calculate the individual's maximal working power (W-max).
The initial work load was 20 watt and this was increased by 20 watt
every minute until a HR of about 110 beats per minute was reached.
Then this work load was maintained for 3 minutes to reach a steady
state of the HR. Thereafter the work load was again increased in the
same way until a HR of about 130 beats per minute was reached, which
was again stabilized for 3 minutes. After 3 minutes of exercise at a
HR of 150 beats per minute the test was terminated. So, each subject

exercised at three incremental work load levels. The mean HR of every level was plotted against the three corresponding work loads. Extrapolation from this plot and the expected maximal HR for a given age (12) resulted in the extrapolated W-max. In a pilot study, 20 healthy volunteers performed both this submaximal exercise test from which the W-max was extrapolated and a maximal exercise test. The measured W-max from the maximal exercise test appeared to be systematically about 10% higher than the extrapolated W-max. So, for all subjects the W-max was calculated to be the extrapolated W-max + 10%. The mean residual difference between the two methods amounted to 5.2% (range -8.3-12.1%) of the measured W-max. The measured W-max and the calculated W-max values of the 20 volunteers have been plotted in figure 2-4.

In the ultimate exercise test, basal measurements of BP, HR, plasma catecholamines and lactate were carried out after a rest period of 10 minutes of sitting on the bicycle. The ECG (lead V5) was monitored throughout the test. All subjects exercised continuously for three periods of 6 minutes at work loads of 25%, 50% and 75% of the previously calculated individual W-max. BP and HR recordings in the fourth and sixth minute of the last period were used in the analysis (figure 2-5). In the last 30 seconds of the final period a blood sample for plasma catecholamines was taken. After the final period the
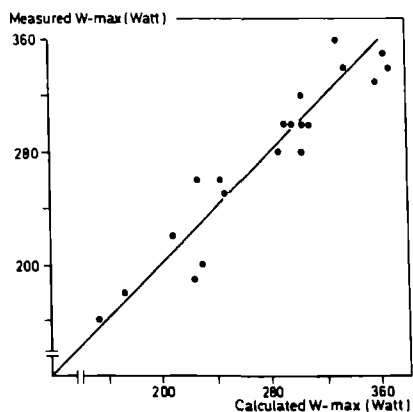
Figure 2-4
The measured W-max plotted against the calculated W-max in 20 normotensives.

work load was decreased to 50% (3 minutes) and 25% (3 minutes) of the work load of the last period. Five minutes after the highest work load, a second blood sample for lactate was drawn. The BP and HR were recorded in the third and sixth minute after decreasing the work load (figure 2-5).
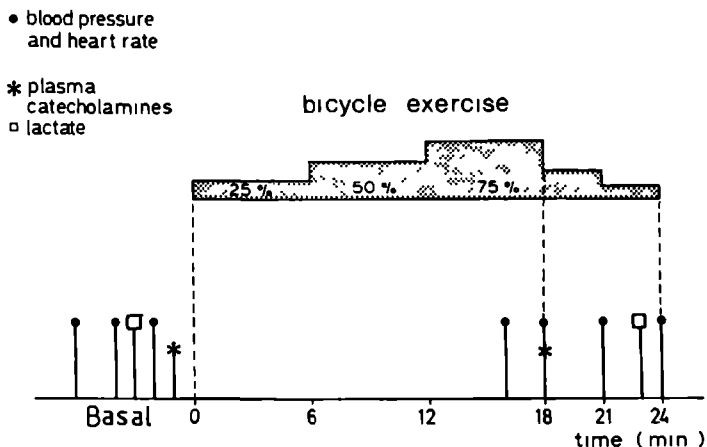
Figure 2-5
The test protocol of the bicycle exercise test

Infusion test with noradrenaline (NA test)

Following a 30 minute equilibration period during which an infusion with NaCl 0.9% was given with an infusion rate of 10 ml/hr, an infusion with a freshly prepared solution of 1 mg l-noradrenaline diluted in 50 ml NaCl 0.9% was given by means of an infusion pump. Utilizing various pump speeds, the infusion rate started at 15 ng/kg/min and doubled every eight minutes until an increase of mean arterial pressure of about 10 mm Hg was reached or if HR fell below 45 beats/min or if ventricular extrasystoles emerged. At the end of the infusion with NaCl 0.9%, baseline values of BP, HR, and FBF were recorded in triplicate and a basal blood sample for plasma catecholamines was drawn (figure 2-6). During the infusion with noradrenaline, BP, HR and FBF were recorded every 2 minutes and in the last 15 seconds of the infusion a blood sample for plasma catecholamines was taken. Only the final three BP and HR values and the last two FBF values at the highest infusion dose were used for the analysis (figure 2-6).
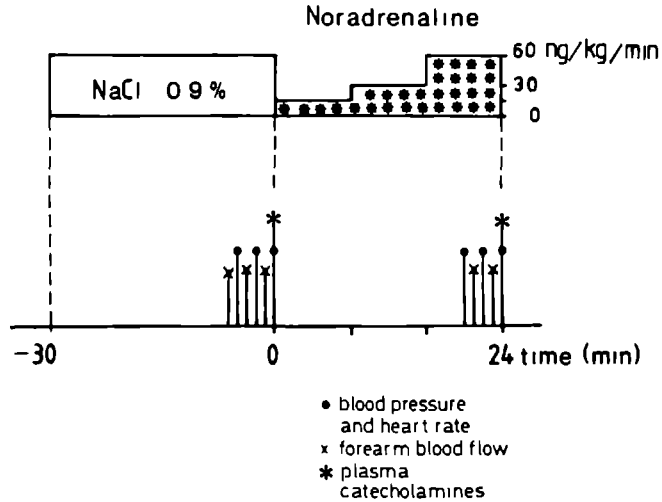
Figure 2-6

The test protocol of the noradrenaline infusion.

Infusion test with adrenaline (A test)

The protocol for infusion of adrenaline (figure 2-7) was exactly the same as for noradrenaline. This infusion was stopped sooner if the increase of heart rate exceeded 25 beats/minute or if the subject experienced complaints of palpitations or anxiety.
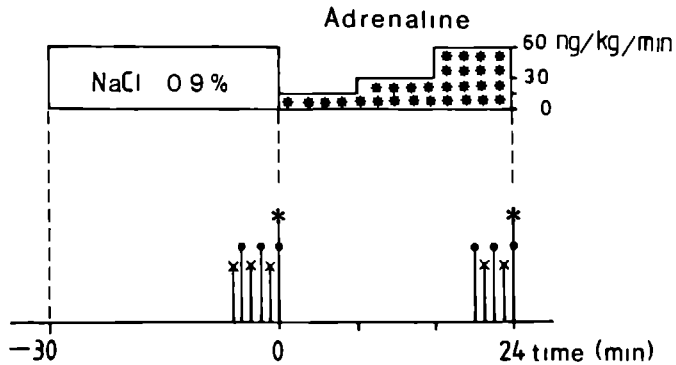
Figure 2-7

The test protocol of adrenaline infusion. For symbols, see figure 2-6.

The cold pressor test (CPT)

After taking a blood sample for plasma catecholamines and 3 basal BP,
HR and FBF readings at the end of a 30 minutes rest, the right foot
(up to the malleolus) of a subject was immersed in a water bath of 5
°C for 6 minutes. This longer lasting test instead of the classic cold
pressor test of only one minute (13) was chosen to have the opportuni-
ty to perform more than one haemodynamic measurement. Haemodynamic and
humoral measurements during and after the test were carried out
according to figure 2-8.
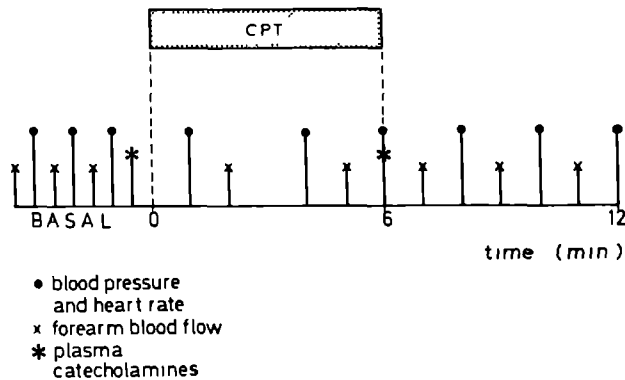
Figure 2-8
The test protocol of the cold pressor test (CPT).

STATISTICAL ANALYSIS

Noradrenaline and adrenaline infusion tests

For each haemodynamic variable the mean of the final 3 values during
NaCl 0.9% and the mean of the final 3 values during catecholamine in-
fusion were calculated. The relative response of every haemodynamic
variable during catecholamine infusion was calculated as a percentage
of the baseline value during saline infusion. The relative haemo-
dynamic responses in every subject of both groups were corrected for
the increase of plasma catecholamine and were expressed as the per-
centage increase of BP, HR and FVR per nmol/l increase of plasma cate-
cholamine. The Kruskall-Wallis test was used to explore the effect of
age and sex on the haemodynamic responses to the catecholamine in-

fusion. Differences between normo- and hypertensives were analysed using the Wilcoxon's two sample test with 0.05 as the level of significance.
Correlation coefficients were calculated according to Spearman.

The other 5 tests

Haemodynamic variables
For all tests the average of the three baseline values of every haemo-dynamic variable was calculated. Subsequently, the relative response of every haemodynamic variable on a certain time point during a test was calculated as a percentage of the baseline value. Mean arterial pressure (MAP) was calculated as the sum of the diastolic BP and one-third of the pulse pressure. Forearm vascular resistance (FVR) was calculated by dividing MAP by the FBF and was expressed as peripheral resistance units (PRU's).
To determine whether age and sex were determinants for the haemodyna-mic response to a given test, the following statistical method was applied to all tests, except for the two infusion tests. Multiple re-gression analysis was used for the dependent variables systolic and diastolic BP, HR and mean arterial pressure and as independent vari-ables: sex, age and their interaction (cross-product). This was done for each time point that a haemodynamic variable was measured. It appeared that age and sex did not contribute to the variance of any haemodynamic variable in the mental arithmetic and cold pressor test. For the three other tests, age and sex contributed to the variance of the response in at least 20% of the cases. So, in these tests the haemodynamic response was related to sex, age and/or their inter-action. For these tests the following procedure was applied: estimates of expected values and their standard errors at every time point during a test were determined by regression analysis. This was done for males and females of 25 and 50 years old separately. These (arbi-trary) age levels were chosen te enable comparison between two extreme age levels. Differences between NT and HT's were tested with Welch's test (14). (The usual t-test could not be used because the standard deviations of the NT and the HT groups differed frequently). Because we were interested in differences with regard to the course of the haemodynamic response rather than the difference at one particular

time point during a test, the level of significance per time point was taken to be 0.10/k, k being the total number of time points at which was measured during a test. Due to the interdependence of the values of subsequent time points during a test, the overall type I error is probably nearer to 5% than to 10%.

Plasma catecholamines

Assuming that age and sex might influence plasma catecholamines, comparisons between normo- and hypertensives were done apart for each sex and age class, using the Wilcoxon test with 0.05 as level of significance.

Means $\pm$ SE are given unless indicated otherwise.

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REPRODUCIBILITY OF HAEMODYNAMIC AND PLASMA CATHECHOLAMINE RESPONSES TO HANDGRIP EXERCISE, MENTAL ARITHMETIC, COLD EXPOSURE AND HEAD-UP TILT IN NORMO- AND HYPERTENSIVE SUBJECTS.

INTRODUCTION

Handgrip isometric exercise (HG), mental arithmetic (MA), cold pressor
test (CPT) and head-up tilt (T) are widely used stress tests in car-
diovascular and pharmacotherapeutic research. In particular, they are
used to study haemodynamic and sympathoadrenal reactivity in a variety
of disorders like hypertension (1,2), congestive heart failure (3) and
autonomic neuropathy (4). In addition to pathophysiological studies
they are often employed for investigation of the effects of pharmaco-
logical intervention in various disorders (5,6). Although it is clear-
ly important to know the variability of the responses to these tests
on repeated application, until now this has not been studied in
healthy subjects or patients with essential hypertension. Therefore,
we carried out these tests twice on two separate days to study the
reproducibility of blood pressure (BP), heart rate (HR) and forearm
blood flow (FBF) responses. Further, the reproducibility of the plasma
catecholamine responses to MA and HG test was studied in normo-
tensives.

SUBJECTS/METHODS

The study was performed in 51 normotensive (NT) and 22 subjects with
essential hypertension (HT) (Table 3-1) who gave informed consent. The
NT group was recruited by a newspaper announcement. The antihyper-
tensive treatment in the HT patients was stopped for at least 4 weeks
prior to the study. Twenty-four NT and 22 HT subjects underwent two
vigorously standardized stress tests in the morning and in the same
sequence: a mental arithmetic test and a handgrip isometric exercise.
This protocol was repeated on a second occasion after at least one
week. Nine NT subjects performed the CPT twice as did another 18 NT
subjects who underwent the T test.
Each test in a subject was carried out by the same investigator and
care was taken to avoid any interfering disturbance of the experiment-
al conditions. All tests were carried out as described in the previous
chapter (CHAPTER 2) and the circulatory variables were measured in the
same manner. Throughout the study the same Arteriosonde BP monitor and
plethysmograph were used. In a given subject the size of the used mer-
cury strain gauge for measurement of forearm blood flow was kept

table 3-1

Characteristics of normo- and hypertensive subjects.

	Normotensives			Hypertensives
Test	MA+HG	T	CPT	MA+HG
n	24	18	9	22
Age (years)	28.5	33.6	26.1	30.4
range	20-57	21-45	20-37	15-54
Sex (males/females)	22/2	12/6	3/6	14/8
Blood pressure (mmHg)				
supine	106/69	112/70	116/72	136/90
(SD)	(10/5)	(8/8)	(9/6)	(14/9)

The given blood pressure value is the mean of three blood pressure values after 20 minutes supine rest.

MA = mental arithmetic   HG = handgrip exercise
CPT = cold pressor test   T = head-up tilt

constant during the study. In 10 normotensive subjects an in-dwelling catheter was inserted in an antecubital vein of the non-dominant arm for taking blood samples for plasma catecholamines (plasma noradrenaline=NORADR, plasma adrenaline=ADR) (CHAPTER 2). The MA and the HG test were carried out on the same morning.

DATA ANALYSIS

The mean arterial blood pressure (MAP) was calculated as the sum of the diastolic BP and one-third of the pulse pressure.
The maximal haemodynamic response of each test has been used for analysis: that is of the first minute of the MA and CPT test and of the last minute of the HG test. Because the haemodynamic changes

during T were stable, the average of all measured haemodynamic values was used for the analysis. Since the three basal values of each haemo-dynamic parameter were stable, the responses during each test have been expressed as the percentage change with respect to the mean of the three basal values. The reproducibility is expressed as the standard deviation of a single observation according to the formula:

$$S = \sqrt{\frac{\sum\limits_{i=1}^{n} (X_i - Y_i)^2}{2n}}$$

X_i= result of the first test and Y_i= result of the second test of subject i. n = number of paired observations. i = 1 to n.

Test performance during MA was assessed by calculating the number of mistakes made and the level that was ultimately reached during sub-traction. Differences between the first and second test were analysed by means of the Wilcoxon's two sample test. The Spearman correlation coefficient was calculated for the relation of test performance with the basal BP and the BP and HR responses during MA.

RESULTS

There were no significant differences in the baseline values of blood pressure and heart rate between the first and second test (table 3-2) for all four stress conditions.

Table 3-2
Baseline blood pressure (BP), heart rate and forearm blood flow values of the first and second test in both groups (mean ± SE).

	Normotensives		Hypertensives	
	First test	Second test	First test	Second test
Systolic BP (mmHg)				
- MA+HG	106 ± 2	107 ± 3	136 ± 3	135 ± 4
- TILT	112 ± 2	111 ± 2	--	--
- CPT	116 ± 3	116 ± 3	--	--
Diastolic BP (mmHg)				
- MA+HG	69 ± 1	68 ± 2	90 ± 2	91 ± 3
- TILT	70 ± 2	67 ± 2	--	--
- CPT	72 ± 2	70 ± 2	--	--
Heart rate (beats/minute)				
- MA+HG	63 ± 2	62 ± 3	71 ± 2	67 ± 2
- TILT	62 ± 3	59 ± 3	--	--
- CPT	63 ± 3	65 ± 2	--	--
Forearm bloodflow (ml/100 ml.min)				
- MA	2.7 ± 0.7	2.7 ± 0.4	3.4 ± 0.3	3.3 ± 0.3
- CPT	5.7 ± 0.8	4.8 ± 0.7	--	--

Mental arithmetic and handgrip exercise

Figure 3-1 shows that in both normotensive and hypertensive subjects, MA caused similar percentage increases of MAP during the first and second test. The same applied to the HR. During HG exercise, the NT group showed a larger increase of MAP than the HT subjects, but there was no difference between the first and second test. The rather large standard deviations of both MAP and HR responses in both groups point to a marked interindividual variability of the responses to both tests. Considering each total group, there was no sequence effect in either test (figure 3-1).

⊠ First test
☐ Second test

Figure 3-1
The mean percentage in-
crease (+ SD) of mean
arterial pressure (MAP)
and heart rate (HR) in
the first and second
test in normotensives
(NT) and hypertensives
(HT).
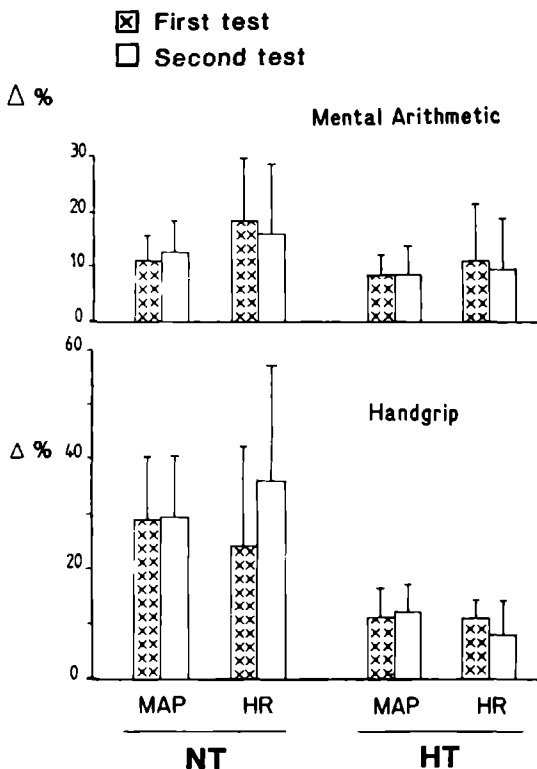
The standard deviation of a single observation for the blood pressure responses ranged from 3.9-9.3% in the NT and from 3.9-6.3% in the HT group. (Table 3-3). With regard to the HR, the NT group showed

Table 3-3

The percentage haemodynamic changes in the first and second test (mean $\pm$ SE) and the standard deviation (S) of a single observation are given for mental arithmetic and handgrip exercise.

BP = blood pressure   FBF = forearm blood flow.

	Mental arithmetic test			Handgrip test		
	1° test	2° test	S	1° test	2° test	S
Normotensives						
Δ systolic BP (%)	11 $\pm$ 3	12 $\pm$ 2	5.5%	24 $\pm$ 3	23 $\pm$ 2	5.6%
Δ diastolic BP (%)	14 $\pm$ 3	17 $\pm$ 4	7.4%	34 $\pm$ 4	36 $\pm$ 4	9.3%
Δ mean arterial BP (%)	11 $\pm$ 1	13 $\pm$ 1	3.9%	30 $\pm$ 2	30 $\pm$ 2	6.9%
Δ heart rate (%)	18 $\pm$ 3	16 $\pm$ 3	4.9%	25 $\pm$ 6	37 $\pm$ 7	12.3%
Δ FBF (%)	61 $\pm$ 19	62 $\pm$ 20	33.7%	-	-	-
Hypertensives						
Δ systolic BP (%)	6 $\pm$ 1	6 $\pm$ 1	4.2%	8 $\pm$ 1	8 $\pm$ 1	3.9%
Δ diastolic BP (%)	10 $\pm$ 1	10 $\pm$ 2	6.1%	15 $\pm$ 2	16 $\pm$ 2	6.3%
Δ mean arterial BP (%)	8 $\pm$ 1	8 $\pm$ 1	4.6%	11 $\pm$ 1	12 $\pm$ 1	4.8%
Δ heart rate (%)	11 $\pm$ 2	10 $\pm$ 2	4.8%	11 $\pm$ 2	8 $\pm$ 2	5.7%
Δ FBF (%)	72 $\pm$ 11	66 $\pm$ 14	33.8%	-	-	-

the highest standard deviation of 12.3% during the HG. The FBF response had the highest standard deviation of a single observation (Table 3-3). Albeit the low standard deviation of a single observation for blood pressure and heart rate changes, figure 3-2 illustrates the large scatter of the intraindividual MAP responses.

In the 10 NT subjects from whom plasma catecholamines were sampled, there was no significant difference between the baseline values of plasma NORADR of the first and second test. The same applies to the baseline plasma ADR values (table 3-4). The average plasma catecholamine response of the first and second test was not different during both MA and HG.

Although the standard deviation of a single observation was lower for the plasma ADR response, the reproducibility of the plasma ADR was worse than that of the plasma NORADR response if the standard errors are related to the mean responses (table 3-4).

The total number of mistakes and the level reached during subtraction did not differ between the first and second test in the 22 HT subjects. In addition there was no relation between performance and the basal BP or the BP and HR responses.

Figure 3-2

The individual mean arterial pressure (Map) responses of the first and second test in the normotensives (NT) and hypertensives (HT).

30

Table 3-4

The baseline plasma catecholamine levels, plasma catecholamine responses and the standard deviation of a single observation of the responses in 10 normotensive subjects in the mental arithmetic (MA) and handgrip test (HG) (mean $\pm$ SE).

	MA		HG	
	1° test	2° test	1° test	2° test
Baseline plasma noradrenaline (nmol/l)	0.80+0.08	0.71+0.04	0.82+0.09	0.72+0.06
Δ plasma noradrenaline (nmol/l)	0.12+0.05	0.07+0.05	0.44+0.11	0.31+0.09
Standard deviation of a single observation (nmol/l)	0.09		0.16	
Baseline plasma adrenaline (nmol/l)	0.10+0.03	0.09+0.02	0.09+0.01	0.12+0.02
Δ plasma adrenaline (nmol/l)	0.06+0.02	0.07+0.02	0.09+0.01	0.06+0.02
Standard deviation of a single observation (nmol/l)	0.05		0.04	

Cold pressor test

The mean increase of BP was not different between the first and second test (table 3-5) but 6 out of 9 subjects showed a higher BP response during the first test than during the second test. The standard deviation of a single observation was 8.4% for the MAP but was even 11.5% for diastolic BP (table 3-5). In this test, too, FBF had a high standard deviation of a single observation of 33.5%.

Table 3-5

The percentage haemodynamic changes in the first and second cold pressor test and the standard deviation of a single observation (S) of the responses of systolic (SBP), diastolic (DBP) blood pressure, mean arterial blood pressure (MAP), heart rate (HR) and forearm blood flow (FBF) (mean $\pm$ SE).

Cold pressor test

	$1°$ test	$2°$ test	S
Normotensives			
Δ SBP (%)	19.9 $\pm$ 3.8	15.1 $\pm$ 3.4	8.2
Δ DBP (%)	31.8 $\pm$ 7.2	35.1 $\pm$ 7.3	11.5
Δ MAP (%)	26.3 $\pm$ 5.1	25.9 $\pm$ 5.4	8.4
Δ HR (%)	30.3 $\pm$ 5.9	21.3 $\pm$ 5.9	9.6
Δ FBF (%)	-15.2 $\pm$ 10.2	8.8 $\pm$ 15.5	33.5

Head-up tilt

The mean BP response was not different between the first and second tilt test, but the HR increase was larger in the second test than in the first test ($p < 0.05$)(table 3-6). As related to the magnitude of the responses, the standard deviation of a single observation was high (table 3-6).

Table 3-6

The percentage haemodynamic changes in the first and second tilt test (mean $\pm$ SE) and the standard deviation of a single observation (S) of the responses of systolic (SBP), diastolic (DBP) blood pressure, mean arterial pressure (MAP), heart rate (HR).

Tilt test

	1° test	2° test	S
Normotensives			
Δ SBP (%)	-7.2 $\pm$ 1.3	-8.2 $\pm$ 4.9	3.7
Δ DBP (%)	-0.9 $\pm$ 2.3	-0.1 $\pm$ 2.0	6.7
Δ MAP (%)	-4.1 $\pm$ 1.5	-3.6 $\pm$ 1.2	4.3
Δ HR (%)	18.8 $\pm$ 3.0 *	24.0 $\pm$ 3.3	7.0

*p<0.05

DISCUSSION

Isometric (handgrip) exercise, mental arithmetic, cold exposure and gravitational stress are commonly encountered adrenergic stimuli in daily life and they elicit significant sympathoadrenal responses and increments of blood pressure and heart rate.

In the past years these tests have been widely used for studying cardiovascular reactivity in a wide spectrum of disorders including hypertension (1,2) and diabetic autonomic neuropathy (4). In particular it has been suggested that cardiovascular reactivity to mental stress is related to the development of hypertension, coronary atherosclerosis and arrhythmias (7). In addition both tests have been used in longterm pharmacotherapeutic trials to demonstrate the influence of a given drug on sympathoadrenal and cardiovascular reactivity (6). From a methodological point of view this supposes knowledge of the reproducibility of these tests, but until now only one study has reported on the reproducibility of the haemodynamic responses to HG and CPT (8). Even less is known about the reproducibility of the responses to

T and MA, and in particular, the reproducibility of the venous plasma catecholamine responses has never been studied systematically.

Although the standard deviation of a single observation seems low for BP and HR responses to MA, HG and T in both normo- and hypertensive subjects, it is clear that the standard deviation of a single observation is considerable if it is related to the mean response in a test. Of all tests, the CPT had the best reproducibility of the BP response. The wide intraindividual scatter of the BP responses clearly limits the use of these tests. Taking into account the vigorously standardized test protocol of our study, it is likely that the reproducibility would be worse in less ideal experimental conditions. We observed no evidence for habituation to either test. This might be expected for the mental arithmetic test, but it is conceivable that it had been eliminated because all subjects were made familiar with the investigational protocol prior to the experiments. The results of HG exercise and CPT are in accordance with a report of Parati et al (8). However, these authors studied the reproducibility in only 8 subjects by performing both tests six times on the same day. In contrast, we studied the reproducibility of each test on two different days at least one week apart. There are no other studies reporting the day-to-day variability of the haemodynamic responses to adrenergic stimuli. Except a wide intraindividual variability, our results again illustrate the wide interindividual variability of the responses to the tests.

For studying reproducibility it is crucial to standardize both the given stimulus and the experimental conditions. This can be accomplished fairly well for physical stimuli as used in the HG, CPT and T, but despite the fact that the MA test seems easy to use, this is more difficult for the mental stress that is experienced during this test. Although the reproducibility of the haemodynamic responses to this test have never been studied systematically, it is generally assumed that a haemodynamic reactivity to this test is well reproducible and stable in time (9). However our results demonstrate that this is only true for a whole group and that the reproducibility in a given subject is rather poor.

The reproducibility of the response of plasma catecholamines is as worse as that of the haemodynamic response. In particular, this applies to plasma ADR. In addition, there is also a wide interindivid-

ual variability of the plasma catecholamine responses to these tests. It is clear that these results indicate that it is difficult to draw conclusions from the changes in plasma catecholamine responses to adrenergic stimulation with regard to changes of sympathoadrenal reactivity.

How can this limited reproducibility of all tests be explained? It is obvious that a cognitive stress task like mental arithmetic is difficult to standardize in a laboratory setting since psychological factors which influence the active coping behaviour, can not be controlled. In contrast, a physical stress stimulus like isometric exercise can be better controlled and standardized better because the individual workload was proportional to the maximal voluntary contraction, which was determined before each experiment. In fact, this also applies to the cold and gravitational stimuli that can be standardized strictly. Except for the CPT, the reproducibility of both tests is nearly similar, so the kind of stimulus seems not to be involved. The baseline blood pressure or heart rate level also does not seem to play an important role since we used the relative changes during a test and the reproducibility was nearly similar in normo- and hypertensives.

Differences in performance in the MA test between the first and second test were not significant. Moreover, there was no relation between haemodynamic response and performance. So, it is unlikely that performance plays an important role with regard to the haemodynamic response variability.

As far as possible, other factors that might have influenced reproducibility were strictly standardized (the time of the day the experiments were carried out and the same investigator and the same instruments). A factor that was not controlled was the sodium intake but it is unlikely that this explains the low reproducibility of the haemodynamic and plasma catecholamine responses, because we could not demonstrate a correlation between the BP response during the tests and the 24-h urinary sodium excretion in a larger normotensive and hypertensive population (chapter 6).

As suggested by Parati et al (8), it is likely that the low reproducibility depends on the complex central neural processes which are involved during tests of adrenergic stimulation. Therefore, if one accepts that response variability is an inherent feature of adrenergic stimulation, one should be very careful and cautious in interpreting

the haemodynamic and plasma catecholamine responses to adrenergic stimulation in pharmacological intervention studies or in defining sympathoadrenal reactivity in cardiovascular disorders.

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BASELINE CIRCULATORY VARIABLES AND PLASMA CATECHOLAMINES

BASELINE CIRCULATORY VARIABLES AND PLASMA CATECHOLAMINES

BLOOD PRESSURE AND HEART RATE

The frequency distribution of the baseline blood pressure (BP) and heart rate (HR) values as measured in the outpatient clinic of both normotensive (NT) and hypertensive (HT) subjects, is shown in figure 4-1. The average supine BP in the NT group was 118±11/72±7 mmHg (standing 118±11/79±9) and in the HT group 146±9/91±8 mmHg (standing 147±11/100±8)(SD). Both in the NT and HT group, there was no sex difference concerning both basal supine and standing BP (table 4-1). Although the average supine HR was higher in the HT's (77±11 beats/minute) than in the NT's (64±10), as is also demonstrated by the shift of the frequency distribution curve of the HR to the right in the hypertensives (figure 4-1), there was a considerable overlap with NT subjects. Only HT women had a higher basal HR than HT men (table 4-1).
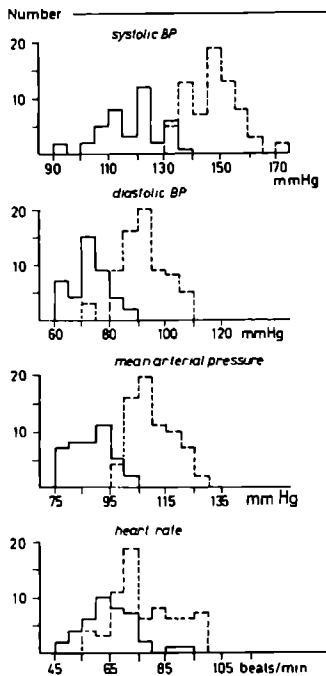
Figure 4-1
The frequency distribution histogram of the supine outpatient clinic blood pressure (BP) and heart rate of the normotensives (___) and hypertensives (---).

Table 4-1

Blood pressure (BP) and heart rate (HR) values of male and female normo- and hypertensive subjects in the supine and standing position in the outpatient clinic (mean $\pm$ SD).

	Males		Females
Normotensives: number	22		19
Age (years)	35.5 $\pm$ 8.2		33.9 $\pm$ 10.9
BP (mmHg)			
– supine	120/73 $\pm$ 9/8		115/71 $\pm$ 12/7
– standing	119/80 $\pm$ 9/10		116/78 $\pm$ 13/8
HR (beats/min)			
– supine	64 $\pm$ 10		65 $\pm$ 10
– standing	74 $\pm$ 12		76 $\pm$ 12
Hypertensives: number	40		30
Age (years)	36.7 $\pm$ 10.5		33.2 $\pm$ 8.6
BP (mmHg)			
– supine	146/90 $\pm$ 10/9		147/93 $\pm$ 8/8
– standing	147/100 $\pm$ 10/8		147/100 $\pm$ 12/7
HR (beats/min)			
– supine	74 $\pm$ 10	*	81 $\pm$ 11
– standing	83 $\pm$ 11	*	91 $\pm$ 12

* $p<0.05$

In both groups, the baseline BP values, as recorded with the Arterio-
sonde before each test, were clearly lower (figure 4-2) than the
values of the outpatient measurements (table 4-1). There are some
possible explanations for this frequently encountered discrepancy in
clinical studies. First, the pretest rest period was longer (20
minutes) than during outpatient measurement (5 minutes). Second, the
arm at which the BP measurement was performed, was supported 10 cm
above heart level for the forearm blood flow (FBF) measurement.
Finally, it is well-known that semiautomatic BP recording detects
lower values than the sphygmanometer. This holds especially for the
systolic BP value.
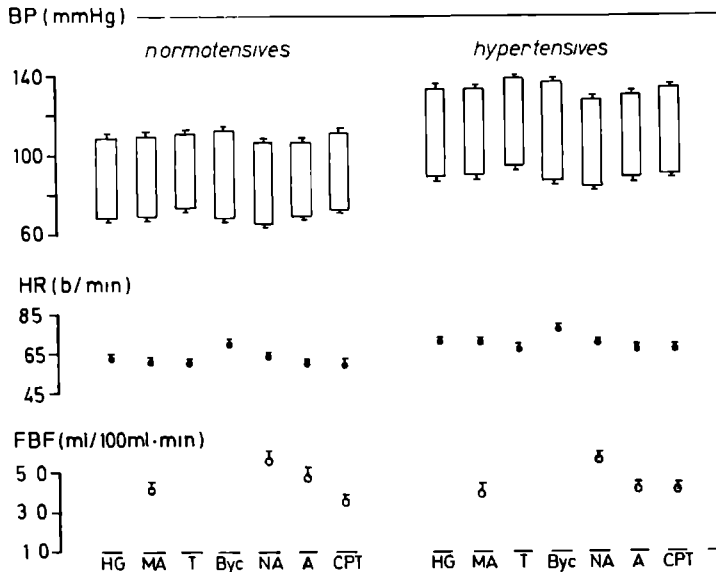
Figure 4-2
Baseline blood pressure (BP), heart rate (HR) and forearm blood flow
(FBF) before each test in the normo- an hypertensives as measured with
the Arteriosonde.
For the abbreviations of the test names see chapter 2.

Figure 4-2 shows that the baseline BP and HR values before each test remained fairly stable throughout the two experimental days. The baseline HR before the bicycle test was higher than that of the other tests, problably because this test was carried out in the sitting position. The baseline FBF was higher before the first test on the second day than before the first test on the first day.

PLASMA CATECHOLAMINES

The day-to-day variability of plasma catecholamines.

As described in chapter 2, baseline plasma catecholamine samples were collected on both the first and the second experimental day before the first test of that day. Since the experimental conditions were strictly standardized, the blood samples from two separate days enables to observe what is the day-to-day variability of plasma catecholamines. The scatters of the individual plasma noradrenaline (NORADR) and adrenaline (ADR) values of the first and second experimental day are shown in figure 4-3. Due to difficulties with blood sampling, basal plasma catecholamine values were not available in 1 NT and 3 HT subjects. The standard deviation of a single observation of baseline plasma NORADR in the NT was 0.36 nmol/l (mean baseline level 1.29± 0.52)(SD) and in the HT's 0.43 nmol/l (mean baseline level 1.44±0.70) (SD). There was no difference between the mean baseline plasma NORADR levels of the two days. The standard deviation of a single observation of baseline plasma ADR in the NT group was 0.04 nmol/l (mean baseline level 0.10±0.06) and in the HT group 0.05 nmol/l (mean baseline level 0.12± 0.08 nmol/l). No difference of mean baseline plasma ADR level between the first and second day could be detected. The standard deviation of a single observation of plasma NORADR and ADR were not significantly different between NT and HT subjects.
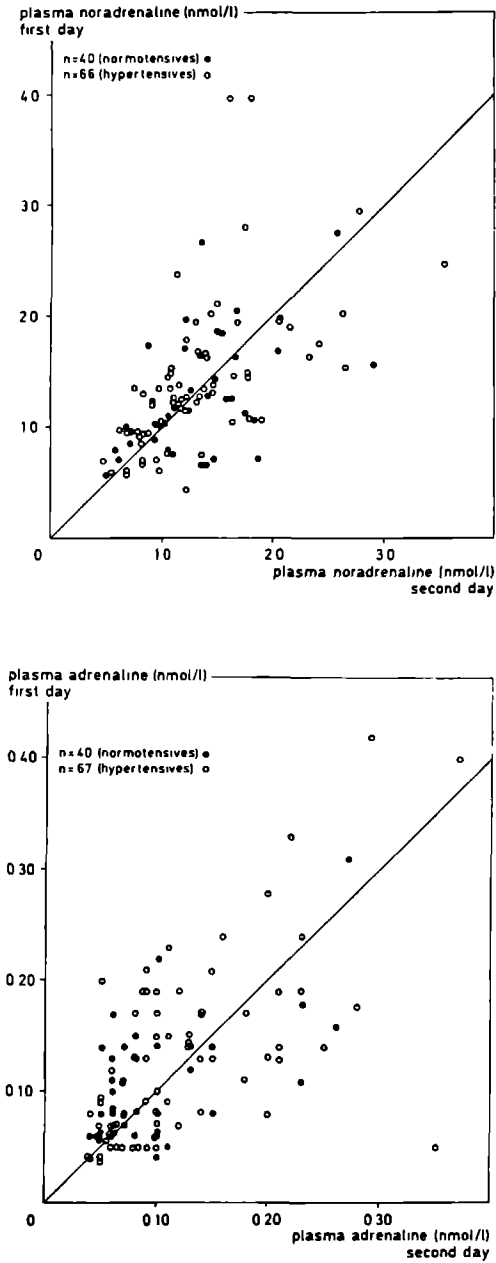
Figure 4-3

The baseline plasma noradrenaline levels (upper panel) and plasma adrenaline levels (lower panel) on the first and second experimental day.

Finally, table 4-2 shows that the plasma NORADR and ADR values as determined <u>before</u> each test remained stable. The only exception is the bicycle exercise test, demonstrating higher baseline plasma catecholamine levels. This is probably caused by the fact that the bicycle exercise test was the only test that was not carried out in the supine but in the upright position. In addition, it is conceivable that the anticipatory arousal, before starting the dynamic exercise test (1), contributes to the higher baseline plasma catecholamine levels.

plasma adrenaline (nmol/l)	NT	HT
HG	0.11±0.06	0.12±0.08
MA	0.09±0.04	0.13±0.10
T	0.08±0.04	0.13±0.10
BYC	0.14±0.07	0.21±0.17
NA inf	0.10±0.06	0.12±0.08
A inf	0.09±0.06	0.13±0.08
CPT	0.14±0.10	0.14±0.10
plasma noradrenaline (nmol/l)		
HG	1.29±0.52	1.44±0.70
MA	1.47±0.58	1.45±0.63
T	1.44±0.53	1.45±0.65
BYC	3.42±1.75	3.49±1.51
NA inf	1.33±0.52	1.33±0.59
A inf	1.42±0.44	1.45±0.71
CPT	1.65±0.70	1.73±1.20

Table 4-2

The baseline values of the plasma catecholamines before each test in the normotensives (NT) and hypertensives (HT) (mean ± SD).
The abbreviations of the tests refer to chapter 2.

Plasma catecholamines in NT and HT subjects.

Do HT subjects have higher baseline plasma catecholamine levels than NT subjects? No matter whether only one single baseline plasma cate- cholamine value is used for analysis or whether the average of the two baseline plasma catecholamine values of two separate days is used, HT subjects do not have significantly higher baseline plasma catechol- amines. This applies to both plasma NORADR and ADR (table 4-3). Besides, within each sex there is no NT-HT difference. Sex itself does not affect baseline plasma NORADR levels in NT and HT subjects, but with regard to the plasma ADR, only HT males show a higher plasma ADR than HT females (0.15+0.08 vs 0.10+0.06 nmol/l, p<0.05) (mean +SD).

Table 4-3

Mean baseline plasma catecholamines in normotensives (NT) and hyper- tensives (HT) according to sex/age class (mean + SD).

	plasma adrenaline (nmol/l)		plasma noradrenaline (nmol/l)	
	NT	HT	NT	HT
All subjects	0.10 + 0.06	0.12 + 0.08	1.29 + 0.52	1.44 + 0.70
range	0.05 - 0.31	0.05 - 0.42	0.58 - 2.75	0.41 - 4.07
20-29 years				
-males	0.10 + 0.05	0.18 + 0.12	1.15 + 0.53	1.39 + 0.57
-females	0.09 + 0.04	0.10 + 0.07	1.27 + 0.59	0.94 + 0.30
30-39 years				
-males	0.10 + 0.04	0.15 + 0.10	1.12 + 0.43	1.19 + 0.56
-females	0.07 + 0.04	0.11 + 0.05	0.86 + 0.27	1.67 + 0.96
40-55 years				
-males	0.15 + 0.09	0.13 + 0.06	1.50 + 0.41	1.49 + 0.39
-females	0.12 + 0.06	0.09 + 0.05	1.77 + 0.51	2.19 + 0.93

Concerning the effect of age on baseline plasma catecholamine levels, there was a moderate correlation between age and baseline plasma NORADR in both NT (r=0.45, p<0.01) and HT subjects (r=0.46, p<0.01) but when analysed by sex, this only applied to female NT (r=0.62, p<0.01) and HT subjects (r=0.69, p<0.001). Plasma ADR also tended to rise with increasing age but this was only the case in the NT's (r=0.32, p<0.05). This correlation was absent in the HT's, possibly as consequence of the higher plasma ADR levels in young HT males (table 4-3). In the NT's, there was a weak correlation between the baseline plasma NORADR level and the mean arterial pressure (r=0.32 p<0.05), whereas in the HT's the baseline plasma ADR level was correlated with the heart rate (r=0.35, p<0.01).

Twenty-four hour sodium excretion was not correlated to the baseline plasma catecholamine levels.

DISCUSSION

The first point to be discussed is the basal BP level in the HT sub-jects. Although all subjects met the BP criterion of a systolic BP of higher than 140 mmHg systolic and/or higher than 90 mmHg diastolic as defined by "The Joint National Committee (JNC) on Detection, Evalua-tion and Treatment of High Blood Pressure in 1984" (2), there is a small overlap with the NT group. Both groups are separated best by the mean arterial pressure (MAP). According to these JNC criteria the HT group can be classified as having mild hypertension although some had borderline hypertension. For classifying hypertensive subjects, any interfering effect of prior antihypertensive therapy on baseline BP and HR should be excluded as much as possible. Unfortunately, it is not known how long therapy should be discontinued to reach this goal. In contrast to some other studies where therapy was stopped only 2-4 weeks before the study (3-6), we maintained a drug free period of 3 months before a previously treated subject was admitted to the study.

The higher baseline HR in HT subjects has been reported in pre-vious studies (4,7) and is predominantly related to a decrease of vagal efferent activity and to a lesser degree to an increased sympa-thetic discharge to the heart (7,8). The reduced vagal efferent activity may be due to an increased inhibitory effect of cardiopulmon-

ary baroreceptors on the arterial baroreceptor reflex as a consequence of a higher central blood volume in HT's. An increased cardiac beta-adrenoceptor sensitivity probably does not play an essential role (7).

The day-to-day variability of both basal plasma catecholamines was considerable if the standard deviation of a single observation is related to the mean basal plasma catecholamine levels. In particular this was the case for plasma ADR. The day-to-day variability of plasma catecholamine levels not only reflects biological variability but it also partially reflects "measurement" variability. Since the inter-assay coefficient of variation for plasma NORADR is 7.5% and for ADR is 9.0%, biological variability is considerably larger than "measure-ment" variability, which in particular applies to plasma ADR. Although two previous studies (9,10) reported no difference in the average levels of plasma catecholamines after repeated sampling after 1 and 2 weeks, no data about the variability were supplied. In view of the fact that variability is an inherent feature of sympathoadrenal activ-ity, the considerable intra-individual variability of the baseline plasma catecholamines is not surprising.

In this study we could not demonstrate increased basal levels of plasma catecholamines for the whole group of patients with mild essen-tial hypertension. This was also the case within each age class and within each sex. The average baseline plasma NORADR value was very similar to those previously reported (11), but plasma ADR levels were clearly lower both in the NT and HT group. Literature data concerning NT-HT differences in basal plasma catecholamines are conflicting but from a review by Goldstein (11), several factors can be identified which, at least partially, determine the chance of detecting a NT-HT difference. Of 34 studies using the COMT based radioenzymatic assay technique, only 12 reported significantly higher plasma NORADR levels in patients with essential HT than in NT subjects of comparable age (11). On the other hand, if other types of assay were included and if all data were pooled, the HT's had a significantly higher plasma NORADR than the NT's. However it is important to realize that the average plasma NORADR in the HT's was higher in those studies that did than in those that did not detect a difference. Also, the standard deviation in the HT's was larger than that of the NT's in the positive

studies, whereas the standard deviation of both groups was similar in the negative studies. So, the positive studies probably comprised an excess of hypernoradrenergic subjects. Our data are in line with the observation that studies using NT controls which were not previously exposed to biomedical research, were usually negative, since the NT controls in our study were also unfamiliar with medical experiments (12).

What about age? In NT's, plasma NORADR is known to rise with increasing age. So positive studies might have been flawed by inadequate age-matching. However, it has firmly been demonstrated that poor age-matching alone can not account for the NT-HT difference in the positive studies (11). Nevertheless most positive studies comprised young HT subjects; so, it is probably the group of young HT subjects that is hypernoradrenergic. Yet, we can not confirm higher plasma NORADR levels in the youngest age group of 20-29 years. Two other factors potentially affecting plasma NORADR levels like sodium balance and the blood pressure level deserve comment. No relationship has been established between sodium intake and the likelihood of finding higher plasma NORADR levels in HT's (11). In our study sodium excretion was not different in subgroups of NT and HT's (table 1 chapter 2) and in addition no correlation was present between sodium excretion and baseline plasma NORADR or ADR in a subset of NT and HT subjects.

Concerning the influence of the blood pressure level it has consistently been shown that studies with patients with established hypertension are more likely to detect a NT-HT difference with regard to plasma NORADR, than studies with borderline HT's (11). However, although most studies also found a weak correlation between the basal mean arterial pressure and plasma NORADR, differences in mean arterial pressure could not differentiate positive from negative studies (11). Nevertheless it remains possible that the normal basal plasma NORADR level in our HT's is the result of the fact that this group contained patients with borderline hypertension.

In addition, in 50% of the studies (11), it has been reported that plasma ADR levels were higher in HT than in NT subjects. Although there was no correlation between plasma ADR and age in the HT in contrast to the NT group, we could not establish significantly higher plasma ADR levels in the young HT's as compared to young NT's. The positive correlation with age in the NT's is at variance with other

studies reporting no positive age-ADR relationship in NT's but the absence of such correlation in the HT's has commonly been found (11). Finally, those studies that detected a higher plasma NORADR level in the HT's failed to detect higher plasma ADR levels in the same group of HT's.

In conclusion, in a large group of patients with, on the average, mild essential hypertension and with an increased basal heart rate, we could not demonstrate significantly higher basal levels of plasma catecholamines as compared to a normotensive control group. This can not be explained by age or sex differences, an inappropriate normotensive control group or a difference in sodium intake. The most probable explanation might be the fact that BP in our HT subjects was not consistently elevated because the inclusion BP criterion for hypertension was defined as the mean of three outpatient measurements higher than 140 and/or 90 mmHg. When plasma catecholamine levels at rest are considered to reflect sympathoadrenal activity, our data are not consistent with an increased basal sympathoadrenal activity in young hypertensives.

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THE HANDGRIP EXERCISE TEST

THE HANDGRIP EXERCISE TEST

PHYSIOLOGY

Although it was Asmussen (1) in 1938 who demonstrated an increase of blood pressure (BP) during isometric exercise, more detailed insight concerning the cardiovascular alterations during isometric exercise was acquired in particular by the comprehensive studies of Lind et al (2). Since then, a consistent and characteristic haemodynamic response to isometric exercise has been recognized. During the handgrip exercise test (HG), systolic and diastolic blood pressure (BP) and heart rate (HR) increase instantaneously in a gradual way and immediately after cessation of exercise, BP and HR fall abruptly to their basal levels. This response is qualitatively and quantitatively quite different from that during dynamic exercise like cycling for instance. During dynamic exercise there is a larger increase of systolic BP, but since diastolic BP does not change, this results in a smaller increase of the mean arterial blood pressure (MAP) during dynamic exercise as compared to handgrip exercise. Nevertheless, the increase of cardiac output and oxygen consumption is larger during dynamic exercise. Both types of exercise usually occur simultaneously in daily life.

In normotensive subjects, the immediate increase of BP during HG is caused by an increase of cardiac output rather than by an increase of total peripheral vascular resistance (2). It has been demonstrated that it is the prompt increase of HR which accounts for the increase of cardiac output, because stroke volume and left-ventricular end-diastolic volume do not change appreciably (3,4). This also applies to hypertensive patients (5) provided that there is no left ventricular hypertrophy. In hypertensives with left ventricular hypertrophy, in cardiac transplant patients and in subjects with beta-adrenergic and parasympathetic blockade the BP response is not due to an increase of cardiac output but merely to an increase of total peripheral vascular resistance (5,6,7,8).

What is the mechanism which causes such abrupt increase of HR? It is well established now that the primary and predominant mechanism responsible for the increase of HR during HG is the withdrawal of parasympathetic activity (9) and not the concomitant increment of sym-

pathetic activity which is only operative later during HG exercise
(7). The sensory information needed for the parasympathetic withdrawal
and sympathetic activation reaches the brainstem cardiovascular con-
trol centers by group III (small myelinated) and group IV (unmyelinat-
ed) afferent nerve fibers which are mechanically or chemically
activated in the skeletal muscle (10). Additionally, but probably less
important, there is a role for impulses from the cerebral cortex
("central command") (11), representing a subject's effect to perform
the HG exercise. Humoral factors like catecholamines do not play a
causative role, since the haemodynamic response to exercise is imme-
diate and disappears promptly after cessation of exercise.

It is still debated whether the haemodynamic response is related
to the muscle mass or to the generated tension of the muscle involv-
ed. In earlier studies (12,13), it was demonstrated that it was rather
the relative tension generated in the muscle than the absolute muscle
tension or the muscle mass which was related to the haemodynamic re-
sponse during isometric exercise. Particularly, if more than one
muscle group was operative, no additive haemodynamic response could be
recorded. However, it has recently been shown that there is a larger
pressor response with a larger muscle mass (14). So, despite the fact
that the relative muscle tension is probably the major factor deter-
mining the magnitude of the haemodynamic response to isometric exer-
cise, it seems likely that muscle mass and absolute muscle tension
play a role too.

In our experiments the subjects exerted a force of 30% of the
maximal voluntary strength. This level was chosen to attain a marked
BP response which can readily be maintained for 3 minutes. Higher
levels of strength are difficult to maintain for more than one minute
since the blood flow through the working muscle decreases with higher
muscle tension (2). Moreover, the 30% level of exerted strength
makes comparison possible with data from most previous studies in
hypertensive patients.

RESULTS

Circulatory measurements

Figure 5-1 displays the course of BP and HR before, during and after
HG exercise. In the HT group, BP increased progressively in a similar

way as in the NT group but at a clearly higher level. In addition, both groups showed an immediate drop of BP after exercise. A similar pattern was seen for the HR response. Age, sex or their interaction, affected the haemodynamic response to HG exercise. The HT subjects at the low age level of 25 years, showed only a smaller increase of the diastolic BP as compared to the NT subjects which applied to both men and women (figure 5-2). If the absolute responses were considered, there was no significant difference between NT and HT subjects. The systolic BP and the HR responses in the HT group were not different from those of the NT-group. At an older age there was no NT-HT differ-ence for any of the haemodynamic responses in any sex.
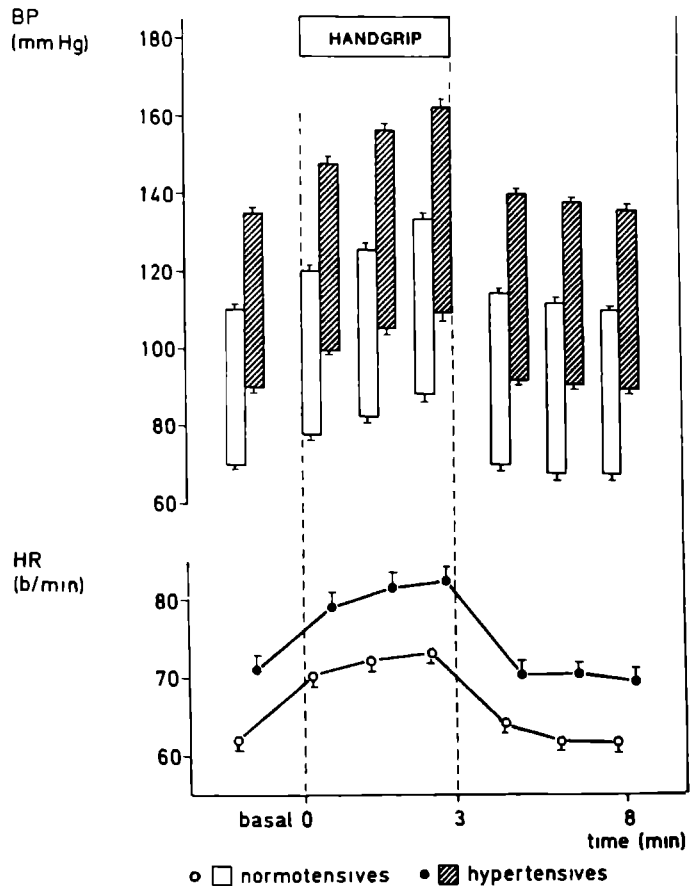
Figure 5-1
The course of blood pressure (BP) and heart rate (HR) before, during and after the handgrip exercise in all normo- and hypertensives (mean ± SE).
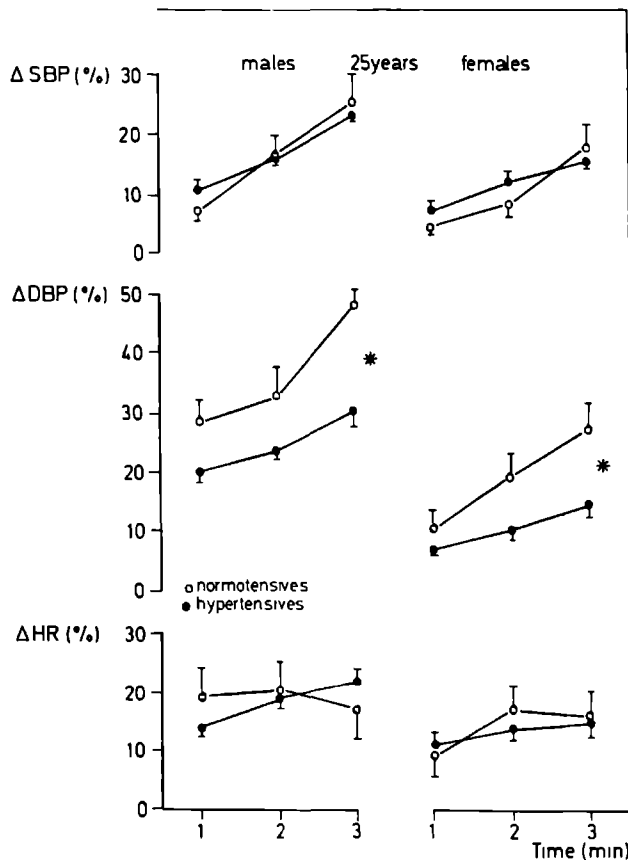
Figure 5-2

The estimated percentage change of systolic (SBP), diastolic blood pressure (DBP) and heart rate (HR) during the handgrip exercise in normo- and hypertensive males and females of 25 years old (mean + SE). *: curves differ significantly.

As shown in table 5-1, within the NT and the HT group, it was in particular young men that showed a higher increase of the diastolic BP and HR rather than young women, whereas the same relative force was exerted. At an older age the diastolic BP response was lower than at a younger age but mainly in male subjects (table 5-1). So, young male subjects showed the strongest BP response. The HR response decreased with increasing age in female NT and HT subjects only (table 5-1).

Table 5-1

The (estimated) expected responses after 3 minutes of diastolic blood
pressure and heart rate in normo (NT)- and hypertensive (HT) males and
females of young and old age (mean $\pm$ SE).

	young (25 years)		old (50 years)	
	Males	Females	Males	Females
ΔDBP (%)				
NT	47.9 $\pm$ 4.5 *	27.8 $\pm$ 3.8 *	17.4 $\pm$ 5.6	18.1 $\pm$ 5.3
HT	30.2 $\pm$ 2.5	14.8 $\pm$ 2.6	22.0 $\pm$ 2.7	23.0 $\pm$ 4.2
ΔHR (%)				
NT	16.4 $\pm$ 4.4	16.1 $\pm$ 3.7	20.0 $\pm$ 5.4	9.9 $\pm$ 5.2
HT	21.4 $\pm$ 2.6	14.6 $\pm$ 2.8	16.9 $\pm$ 2.8	10.8 $\pm$ 4.5

DBP= diastolic blood pressure
HR= heart rate
*p<0.05

Neither in NT (n=16) nor in HT (n=31) subjects, a relation between the
maximal BP response and the 24-h urinary sodium excretion could be
demonstrated.
The calculated absolute strength as exerted during the handgrip exer-
cise, (that is 30% of the maximal voluntary contraction), was not
different between the NT and HT subjects, but as expected, the abso-
lute strength in women was about 65% of that in men. This applied to
both groups. There was a significant correlation between the absolute
strength and the mean arterial BP increase in the NT group (r=0.51,
p<0.001) and the HT group (r=0.38, p<0.01). In addition, as could be
expected, in both men (r=-0.25, p<0.05) and women (r=-0.41, p<0.01),
the absolute strength tended to decrease with increasing age.

Plasma catecholamine responses

Baseline plasma catecholamine levels were not significantly different between NT and HT subjects. As depicted in table 5-2, both the NT and HT group showed a significant increase of plasma noradrenaline (NORADR) and adrenaline (ADR) ($p<0.01$). Concerning the plasma NORADR response, there was no NT-HT difference for each age-sex class. In the lowest age class the plasma ADR response was larger in HT than in NT subjects, but this difference was only significant in the females (table 5-2). In addition, NT (20-29 years) and HT males (20-29 and 30-39 years) showed a larger increase of plasma ADR than the corresponding females.

There was no correlation between the plasma NORADR response and the absolute maximal muscle strength in the NT, whereas there was a weak correlation ($r=0.30$, $p<0.05$) in the HT group.

Table 5-2

The changes of plasma adrenaline (ADR) and noradrenaline (NORADR) during handgrip exercise in normotensives (NT) and hypertensives (HT) according to sex/age class (mean $\pm$ SE).

	Δ plasma ADR (nmol/l)		Δ plasma NORADR (nmol/l)	
	NT	HT	NT	HT
All subjects	0.07 ± 0.02	0.09 ± 0.01	0.20 ± 0.06	0.27 ± 0.04
20-29 years				
– males	0.08 ± 0.02 **	0.18 ± 0.07 *	0.15 ± 0.15	0.32 ± 0.11
– females	0.01 ± 0.01*	0.05 ± 0.01	-0.01 ± 0.10	0.23 ± 0.06
30-39 years				
– males	0.07 ± 0.02	0.10 ± 0.03 *	0.26 ± 0.12	0.39 ± 0.09
– females	0.05 ± 0.03	0.03 ± 0.01	0.46 ± 0.31	0.19 ± 0.08
40-55 years				
– males	0.17 ± 0.07	0.09 ± 0.01	0.30 ± 0.07	0.32 ± 0.08
– females	0.04 ± 0.03	0.07 ± 0.02	0.19 ± 0.19	0.07 ± 0.19

* $p<0.05$

** $p<0.01$

DISCUSSION

The results of this study clearly indicate that HT subjects do not have an enhanced haemodynamic reactivity to isometric exercise. In fact, the relative and not the absolute diastolic BP response was lower in young HT than in young NT subjects. Since the baseline BP level differed between the NT and HT groups, the relative responses not only are more relevant than the absolute changes but also more appropriate because structural adaptation of the vessels in hypertension causes a non-specific vascular hyperreactivity (15).

Considering literature data, only two studies reported a significantly higher percentage increase of BP in HT subjects (16,17). One study investigated a small group of only 14 patients with essential hypertension and the stimulus was weak since exercise was sustained for 1 minute only (16). A recently published report (17) described higher percentage increments of BP in HT subjects, but the validity of the NT control group can be questioned since these subjects were selected from a population which underwent cardiac catheterisation for chest pain but who had normal coronary arteriograms. Except for one study (18), all other studies, examining absolute responses only, could not demonstrate a higher BP response to isometric exercise in HT subjects. So, our results support most other studies reporting normal haemodynamic reactivity to isometric exercise in borderline or essential hypertension (table 5-3).

As demonstrated in this study there is a clear effect of age and sex on the haemodynamic response to HG exercise. In particular, in both the NT and HT group it is the young male subject who responds with the strongest increase of the diastolic BP. This latter finding is in agreement with data of Ordway and Wekstein (19), but seems at variance with two other studies which could not demonstrate an effect of age on the BP response although this only applied to the absolute response (20,21). The observed somewhat smaller heart rate increase in the older female subjects confirms earlier reports (19,20,22). This might be due to a reduced afferent input from the involved muscle at older age or to a decline of the autonomic nervous system function with increasing age (23).

Table 5-3

Literature review of the results of handgrip exercise in hypertensive subjects.

Author (year)	Reference	Subjects(n)			Mean age (yrs)			Males/Females			Study protocol		Difference NT-HT Δ Blood pressure	
		NT	BHT	HT	NT	BHT	HT	NT	BHT	HT	%MVC	Time (min)	Abs	%
Sannerstedt (1972)	29	17	17	-	25	24	-	15/2	16/1	-	50	2	NS	-
Nyberg (1976)	30	19	21	-	30	45	-	10/9	9/12	-	50	1	-	NS
Brorson (1978)	18	7	9	11	25	30	40	7/0	9/0	11/0	30	4	HT>NT	-
Robertson (1979)	31	10	9	-	27	25	-	?	?	-	30	3	NS	-
Nazar (1979)	32	25	30	-	29	31	-	25/0	30/0	-	30	?	NS	-
Vlachakis (1979)	33	14	14	24	49	41	52	10/4	8/6	12/12	66	3	NS	-
McAllister (1979)	34	32	-	35	40	-	44	32/0	-	35/0	30	3	NS	-
Watson (1980)	25	4	-	12	29	-	39	?	-	?	30	3	NS	-
Sullivan (1981)	26	13	-	15	36	-	37	9/4	-	6/9	30	3	-	NS
Frederikson (1985)	16	14	-	14	40	-	47	13/1	-	13/1	33	1	HT>NT	HT>NT
Welsh (1985)	35	12	17	-	27	25	-	12/0	17/0	-	50	1.5	NS	-
Hamada (1987)	17	12	-	46	49	-	48	8/4	-	30/16	30	3	HT>NT	HT>NT
Lenders (1987)	-	40		71	35		35	22/19	-	40/30	30	3	NS	HT<NT

NT = normotensives

BHT = borderline hypertensives

HT = hypertensives

MVC = maximal voluntary contraction

NS = not significant

With regard to sex, our results confirm a recent report of Messerli et al (24) who could also demonstrate a higher relative BP response to isometric exercise in men as compared to premenopausal women. These data suggest an interfering role of estrogens with haemodynamic reactivity.

The response of plasma NORADR was not different between the NT and HT subjects, confirming previous studies in smaller groups of subjects (25,26). However, the plasma ADR response was larger in young HT's than in young NT's, although the difference was only significant in females, supporting comparable data of Sullivan et al (26). Since circulating adrenaline is almost exclusively released from the adrenal medulla and since blood flow does not appreciably change in the resting arm during HG exercise (2), the significant increase of plasma adrenaline in HT subjects during HG exercise points to an increase of adrenomedullary activity in HT subjects.
With regard to the effect of sex, our data partially reinforce a study of Gustafson et al (27), reporting higher increments of both plasma catecholamines in men than in women. In contrast, another study (28) could not detect a significant sex difference with regard to plasma catecholamine response to sustained HG exercise.

In conclusion, HT subjects do not have an enhanced haemodynamic reactivity to HG exercise. Actually, the relative diastolic blood pressure response was lower in young HT subjects than in young NT subjects. There was no significant difference in plasma NORADR response between the two groups but the plasma ADR increment was slightly higher in the young HT than in the young NT subjects, indicating an increased adrenomedullary activity during HG exercise in young HT's.

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THE MENTAL ARITHMETIC TEST

THE MENTAL ARITHMETIC TEST

PHYSIOLOGY

Mental arithmetic, performed as serial subtraction, is a powerful cog-
nitive stressor, requiring an active coping behaviour. As a special
mode of mental stress, it elicits a circulatory reaction pattern which
is similar to that evoked by hypothalamic stimulation in animals (1)
and consists of a strong and instantaneous increase of systolic and
diastolic blood pressure (BP), heart rate (HR) and cardiac output,
which all taper off in the course of the test (2). These haemodynamic
alterations are due to a centrally-mediated and differentiated but not
a generalized activation of sympathetic nerves. So, the increase of
sympathetic discharge is confined to certain organs like heart, kidney
and splanchnic area, whereas it decreases to others like the skeletal
muscle (3). The decrease of sympathetic discharge to the forearm
skeletal muscle causes an increase of forearm muscle blood flow by a
fall in vascular resistance. In contrast, vascular resistance does not
fall in muscle vessels of the calf (4). So, it is likely that another
or additional mechanism might be responsible for the decrease of fore-
arm vascular resistance during mental stress. As suggested by Blair et
al (5) there may be a role for sympathetic cholinergic nerves, dis-
tributed to the forearm but not to calf vessels.
This pattern of an increment and redistribution of cardiac output
seems similar to that during dynamic exercise, although the mechanism
is different. It has been suggested that the subject prepares himself
this way to "fight or flight" (6). This so-called defense reaction (1)
is predominantly accompanied by an increase of peripheral venous
plasma adrenaline (ADR) whereas the peripheral venous plasma nor-
adrenaline (NORADR) does not change appreciably (7), because sympa-
thetic discharge to the forearm skeletal muscles does not increase
during mental stress (3). It has been demonstrated that this circula-
tory reaction pattern to mental stress in NT subjects, is very similar
to the increased basal cardiac output and heart rate, which has been
demonstrated in a substantial number of patients with early or border-
line hypertension (6,8). The link between the haemodynamic response
during mental stress and analogue haemodynamics at rest in early
hypertension has led to the view that neurogenic factors play a role

in the pathogenesis of essential hypertension (1,6).

The MA test was chosen because this test was also used in the classic studies of Brod et al (2) and because this test is relatively easy to use in an experimental setting. However, some methodological drawbacks of the test deserve attention. First, since the subjects have to perform the calculations aloud, speaking might interfere with the haemodynamic response (9). Secondly, although the test stimulus itself can be standardized in the laboratory, it is likely that there is a wide interindividual variability of task performance which may confound the haemodynamic responses. Finally, except for mental effort, possible other psychological factors like anxiety may play an important role. However, other forms of mental stress like the Stroop's color word conflict test, video games or solution of anagrams have more or less the same disadvantages.

RESULTS

Circulatory measurements

Neither age nor sex were related to changes in any of the haemodynamic variables.

The course of BP, HR and forearm vascular resistance (FVR) during MA was similar in the NT and HT groups, although for BP and HR at a substantial lower level in the NT group (figure 6-1). After finishing the MA test, BP and HR decreased in a similar way in both groups, but BP remained significantly (p<0.05) above the baseline value in the HT (+4/+3 mmHg), in contrast to the NT group which regained the baseline level within six minutes after MA.
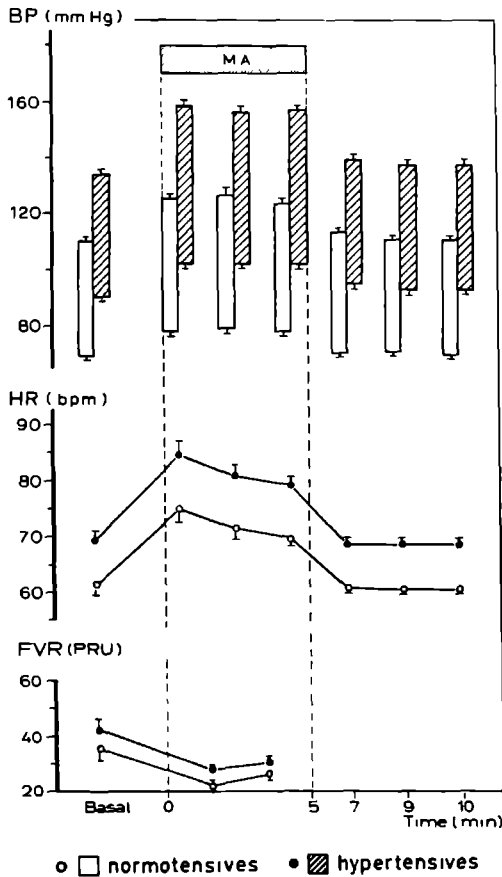
Figure 6-1
The course of blood pressure (BP), heart rate (HR) and forearm vascular resistance (FVR) before, during and after mental arithmetic (MA) in all normo- and hypertensive subjects (mean ± SE).

The relative haemodynamic changes in the HT group showed a significantly higher increase of systolic BP (+17-19%) than those in the NT group (+12-15%) (p<0.05) during the whole test session (figure 6-2). The slightly higher increase of diastolic BP in the HT's did not reach significance. Despite a higher baseline HR, the HT group showed the same increase of HR during MA as compared to the NT group. Baseline FVR and the decrease of FVR were also similar in both groups (figure 6-1).
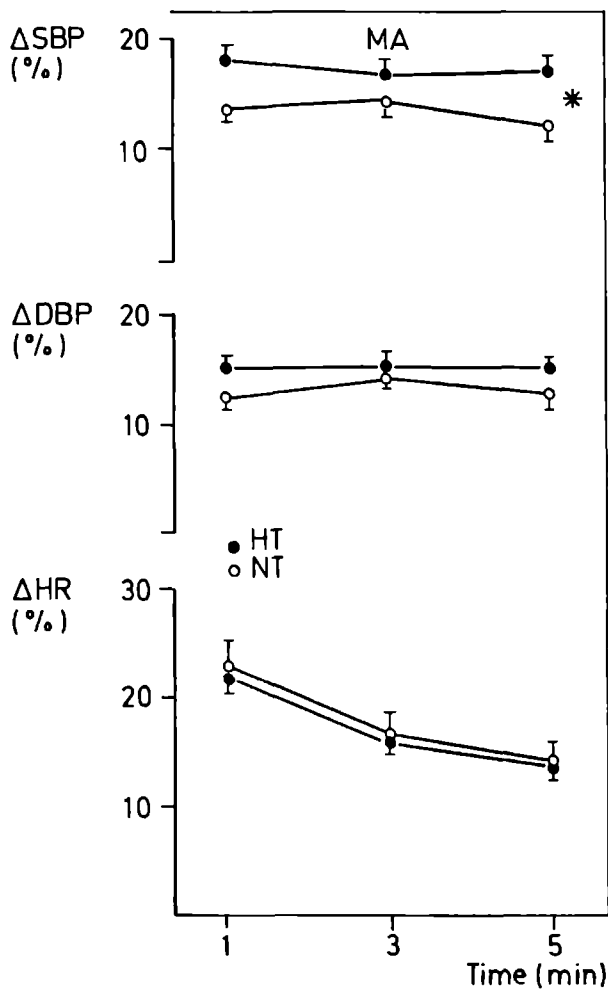
Figure 6-2

The percentage change of systolic (SBP), diastolic (DBP) blood pressure and heart rate (HR) during mental arithmetic in all normo- and hypertensive subjects (mean ± SE).

*: curves differ significantly

Plasma catecholamines

As expected, plasma ADR increased: in the NT group by 0.04 nmol/l (p<0.01) and in the HT group by 0.07 nmol/l (p<0.01) but there was no significant difference between both groups (table 6-1). Both NT and HT men showed a higher increase of plasma ADR than women but only in the lowest age class (20-29 years). There was no overall correlation of age with plasma ADR response.

Table 6-1

The changes of plasma adrenaline (ADR) and noradrenaline (NORADR) during <u>mental arithmetic</u> in normotensives (NT) and hypertensives (HT) according to sex/age class (mean ± SE).

	Δ plasma ADR (nmol/l)		Δ plasma NORADR (nmol/l)	
	NT	HT	NT	HT
All subjects	0.04 ± 0.01	0.07 ± 0.01	-0.12 ± 0.05	* 0.10 ± 0.05
20 - 29 years				
- males	0.08 ± 0.02 *	0.13 ± 0.04 *	-0.08 ± 0.07	* 0.17 ± 0.07
- females	0.01 ± 0.01	0.03 ± 0.02	-0.28 ± 0.11	** 0.11 ± 0.06
30 - 39 years				
- males	0.03 ± 0.02	0.05 ± 0.02	0.16 ± 0.11	0.12 ± 0.10
- females	0.02 ± 0.01	0.03 ± 0.01	-0.20 ± 0.12	0.06 ± 0.15
40 - 55 years				
- males	0.08 ± 0.02	0.08 ± 0.03	-0.14 ± 0.13	0.05 ± 0.16
- females	0.06 ± 0.02	0.08 ± 0.01	-0.25 ± 0.19	0.11 ± 0.13

* p<0.05

** p<0.01

Plasma NORADR decreased slightly in the NT's (-0.12 nmol/l) (p<0.01)
but increased slightly in the HT's (0.10 nmol/l) (p<0.01). This di-
verging response between the groups was significant (table 6-1). Con-
sidering age-related responses however, plasma NORADR changed signi-
ficantly in the age class of 20-29 years only. In this youngest age
class, plasma NORADR fell slightly in the NT's (-0.20 nmol/l) and in-
creased slightly in the HT's (0.14 nmol/l). This difference was
present in both sexes (table 6-1). Plasma NORADR increased in 17 of
the 22 HT but in only 2 of the 15 NT subjects (figure 6-3).

In NT and HT groups there was a weak but significant correlation
between the responses of HR and plasma ADR (NT: r=0.33, HT: r=0.26,
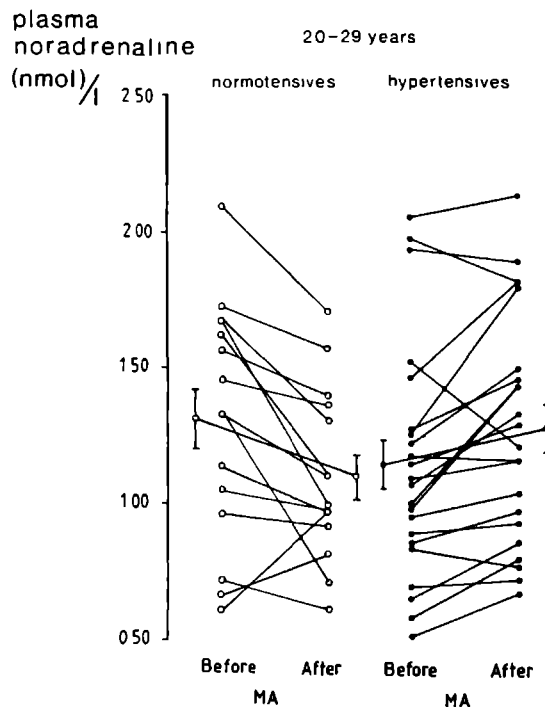p<0.05) and there was no correlation between the BP and plasma cate-
cholamine responses.

Figure 6-3
The individual plasma noradrenaline levels before and after mental
arithmetic (MA) in the youngest normo- and hypertensive subjects of
20-29 years.

DISCUSSION

Circulatory variables

Up to now, many studies have been carried out to detect NT-HT differences concerning haemodynamic reactivity to mental stress. Although there is considerable disparity regarding the used mental stress protocol, data analysis and the selection and number of patients and control subjects, most studies agree that HT subjects show a stronger BP response to mental stress than do NT controls (table 6-2). Out of twelve studies, three negative studies used a MA test (2,10,11). Some positive studies reported a stronger increase of only diastolic BP (12,13) whereas others reported a stronger increase of systolic BP too (14-19). Only 3 studies showed a stronger HR response in HT subjects (14,17,19). Our results are at variance with previous reports since we demonstrated a higher responsiveness of only systolic BP in the HT group. A comparison of the reported results is hampered by differences in the used study protocol, but more importantly by the heterogeneity of the studied hypertensive populations.

It has been suggested that this increased haemodynamic reactivity is only limited to provocative stimuli that require an active coping behaviour of a subject. It does not apply to passive stress experiences like cold exposure for instance (14).

How should the difference of pressor response between NT's and HT's be explained? First, the possibility of a different test performance should be considered. Although test performance actually was not measured in this study; in a previous study of 22 subjects we could not demonstrate a relation between the total number or the number of correct test responses with the increase of BP or HR or with the baseline BP. This observation is supported by Eliasson et al (12) who could not demonstrate a difference between NT and HT groups as far as test performance was concerned. Second, the enhanced pressor responsiveness might be caused by an increased responsiveness of the target organs due to structural changes in the heart and the vascular wall by the high blood pressure. However, it has been demonstrated that normotensive adolescents with a positive family history for hypertension, show an augmented diastolic BP and HR response to mental arithmetic (17). Apparently, the enhanced pressor response predates the onset of hypertension; so, it is unlikely that this pressor response is only

Table 6-2

Literature review of the results of mental stress testing in hypertensive subjects.

| Author (year) | Reference | Subjects(n) | | | Test protocol | | | Response difference between NT-HT | | | | |
		NT	BHT	HT	Test	Minutes		SBP	DBP	HR	plasma ADR	urinary ADR
Brod (1959)	2	8	-	10	MA	4	NS					
Nestel (1969)	15	17	20	-	puzzle	40	BHT>NT	+	+	?		+
Lorimer (1971)	16	15	-	15	game	?	HT>NT	+	+	?		-
Falkner (1979)	17	25	17	-	MA	10	BHT>NT	+	+	+		
Sullivan (1981)	10	13	-	15	MA	10	NS				-	
Jern (1982)	13	11	24	-	MA	2	BHT>NT	-	+	-		
Drummond (1983)	18	18	-	18	MA	2	HT>NT	+	+	-		
Schulte (1984)	19	10	10	10	MA	5	HT>NT	+	+	+		
Eliasson (1983)	12	17	16	33	SWC	20	BHT>NT	-	+	-	+	
							HT>NT				+	
Steptoe (1984)	14	12	12	12	SWC	4	HT>NT,BHT	+	-	-		
					video-		HT,BHT>NT	-	+	-		
					game	4	BHT>NT, HT	-	-	+		
Frederikson (1985)	11	14	-	14	MA	2	NS					-
Lenders (1988)	-	40	-	71	MA	5	HT>NT	+	-	-	-	

NT = normotensives
BHT = borderline hypertensives
HT = essential hypertensives
MA = mental arithmetic
SWC = Stroop's color word conflict test

SBP = systolic blood pressure
DBP = diastolic blood pressure
HR = heart rate
ADR = adrenaline

+ : significant difference
- : no significant difference

due to structural vascular changes as a consequence of hypertension. Third, the higher increment of systolic BP might result from a higher increment of cardiac output in the HT during mental stress since the increase of BP during mental stress is predominantly caused by an increase of cardiac output (2,20). Since both groups showed similar increments of HR, the most plausible inference is that the HT subjects have a stronger increase of stroke volume. This is more likely due to a higher sympathetic outflow to the heart (8) than to a higher beta-adrenoceptor responsiveness of the myocardium in the HT's. The similar increase of HR also argues for a greater sympathetic discharge to the heart in the HT group during MA, because the higher baseline HR requires a stronger increase in sympathetic nerve activity to reach a similar increase of HR as the NT group (21).

Plasma catecholamines

Up to now only, few studies have reported on plasma catecholamine responses to mental stress as laboratory stressor. The similar increase of plasma ADR in NT and HT subjects confirms other reports (10,22). In contrast, data of Eliasson et al (12) showed no increase of plasma ADR in NT but only in the HT subjects. This result is at variance with two previous studies of the same group showing an increase of plasma ADR in NT's too (7,20). Falkner et al (17) measured a higher plasma ADR response in HT, but samples were taken 5 minutes after finishing MA. The smaller increase of plasma ADR in young women than in young men was also found in a previous study (12). A possible explanation for this sex difference might be that women have a lower central sympathetic nerve activity, as is suggested by a lower plasma ADR response to hypoglycemia in women (23). In addition, it has been suggested that estrogens may inhibit the acetylcholine-induced adrenal secretion of ADR (24). Obviously, the role of estrogens in catecholamine metabolism deserves further investigation.

The weak correlation between the HR and plasma ADR responses to MA in both NT and HT subjects has been described previously (12) and does not necessarily imply a causal relationship.

Although a venous plasma NORADR sample is the net outcome of the release of NORADR from sympathetic nerve endings to an organ, neuronal reuptake and metabolic clearance, an antecubital venous plasma NORADR sample drawn at rest is predominantly composed of released NORADR from

the sympathetically innervated forearm skeletal muscles (25). It is therefore not surprising that antecubital venous plasma NORADR closely relates to the direct microelectrode recording of sympathetic neural activity (26). During mental stress, sympathetic discharge to the forearm muscle decreases. Indeed, in the NT group there was a slight decrease of plasma NORADR. In contrast, in our HT subjects in the youngest age class, we demonstrated a small but significant increase of plasma NORADR. This might be explained by a diminished removal of NORADR from the forearm, an increased sympathetic outflow to the forearm muscle or a higher arterial NORADR inflow as a consequence of an increment of the sympathetic discharge to other vascular beds. The first possibility is least likely since the forearm blood flow, being an important determinant of the extraction of NORADR, increased similarly in both groups. The second possibility is also unlikely since the sympathetic discharge to the forearm muscles decreases during mental stress (3). The third possibility seems most likely and is supported by a previously demonstrated stronger increment of arterial over venous plasma NORADR during a MA test in a small group of hypertensive subjects (27).

Our finding of an increase of plasma NORADR during mental stress in young HT subjects was not found in a similar study of Eliasson et al (12). Apart from the fact that they used another mental stress test (Stroop's color word test) than we did, it may be more important that their test was carried out in the sitting position in contrast to the supine position of our study. A higher basal sympathetic activity in the sitting than in the supine position (4), also suggested by their higher basal plasma catecholamine levels, might have prevented unmasking slight differences in alterations of plasma NORADR. Unfortunately, other studies with an adequate number of patients, comparing both haemodynamic and plasma catecholamine responses between NT and HT subjects, are lacking.

In conclusion, this study confirms that patients with essential hypertension exhibit an enhanced pressor response to a mental arithmetic test. In addition, the HT group disclosed a similar heart rate response despite a higher baseline heart rate than the NT group. Together with the demonstrated increase of plasma NORADR in the youngest HT subjects, these data support the concept that HT subjects have an increased haemodynamic reactivity during mental stress, probably on the basis of increased sympathetic reactivity.

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CHAPTER 7

THE HEAD-UP TILT TEST

THE HEAD-UP TILT TEST

PHYSIOLOGY

Assuming the upright position from recumbency elicits complex cardio-
vascular reflex and hormonal responses leading to various haemodynamic
adjustments with the purpose to maintain systemic blood pressure
(BP). Concerning cardiovascular adaptation, it is important to realize
that there are differences between (passive) head-up tilt (tilt) and
(active) free standing. First, active standing elicits the exercise
reflex giving rise to an immediate cardioacceleration. Since this
exercise reflex is not operative during tilt, the HR increase is more
gradual (1). Second, contraction of the skeletal and abdominal muscles
by (active) standing leads to an increase of peripheral resistance by
compressing the muscle arteries. It has been suggested that this is
the cause of the instantaneous increase of BP during active standing.
This BP increase and the secondary baroreceptor-mediated BP decrease
are nearly absent during tilt (2).
The gravitational effect on pooling of blood in capacitance vessels of
the lower extremities decreases venous return to the right heart. The
ensuing reduction in right and left ventricular filling pressures is
the cause of the fall of stroke volume and despite the reflex increase
of HR, cardiac output is reduced (3,4). The impending progressive fall
of BP is prevented by unloading of arterial baroreceptors and cardio-
pulmonary receptors (5), thus giving rise to an increase of sympathe-
tic and a decrease of parasympathetic nerve activity (1,6). This
results in an increase of heart rate and of total peripheral vascular
resistance. Systolic BP falls slightly (7) or remains unaltered (3),
whereas diastolic BP does not change (7) or increases (3). Despite the
fact that mean arterial pressure does not change considerably, renal
(8) and forearm blood flow (7) decrease. The increased sympatho-
adrenal activity is reflected by increments of both plasma catechol-
amines (9,10). However there is strong evidence that the increase of
plasma noradrenaline (NORADR) not only reflects an increased NORADR
spill-over from synaptic clefts but also a reduced NORADR clearance
during tilt (11).
What can be expected to happen during a tilt test to 45 degrees for 10
minutes as used in this study?

The gravitational effect on the circulation during 45 degrees tilt is about 70% of that during free standing. Cardiac output decreases by about 20-30%, stroke volume by about 30-40% and peripheral vascular resistance increases by about 30-40% (3,12,13). At a given tilt angle, the decrease of cardiac output is fairly stabilized within 6 minutes (4,12). The HR response increases linearly with increasing tilt angle but tends to level off beyond an angle of 45 degrees (13). Plasma NORADR increases linearly with the angle of tilt and the response is maximal at an angle of 45 degrees and after a period of 10 minutes (9).

So our protocol elicits nearly maximal HR (13) and plasma NORADR responses (9). Higher tilt angles might evoke unwanted vasovagal episodes (14). In addition it has previously been demonstrated that muscular activity is almost absent during tilt in contrast to active standing (1). So, an interference of somatic reflexes as a result of static muscle activity seems less likely.

RESULTS

Circulatory measurements

During tilt, systolic BP hardly changed, whereas both diastolic BP and HR increased in both groups (figure 7-1). However analysis of all data disclosed involvement of both age and sex in the haemodynamic response to tilt (chapter 2). So, the results accounting for age and sex are presented.
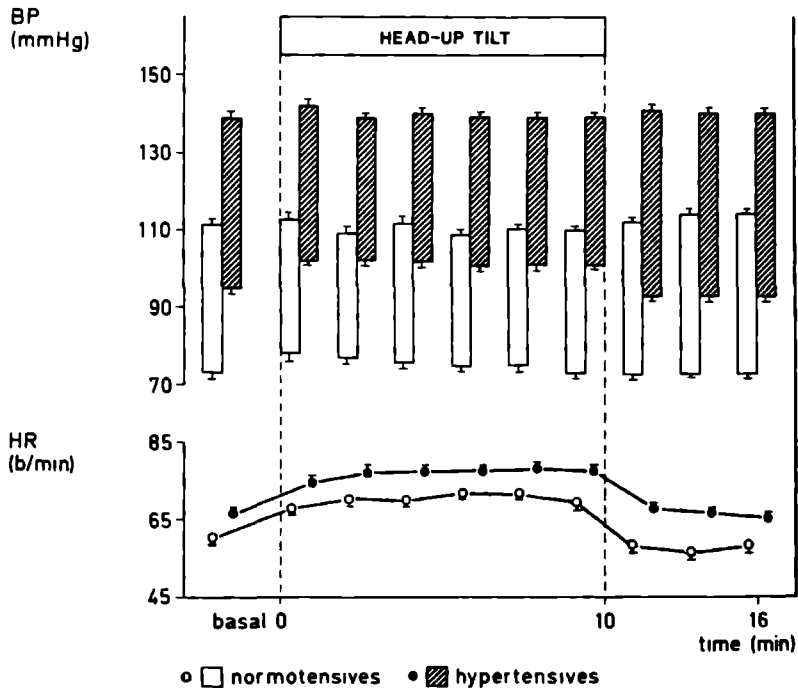
Figure 7-1
The course of blood pressure (BP) and heart rate (HR) before, during
and after head-up tilt in all normo- and hypertensive subjects (mean +
SE).

There was a clear difference between NT and HT men of the lowest age
level (25 years) concerning the response of BP and HR to tilt (figure
7-2). In the NT's, systolic BP showed a decline of 5-10%, whereas it
did not change in the HT's.
In the first minute, both NT's and HT's showed an increase in diastol-
ic BP, which was about two times as high in the NT's as in the HT's.

Thereafter, the diastolic BP level of the HT's remained elevated, whereas it rapidly decreased in the NT's. The relative increment of HR was larger in the NT than in the HT group during the whole tilt test (figure 7-2).

No NT-HT difference emerged in women of the youngest age level, as was also the case for both sexes at the highest age level.
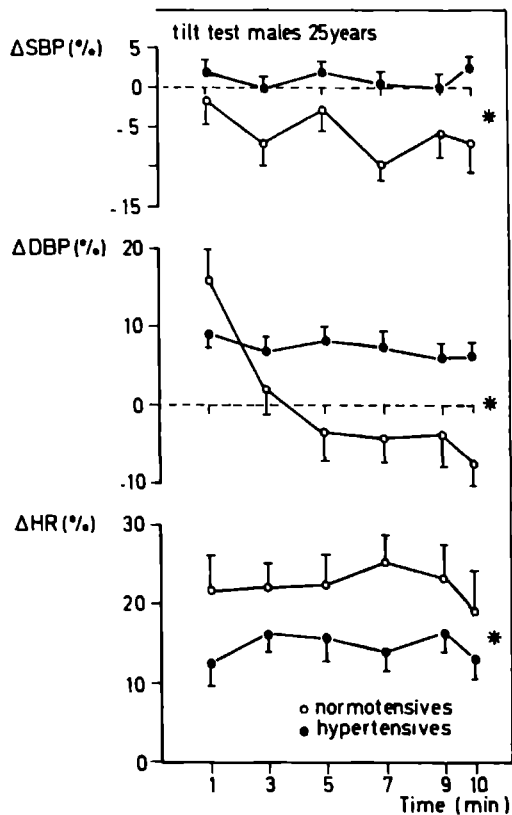
Figure 7-2

The estimated percentage changes of systolic (SBP), diastolic (DBP) blood pressure and heart rate (HR) in normo- and hypertensive males of 25 years (mean ± SE).

*: curves differ significantly

Plasma catecholamines

Both plasma catecholamines increased significantly during tilt. The HT group showed a larger increase of plasma ADR than the NT group (table 7-1). However, if accounted for sex and age, only HT women of the youngest age class (20-29 years) showed a stronger increment of plasma ADR (0.14 ± 0.03 nmol/l) than the corresponding NT controls (0.03 ± 0.01 nmol/l) ($p<0.01$). Within the young NT group the rise of ADR was larger in men than in women, but this difference was not significant in the HT group (table 7-1). In addition, in the HT females there was a weak but significant inverse correlation between plasma ADR response and age (-0.37, $p<0.05$). Only in the HT's, the plasma ADR response was weakly correlated with the increase of HR (0.31, $p<0.01$) and diastolic BP (0.28, $p<0.05$).

Table 7-1

The changes of plasma adrenaline (ADR) and noradrenaline (NORADR) during head-up tilt in normotensives (NT) and hypertensives (HT) according to sex/age class (mean $\pm$ SE).

	Δ plasma ADR (nmol/l)		Δ plasma NORADR (nmol/l)	
	NT	HT	NT	HT
All subjects	0.07 ± 0.01 *	0.11 ± 0.01	1.18 ± 0.11	1.22 ± 0.09
20-29 years				
-males	0.07 ± 0.02 *	0.17 ± 0.04	1.14 ± 0.22	1.10 ± 0.09
-females	0.03 ± 0.01 **	0.14 ± 0.03	0.68 ± 0.21	0.81 ± 0.17
30-39 years				
-males	0.11 ± 0.04	0.07 ± 0.03	1.48 ± 0.13 *	1.53 ± 0.20 *
-females	0.07 ± 0.03	0.07 ± 0.02	0.67 ± 0.15	0.89 ± 0.16
40-55 years				
-males	0.11 ± 0.03	0.10 ± 0.03	1.70 ± 0.26	1.50 ± 0.24
-females	0.04 ± 0.02	0.08 ± 0.02	1.24 ± 0.32	1.34 ± 0.21

* $p<0.05$

** $p<0.01$

For NORADR, no NT-HT difference could be detected (table 7-1) and this applied also to either sex. The effect of sex on the plasma NORADR response to tilt was important since plasma NORADR rose more strongly in men than in women, which applied both to NT and HT's (table 7-1). The plasma NORADR response was not significantly related to BP or HR response or to age.

DISCUSSION

In this study we could demonstrate that in young HT males, systolic BP did not fall when compared to young NT males whereas diastolic BP increased in the HT but not in the NT males during tilt. This enhanced BP response to gravitational stress in young male hypertensives could not be demonstrated in young female hypertensives and older hypertensives of both sexes. Comparison of our results with previous studies is difficult because of the considerable methodological variability. This might be ascribed to differences in the used stimulus (tilt or active standing), the used tilt angle or the duration of tilt, the method used for data analysis and the heterogeneity of the investigated NT and HT groups. Only few studies reporting NT-HT differences concerning the haemodynamic response to tilt (15-19) are eligible for comparison. Fröhlich et al (15) demonstrated an enhanced mean arterial BP response to 5 minutes tilt (70 °) in nearly one-third of a heterogeneous group of 51 hypertensive subjects, whereas about 50% had a normal response and 20% was classified as having orthostatic hypotension. The hyperresponders, having the mildest hypertension and the highest cardiac output at rest, showed the largest increment of total peripheral resistance, whereas cardiac output decreased to the same degree as the HT's who showed a normal BP response to tilt. In contrast, the HT subjects with orthostatic hypotension, having the most severe hypertension and the highest total peripheral resistance at rest, showed the largest decrease of cardiac output and were unable to increase their total peripheral resistance to the same degree as the HT's with a normal pressor response. So, the hyperresponsiveness of BP to tilt in mild HT's was probably causally related to an abnormal increase in total peripheral resistance. From that study it was concluded that an enhanced sympathetic responsiveness to orthostatic stress might play a role in mild hypertensives only. These results

were supported by a report of Sannerstedt et al (17), who could not demonstrate a decrease of mean arterial BP in 17 young borderline HT's during 10 minutes tilt (45 °) when compared to a group of 18 NT subjects. Unfortunately, no separate data of systolic and diastolic BP were supplied. Both our test protocol and our results agree fairly well with this study. Additional support for the conclusions of Fröhlich et al (15) can also be derived from a study of Esler and Nestel (18). A subgroup of 10 out of 41 HT subjects showed an enhanced diastolic BP response to a 75 minutes lasting tilt (25 °) and these were the subjecs with the mildest HT. In addition, there was a correlation between the diastolic BP response and the urinary noradrenaline excretion. Another study (16) demonstrated an increment of diastolic BP in 23 borderline HT's, which was twice as large as in a group of 28 NT's. A similar study in 35 subjects with sustained hypertension (BP consistently 100 mmHg) disclosed a small but significant increase of diastolic BP (+ 7 mmHg) during 5 minutes tilt (50 °), whereas this increase was absent in a control group of 21 NT's (19).

So, up to now, there has been strong evidence that the pressor response is enhanced in subjects with borderline and mild hypertension, whereas in subjects with sustained and more severe hypertension this pressor response may be absent or BP may even decrease during orthostatic stress.

The increased pressor response to gravitational stress that is related to an increased response of the peripheral vascular resistance in HT subjects is difficult to explain.

1. An enhanced arterial baroreceptor activity should be considered. Although it has been demonstrated that arterial baroreceptor control of HR is impaired in borderline HT's (20), it can be derived from experiments in animal and in human hypertension that baroreflex control of the peripheral resistance is preserved or even augmented (21). On the other hand, it has been reported (22) that pressor and vasoconstrictor responses to inhibition of arterial baroreceptors is impaired in borderline hypertensives. So, it remains doubtful whether an elevated arterial baroreceptor activity can explain the increased pressor response in the HT's.

2. It might be possible that cardiopulmonary receptor activity with vagal afferents is enhanced in the HT's. Cardiopulmonary re —

ceptors are sensitive to changes in cardiac filling pressure and an increase of cardiac filling pressure inhibits sympathetic outflow. Thus, a fall of cardiac filling pressure during tilt decreases this inhibitory effect resulting in an increase of sympathetic outflow. It has been shown that it is likely that cardiopulmonary afferent activity is increased in HT subjects (23), so this could explain why HT subjects reveal a higher pressor reactivity than NT subjects when this enhanced inhibitory activity is reduced during tilt.

3. A higher central sympathetic outflow in HT's at rest has been demonstrated (24), but it remains to be established whether this is also the operative mechanism that is responsible for the increased pressor response in HT's during tilt. This possibility is difficult to prove or to exclude.

4. There might be a higher efferent sympathetic activity in HT's at the site of the neuronal nerve endings resulting in an increased NORADR release during tilt. The increase of both plasma NORADR and ADR is in agreement with previous studies (9,10,14). However, we were unable to demonstrate a stronger increase of plasma NORADR in HT than in NT subjects, which agrees with some (14,25) but not all studies, some of which demonstrate enchanced plasma NORADR responses in hypertensive subgroups (26). It should be noted that active standing instead of tilt was used in some studies. The clearly larger increase of plasma NORADR in men than in women confirms a previous report (25). With regard to plasma ADR, only young HT's showed a stronger response than the young NT's, although this was only significant in the females. This is in agreement with a previous study (25) and may be due to a decreased clearance of ADR from the forearm. It has been demonstrated in NT's that the clearance of ADR from the forearm increases during orthostasis, probably as a result of the fall in forearm blood flow (10). However, HT subjects show a similar fall in forearm blood flow during orthostatic stress as NT's (23). So, it seems unlikely that the enhanced plasma ADR response in the young HT's can be attributed to a lower clearance of ADR from the forearm. A more likely explanation is that HT's have a stronger adrenomedullary release of ADR as a result of stronger sympathetic efferent activity towards the adrenal medulla.

5. An increased alpha-adrenoceptor density or an increased sensitivity of alpha-adrenoceptors to NORADR in hypertension might account for the enhanced pressor response. However, it has been shown that mild hypertensives have a normal alpha-adrenoceptor sensitivity (24) to NORADR, so this possibility seems unlikely.

6. Finally, nonspecific vascular hyperreactivity in the HT's as a result of structural vessel wall changes should be discussed but the normal pressor responsiveness to cold exposure in HT's (23,25, chapter 11 of this thesis) argues strongly against this possibility.

In conclusion, we were able to demonstrate an enhanced blood pressure responsiveness to head-up tilt in young males with mild HT as compared to young NT males. The HT's showed a normal plasma NORADR response but the young HT's showed a stronger increment of plasma ADR than the young NT's. These observations are consistent with the existing concept of an increased sympathoadrenal reactivity in young HT's during orthostatic stress.

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THE BICYCLE EXERCISE TEST

THE BICYCLE EXERCISE TEST

PHYSIOLOGY

Bicycle (BYC) exercise is a mode of dynamic exercise involving large
skeletal muscles. Complex central and peripheral circulatory adjust-
ments become operative to ensure the exercising muscles with suffi-
cient blood. During the anticipation phase before starting exercise on
a bicycle ergometer, an increase of central sympathetic activity al-
ready increases heart rate (HR), blood pressure (BP) and cardiac out-
put (1). Immediately after the onset of exercise, central command from
cortical areas is probably the most important mechanism responsible
for vagal withdrawal, causing an instantaneous rise of HR. Afferent
information from muscle chemoreceptors causes an increase of sym-
pathetic outflow to the heart and vessels, but this occurs consider-
ably later than the vagal withdrawal (2).

The increase of sympathetic neural activity to the vessels not only
modulates the increase of local blood flow in the exercising muscles
that is due to local vasodilation, but also elicits vasoconstriction
in the non-exercising muscles, the resistance vessels of the splanch-
nic and renal vascular bed and of the capacitance veins. This con-
tributes to the pressor response and to an adequate redistribution of
the increased cardiac output towards the exercising muscles. An
additional consequence of the increased sympathoadrenal stimulation to
the heart is an increase of myocardial contractility. Nevertheless it
is well established that the rise of HR is more important for the rise
of cardiac output than for the increase of stroke volume.

Both plasma catecholamines rise during incremental work loads,
reflecting sympathoadrenal activation (3,4). After reaching the an-
aerobic threshold at about 75 % of an individual's maximal work load,
both plasma catecholamines increase steeply (5).

RESULTS

Circulatory measurements

Five out of 41 NT and 4 out of 70 HT subjects were unable to finish
the exercise protocol because of tiredness.

As expected, systolic BP increased gradually, reaching a steady state
in the last three minutes of the final workload and the diastolic BP
showed a small decrease (figure 8-1). HR rose in both groups to about
160 beats per minute and the difference in baseline HR between NT and
HT's disappeared during exercise (figure 8-1).
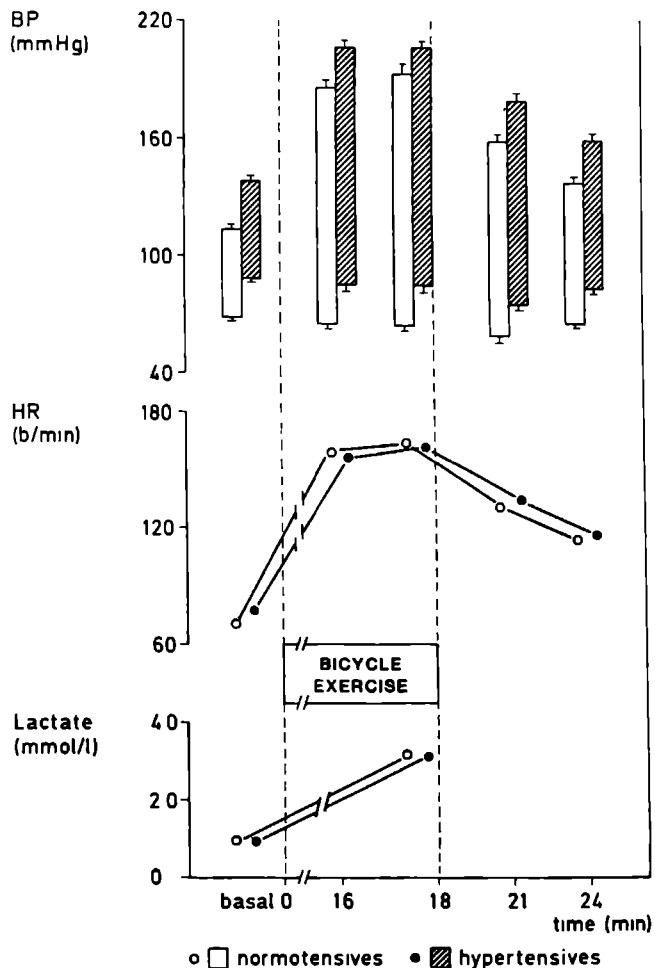
Figure 8-1
The course of blood pressure (BP), heart rate (HR) and blood lactate
before, during and after bicycle exercise in all normo- and hyperten-
sive subjects (mean $\pm$ SE are given. The SE of HR and blood lactate are
omitted because they are too small for the given scale).

The percentage changes in the young HT males and females showed a lower increase of systolic BP than those in the young NT males and females (figure 8-2). Systolic BP rose less in females than in males and this applied to the NT and HT subjects. There was no difference between NT and HT subjects with regard to the diastolic BP response. The HR response was higher in the NT than in the HT subjects but this difference only reached significance in the females. In the older age group there were no differences between NT and HT subjects concerning the BP or HR responses.
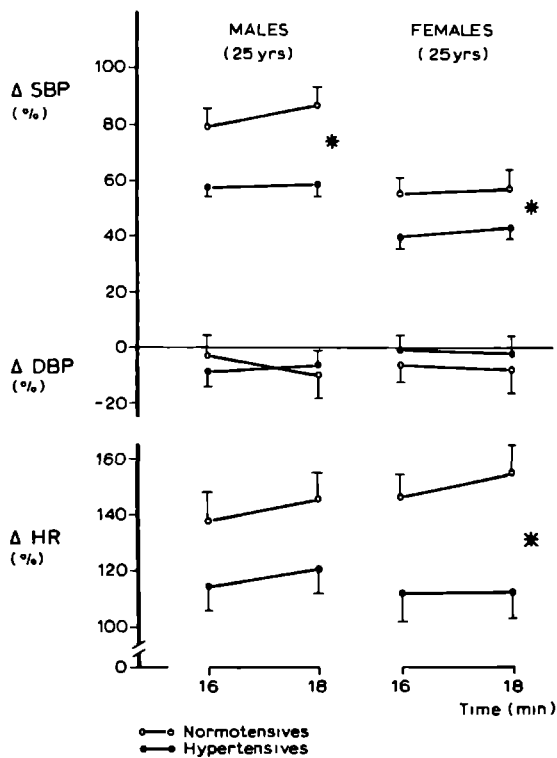
Figure 8-2
The estimated percentage changes of systolic (SBP), diastolic (DBP) blood pressure and heart rate (HR) in normotensive and hypertensive males and females of 25 years (mean ± SE are given).
*: curves differ significantly

Plasma catecholamines.

Plasma ADR increased from 0.14±0.01 to 0.70±0.06 nmol/l in the NT and from 0.21±0.02 to 0.77±0.06 nmol/l in the HT group. Plasma NORADR increased from 3.42±0.28 to 10.04±0.51 nmol/l in the NT and from 3.49± 0.18 to 9.50±0.72 nmol/l in the HT group (table 8-1). In both groups there was no sex- or age effect on the responses of either ADR or NORADR. Plasma NORADR but not ADR response correlated weakly with the HR response in both groups (NT r=0.38, HT r=0.29, p<0.05).

Blood lactate.

Basal blood lactate levels were not different between NT and HT subjects, nor was the increase of blood lactate during exercise (table 8-1). The blood lactate response was weakly correlated with the plasma NORADR response in NT (r=0.34, p<0.05) and HT group (r=0.49, p<0.01).

Table 8-1

The increase of plasma ADR (adrenaline) and noradrenaline (NORADR), the baseline blood lactate levels, the increments of blood lactate and the workload (at 75% of the W-max) in the normotensives (NT) and hypertensives (HT). (Mean ± SE are given)

	NT	HT
Δ plasma ADR (nmol/l)	0.56±0.06	0.55±0.05
Δ plasma NORADR (nmol/l)	6.66±0.50	6.02±0.66
blood lactate (rest) (mmol/l)	0.89±0.03	0.89±0.02
Δ blood lactate (mmol/l)	2.24±0.17	2.22±0.17
work load (watts)	174±7 *	142±5

* p<0.05

There was a considerable inter-individual variablity in the absolute work load (at 75% of the W-max). NT's exercised with a higher average work load than the HT subjects (table 8-1), and as expected it was higher in male than in female subjects. Age was negatively correlated with work load in the NT's (males r=-0.52, p<0.01; females r=-0.46, p<0.05).

DISCUSSION

In this study we used a standardized submaximal exercise test with 3 incremental work loads of 25, 50 and 75% of the W-max of a subject. To reach a steady state during each work load level, the exercise time of 6 minutes is considered to be sufficient (6). This design of relative work loads allows elimination of differences in physical condition as a confounding factor for the haemodynamic responses. The attained HR during the final level of exercise of about 160 beats per minute is in agreement with previous data in healthy subjects (7).

If HT subjects exhibited a stronger sympathetic neural activity during dynamic exercise, one could expect that HT subjects would show exaggerated responses of BP, HR and plasma catecholamines during exercise than NT's. However, in this study we found a smaller relative response of systolic BP and HR in young HT's than in young NT's, but there was no difference in the responses of plasma catecholamines and of blood lactate, indicating similar levels of sympathoadrenal stimulation and similar levels of exertion during exercise in NT and HT subjects. Our data are at variance with some (8-12) but not all (13-16) earlier reports demonstrating higher sympathetic responses during exercise in HT subjects. It should be noted however, that some positive studies may be flawed by giving the same absolute work load to NT and HT subjects, thus not accounting for differences in physical condition. Although the used work load was higher for NT's than for HT's, the difference in BP response in our study can not be explained in terms of a worse physical condition of the HT's than the NT's since the work load was related to the maximal working power of each individual subject. The relative HR response was lower in the young HT's than in the young NT's. However, from a physiological point of view it would be more appropriate to express the HR response in absolute values because the HR response to sympathetic stimulation is not amplified as is the case with the vascular response (17). Even if the HR response is expressed in absolute values, young HT subjects did not show a larger HR increase than young NT subjects. This suggests that the sympathetic response to exercise is not enhanced in young hypertensives. The lower relative HR response in the young hypertensives might be explained by a reduced cardiac beta-1-adrenoceptor sensitivity (8).

However, we have demonstrated an increased beta-1-adrenoceptor sensi-
tivity in HT subjects (chapter 10), but this was only the case in the
male subjects.

The weak correlations between HR and plasma NORADR responses during
exercise confirm previous studies (3,18) and reflect sympathetic
reactivity during dynamic exercise. In contrast, we could not confirm
the previously established correlation between BP response and plasma
NORADR response (3,18).

In conclusion, young hypertensives showed lower relative increments of
systolic BP and HR than young normotensives but there was no differ-
ence concerning the plasma catecholamine responses. These data do not
point to an exaggerated sympathoadrenal activity during dynamic exer-
cise in hypertensive subjects.

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CHAPTER 9

NORADRENALINE INFUSION

NORADRENALINE INFUSION

INTRODUCTION

Noradrenaline (NORADR) is a potent vasoconstricting amine which is released from postganglionic sympathetic nerve endings into the synaptic cleft in response to neuronal impulses (1). For a long time, NORADR, at physiological plasma levels, has been considered as a sympathetic neurotransmitter and not as a hormone (2). However, more recently it has unequivocally been demonstrated that infused NORADR has clear haemodynamic effects at much lower plasma levels than previously demonstrated (3). So, it could be shown that the threshold for a pressor effect is already reached at plasma levels which occur during physiological stimulation like standing.

When NORADR is given intravenously in increasing doses, both systolic and diastolic blood pressure (BP) increase linearly (4) as a result of an alpha-adrenoceptor-mediated rise in peripheral vascular resistance. Cardiac output does not change appreciably and heart rate falls due to activation of the baroreceptor reflex (5).

NORADR infusion has frequently been used to study haemodynamic reactivity in hypertensive patients but the results were rather conflicting (4-10). Instead of the commonly employed pressor-dose relationship, we studied the pressor-plasma level relationship to determine whether there is a difference between NT and HT subjects concerning the haemodynamic sensitivity to infused NORADR to levels that are encountered during various kinds of daily life stress.

RESULTS

In 1 NT and in 4 HT subjects the NORADR infusion test was not possible due to technical difficulties with blood sampling. In the other subjects the ultimately infused dose of NORADR amounted to 51 ± 19 ng/kg/minute (SD) in the NT and 37 ± 24 ng/kg/minute in the HT subjects. As expected the increase of plasma NORADR was larger in the NT ($+2.14 \pm 0.30$ nmol/l) than in the HT group ($+1.63 \pm 0.16$ nmol/l).

As described in chapter 2, the individual haemodynamic responses were corrected for the increase of plasma NORADR. Age, sex or their inter-

action only affected the percentage haemodynamic response per nmol increment of plasma NORADR only in the normotensives. Therefore, data for each age/sex class are presented (table 9-1). Since there were no NT-HT differences within each age/sex class except for females of 20-29 years old, one must conclude that there is no important difference between NT and HT subjects concerning the haemodynamic responses/nmol increment NORADR during NORADR infusion. The overall responses of the whole groups show that only the diastolic BP response in the NT group was larger than that of the HT group but this difference did not reach significance (table 9-2).

Table 9-1

The percentage changes of systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and forearm vascular resistance (FVR) per nmol noradrenaline (NORADR) increment in normotensive (NT) and hypertensive (HT) subjects according to each age/sex class (mean $\pm$ SE are given).

Δ SBP/NORADR (%/nmol/1)		NT		HT
Age 20-29 years	- males	0.8 + 0.8		4.6 + 1.4
	- females	6.4 + 2.7		2.8 + 0.4
,, 30-39 years	- males	3.6 + 0.8		3.2 + 1.1
	- females	3.9 + 1.8		5.5 + 1.6
,, 40-55 years	- males	3.1 + 1.0		3.5 + 4.4
	- females	6.9 + 2.5		7.9 + 1.9

Δ DBP/NORADR (%/nmol/1)		NT		HT
Age 20-29 years	- males	4.8 + 0.9		6.3 + 1.5
	- females	25.0 + 7.2	*	7.7 + 1.7
,, 30-39 years	- males	13.6 + 3.5		6.6 + 0.9
	- females	10.7 + 4.7		6.4 + 1.8
,, 40-55 years	- males	1.9 + 0.8		5.0 + 2.5
	- females	9.9 + 7.3		11.8 + 3.8

Δ HR/NORADR (%/nmol/1)		NT		HT
Age 20-29 years	- males	-5.2 + 1.6		-6.0 + 1.0
	- females	-22.0 + 5.9		-11.7 + 2.6
,, 30-39 years	- males	-9.7 + 3.3		-8.8 + 1.3
	- females	-8.7 + 3.2		-6.7 + 1.3
,, 40-55 years	- males	-6.3 + 0.5		-4.7 + 3.9
	- females	-8.2 + 3.3		-8.5 + 2.1

Δ FVR/NORADR (%/nmol/1)		NT		HT
Age 20-29 years	- males	12.6 + 4.8		22.9 + 6.4
	- females	101.8 + 42.2		33.9 + 9.8
,, 30-39 years	- males	52.2 + 12.1		39.9 + 8.1
	- females	37.7 + 20.1		44.7 + 14.5
,, 40-55 years	- males	49.1 + 13.1		19.2 + 22.9
	- females	68.8 + 31.3		59.8 + 22.1

*p<0.05

Table 9-2

The percentage changes of systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and forearm vascular resistance (FVR) per nmol noradrenaline (NORADR) increase in all normo- (NT) and hypertensives (HT) during NORADR infusion.

	Normotensives	Hypertensives
Δ SBP/NORADR (%/nmol/1)	4.2 + 0.8	4.3 + 1.1
Δ DBP/NORADR (%/nmol/1)	12.1 + 2.3	6.8 + 0.9
Δ HR/NORADR (%/nmol/1)	-10.9 + 1.8	-7.4 + 1.1
Δ FVR/NORADR (%/nmol/1)	55.1 + 10.4	33.2 + 6.4

DISCUSSION

In this study we demonstrated that HT subjects do not have a significantly stronger blood pressure response per nmol increment of plasma NORADR than NT subjects.

The given doses of NORADR were low in order to attain similar plasma NORADR levels as during adrenergic stimulation like head-up tilt, cold pressor test and isometric exercise. Every dose was given for 8 minutes, which is long enough to achieve a steady state (2). Instead of the conventional approach to derive vascular sensitivity from a dose-pressor relationship, we were merely interested in the relationship between the increment of plasma NORADR and the pressor response, since it is the ultimately attained plasma level that determines the haemodynamic effects. Ideally, it would be more appropriate to use arterial instead of venous plasma NORADR responses because it is the arterial plasma level to which the vessels are exposed.

This approach makes it difficult to compare our results with previous studies since in those studies dose-pressor response curves were used instead of the plasma level-pressor response as we used. Some studies reported enhanced BP responses (5-7) or enhanced reactivity of peripheral vessels (11-13) to infused NORADR in hypertensive patients but others could not establish such an increased BP response (4,8-10). Our data are in agreement with the recent study of Dimsdale et al (4) which found no evidence for an increased sensitivity to infused

NORADR in mildly HT's. As emphasized in that study (4), the conflicting results might be due to confounding factors like age, sodium intake, race or inadequate assessment of the dose-response relationship.

Interpretation of the BP responses to systemic administrations of NORADR is hampered by activation of the baroreceptor reflex. However, if activation of the baroreceptor reflex would have flawed the BP responses, one should expect a stronger BP increase in the HT's as a consequence of the impaired baroreceptor reflex in the HT's (14). Age can be ruled out since there was no difference in age between both groups, and in addition there were no NT-HT differences within each age class. In contrast, it has recently been shown that older subjects had a stronger BP response to NORADR but this was only apparent during a high salt diet (4). Previous studies indicate that age does not affect alpha-2-adrenoceptor density on human platelets (15) or alpha-adrenoceptor sensitivity to NORADR in isolated human arteries (16). At an older age the plasma clearance rate of NORADR is diminished (17). Finally, a difference in sodium intake must be considered (4) but this seems unlikely since the 24-hour sodium excretion was similar in a subset of 16 NT and 31 HT subjects.

In conclusion, we could not demonstrate an abnormally strong BP increase per nmol increment of plasma NORADR during infusion with NORADR in HT subjects. These results are at variance with some but not all previous studies which only reported a dose-pressor relationship. Our data suggest that HT subjects do not have an enhanced vascular sensitivity to NORADR as compared to NT's but one should take into account that venous plasma NORADR levels were used in this study.

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ADRENALINE INFUSION

ADRENALINE INFUSION

INTRODUCTION

The adrenal medulla is the predominant source of circulating adrena-
line (ADR) since it is undetectable in adrenalectomised subjects, even
if a very sensitive assay is used. As replacement therapy is not
necessary after adrenalectomy, ADR is not an essential hormone. Never-
theless, ADR has a variety of physiological effects in particular
under stressful circumstances. Obviously, the circulatory effects of
ADR are related to the height of the plasma ADR levels. During stress-
ful physiological conditions like exercise or during surgery, a five
to tenfold increase of venous plasma ADR levels to about 1 nmol/l may
be reached (1). A similar plasma ADR level can also be attained by an
intravenous infusion of a low dose of ADR. In contrast to a previous
study (2), reporting similar plasma ADR threshold levels for systolic
and diastolic blood pressure (BP) responses, it has recently been
demonstrated recently that the threshold for the diastolic BP response
is considerably lower than that for systolic BP (3). So, diastolic BP
is probably more sensitive to ADR than systolic BP. If infused intra-
venously, ADR decreases diastolic BP and systemic vascular resistance
and increases heart rate (HR) and stroke volume (3). Higher doses are
required to increase systolic BP.
In contrast to noradrenaline infusion, ADR infusion has been used less
frequently to study haemodynamic reactivity in patients with essential
hypertension, and if so, such studies entailed small patient samples
and ADR doses beyond the physiological range were administered (4,5).
This study was carried out to determine whether there is a difference
between NT and HT subjects concerning the haemodynamic sensitivity
during infusion of low incremental doses of ADR to plasma levels which
are commonly attained during various kinds of daily life stress.

RESULTS

In 4 NT and 7 HT subjects completion of the ADR infusion test was im-
possible because of technical difficulties with blood sampling. Base-
line plasma ADR was not significantly different between NT and HT's

(0.09+0.01 and 0.13+0.01 nmol/l). The ultimate infused dose of ADR was higher in the NT (45+4 ng/kg/min) than in the HT subjects (30+2 ng/kg/min). The resulting increment of plasma ADR was larger in the NT (+1.15+0.11 nmol/l) than in the HT group (+0.90+0.07 nmol/l). As described in chapter 2, the individual haemodynamic responses were corrected for the increase of plasma ADR. Sex, age or their inter-action appeared to affect the percentage haemodynamic response per nmol increase of plasma ADR. Therefore, data for each age/sex class are presented (table 10-1).

The effect of age was confined to the systolic blood pressure response in both NT and HT male subjects. No consistent age effects on the other variables were apparent (table 10-1). Therefore, all data were reanalysed separately for male and female subjects (table 10-2). The HT males showed a larger decrease of the diastolic BP and of the fore-arm vascular resistance (FVR), whereas the HR increased more than in the NT males. In addition, the HR response was significantly larger in the NT and HT females as compared to the males. Within the NT and within the HT group, the BP responses were not different between males and females, but the HR response was significantly larger in female than in male subjects (table 10-2).

DISCUSSION

In this study we have demonstrated a stronger decrease of diastolic BP and FVR and a stronger increase of HR per nmol increase of plasma ADR in HT as compared to NT males. These data suggest that HT males are more sensitive to exogenous ADR than NT males. Since the decrease of diastolic BP and of FVR reflects vasodilation by stimulation of vascu-lar beta-2-adrenoceptors, these data might indicate that HT males have (1) a higher density of beta-2-adrenoceptors on the vascular smooth muscle cells, (2) a higher beta-2-adrenoceptor sensitivity to ADR, (3) or a nonspecific vascular hypersensitivity due to the structurally altered vascular wall. Actually, it is not known whether HT subjects have a higher density of beta-2-adrenoceptors in the vascular wall. The results of studies using mononuclear lymphocytes for assessment of beta-adrenoceptor density are contradictory. Brodde et al (6) found an

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Table 10-1

The percentage changes of systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and forearm vascular resistance (FVR) per nmol adrenaline (ADR) increment in normotensive (NT) and hypertensive (HT) subjects according to each age/sex class (mean $\pm$ SE are given).

Δ SBP/ADR (%/nmol/l)		NT		HT
Age 20-29 years	- males	9.7 $\pm$ 1.7		9.6 $\pm$ 2.0
	- females	19.5 $\pm$ 9.0		5.7 $\pm$ 2.2
,, 30-39 years	- males	11.2 $\pm$ 2.2	*	5.1 $\pm$ 1.4
	- females	0.9 $\pm$ 3.1		1.3 $\pm$ 1.3
,, 40-55 years	- males	1.6 $\pm$ 1.1		1.7 $\pm$ 1.3
	- females	-0.6 $\pm$ 4.3		0.6 $\pm$ 1.9

Δ DBP/ADR (%/nmol/l)				
Age 20-29 years	- males	-4.4 $\pm$ 1.9	*	-17.5 $\pm$ 3.8
	- females	-26.1 $\pm$ 16.7		-13.2 $\pm$ 2.7
,, 30-39 years	- males	-10.3 $\pm$ 4.4		-16.3 $\pm$ 3.6
	- females	-3.5 $\pm$ 4.0		-10.1 $\pm$ 3.0
,, 40-55 years	- males	-3.9 $\pm$ 1.8		-7.8 $\pm$ 1.5
	- females	-6.8 $\pm$ 8.2		-10.8 $\pm$ 6.0

Δ HR/ADR (%/nmol/l)				
Age 20-29 years	- males	8.6 $\pm$ 1.9	*	26.7 $\pm$ 5.2
	- females	75.5 $\pm$ 23.7		52.8 $\pm$ 11.6
,, 30-39 years	- males	18.4 $\pm$ 5.8		23.1 $\pm$ 3.5
	- females	19.0 $\pm$ 8.2		34.8 $\pm$ 8.4
,, 40-55 years	- males	5.8 $\pm$ 0.7	*	18.5 $\pm$ 3.4
	- females	39.7 $\pm$ 5.8		26.5 $\pm$ 6.7

Δ FVR/ADR (%/nmol/l)				
Age 20-29 years	- males	8.9 $\pm$ 9.9		-12.9 $\pm$ 10.9
	- females	54.8 $\pm$ 92.9		-50.0 $\pm$ 27.5
,, 30-39 years	- males	7.3 $\pm$ 19.7	*	-27.9 $\pm$ 11.3
	- females	9.2 $\pm$ 4.7		-34.8 $\pm$ 16.6
,, 40-55 years	- males	13.1 $\pm$ 16.5		-16.6 $\pm$ 6.8
	- females	-68.2 $\pm$ 35.1		-19.5 $\pm$ 14.0

* p<0.05

Table 10-2

The dose of adrenaline, the plasma adrenaline (ADR) response and the percentage changes of systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and forearm vascular resistance per nmol ADR increase in the NT (normotensives) and HT (hypertensives) according to each sex (mean $\pm$ SE are given).

	NT		HT
Dose (ng/kg/min)			
–males	52 $\pm$ 6		30 $\pm$ 2
	*		
–females	38 $\pm$ 4		30 $\pm$ 2
Δ plasma ADR (nmol/l)			
–males	1.52 $\pm$ 0.11		1.04 $\pm$ 0.09
	**		*
–females	0.63 $\pm$ 0.11		0.67 $\pm$ 0.09
Δ SBP/ADR (%/nmol/l)			
–males	8.4 $\pm$ 1.4		4.9 $\pm$ 1.0
–females	9.8 $\pm$ 5.2		3.0 $\pm$ 1.2
Δ DBP/ADR (%/nmol/l)			
–males	-6.9 $\pm$ 2.2	*	-13.1 $\pm$ 1.8
–females	-15.8 $\pm$ 8.8		-11.5 $\pm$ 2.0
Δ HR/ADR (%/nmol/l)			
–males	12.3 $\pm$ 2.9	*	22.1 $\pm$ 2.3
	*		*
–females	53.2 $\pm$ 13.3		40.6 $\pm$ 6.2
Δ FVR/ADR (%/nmol/l)			
–males	9.3 $\pm$ 9.8	**	-19.2 $\pm$ 5.4
–females	-3.5 $\pm$ 40.7		-39.6 $\pm$ 14.3

  * $p < 0.05$

 ** $p < 0.01$

increased beta-adrenoceptor density in the HT's, whereas others could not confirm these results (Graafsma et al, unpublished observations). As far as we know, no reliable data have been published on the vascular beta-2-adrenoceptor sensitivity of adrenaline. Finally, it is conceivable that the stronger haemodynamic response is due to the structurally altered vascular wall in the HT males (7). Since we could not establish an abnormal haemodynamic response in the HT females, this explanation seems unlikely because this would also apply to the HT females.

Our data are, at least partially, consistent with a those of Goldenberg et al (4) who found a stronger drop in diastolic BP and total peripheral vascular resistance in 3 HT subjects (2 males, 1 female) as compared to 4 male NT's. Fatherree and Hines (5) reported similar findings in 12 NT's and 10 HT's but unfortunately no sex distribution was given. On the other hand, Duff (8) described a stronger vasoconstriction in the hand vessels during intra-arterial administration of ADR in HT's as compared to NT's. Indeed, ADR has opposite effects on the forearm blood flow and the hand blood flow (9) because alpha-adrenoceptors prevail against beta-adrenoceptors in the skin vessels of the hand. So, the study of Duff (8) merely supports for an increased alpha-adrenoceptor sensitivity or density in the hand skin vessels in HT's.

Apart from a larger decrease of diastolic BP and FVR, HT males also showed a larger increment of HR as compared to NT males. Although ADR lowers BP slightly with subsequent deactivation of the baroreceptor reflex and vagal withdrawal, the HR response to infused ADR can be considered to reflect cardiac beta-1-adrenoceptor sensitivity. Thus, our results suggest that HT males have a higher cardiac beta-1-adrenoceptor sensitivity or density than NT males. This finding is at variance with the repeatedly reported normal or even reduced cardiac beta-1-adrenoceptor sensitivity in HT's (10). It seems unlikely that this can be explained by the fact that nearly all studies used isoproterenol instead of ADR. A probably more important methodological difference is the fact that we have studied the plasma level-response relationship instead of the dose-response relationship. However, even if the dose-response relationship is considered in our study, it is clear that the HT males show a significantly higher HR response than the NT males who received a higher dose. With regard to the role of

sex, we have demonstrated that the response, expressed as the BP change per nmol increment of plasma ADR, was similar in HT men and women who received a similar dose of ADR. However, also between NT men and NT women there was no difference in response despite the fact that they received different doses of ADR. These data indicate that vascular sensitivity for ADR is similar in males and females of both groups. In contrast, the HR response per nmol increment of plasma ADR was higher in both NT and HT females as compared to males, suggesting a higher cardiac beta-1-adrenoceptor sensitivity or density in women than in men. It can be speculated whether this attributes to the higher basal HR in HT females than in HT males (chapter 4).

Despite the fact that the HT male and female subjects received the same dose of ADR, the increase of plasma ADR was higher in the male than in the female subjects. This can not be ascribed to an effect of age since both groups had a similar age and in addition it has recently been demonstrated that age has no effect on the plasma clearance of ADR (11). The most obvious explanation might be that HT men have a lower clearance of ADR from the circulation than HT women. However, no definite conclusion concerning a possible difference in plasma clearance of ADR between men and women is allowed. For the study of basal plasma ADR kinetics a radiotracer infusion with arterial plasma ADR sampling is necessary since there is a considerable extraction of ADR from the plasma by peripheral tissues.

Finally, the method of correcting the haemodynamic responses by the increment of plasma ADR deserves discussion. It may be questioned whether it is appropriate to correct the haemodynamic responses by the venous plasma ADR level, since it is the arterial plasma ADR level to which the tissue is exposed. However, venous and arterial plasma ADR levels are closely correlated both at rest (12) and during ADR infusion (13). Nevertheless, it remains possible that differences in plasma ADR clearance between NT and HT subjects might have confounded our results.

In conclusion, during ADR infusion HT males showed a larger decrease of diastolic BP and FVR and a larger increase of the HR per nmol increment of plasma ADR during ADR infusion than NT males. This difference was not apparent in females. It remains to be elucidated whether this is due to a higher beta-2-adrenoceptor sensitivity or density, or whether this has to be ascribed to the structurally altered vascular wall. Finally both NT and HT females disclosed a more pronounced rise of HR than males.

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CHAPTER 11

THE COLD PRESSOR TEST

THE COLD PRESSOR TEST

PHYSIOLOGY

In this study we used a previously published (1) modified version of the classic cold pressor test (CPT) as initially described by Hines (2). In view of the fact that there is no difference between blood pressure (BP) responses to hand or foot immersion (3) and in order to permit measurements at both arms, immersing a foot was more feasible. In addition, the longer duration of the test gave the opportunity to perform more than one haemodynamic measurement.

Immersing one foot in an ice cold water bath elicits an instantaneous local and generalized vasoconstriction in the skin and the skeletal muscle (4). This is not only due to a direct effect of cold on the local skin vessels, but also to activated spinal cord and hypothalamic reflexes. The increased sympathetic neural activity to skin (5) and skeletal muscle (6) gives rise to an increase of total peripheral vascular resistance. This is probably not the only mechanism of the BP increase during local cold exposure since also an increase of cardiac output has been reported (7). However, the relative contribution of vascular resistance and cardiac output to the BP response remains disputed. Both systolic and diastolic BP increase during the CPT and reach a peak value in the first (8) or second (6) minute. This pressor response is strongly correlated with the increase of muscle sympathetic neural activity as measured by direct recording of sympathetic neural activity. It has been suggested that the pressor response of the CPT is an approximate index of sympathetic reactivity (6).

The CPT, carried out according to our protocol, also evokes a painful sensation which is maximal during the first minute of the test and thereafter tapers off due to cold habituation (9). It has been shown that this pain sensation is related to the BP increase (9) and to the heart rate (HR) increase, which is also apparent only during the first minute of the test (6). The small increment of HR is due to sympathetic stimulation of the heart since it can be suppressed by betablockade (6). Up to now it has not been clarified definitely whether the increase of sympathetic activity is caused by the cold or by the pain sensation. Habituation to recurrent exposure to cold decreases the pressor response to a cold pressor test as has been demonstrated in Eskimos (10).

The expected increase of plasma noradrenaline (NORADR) during cold ex-
posure is correlated with the increase of BP (11) and sympathetic
neural activity during cold exposure (6), but the magnitude of the
response varies from 20-240% (12,13). Nevertheless, the plasma NORADR
response during the CPT is not suitable for measuring sympathetic
neural activity since direct measurement of sympathetic activity de-
monstrated inconsistent quantitative responses of both parameters
(6). In contrast to plasma NORADR, plasma adrenaline (ADR) does not
increase or increases only slightly, during cold exposure (11,13).
After bilateral adrenalectomy, the pressor response to cold is un-
altered (14).

RESULTS

Circulatory measurements

No differences between age classes could be demonstrated for any of
the haemodynamic variables. The course of BP during and after cold ex-
posure was similar in normo (NT)- and hypertensives (HT), although the
BP level is higher in the HT's (figure 11-1). The peak increase of BP
of 10-15% was already reached in the first minute. The percentage
response of BP was not different between the two groups (figure 11-
2). After the waterbath, BP did not show an immediate fall as is the
case after exercise or mental arithmetic, but decreased gradually
(figure 11-1). HR increased similarly in both groups but this was only
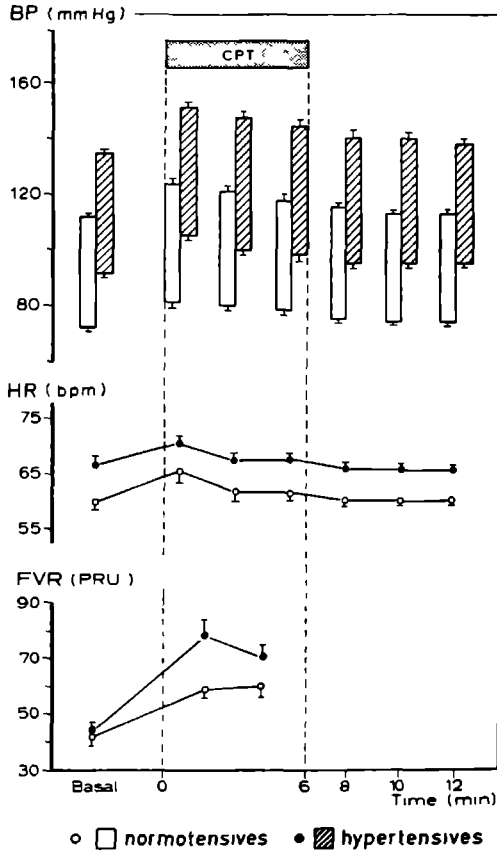apparent in the first minute of the test (figure 11-1).

Figure 11-1

The course of blood pressure (BP), heart rate (HR) and fore-arm vascular resistance (FVR) before, during and after the cold pressor test (CPT) in all normo- and hypertensive subjects (mean ± SE).

As expected, forearm blood flow decreased from 2.6±0.3 to 2.0±0.2 ml/100 ml.minute in the NT's and from 3.1±0.2 to 2.1±0.1 ml/100 ml.minute in the HT's. The resultant increase of FVR in both groups was not significantly different (figure 11-1).
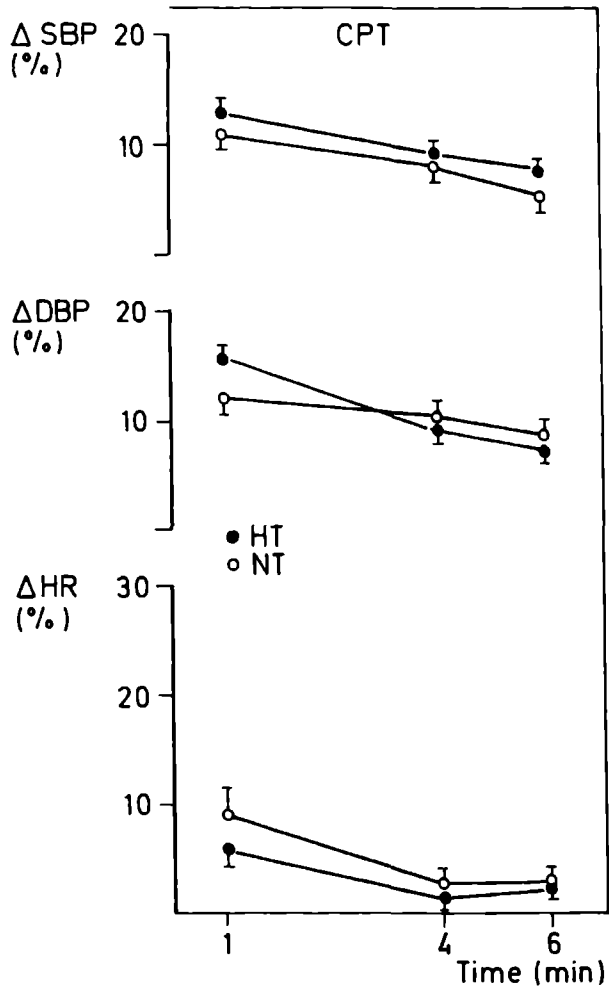
Figure 11-2

The percentage change of systolic (SBP), diastolic (DBP) blood pressure and heart rate (HR) during the cold pressor test in all normo (NT)- and hypertensive (HT) subjects (mean ± SE).

Plasma catecholamines

Plasma NORADR increased from 1.65+0.11 to 2.30+0.17 nmol/l in the NT's (p<0.001) and from 1.73+0.14 to 2.29+0.16 nmol/l (p<0.001) in the HT's. The plasma NORADR response was not different between the NT and HT groups, which also applied to every age/sex class (table 11-1). In the youngest NT males, the plasma NORADR response was larger than in the youngest NT females (table 11-1). The very small plasma ADR responses were similar in NT and HT subjects (table 11-1).

Plasma catecholamine responses were neither correlated with age nor with the circulatory responses.

Table 11-1

The changes of plasma catecholamines during the cold pressor test in normotensives (NT) and hypertensives (HT) according to sex/age class (mean + SE).

	Δ plasma adrenaline (nmol/l)		Δ plasma noradrenaline (nmol/l)	
	NT	HT	NT	HT
All subjects	0.04 + 0.02	0.01 + 0.01	0.65 + 0.13	0.56 + 0.09
20-29 years				
-males	0.13 + 0.08	0.01 + 0.02	1.09 + 0.21 *	0.65 + 0.18
-females	0.01 + 0.01	-0.05 + 0.05	0.34 + 0.10	0.51 + 0.13
30-39 years				
-males	0.01 + 0.07	0.00 + 0.01	1.06 + 0.46	0.70 + 0.13
-females	0.03 + 0.01	0.02 + 0.02	0.42 + 0.17	0.90 + 0.40
40-55 years				
-males	0.06 + 0.05	0.02 + 0.01	0.61 + 0.17	0.51 + 0.12
-females	0.02 + 0.01	0.03 + 0.02	0.18 + 0.25	-0.05 + 0.28

*p<0.05

DISCUSSION

The maximal BP response in the first minute in the NT's is clearly lower than reported in previous studies (6,11). This can not be explained by BP measurement technique or by the used limb (3,7). Our data correspond fairly well with the non- or hyporeactors in the original study of Hines (2), suggesting that our NT group was mainly composed of so-called hyporeactors. However, also the HT's showed less response than reported in literature (2,15,16). Nevertheless, the principal finding that HT's show a BP response not significantly different from that in NT's, supports similar findings in earlier studies (table 11-2).

Table 11-2

Literature review of the results of a <u>cold pressor test</u> in hypertensive subjects.

Author	(year)	Reference	Number subjects		NT - HT Difference of BP response
			NT	HT	
Greene	(1965)	16	10	10	NS
Robertson	(1979)	19	10	9	NS
Bolli	(1981)	20	15	16	NS
Eliasson	(1983)	15	7	42	NS
Frederikson	(1985)	21	14	14	NS
Lenders	(1988)		41	70	NS

NT = normotensives   NS = not significant

HT = hypertensives

So, BP reactivity to cold exposure is not increased in the HT's and as derived from a recent study (6), this should imply a normal sympathet-

ic response to the aspecific cold stimulus in HT subjects. This is corroborated by the similar increase of FVR and the similar increase of plasma NORADR in the NT and HT group. In contrast to a previous study (11) we could not demonstrate a correlation between the pressor response and plasma NORADR response.

The plasma NORADR response as derived from literature data widely varies widely from 20-240%. This is difficult to explain since neither the used water temperature, duration of immersion, the used limb nor sample size of the studies can be blamed. Since the earliest studies (12,17) showed the largest plasma NORADR responses in contrast to the more recent ones (13,18), it may be possible that the method of the catecholamine assay is responsible for the wide variation of the plasma NORADR responses. Our result of an increase of plasma NORADR of 35-40% concurs with the more recent studies.

Since the small increment of HR in the first minute is due to the increased sympathetic activity to the heart as a result of arousal and/ or pain (6), the similar HR response together with the similar plasma ADR response, suggest that arousal and/or pain is not enhanced in the HT's when exposed to cold stress.

In conclusion, subjects with mild essential hypertension have a normal pressor response to acute local cold exposure as is the case in the CPT. Together with the normal increase of forearm vascular resistance and the normal increase of plasma NORADR, these data extend the previously demonstrated normal sympathetic neural reactivity to cold exposure in smaller groups of patients with essential hypertension.

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HAEMODYNAMIC REACTIVITY TO ADRENERGIC STIMULATION
IN ADRENALECTOMISED WOMEN

HAEMODYNAMIC REACTIVITY TO ADRENERGIC STIMULATION IN ADRENALECTOMISED
WOMEN

INTRODUCTION

Circulating adrenaline (ADR) secreted from the adrenal medulla is in-
volved in the sympathetic response to various kinds of physical and
emotional stress (1). However, absence of circulating ADR after bi-
lateral adrenalectomy is apparently well tolerated well and compatible
with normal life. Nevertheless, ADR probably has a physiological role
in the control of sympathetic nerve activity. By a stimulatory effect
on presynaptic beta-adrenergic receptors, ADR can facilitate the re-
lease of noradrenaline (NORADR) from sympathetic nerve endings (2,3).
In addition, increased plasma ADR levels have been found in some groups
of hypertensive patients (4) and it was subsequently hypothesised that
ADR might play a pathogenetic role in the development of essential
hypertension (5). If the presynaptic stimulatory effect of ADR is
indeed operative in man, the cardiovascular and plasma NORADR responses
to various kinds of sympathetic stimulation should be attenuated in
adrenalectomised subjects who have no measurable circulating ADR. We
tested this hypothesis by comparing the blood pressure, heart rate,
forearm vascular resistance and plasma catecholamine responses to
mental arithmetic, head-up tilt and cold exposure in adrenalectomised
women and in a control group of normal women.

SUBJECTS AND METHODS

Subjects

Ten adrenalectomised females participated in this study on a voluntary
basis after giving informed consent (table 12-1). All women had under-
gone bilateral adrenalectomy because of Cushing's disease 1-18 years
prior to the study (mean $\pm$ SD: 6.5 $\pm$ 4.9 years). All subjects used a
glucocorticoid and 9-alpha-fluorocortisol at the time of the study. Ten
normotensive age-matched females served as a control group (table 12-
1). The normal women were recruited by means of a newspaper announce-
ment and were not familiar with any investigational procedure. All had
a normal physical examination, normal renal function and a normal ECG.
The study protocol was approved by the hospital ethical committee.

Table 12-1

Clinical characteristics (mean $\pm$ SD) of the adrenalectomised and normal women.

	ADRENALECTOMISED	CONTROLS
Subjects (N)	10	10
Age (yrs)	38.2+10.4	37.0+11.1
Body mass index (kg/m^2)	24.3+4.7	23.2+ 1.9
Systolic blood pressure (mm Hg)	115+22	110+9
Diastolic blood pressure (mm Hg)	80+16 *	68+6
Heart rate (beats/min)	72+9	64+8
24 hour urinary sodium excretion (mmol/mmol creatinine)	11+5	12+5

*p<0.05

Study protocol

Both groups underwent 3 standardized stress tests always in the same sequence: a mental arithmetic test, a head-up tilt and a cold pressor test. All tests were carried out as described in chapter 2. The adrenalectomised women took their medication before breakfast. A 24-hour urine was collected on the day prior to the experimental day to estimate sodium intake.

DATA ANALYSIS

The haemodynamic results in the adrenalectomised and normal women were analysed with the Student's two sample t-test. The plasma catecholamine responses in the two groups were analysed using Wilcoxon's two sample test and the results were considered to be statistically significant if $p<0.05$ (two-sided). Correlation coefficients were calculated according to the non-parametric Spearman's rank correlation test.

RESULTS

Baseline measurements. The adrenalectomised women had a significantly higher mean diastolic BP than the controls (table 12-1). There was no difference between both groups with regard to systolic BP, HR and body mass index. The FBF was slightly but not significantly lower in the adrenalectomised (2.0 ml/100 ml.min) than in the controls (3.7 ml/100 ml.min). The mean baseline plasma NORADR levels were similar but as expected the plasma ADR levels were consistently below the level of detection in all adrenalectomised women (table 12-2). There was no correlation between the baseline plasma NORADR level and the baseline FBF or FVR values in either group.

Mental arithmetic. During MA blood pressure rose in both groups to the same extent (figure 12-1). However, the HR response was significantly smaller in the adrenalectomised women than in the normal women. In the normal women the increase in HR correlated with the increase in systolic (r:0.75 p<0.05) and diastolic (r:0.66 p<0.05) BP and with the decrease of FVR (r:-0.75 p<0.05). In the adrenalectomised women no such correlations were found. The FBF increased by 1.4 ± 0.5 (SE) ml/100 ml.min. in the normal and 0.6 ± 0.2 (SE) ml/100 ml.min. in the adrenalectomised women. This difference was not significant. The decrease in FVR was similar in the two groups (normal -10 ± 3 (SE) PRU's, adrenalectomised -7 ± 4 (SE) PRU's). Plasma NORADR levels did not change during MA in either group. Plasma ADR rose in the normal women and remained undetectable in the adrenalectomised women (Table 12-2).

Table 12-2

Plasma adrenaline and noradrenaline levels (nmol/l) before and at the end of the tests and the percentage changes of plasma noradrenaline during each test (mean $\pm$ SE).

PLASMA ADRENALINE		BEFORE	END	
Mental arithmetic				
	AEX	< 0.05	< 0.05	
	controls	0.09+0.01	0.12+0.01	
Head-up tilt				
	AEX	< 0.05	< 0.05	
	controls	0.08+0.01	0.13+0.02	
Cold pressor test				
	AEX	< 0.05	< 0.05	
	controls	0.08+0.01	0.11+0.01	
PLASMA NORADRENALINE				Δ (%)
Mental arithmetic				
	AEX	1.48+0.17	1.49+0.21	4.1+11.9
	controls	1.61+0.23	1.46+0.20	-9.1+4.5
Head-up tilt				
	AEX	1.47+0.16	2.77+0.41	84.6+11.1**
	controls	1.49+0.20	2.35+0.25	60.0+2.7**
Cold pressor test				
	AEX	1.52+0.22	2.12+0.30	36.9+9.5*
	controls	1.49+0.26	1.82+0.26	31.5+12.0**

AEX = adrenalectomised women

* $p<0.05$
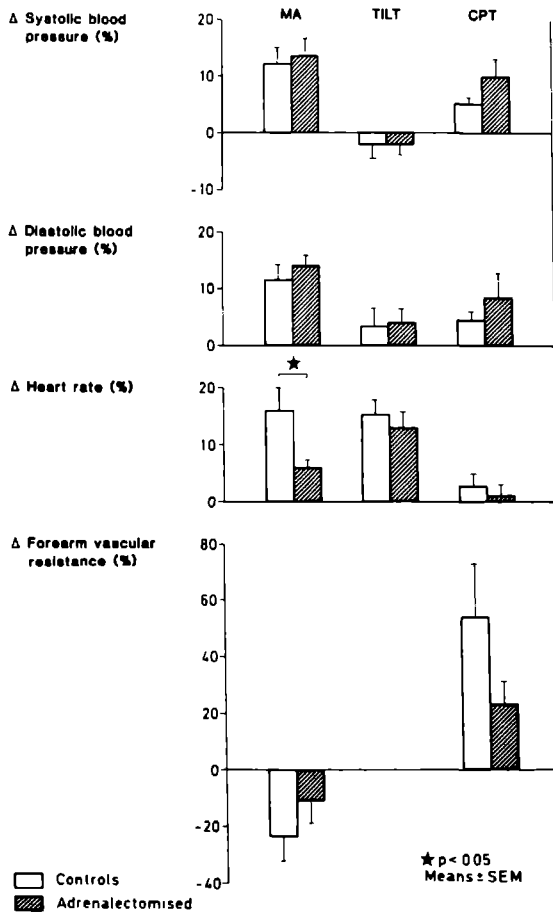** $p<0.01$ as compared to before the test

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Figure 12-1

The mean percentage changes of blood pressure, heart rate and forearm vascular resistance during mental arithmetic (MA), head-up tilt (Tilt) and cold pressor test (CPT) in 10 normal and in 10 adrenalectomised women.

Head-up-tilt. Tilting had no significant effect on BP in either group but HR increased significantly in both groups to a similar extent (figure 12-1). The adrenalectomised women had a rise of plasma NORADR similar to that in the normal women but plasma ADR remained undetectable (table 12-2).

Cold pressor test. Exposure to cold elicited a similarly small but significant increment of BP in both groups (figure 12-1). HR did not change in either group. The rise of FVR was slightly, but not significantly, less in the adrenalectomised as compared to the normal women (controls 15+4 PRUs, adrenalectomised 8+4 PRUs). Plasma NORADR increased to the same degree in both groups (table 12-2) and plasma ADR could not be detected during cold exposure in the adrenalectomised patients.

DISCUSSION

The main purpose of our study was to determine the role of plasma ADR in cardiovascular reactivity during different kinds of sympathoadrenal stimulation. Since virtually all plasma ADR is secreted from the adrenals, adrenalectomised subjects are an appropriate model for studying the effect of several kinds of sympathoadrenal stimulation on cardiovascular reactivity. Indeed, in contrast to the normal women, no one of the adrenalectomised group had detectable levels of plasma ADR, neither at rest nor during adrenergic stimulation. Nevertheless, since the lower limit of detection in our assay is 0.05 nmol/l, minute amounts of ADR might have been present. In fact, two previous studies (6,7) demonstrated very low basal plasma ADR levels and small increments of plasma ADR during hypoglycaemia and submaximal dynamic exercise in adrenalectomised subjects. However, the stimulated plasma ADR levels were not high enough to elicit haemodynamic effects (8).

We used several kinds of adrenergic stimulation because these differ in some respects concerning the evoked reaction patterns. Mental stress elicits an increase of blood pressure, heart rate and plasma ADR but vascular resistance is reduced as is confirmed in our normal women. However, muscle sympathetic activity and plasma NORADR do not increase. In contrast, to maintain blood pressure, head-up tilt evokes generalized vasoconstriction by an increase of sympathoadrenal activity as is demonstrated by the increase of both plasma catecholamines in the

controls. Cold exposure is also a strong stimulus to muscle sympathetic nerve activity leading to a pressor and plasma NORADR response but no significant heart rate response, as was the case in our control group.

Although bilateral adrenalectomy has been widely used as treatment for patients with Cushing's disease, the physiological consequences of a nearly complete lack of circulating ADR regarding cardiovascular homeostasis during physical and mental stress has scarcely been studied. In experiments in dogs, blunted pressor responses to exogenous catecholamines have been demonstrated after acute bilateral adrenalectomy (9). In spontaneous hypertensive rats the pressor response to sympathetic nerve stimulation was attenuated after bilateral adrenal demedullation which could be restored by infusion of ADR (10). In contrast to these animal experiments, we demonstrated normal responses of blood pressure and plasma NORADR to adrenergic stimulation in adrenalectomised females. The only significant finding was a smaller increase of heart rate in the adrenalectomised subjects during mental stress. As previously reported, plasma NORADR also showed a normal increase during moderate exercise (7) and standing (6) in adrenalectomised subjects.

How can the normal pressor responses be explained? First, the possibility that the facilitating role of ADR on NORADR release by direct stimulation of presynaptic beta-adrenoceptors has no physiological relevance at all during periods of recurrent stress in every day life should be considered. Although the venous plasma NORADR level does not only reflect the release of neuronal NORADR (4,11), both the normal plasma NORADR levels at rest and the increase of venous plasma NORADR do not conflict with this possibility. Our results support a report of Eliasson et al (12) that ADR plays no role in the haemodynamic response to mental stress. Second, except for the fact that it has been well established that ADR has a facilitating effect on NORADR release by direct stimulation of presynaptic beta-adrenoceptors both in isolated tissues and in vivo, ADR is also incorporated in the terminal nerve endings and is subsequently released as co-transmitter with NORADR in the synaptic cleft where it facilitates the NORADR release again (3). As a result of this co-transmitter mechanism and because ADR had a very short half-life in plasma of about 2 minutes and of about 4 hours in sympathetically innervated tissues (3), it can not be excluded that very minute amounts of circulating ADR, which can not be detected by

our assay, might still facilitate the NORADR release. Thus it may be that it is not the quantity of circulating ADR that is the major determinant of the pressor response to stress but the amount of ADR incorporated in the sympathetic nerve endings. Third, very low or even absent plasma ADR levels result in up-regulation of beta-adrenoceptors (13), thus maintaining haemodynamic reactivity during stressful situations. Finally, the interplay of substitution therapy with gluco- and mineralocorticosteroids with the results of our study has to be considered. Glucocorticoids play an important role in the biosynthesis of ADR in the adrenal medulla (14). Both glucocorticosteroids (15) and mineralocorticoids (16) suppress plasma NORADR levels either by the subsequent volume expansion, or by inhibition of release of NORADR from terminal nerve endings or by suppression of adrenocorticotrophic hormone (ACTH) or corticotropinreleasing (CRF) hormone secretion. Furthermore, glucocorticosteroids may alter adrenergic receptor density and function (17). Administration of glucocorticosteroids and mineralocorticosteroids to normal subjects causes an enhanced vascular reactivity to ADR and NORADR (18) and a lack of glucocorticosteroids gives rise to blunted responses to catecholamines in most tissues (19). Since we did not investigate the effects of adrenergic stimulation in adrenalectomised subjects without substitution therapy, we can not precisely define the influence of substitution therapy on our results. Nevertheless we could not demonstrate an enhanced vascular reactivity nor did we find suppressed plasma NORADR levels.

How should the smaller increase of HR during mental stress in the adrenalectomised group be interpreted? It is tempting to speculate that the lack of circulating ADR resulted in this smaller HR response. However, there was no correlation between the increase of HR and plasma ADR increase in the normal women. In addition, in a previous study (12) no causal relationship was found between the HR and plasma ADR responses during mental stress. Nevertheless, the smaller HR response in the adrenalectomised women suggests that circulating ADR contributes to the HR response during mental stress in non-adrenalectomised females.

From a methodological point of view several points deserve further discussion. First, age and sex can not have confounded the results of our study since the study subjects were sex- and age-matched. However, since sex is an important determinant of haemodynamic and plasma catecholamine responses to stress (20,21), our results can not be extrapo-

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lated to men. Finally, although it would be more appropriate to study
the same subjects before and after adrenalectomy instead of comparing
different groups, the confounding effect of the preexisting Cushing's
disease would make such a comparison impossible.

In conclusion, our results demonstrate that blood pressure respon-
ses to 3 different types of adrenergic stress were similar in adrenal-
ectomised and normal women. Only during mental stress did the adrenal-
ectomised women have a smaller increase of heart rate. The response of
plasma NORADR during head-up tilt and cold exposure was not impaired in
the adrenalectomised women. Despite some methodological limitations,
our results challenge the view that the presynaptic facilitating effect
of ADR on neuronal release of NORADR plays an important physiological
role in haemodynamic regulation during sympathetic stress.

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THE EFFECT OF BETA-ADRENOCEPTOR BLOCKADE ON HAEMODYNAMIC AND PLASMA CATECHOLAMINE REACTIVITY DURING ADRENERGIC STIMULATION

THE EFFECT OF BETA-ADRENOCEPTOR BLOCKADE ON HAEMODYNAMIC AND PLASMA
CATECHOLAMINE REACTIVITY DURING ADRENERGIC STIMULATION

INTRODUCTION

Beta-adrenoceptor antagonists, shortly referred to as betablockers,
still belong to the most frequently prescribed antihypertensive
agents. Although the hypotensive efficacy is similar for beta-1-
selective and non-selective betablockers, beta-1-selective beta-
blockers have been given preference because of the lack of unfavour-
able pressor responses during adrenaline-mediated stress situations
(1). However, during daily life stresses like mental arithmetic and
isometric exercise, this difference between the beta-1-selective and
non-selective betablockers did not emerge (2). The exact hypotensive
mechanism of betablockers has not definitely been resolved yet. The
haemodynamic response during long term betablockade with betablockers
without intrinsic sympaticomimetic activity (ISA) consists of a de-
crease in cardiac output, whereas systemic vascular resistance remains
largely unchanged (3). Thus, the increased systemic vascular resis-
tance, being the principal haemodynamic derangement in essential
hypertension, is not appreciably altered by treatment with beta-
blockers without ISA.

In the past, it has been tried to predict the hypotensive response to
betablocker therapy on the basis of plasma catecholamines at rest or
during exercise. It appeared to be impossible to predict the hypo-
tensive response from basal or exercise plasma catecholamines con-
sistently (4). Less is known about the value of the haemodynamic and
plasma catecholamine responses to other stress tests than exercise to
predict the hypotensive efficacy of betablocker therapy.

In an open study in a small group of 8 subjects with mild essential
hypertension, we investigated the haemodynamic and plasma catechola-
mine responses to 7 different stresses before and during treatment
with 50 mg atenolol once daily for a period of 6 months. In addition,
the predictive value of the haemodynamic and plasma catecholamine
responses to different stress tests for the chronic hypotensive
response to atenolol was investigated.

SUBJECTS AND METHODS

In 8 hypertensive subjects (6 men, 2 women) (age 34.8+7.5 years) all 7
tests were repeated after treatment with 50 mg atenolol for 6 months.
The mean blood pressure (BP) (+ SD) before treatment was 151+8/94+6 mm
Hg and the heart rate (HR) was 80+11 beats/minute. In these patients
the BP was measured with the Hawksley Random Zero Sphygmomanometer.
The tests were carried out as described in chapter 2. The latest dose
of atenolol was taken 1 hour before the start of the tests.
The given work load, both in the handgrip exercise and in the bicycle
exercise test, were identical before and during atenolol. The mean in-
fused dose of noradrenaline (NORADR) was 44+14 ng/kg/min and the dose
of adrenaline (ADR) was 30 ng/kg/min before and during atenolol.
For all haemodynamic variables, differences were tested using the
Student's t-test for paired observations; differences in plasma cate-
cholamines were tested with Wilcoxon's signed rank test. The level of
significance was set at 0.10/k per time point (k being the total
number of time points at which was measured during a test) to avoid
type I error. Correlation coefficients were calculated according to
Spearman. Means + SE are given unless indicated otherwise.

RESULTS

Baseline values
After 6 months of treatment with 50 mg atenolol once daily, the base-
line supine blood pressure (BP) had decreased from 151+3/94+2 to
128+3/79+3 mm Hg and the baseline heart rate (HR) from 80+4 to 63+4
beats/minute. Baseline plasma NORADR level was 1.44+0.23 before and
1.40+0.23 nmol/l during chronic treatment. Plasma ADR amounted to
0.11+0.02 and 0.09+0.02 nmol/l respectively. The decrease of the
supine systolic BP by atenolol was related to the baseline plasma ADR
(r=-0.80, p<0.05) but not to the baseline plasma NORADR level before
treatment. The fall of BP after 6 months treatment with atenolol was
not related to the baseline BP or HR.

The handgrip exercise test
Before the atenolol treatment the handgrip exercise (HG) resulted in
an increase of BP from 138+3/94+3 to 165+5/116+5 mm Hg in the last

minute of the test and the HR increased from 73±4 to 82±4 beats/ minute. During treatment BP rose from 126±5/83±3 to 149±8/102±3 mm Hg and the HR from 59±3 to 66±3 beats/minute. As shown in figure 13-1, the percentage increment of BP was similar before and during atenolol. The increment of HR was slightly attenuated during atenolol, particularly apparent in the first minute of the test (figure 13-1).

The increase of systolic BP in the last minute of the test before treatment was related to the decrease of the supine systolic BP by atenolol (r=-0.76, p<0.05).

The plasma catecholamine responses to HG exercise were not different before and during atenolol (table 13-1). The plasma catecholamine responses were not related to the chronic hypotensive effect of atenolol.

The mental arithmetic test

Before atenolol treatment, mental arithmetic (MA) resulted in a rise of BP from 134±4/94±4 to 158±6/104±5 mm Hg in the first minute of the test. HR increased from 73±3 to 85±4 beats/minute and forearm vascular resistance (FVR) decreased from 52±7 to 29±6 units. During treatment with atenolol for 6 months, BP rose from 120±4/83±2 to 136±5/95±2 mm Hg with a rise of HR from 59±2 to 65±3 beats/minute. FVR decreased from 41±6 to 25±3 units. If the percentage changes are considered, atenolol only attenuated the HR response (figure 13-1). The BP and FVR responses were similar before and during atenolol. The haemodynamic responses to MA before treatment were not related to the hypotensive response to treatment with atenolol.

The plasma catecholamine responses were not different before and during atenolol (table 13-1) and were not related to the hypotensive response by atenolol at 6 months.

The cold pressor test

Before atenolol, BP rose from 143±4/98±3 to 155±6/107±4 mm Hg in the first minute of the water bath. The HR did not change: 72±4 and 73±4 beats/minute. FVR increased strongly from 55±8 to 91±19 units. During atenolol, BP rose from 129±5/87±2 to 146±9/97±3 mm Hg. Again the HR did not change. FVR increased from 42±4 to 74±10 units. There were no differences in the percentage haemodynamic responses to cold exposure before and during atenolol (figure 13-1). So, atenolol did not change
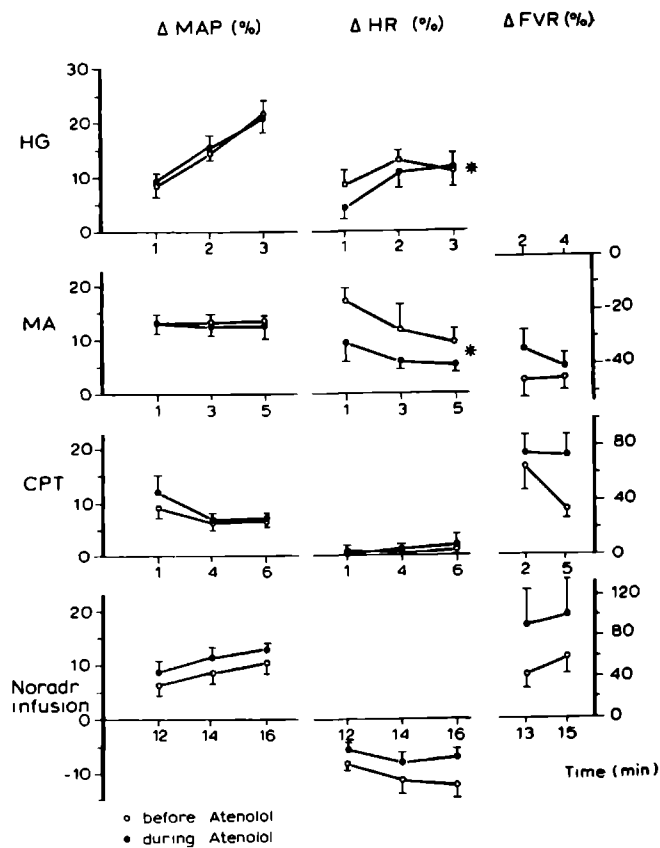
Figure 13-1

The percentage changes of mean arterial pressure (MAP), heart rate (HR) and forearm vascular resistance (FVR) before and during atenolol for the handgrip exercise (HG), mental arithmetic (MA), cold pressor test (CPT) and noradrenaline infusion (Noradr). Mean ± SE are given. For the time points of each test is referred to chapter 2.

*: curves differ significantly

Table 13-1

The plasma catecholamine levels before and at the end of each test, before and during atenolol (mean $\pm$ SE are given).

	plasma adrenaline (nmol/l)		plasma noradrenaline (nmol/l)	
	before atenolol	during atenolol	before atenolol	during atenolol
Handgrip				
-before	0.11+0.02	0.09+0.02	1.44+0.23	1.40+0.23
-end	0.17+0.02	0.18+0.04	1.69+0.31	1.79+0.29
Mental arithm				
-before	0.09+0.02	0.08+0.01	1.59+0.23	1.45+0.30
-end	0.17+0.02	0.15+0.02	1.47+0.21	1.47+0.25
Cold pressor test				
-before	0.14+0.01	0.11+0.02	1.97+0.37	1.79+0.27
-end	0.14+0.01	0.11+0.02	2.65+0.36	2.33+0.35
Noradrenaline infusion				
-before	0.13+0.03	0.09+0.02	1.68+0.31	1.42+0.20
-end	0.08+0.01	0.09+0.01	2.78+0.26	3.11+0.39
Adrenaline infusion				
-before	0.09+0.01	0.09+0.01	1.65+0.41	1.66+0.25
-end	1.09+0.16	1.10+0.25	2.26+0.42	2.06+0.31
Bicycle exercise				
-before	0.20+0.01	0.20+0.05	3.79+0.48	4.22+0.35
-end	0.72+0.15	0.80+0.20	9.93+1.01	10.23+1.02
Head-up tilt				
-before	0.10+0.02	0.10+0.02	1.60+0.22	1.60+0.31
-end	0.18+0.04	0.17+0.03	3.07+0.32	2.87+0.35

the haemodynamic responses to cold exposure. Also, the plasma NORADR response was unaltered by atenolol whereas the plasma ADR did not change both before and during atenolol (table 13-1).

The increase of the systolic BP during cold exposure before treatment was related to the decrease of the systolic BP by atenolol treatment (r=-0.79, p<0.05), but this was only the case in the fourth minute of the cold pressure test. The plasma NORADR response to cold was not related to the long-term hypotensive effect of atenolol.

The noradrenaline infusion

Before atenolol, BP rose from 137+5/92+2 to 151+6/101+3 mm Hg, the HR decreased from 74+5 to 65+4 beats/minute and FVR increased from 41+7 to 60+9 units during NORADR infusion. During atenolol, BP increased from 123+5/80+2 to 135+6/92+3 mm Hg and HR decreased from 57+2 to 53+2 beats/minute. FVR increased from 27+6 to 49+8 units. There was no significant difference in the percentage haemodynamic responses before and during atenolol (figure 13-1). The plasma NORADR response was not significantly altered by treatment with atenolol (table 13-1). The haemodynamic responses to the NORADR infusion before treatment were not related to the hypotensive effect of atenolol after 6 months of treatment.

The adrenaline infusion

Before atenolol, ADR infusion resulted in a decrease of diastolic BP from 95+3 to 85+3 mm Hg whereas the sytolic BP did not significantly change. The HR increased from 70+4 to 85+4 beats/minute and the FVR fell from 52+9 to 37+6 units. During atenolol, both systolic and diastolic BP did not significantly change during ADR infusion but the HR increased from 58+2 to 66+3 beats/minute. The FVR decreased from 39+6 to 28+6 units. The decrease of diastolic BP nearly disappeared and the HR increment was attenuated during atenolol (figure 13-2). The increase of plasma ADR during infusion was similar during atenolol treatment (table 13-1). The haemodynamic responses to the ADR infusion before treatment were not related to the chronic hypotensive effect of atenolol.
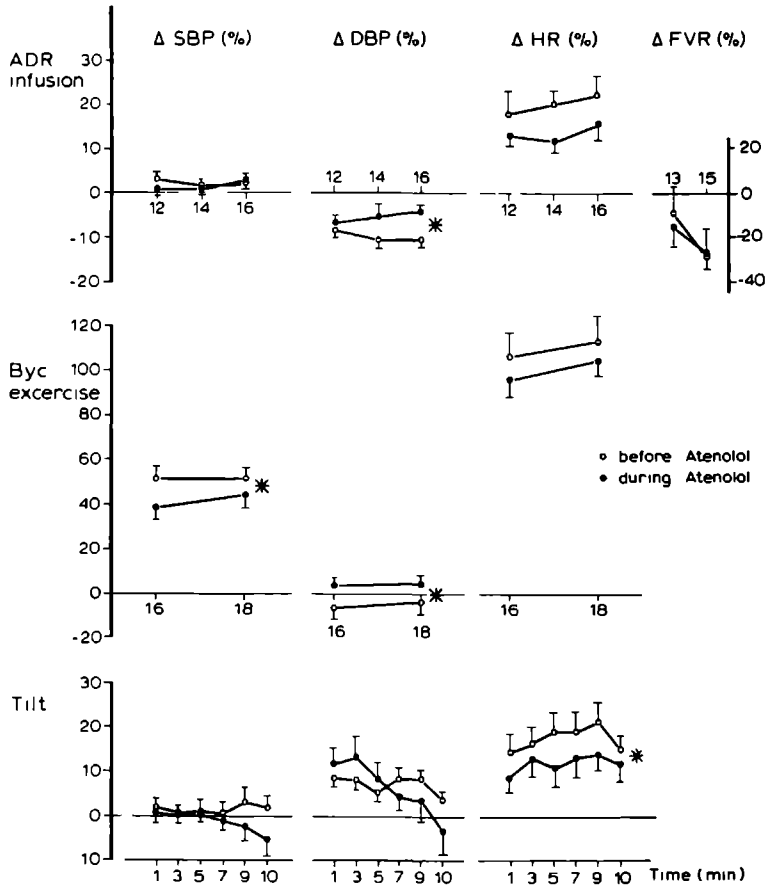
Figure 13-2

The percentage changes of systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and forearm vascular resistance (FVR) before and during atenolol for the adrenaline (ADR) infusion, bicycle exercise (BYC) and head-up tilt (Tilt) (mean $\pm$ SE and given). For the time points is referred to chapter 2.

*: curves differ significantly

The bicycle exercise test

Before atenolol, bicycle exercise (BYC) increased BP from 149+4/97+4
to 224+5/92+5 mm Hg and the HR from 82+4 to 169+6 beats/minute. During
atenolol, BP increased from 133+3/85+2 mm Hg to 191+7/87+3 mm Hg. The
percentage increment of the systolic BP was lower and the small de-
crease of diastolic BP had disappeared during atenolol (figure 13-2).
No relation between the haemodynamic or plasma catecholamine responses
to BYC exercise test before treatment and the hypotensive effect of 6
months atenolol treatment could be established. The increments of both
plasma catecholamines were not significantly altered by atenolol
(table 13-1). Before atenolol, blood lactate increased from 0.91+0.06
to 3.36+0.42 mmol/l and during atenolol from 0.95+ 0.12 to 3.25+0.48
mmol/l.

The head-up tilt test

Systolic BP did not significantly change both before and during ateno-
lol. Before atenolol, the diastolic BP significantly increased from
100+3 to 108+4 mm Hg and the HR from 68+4 to 81+4 beats/minute. During
atenolol, the diastolic BP increased from 87+3 to 97+3 mm Hg in the
third minute of the test, but thereafter the diastolic BP was not sig-
nificantly different from the baseline BP anymore (figure 13-2). The
HR significantly rose from 57+3 to 64+3 beats/minute but this increase
was significantly smaller than before atenolol. The increment of
diastolic BP during tilt before treatment was related to the decrease
of diastolic BP in the upright position after 6 months atenolol treat-
ment, but it was significant only for the third and fifth minute of
the tilt test (r=-0.84, p<0.01). The rise of both plasma catechol-
amines was not different before and during atenolol (table 13-1) and
the plasma catecholamine response to head-up tilt before atenolol was
not related to the long-term hypotensive effect of atenolol.

DISCUSSION

In this study, in a small group of mildly hypertensives, baseline BP
fell with about 20/15 mm Hg during prolonged treatment with the beta-
1-selective adrenoceptor blocking drug atenolol in a dose that is com-
monly used in the treatment of hypertension. This is in agreement with

previous placebo controlled studies (5). The basal plasma catecholamine levels were unaltered during atenolol treatment which is in accordance with some (6,7) but not all (8) earlier observations.
The inhibition of exercise-induced tachycardia of about 25% demonstrates adequate betablockade. Although desirable from a methodological point of view, obviously, for ethical reasons it was not feasible to include a placebo period of 6 months because hypertensive patients can not be left untreated for such a long time. However, haemodynamics and plasma catecholamines were monitored by methods minimizing observer bias.

As expected, during atenolol treatment, the attained BP and HR levels during each stress test were lower than those without treatment owing to the lower basal levels during atenolol. This is an important difference with other antihypertensive drugs like thiazide diuretics. Indeed, diuretic therapy decreases basal blood pressure equally as betablockers but the blood pressure and heart rate levels that are attained during stress testing are clearly less affected by thiazide diuretics than by betablockers (9).
We could not establish a relation between the basal plasma NORADR level and the chronic hypotensive effect of atenolol and this is in accordance with other reports (4,7). However, Myers et al (6) demonstrated that hypernoradrenergic subjects showed a larger fall of blood pressure during atenolol treatment than normoadrenergic subjects. Also for metoprolol, Eliasson et al (9) could establish a moderate correlation between the basal plasma NORADR level and the fall of systolic blood pressure. The weak correlation between basal plasma ADR level and the hypotensive response to atenolol is not confirmed by 2 previous studies (7,9) but other beta-1-selective betablockers were used. It is likely that these contradicting results must be ascribed to patient selection and methodological differences.

Handgrip exercise
The unaltered BP response during HG exercise during atenolol treatment confirms the results of previous studies with beta-1-selective and non-selective betablockers (2,10,11). The slightly blunted HR response, although particularly apparent in the first minute of the test, is in agreement with earlier work (2,11). Dreslinsky et al (10)

could not establish a lower HR response but they measured only in the last minute of the test. Since the BP increase during HG exercise is due to an increase of HR and cardiac output, one should expect a lower BP response during atenolol. It has been demonstrated, however, that the unaltered BP response during betablockade is due to a compensatory increase of peripheral vascular resistance (12).

The correlation between the systolic BP increment to HG exercise and the decrease of the supine systolic BP during atenolol treatment has also been reported for metoprolol although this was only apparent for the diastolic BP (13). It remains doubtful whether these inconsistent results are of any relevance in predicting the chronic hypotensive response to a betablocker for an individual subject.

Mental Arithmetic

In view of the blunted HR response during the MA test by betablockade in our study and in other studies (2,9,14), one should also expect an attenuation of the BP response to MA. However, the BP response in the MA test during betablockade is unchanged which is in agreement with previous studies (2,9,14). This may be explained by the recent observation that the BP response to MA during betablockade is preserved by an increase of peripheral vascular resistance (15). However, the nearly similar decrease of forearm vascular resistance in our study does not support this possibility.

No consistent relation between the haemodynamic or plasma catecholamine responses to MA before treatment and the chronic hypotensive effect of atenolol was established.

Cold pressor test

Both the BP and the plasma catecholamine responses to cold remained unchanged during atenolol. Similar findings for metoprolol treatment were recently described (9).

Although the increase of systolic BP during cold was related to the decrease of the systolic BP during atenolol, this was not a consistent relation which was operative at all time points of the test. Thus, it is unlikely that this finding bears any clinical relevance.

The noradrenaline infusion

The unaltered haemodynamic responses to NORADR infusion during ateno-

lol treatment confirms one previous study (16) in hypertensives who were treated with propranolol. In contrast, another study reported potentiation of BP responses to noradrenaline by betablockade. However, that study was carried out in NT's and two different nonselective betablockers were used (17).

The unchanged increment of plasma NORADR during NORADR infusion suggests that long term betablockade with atenolol does not influence the NORADR clearance. However, an earlier study with propranolol demonstrated a reduced clearance of NORADR (18).

The adrenaline infusion

Even at a low dose, infused ADR causes a beta-2-adrenoceptor mediated decrease of diastolic BP and of vascular resistance (19). Despite the fact that the plasma ADR increase during infusion was unchanged during atenolol, the decrease of diastolic BP during ADR infusion was almost completely reduced. Similar findings have recently been reported in normotensives but in that study the betablockers were given intravenously (20). Although the unaltered decrease of forearm vascular resistance provides evidence that atenolol has no appreciable vascular beta-2-blockade.

A possible explanation for the abolished decrease of diastolic BP during atenolol may be that the diminished beta-1-adrenoceptor mediated increase of cardiac output during ADR infusion elicits a reflex mediated vasoconstriction in other than the forearm vascular bed. It can be questioned whether this reduced fall in diastolic BP during adrenaline infusion and betablockade is of any clinical relevance. However, in view of the fact that adrenaline levels as during infusion are also attained during various kinds of daily life stress (21), even beta-1-selective betablockade may have unwanted circulatory effects during daily life stress.

The bicycle exercise test

Although the effect of betablockade on the systolic BP response during exercise has frequently been studied, little is known about the exercise diastolic BP during long term betablockade. With a regular cuff sphygmomanometer it is hardly possible to measure diastolic BP adequately during exercise. The automated exercise BP monitor as used in this study is considered superior to mercury manometers with regard to

the diastolic BP measurement during dynamic exercise (22).

During atenolol treatment the small decrease of diastolic BP during exercise completely disappeared. Similar findings were reported by McLeod et al (23), but they could not be confirmed by another uncontrolled study (24). Although the skeletal muscle vessels possess beta-2-adrenoceptors, the decrease of diastolic BP and the vasodilation during exercise are largely caused by direct acting local metabolites (25). So, one should expect that betablockade does not interfere with the increase of blood flow to the exercising muscles. Another explanation for the disappearance of the fall in exercise diastolic BP during atenolol might be a compensatory vasoconstriction in the non-exercising muscles or in the splanchnic vascular bed. However, during treatment with metoprolol Svensson et al (26) could not establish a larger increment of forearm vascular resistance during leg exercise. Finally, the similar response of plasma catecholamines to exercise rules out a possible role of circulating catecholamines on the diastolic BP response during exercise.

So, the diminished decrease of total peripheral resistance during dynamic exercise, which is already apparent in untreated hypertensives (27) as compared to normotensives, may be amplified by therapy with a low dose of atenolol.

In contrast to Distler et al (8) we were unable to establish a correlation between the plasma NORADR response during exercise and the chronic hypotensive effect of atenolol. This difference cannot only be ascribed to the stimulus intensity as suggested by Birkenhäger and De Leeuw (4) because the HR and plasma NORADR responses in our study were at least as high as in that of Distler et al (8).

The head-up tilt test

As expected, atenolol did not affect the BP or plasma catecholamine responses during tilt. The HR response was lower than before therapy which confirms a similar study by Dreslinski et al (10), although the dose of atenolol was higher in the latter study.

It remains open to speculation whether the significant correlation between the increment of diastolic BP in the third and fifth minute of the tilt test before therapy and the decrease of the standing diastolic BP by atenolol after 6 months treatment is of any clinical significance. We are unaware of previous studies reporting a predict-

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ive value of the haemodynamic response to tilt for the hypotensive
effect of long term betablockade.

In summary, long-term treatment with the beta-1-selective betablocker
atenolol reduced blood pressure and heart rate levels both at rest and
during all stress tests. The blood pressure responses to handgrip
exercise, mental arithmetic, cold pressor test, head-up tilt and nor-
adrenaline infusion were not altered by atenolol. In contrast, the
heart rate responses to stress testing were clearly attenuated. The
decrease of diastolic blood pressure during bicycle exercise and adre-
naline infusion was significantly attenuated by even this low dose of
atenolol and it can be speculated whether this implies an increased
afterload during daily life stress.
In accordance with most literature data, we were unable to demonstrate
a relation between the baseline plasma noradrenaline level or the
plasma catecholamine response to several stress tests and the anti-
hypertensive efficacy of 6 months treatment with atenolol. Only the
basal plasma adrenaline may have some predictive value for the hypo-
tensive effect of atenolol, but the clinical significance of this
finding remains to be confirmed. Despite the fact that there were some
moderate correlations between a haemodynamic response to a stress test
and the chronic hypotensive effect of atenolol, these inconsistent
results render it unlikely that it is feasible to predict the blood
pressure lowering effect of atenolol for a given subject from the
haemodynamic response to a stress test as performed in this study.

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CHAPTER 14

SUMMARY/CONCLUSIONS

GENERAL DISCUSSION AND CONCLUSIONS

In the past, many attempts have been made to prove that the sympathet-
ic nervous system is involved in the pathogenesis of essential hyper-
tension. Evidence for a pathogenetic role of the sympathetic nervous
system has been obtained from studies both in animal and in human
hypertension (1). However, it is uncertain whether the various esta-
blished abnormalities of the sympathetic nervous system are causally
related to the development of essential hypertension in man. In addi-
tion there is still disagreement concerning the principal site of the
derangement within the sympathetic nervous system (1). Methodological
difficulties with a reliable assessment of an abnormal sympathetic
activity is probably the most important factor that hampers unequi-
vocal conclusions.
Although sympathetic nervous system activity can be assessed by direct
microneurography of the peroneal muscle nerve fascicle (2), muscle
sympathetic nerve activity is not representative for the overall sym-
pathetic nerve activity since sympathetic outflow to regional vascular
beds is not uniform. An alternative approach to the assessment of sym-
pathetic nervous activity is the use of plasma noradrenaline levels
(3). Although there is a good correlation to direct microneurography
(4), a peripheral plasma noradrenaline sample is the result not only
from the neuronal noradrenaline release but also from the clearance of
noradrenaline from plasma. In addition, both release and removal of
noradrenaline are different for most organs as has been demonstrated
by regional noradrenaline turnover studies (5). Nevertheless, ante-
cubital plasma noradrenaline samples have frequently been used to
determine whether sympathetic nerve activity is increased in hyper-
tensives (6). Since it might be supposed that differences between
normo- and hypertensives will emerge more clearly when the sympathetic
nervous system is stimulated, both normo- and hypertensives have been
exposed to various adrenergic stimuli (7).

In this study, we investigated the reactivity of blood pressure, heart
rate, forearm blood flow and plasma catecholamines to various kinds of
adrenergic stimulation in 70 patients with mild essential hypertension
and in a control group of 41 normotensives who were not familiar with
medical procedures (chapter 2). Both groups had a comparable age and

sex stratification. In contrast to previous studies in this field, all tests were carried out in the same group of hypertensives. All participants underwent 5 standardized stress tests: an isometric handgrip exercise, a mental arithmetic test, a head-up tilt test, a submaximal bicycle exercise test and a cold pressor test. To determine the sensitivity for catecholamines, two infusions with a low dose of noradrenaline and adrenaline completed the study protocol (chapter 2).

The mental arithmetic test, the head-up tilt test and the cold pressor test were carried out in a small group of 10 adrenalectomised women to investigate the role of adrenaline concerning the haemodynamic responses to these kinds of adrenergic stimulation.

In a small group of 8 hypertensives, the entire study protocol was repeated after 6 months treatment with the beta-adrenoceptor blocker atenolol to evaluate the effect of long-term betablockade on the haemodynamic and plasma catecholamine responses to adrenergic stimulation. In addition, the relation between the haemodynamic and catecholamine responses to a stress test and the hypotensive effect of long-term betablockade was explored.

In a pilot study, reproducibility of the haemodynamic responses to handgrip exercise, mental arithmetic, head-up tilt and cold pressor test were investigated in a separate group of 51 normotensive and 22 hypertensives (chapter 3). Although there was a good reproducibility of the haemodynamic responses for a whole group, the individual reproducibility of the haemodynamic responses, expressed as the standard deviation of a single observation, was rather poor. This was more apparent when relating the standard deviation of a single observation to the mean haemodynamic responses and it applied equally to normo- and hypertensives. The plasma catecholamine responses to handgrip exercise and mental arithmetic revealed a bad reproducibility too. Consequently, interpretation of drug effects on haemodynamic reactivity during these kinds of adrenergic stimulation is possible with the greatest caution only. In view of the fact that these tests are regularly used, it is amazing that reproducibility of the haemodynamic responses to adrenergic stimulation has scarcely been studied.

As described in chapter 4, we could not demonstrate higher plasma noradrenaline or adrenaline levels in patients with mild essential hypertension. Even if analysed by each age/sex class, no normo-hypertensive difference emerged. This is in line with most previous

studies, in which the normotensive control group was also not habituated to medical experiments (6). In addition, with direct microneurography, no difference in basal sympathetic neural activity between normo- and hypertensives could be detected (8) but this applies only to muscle sympathetic activity. Our negative result might partially be explained by the mild blood pressure elevation in the hypertensives we studied (6), although we found only a weak correlation between the baseline plasma noradrenaline and the baseline blood pressure. The previously demonstrated increase of plasma noradrenaline with increasing age (9), could only be demonstrated in female normo- and hypertensive subjects.

Both during handgrip exercise (chapter 5), during bicycle exercise (chapter 8) and during cold exposure (chapter 11), hypertensives did not show an abnormal strong haemodynamic responsiveness in comparison with the normotensives. During handgrip exercise, the plasma adrenaline response was larger in the young hypertensives than young normotensives, pointing to an increased adrenomedullary reactivity. In contrast, during bicycle exercise the plasma catecholamine responses were not different between both groups. Figure 1 demonstrates that bicycle exercise was the strongest adrenergic stimulus in our study.
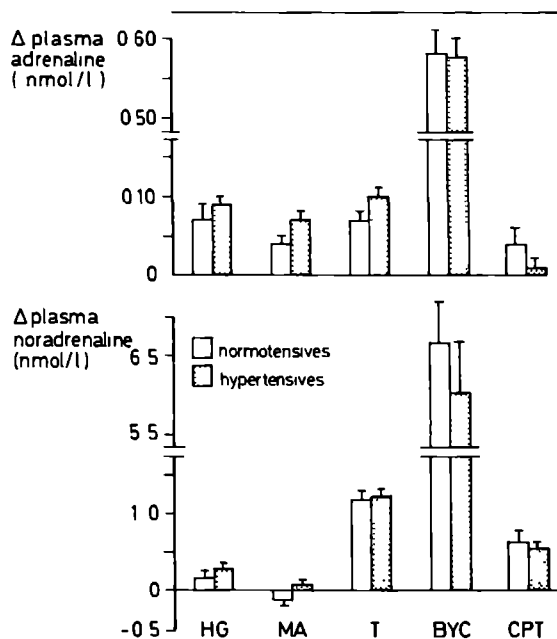

Figure 1
The plasma catecholamine respons to the stress tests in the normo- and hypertensives (mean + SE).
For abbreviation of the test names is referred to chapter 2.

Only during the mental stress (chapter 6) and during the head-up tilt (chapter 7), hypertensives showed enhanced haemodynamic responses as compared to normotensives. The enhanced response during mental stress was accompanied by a small increase of plasma noradrenaline in the hypertensives, in contrast to a small decrease in the normotensives. The mental stress is regarded as the only stimulus that consistently provokes an enhanced blood pressure responsiveness in studies with hypertensives (10). From the earliest experiments of Brod et al (11), it has been shown that mental stress elicits a typical haemodynamic response of an increase of blood pressure, heart rate and skeletal muscle blood flow. Later this response was designated as the 'defense reaction' (12) and the accentuated blood pressure response in the hypertensives to mental stress points to an enhanced 'defense reaction' in the hypertensives. In addition, morphological alterations of the cardiovascular system due to the hypertension itself (13), can give rise to abnormal pressor responsiveness. However, in normotensive offspring of parents with essential hypertension, an exaggerated haemodynamic response to mental stress already exists (14) although they do not yet have structural vascular damage. This suggests an abnormal neurogenic control of the haemodynamic responses to mental stress when there is only a genetic risk for developing hypertension. The enhanced blood pressure response in the young hypertensives during head-up tilt (chapter 7) might be attributed to an abnormal high cardiopulmonary baroreceptor activity in the hypertensives (15).

Adrenaline does not play an essential role in the adaptation to mental arithmetic, head-up tilt and cold exposure since the haemodynamic responses to these tests were normal (chapter 12). More interestingly, the adrenalectomised women had normal baseline plasma noradrenaline levels and the plasma noradrenaline increments during adrenergic stimulation were normal too. This finding challenges the view that the presynaptic facilitating effect of adrenaline on the neuronal release of noradrenaline plays an important physiological role in the haemodynamic regulation during short-lasting sympathetic stress.

In both groups, low dose infusion with noradrenaline evoked a similar haemodynamic response when corrected for the plasma noradrenaline increase (chapter 9). In contrast, infusion with adrenaline elicited a stronger decrease of diastolic blood pressure and forearm vascular resistance and a stronger increase of heart rate per nmol

plasma adrenaline increment in male hypertensives than in male normo-
tensives (chapter 10). These data suggest that hypertensive men have a
higher vascular and cardiac beta-adrenoceptor density or sensitivity
than normotensive men.

Gender is an important determinant of the baseline plasma adrena-
line level (16) and we could also demonstrate a lower baseline plasma
adrenaline level in hypertensive women than in hypertensive men. More
interestingly, women showed a smaller increase of plasma catechol-
amines to several tests (chapter 5-7,11). In view of the fact that
catecholamines itself may induce structural vascular and cardiac
alterations, it can be speculated whether the lower catecholamine
response to stress in women contributes to the previously demonstrated
smaller cardiovascular morbidity and mortality (17). In addition,
females seemed to have a faster clearance of infused adrenaline than
men (chapter 10). On the other hand, females had a higher beta-1-
adrenoceptor sensitivity for adrenaline as was demonstrated by the
stronger heart rate response during adrenaline infusion and this might
partially explain the higher heart rate in women than in men.
In chapter 13, the haemodynamic responses to adrenergic stimulation
during long term betablockade are described in a small group of hyper-
tensives. As could be expected, betablockade reduced the heart rate
responses to isometric exercise, mental arithmetic and head-up tilt
whereas the blood pressure responses during these tests remained un-
altered. More interestingly, the normally occurring decrease of dia-
stolic blood pressure during bicycle exercise and adrenaline infusion
was attenuated. These findings suggest that even a low dose of a
beta-1-adrenoceoptor blocker may impair the physiological vasodilation
during dynamic exercise and during an increase of plasma adrenaline to
levels as occurring during daily life stress.

Baseline plasma adrenaline and not noradrenaline was related to
the hypotensive efficacy of atenolol, suggesting that the higher the
basal plasma ADR level before treatment, the larger the fall in
systolic blood pressure by atenolol. Because of the considerable
variability of baseline plasma adrenaline levels (chapter 4), this
finding should be interpreted with the greatest caution.
Not a single haemodynamic or a plasma catecholamine response during
adrenergic stimulation was consistently related to the chronic hypo-
tensive effect of atenolol. Thus it seems unfeasible to predict the

individual's antihypertensive response to a betablocking drug reliably by measuring haemodynamic or plasma catecholamine responses during adrenergic stimulation.

Conclusions

1. Both age and gender are important determinants of the haemodynamic and plasma catecholamine reactivity in normo- and hypertensives.
2. The intra-individual reproducibility of the haemodynamic alterations during adrenergic stress testing is rather bad.
3. Patients with mild essential hypertension do not have increased baseline plasma catecholamine levels, indicating a normal sympatho-adrenal activity at rest.
4. Both the enhanced blood pressure- and plasma noradrenaline reactivity to mental arithmetic and the enhanced blood pressure and plasma adrenaline reactivity to head-up tilt in young hypertensives, support the concept of an abnormally strong reactivity of the sympathoadrenal system in young subjects with essential hypertension.
5. Circulating adrenaline does not play an important role for the haemodynamic reactivity to some kinds of mild adrenergic stimulation.
6. Hypertensive males exhibit a stronger vascular and cardiac beta-adrenoceptor sensitivity to adrenaline and/or adrenoceptor density than normotensive males. This might partially explain the higher baseline heart rate in patients with essential hypertension.
7. Women have a higher sensitivity of the cardiac beta-adrenoceptor to adrenaline than men and this probably contributes to the higher baseline heart rate in women than in men.
8. It is impossible to predict the hypotensive efficacy of atenolol from the haemodynamic or plasma catecholamine responses during adrenergic stimulation before treatment with atenolol. Patients with the highest baseline plasma adrenaline level showed the largest hypotensive effect of atenolol.
9. The usually occurring vasodilation during submaximal bicycle exercise and during artificially elevated circulating adrenaline as during daily life stress, decreases during treatment with a beta-1-selective betablocker. It is uncertain whether this offsets the beneficial antihypertensive effect of the drug.

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SAMENVATTING EN CONCLUSIES

SAMENVATTING

Het is reeds lang bekend dat de bloeddruk geen statische grootheid is
maar dat deze binnen een kort tijdsbestek zeer sterk kan variëren.
Deze variatie ontstaat doordat allerlei prikkels, waaraan een individu
in het dagelijks leven blootstaat, invloed uitoefenen op het hart-
vaatstelsel. De bloeddruk kan snel en sterk op allerlei stimuli reage-
ren door de intermediërende rol van het autonome zenuwstelsel.

Het belangrijkste doel van het beschreven onderzoek was te onderzoeken
of patiënten met essentiële hypertensie abnormaal sterk reageren met
hun bloeddruk, hartfrequentie en onderarmsdoorbloeding wanneer ze
blootgesteld worden aan verschillende fysieke en mentale stress-situa-
ties. Omdat plasma catecholamines een indruk geven over de activiteit
van het sympatisch zenuwstelsel werd tevens onderzocht of er een ab-
normaal sterke stijging van de plasma catecholamines optrad tijdens
deze stimulatie.
Het onderzoek werd uitgevoerd bij 70 patiënten met lichte hypertensie
en bij 41 gezonde normotensieve vrijwilligers. Alle proefpersonen wer-
den onderworpen aan 5 gestandaardiseerde stress-testen: een handgrip
test (statische spierarbeid), een 'mental arithmetic' test (hoofdre-
kensom), een tilttest (een kleppproef om het effect van de zwaarte-
kracht te bestuderen), een submaximale fietstest (dynamische spier-
arbeid), een 'cold pressor' test (koude provocatie). Bovendien kregen
de proefpersonen een tweetal infusen met de beide endogeen voorkomende
catecholamines: noradrenaline en adrenaline.
De rol van circulerend adrenaline met betrekking tot de hemodynami-
sche reactiviteit werd onderzocht door enkele van bovengenoemde testen
uit te voeren bij 10 normotensieve personen die in het verleden een
dubbelzijdige bijnierextirpatie hadden ondergaan wegens de ziekte van
Cushing.
Bij een kleine groep van 8 patiënten met hypertensie werd het gehele
bovengenoemde protocol herhaald na 6 maanden behandeling met een beta-
blokker. Met name werd gekeken of het bloeddrukverlagend effect bij
chronisch gebruik van de betablokker voorspeld kon worden op grond van
de hemodynamische of plasma catecholamine respons tijdens een van
bovengenoemde testen.

In hoofdstuk 2 worden de proefpersonen en de gebruikte testprocedures beschreven. In tegenstelling tot eerder verricht onderzoek, werden alle testen bij een en dezelfde groep hypertensieven en bij een en dezelfde groep normotensieven uitgevoerd en er werd gestreefd naar een gelijke leeftijds- en geslachtsverdeling binnen beide groepen. Behalve bij de 'mental arithmetic' en 'cold pressor' test bleken leeftijd, geslacht of de interactie tussen deze beide van invloed te zijn op de hemodynamische veranderingen tijdens de testen.

In een afzonderlijke groep normo- en hypertensieve proefpersonen werd de reproduceerbaarheid van de hemodynamische veranderingen tijdens enkele testen bestudeerd (hoofdstuk 3). De reproduceerbaarheid voor een totale groep proefpersonen was weliswaar goed, maar de intra-individuele reproduceerbaarheid was voor alle testen matig tot slecht. Hetzelfde gold voor de plasma catecholaminerespons tijdens de handgrip en de 'mental arithmetic'.

De basale plasma catecholaminespiegels worden beschreven in hoofdstuk 4. De hypertensieve proefpersonen bleken geen verhoogde plasma catecholamines te hebben. Het is niet uitgesloten dat dit het gevolg is van het feit dat de hypertensieve proefpersonen slechts een lichte hypertensie hadden. Een andere mogelijkheid is dat de normotensieve controlegroep bestond uit personen die niet gewend waren aan deelname aan medische onderzoeken. Dit is van belang omdat de meeste onderzoekers die wel verhoogde plasma catecholamines vaststelden bij hypertensieven, gebruik maakten van een controlegroep die wel gewend was aan medische experimenten en mogelijk daardoor lagere basale plasma catecholamines hadden.

In dit soort onderzoeken is het tevens van belang rekening te houden met de geslachtsverdeling. De mannelijke hypertensiepatiënten hadden een hogere basale plasma adrenalinespiegel dan de vrouwelijke hypertensiepatiënten.

Zowel bij de normo- als hypertensieve proefpersonen bestond er een aanzienlijke dag-tot-dag-variabiliteit wat betreft de individuele basale plasma catecholaminewaarden.

Tijdens beide vormen van spierarbeid (handgrip en fietstest) (hoofdstukken 5 en 8) bleek er bij de hypertensiepatiënten geen abnormaal sterke stijging van de bloeddruk en hartfrequentie op te treden. De relatieve stijging was op jonge leeftijd bij de hypertensiepatiënten zelfs lager dan bij de normotensieve proefpersonen. Wel bleek de

plasma adrenalinerespons tijdens de handgriptest bij de jonge hyper-
tensiepatiënten groter te zijn dan bij de jonge normotensieve proef-
personen, hetgeen er mogelijk op wijst dat er bij jonge hypertensie-
patiënten tijdens statische spierarbeid een abnormaal sterke stimula-
tie van het bijniermerg optreedt. Zoals verwacht kon worden bleek de
submaximale fietstest de sterkste adrenerge stimulus te zijn (figuur
1).

Hoewel hypertensiepatiënten een slechtere conditie hadden dan de nor-
motensieven, pleit de gelijke lactaatrespons tijdens de fietstest voor
een vergelijkbare mate van inspanning door beide groepen.
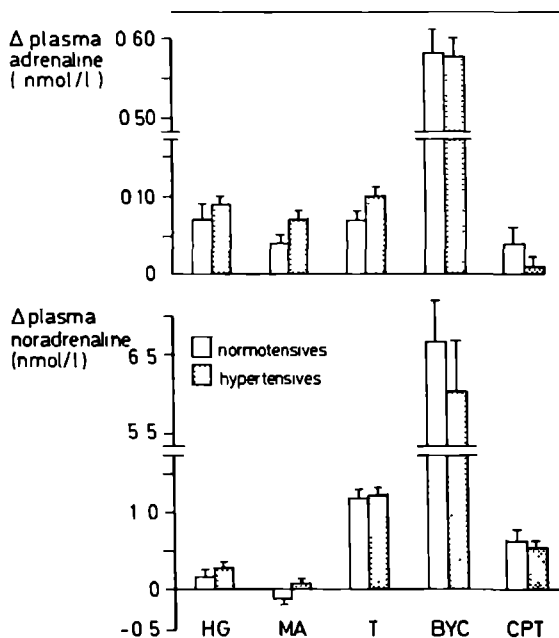
Figuur 1

De veranderingen van beide plasma catecholamines tijdens de stress-
testen bij de normo- en hypertensieve proefpersonen (gemiddelde $\pm$ SE).
Voor de afkortingen van de testnamen zie hoofdstuk 2.

Al tijdens het uitvoeren van een simpele rekensom ('mental arith-
metic') (hoofdstuk 6), bleek de systolische bloeddruk van de hyperten-
siepatiënten iets sterker te stijgen dan die van de controlegroep.
Bovendien bleek het plasma noradrenaline van de jonge hypertensiepa-
tiënten te stijgen terwijl het in geringe mate daalde bij de jonge
normotensieven. Beide gegevens geven enige steun aan de hypothese dat
er bij jonge hypertensiepatiënten mogelijk sprake is van een verhoogde
sympaticus reactiviteit tijdens mentale stress.

Jonge hypertensiepatienten toonden ook een abnormale bloeddruk-
respons tijdens de tilttest (hoofdstuk 7) en dit gold ook voor de
stijging van het plasma adrenaline. Deze abnormale bloeddrukreactie
bij jonge hypertensiepatiënten moet wellicht toegeschreven worden aan
de reeds eerder aangetoonde abnormaal sterke activiteit van de cardio-
pulmonale mechanoreceptoren bij hypertensiepatiënten.

Een andere stimulus die eveneens een sterke adrenerge prikkel is,
is de 'cold pressor' test (hoofdstuk 11). Zowel de hemodynamische als
de plasma catecholaminerespons verliepen echter normaal bij de hyper-
tensiepatiënten.

Infusie met een lage dosis noradrenaline (hoofdstuk 9) leidde in beide
groepen tot eenzelfde hemodynamische reactie wanneer deze gerelateerd
werd aan de stijging van het plasma noradrenaline tijdens de infusie.
Infusie met een lage dosis adrenaline (hoofdstuk 10) veroorzaakte
echter een sterkere daling van de diastolische bloeddruk en van de
onderarmsdoorbloeding en een sterkere stijging van de hartfrequentie
bij mannelijke hypertensiepatiënten dan bij mannelijke normotensie-
ven. Deze gegevens zouden er op kunnen wijzen dat mannelijke hyperten-
siepatiënten een grotere vasculaire (β_2) en cardiale (β_1) beta-adreno-
ceptorgevoeligheid hebben voor adrenaline en/of een grotere receptor-
dichtheid hebben. De sterkere gevoeligheid van de hartfrequentie voor
adrenaline in zowel normo- als hypertensieve vrouwen (in vergelijking
tot mannen) zou ook kunnen wijzen op een grotere cardiale beta-adreno-
ceptorgevoeligheid voor adrenaline en/of een grotere receptordichtheid
bij vrouwen dan bij mannen.

Tien vrouwen zonder bijnieren en dus zonder meetbaar circulerend
plasma adrenaline, toonden een normale bloeddruk reactiviteit tijdens
de 'mental arithmetic' test, tilt test, en 'cold pressor' test (hoofd-
stuk 12). Hieruit kan geconcludeerd worden dat het plasma adrenaline

geen essentiele rol speelt bij de hemodynamische reactie tijdens deze milde vormen van adrenerge stimulatie. Verder suggereren zowel het normale basale plasma noradrenaline als de normale stijging hiervan tijdens de testen, dat het presynaptisch faciliterend effect van adrenaline op de neuronale noradrenalineafgifte wellicht geen belangrijke fysiologische rol speelt tijdens milde vormen van kortdurende adrenerge stimulatie.

In hoofdstuk 13 worden de hemodynamische reacties tijdens alle testen beschreven na 6 maanden behandeling van 8 patienten met de beta-1-selectieve adrenoceptor-antagonist (betablokker) atenolol (een maal daags 50 mg). Tijdens behandeling met de betablokker was de hartfrequentiestijging tijdens de handgrip test, 'mental arithmetic' test en tilt test geringer dan voor behandeling. Hoewel tijdens atenolol het bereikte bloeddrukniveau tijdens stimulatie lager was dan vóór de behandeling met atenolol, bleef de bloeddrukstijging tijdens adrenerge stimulatie onveranderd. De normale daling van de diastolische bloeddruk tijdens de fietstest en tijdens het adrenalineinfuus bleek tijdens behandeling met de betablokker duidelijk verminderd. Dit wijst erop dat de normaal optredende vasodilatatie tijdens fietsen en tijdens een adrenalineinfuus afneemt tijdens langdurige behandeling met een veel gebruikte dosis van een beta-1-selectieve betablokker.

De bloeddrukdaling na 6 maanden gebruik van atenolol bleek gerelateerd aan het basale plasma adrenalinegehalte vóór de start van atenolol; deze relatie was er echter niet met het basale plasma noradrenalinegehalte. Gezien de aanzienlijke intra-individuele variabiliteit van het basale plasma adrenaline, dient dit gegeven echter voorzichtig geïnterpreteerd te worden.

Er bestond geen consistente relatie tussen het bloeddrukverlagend effect van atenolol en de hemodynamische of plasma catecholamine reactiviteit tijdens de stresstesten. Het bloeddrukverlagend effect van atenolol voor een bepaalde patient kan dus niet goed voorspeld worden op grond van de hemodynamische reactiviteit tijdens de in dit onderzoek gebruikte stresstesten.

CONCLUSIES

1. Zowel leeftijd als geslacht zijn belangrijke factoren waarmee rekening gehouden moet worden bij onderzoek van bloeddruk en plasma catecholamine reactiviteit bij normo- en hypertensieven.

2. De intra-individuele reproduceerbaarheid van de hemodynamische veranderingen tijdens stresstesten laat zeer te wensen over.

3. Patiënten met lichte hypertensie hebben in basale toestand geen verhoogde plasma catecholamines in vergelijking met gezonde normotensieve proefpersonen. Dit pleit tegen een verhoogde sympaticusactiviteit in rust bij patiënten met een lichte hypertensie.

4. Zowel de abnormale bloeddruk- en plasma noradrenalinerespons tijdens 'mental arithmetic' als de abnormale bloeddruk- en plasma adrenalinerespons tijdens 'head-up tilt' bij de jonge hypertensiepatiënten, wijzen op een abnormaal sterke sympaticus reactiviteit bij jonge hypertensiepatienten.

5. Hypertensieve mannen hebben mogelijk een grotere vasculaire en cardiale beta-adrenoceptorgevoeligheid voor adrenaline en/of adrenoceptordichtheid dan normotensieve mannen terwijl er geen verschil is in de gevoeligheid voor noradrenaline. Dit zou, althans gedeeltelijk, een mogelijke verklaring kunnen vormen voor de hogere basale hartfrequentie van hypertensiepatiënten.

6. Vrouwen hebben mogelijk een grotere gevoeligheid van cardiale beta-adrenoceptoren voor adrenaline dan mannen en ook hier draagt dit wellicht bij aan de hogere basale hartfrequentie van vrouwen dan van mannen.

7. Het bloeddrukverlagend effect op lange termijn van atenolol kan niet voorspeld worden op grond van de hemodynamische of plasma catecholamine reactiviteit tijdens bepaalde stresstesten. Wel is het bloeddrukverlagend effect van atenolol in deze kleine groep hypertensiepatiënten sterker wanneer het basale plasma adrenalinegehalte vóór behandeling met atenolol hoger is.

8. De normaal optredende vasodilatatie tijdens een submaximale fietstest en tijdens kunstmatige verhoging van het plasma adrenaline tot waarden zoals die vaak voorkomen in dagelijkse stresssituaties, neemt af tijdens behandeling met een beta-1-selectieve betablokker. Het is de vraag of het gunstige effect van de bloeddrukverlaging door de betablokker hierdoor enigszins wordt tegengegaan.

9. Circulerend adrenaline speelt geen belangrijke rol bij het totstandkomen van de hemodynamische reactie tijdens adrenerge stimulatie.

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Parts of this thesis have been or will be published in the following
papers:

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   subjects. Submitted.

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   parate effects of mental stress on plasma norepinephrine in young
   normotensive and hypertensive subjects. Submitted.

8. Jansen RWMM, Lenders JWM, Hoefnagels WHL, Thien Th. The influence
   of age and blood pressure on the hemodynamic and humoral response
   to head-up tilt. Submitted.

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De meeste tekeningen in dit proefschrift werden met zorg vervaardigd door de heer C. Nicolasen van de afdeling Medische Illustratie en werden gefotografeerd door de medewerkers van de afdeling Medische Fotografie.

In het kader van hun wetenschappelijke stage hebben Rudolf van Valderen, Jeroen Peters en G. Wijnands bijgedragen aan hoofdstuk 3 en 12.

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Allen die anderszins aan de totstandkoming van dit proefschrift hebben bijgedragen wil ik hierbij van harte dank zeggen.

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 8 december 1947 te Blerick. Na het behalen van het einddiploma HBS-B aan het Blariacum College te Blerick (1967), studeerde hij geneeskunde aan de Katholieke Universiteit te Nijmegen. Na het artsexamen (1975), werkte hij als assistent op de afdelingen interne geneeskunde (Dr H. Lanting en Dr W. Bos) en chirurgie (Dr S. Oudkerk) van het Prot. Christ. Streek-ziekenhuis te Bennekom. De opleiding tot internist begon in 1977 in het Groot Ziekengasthuis te 's-Hertogenbosch (opleider: Dr J. Lips) en deze werd in 1979 voortgezet in de Universiteitskliniek voor Inwendige Ziekten van het Sint Radboudziekenhuis te Nijmegen (Hoofd destijds Prof.Dr C.L.H. Majoor †, nadien Prof.Dr A. van 't Laar). In 1982 werd hij ingeschreven als internist in het specialistenregister. Vervolgens werkte hij middels een subsidie van de Universitaire Onderzoek Pool tot eind 1985 aan het in dit proefschrift beschreven onderzoek. Sinds-dien is hij als staflid werkzaam op de afdeling algemene interne geneeskunde (Hoofd: Prof.Dr A. van 't Laar) van de Universiteits-kliniek voor Inwendige Ziekten.

STELLINGEN

behorend bij het proefschrift

BLOOD PRESSURE AND CATECHOLAMINE REACTIVITY
TO ADRENERGIC STIMULATION IN ESSENTIAL HYPERTENSION

J.W.M. Lenders

STELLINGEN

1. Patienten met een lichte essentiéle hypertensie reageren tijdens lichamelijke belasting niet, maar tijdens mentale belasting wel met een sterkere bloeddrukstijging dan mensen met een normale bloeddruk.

2. De sterkere stijging van plasma catecholamines bij jonge mannen dan bij jonge vrouwen tijdens adrenerge stimulatie zou de grotere cardio-vasculaire morbiditeit en mortaliteit bij mannen mede kunnen verklaren.

3. De matige tot slechte intraindividuele reproduceerbaarheid van de hemodynamische reactie op sommige vormen van adrenerge stimulatie, is tot nu toe onvoldoende onderkend.

4. Het is onwaarschijnlijk dat het presynaptisch faciliterend effect van adrenaline op de neuronale noradrenaline afgifte van groot belang is voor de hemodynamische reactie tijdens kortdurende adrenerge stress.

5. Het bloeddrukverlagend effect van een betablokker kan niet voorspeld worden op grond van de reacties van de bloeddruk, de hartfrequentie of de catecholamineconcentraties in het plasma op bepaalde adrenerge stresstests.

6. De zeer sterke catecholaminestijging bij een kind tijdens de geboorte is van zeer grote betekenis om de scheiding van de moeder te overleven.

> H. Lagercrantz. The stress of being born.
> The Scientific American 1986;254:92-102.

7. Ernstige hypogammaglobulinemie kan lange tijd vooraf gaan aan een chronische lymphatische leukemie.

> J.W.M. Lenders, B.E. de Pauw, M.J. Bogman,
> C. Haanen. Combined immunodeficiency pre-
> ceeding chronic lymphocytic leukemia. Blut
> 1984;48:171-175.

8. Een electrocardiogram is een te ongevoelige methode om bij hypertensiepatiënten een eventuele hypertrofie van de linker ventrikel vast te stellen.

9. Behandeling met nifedipine voorkomt wel de bloeddrukstijging maar niet de stijging van noradrenaline in het plasma tijdens een hypertensieve crise bij patiënten met een feochromocytoom.

J.W.M. Lenders, H.E. Sluiter, J.J. Willemsen, Th. Thien. Treatment of a phaeochromocytoma of the urinary bladder with nifedipine. Br Med J 1985;290:1624-1625.

10. De tegenstrijdige gegevens over het type-A gedrag als cardiovasculaire risicofactor doen vermoeden dat het gedrag van de meeste mensen type non-A, non-B is.

11. De eis dat kandidaat-huisartsen bereid moeten zijn om alternatieve geneeswijzen toe te passen, zoals soms gesteld in advertenties van gemeentelijke vestigingscommissies, is in strijd met het beleid van de overheid dat de eerstelijnsgezondheidszorg versterkt moet worden.

12. De idee dat het beeld van de deskundige specialist vooral dat van de man zou zijn, is waarschijnlijk niet juist: onder patiënten bestaat evenveel voorkeur voor een mannelijke als voor een vrouwelijke internist. (Ontleend aan onderzoek op de polikliniek voor Inwendige Ziekten, Academisch Ziekenhuis Nijmegen, 1988).

13. De wens van ziekenhuisdirecties om eigen zogenaamde diagnostische centra op te richten berust meer op opportunisme dan op visie.

Nijmegen, 10 juni 1988