# COFFEE AND BLOOD PRESSURE

a pharmacological study on the circulatory effects of coffee and caffeine

Paul Smits

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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN, OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. DR. J.H.G.I. GIESBERS VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN IN HET OPENBAAR TE VERDEDIGEN OP VRIJDAG 20 JUNI 1986 DES NAMIDDAGS TE 2 UUR PRECIES

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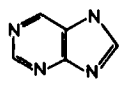
Aan Liesbet, Loek en
aan mijn ouders

CONTENTS

## GENERAL INTRODUCTION AND PROBLEM STATEMENT

Caffeine is a naturally occurring methylxanthine (figure 1), that has been consumed and enjoyed by people throughout the world for many centuries. According to an ancient legend, eastern shepherds were the first to observe pharmacological effects of this



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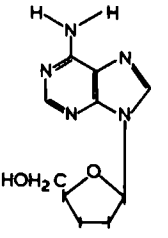

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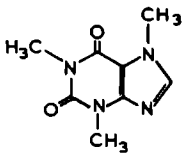
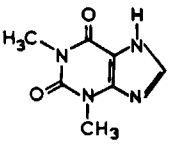
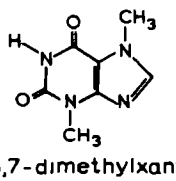


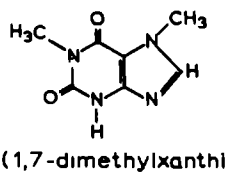
(1,3,7-trimethylxanthine)
CAFFEINE



(1,3-dimethylxanthine)
THEOPHYLLINE



(3,7-dimethylxanthine)
THEOBROMINE



(1,7-dimethylxanthine)
PARAXANTHINE

Figure 1: The structural formula of caffeine and some related compounds.

agent, as several goats showed nocturnal alertness and sleeplessness after eating the berries of coffee plants. Coffee was already a favourite beverage in the Middle East in the 15th century, and via French and Dutch colonies coffee consumption was propagated and spread out to Europe in the 17th century. The isolation of caffeine from beans of the plant "Coffea Arabica" was firstly reported in 1820 (1), and 55 years later its chemical structure was elucidated (2).

The mean daily caffeine intake of adult coffee drinkers is estimated to range from 2.7 to 4 mg/kg (3). For adults weighing 60-70 kg these estimates correspond to a daily intake of about 160-280 mg caffeine. Coffee is the most important caffeine source, accounting for approximately 75% of total caffeine intake (4). In the Netherlands the mean consumption of coffee during 1984 numbered 7.7 kg of coffee for an adult subject. The average caffeine content values per 150 ml (one cup) of coffee and other caffeine sources are: 85, 60 and 3 mg caffeine for ground roasted, instant and decaffeinated coffee respectively, 40 mg for tea, 4 mg for cacao- and chocolate drinks and 15 mg for cola drinks (3). Our own data also show that one cup of coffee of medium strength (7.5 gram coffee/150 ml water) contains about 90 mg caffeine (figure 2). From this figure it also appears that there is an almost linear relation between the quantity of coffee powder used, and the caffeine content per cup of coffee, when coffee is prepared with a coffee machine using a constant quantity of water. Decaffeinated coffee of customary strength hardly contains caffeine (figure 2).

After oral ingestion caffeine is almost completely absorbed, and the apparent volume of distribution is between 400 and 550 ml/kg (5). After drinking 2 cups of regular coffee peak plasma caffeine levels are reached after a mean of 50 minutes, and range between 5 and 15 mg/l (chapter II - VI). The elimination from plasma occurs by demethylation and oxidation in the liver, with a plasma half-life averaging about 4 hr (5). As will be illustrated in chapter III plasma caffeine half-life shows large inter-individual differences. Consequently, certain individuals may be continuously exposed to plasma caffeine concentrations, depending on their daily intake of caffeine.

Because of the widespread use of caffeine, pharmacological aspects of drinking coffee may be of some clinical interest. Around the start of the 20th century, caffeine and other methylxanthines were favourite agents for pharmacological studies. After a period of relative neglection, there has been a renewed interest in caffeine since the past 10 years. This may partly be the result of the increasing consciousness of the importance of the effects on health of all dietary components. Recent hypotheses on the mode of action of caffeine may also have contributed to this renewed interest. Although most pharmacological effects of caffeine are subtle, and consequently hard to measure, they are not necessarily trivial, as the daily intake of caffeine by large numbers of people, in the long run, could bring about substantial effects.

Caffeine has been reported to exert pharmacological effects in several organ systems: the gastrointestinal tract, the kidneys,

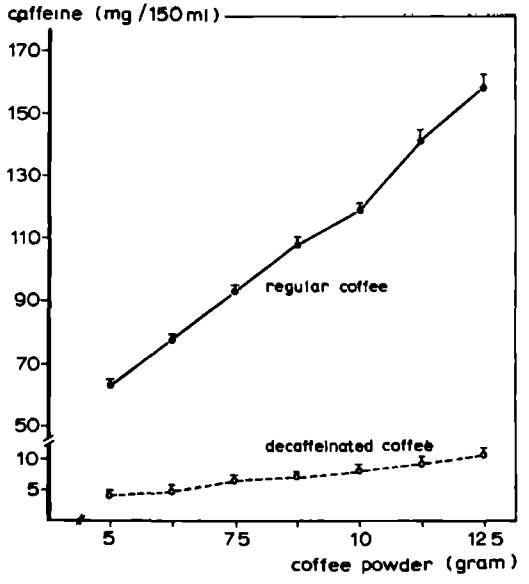



Figure 2: Caffeine content of one cup of regular or decaffeinated coffee, prepared by 150 ml water and different amounts of coffee powder (mean±SEM, n=2)

skeletal muscles, the central nervous system and the cardiovascular system (6). Whether these effects are harmful or not has recently been discussed by Curatolo et al (7). With respect to the cardiovascular system only few pharmacological studies have been performed with controversial results. In 1978 important data on this item were published by Robertson et al (8). He observed an increase in blood pressure, plasma catecholamines and plasma renin activity after oral administration of 250 mg caffeine in non-coffee users, who had abstained from all caffeine-containing products for 3 weeks. As it is not justified to extrapolate these results to the effects of drinking coffee in a daily life pattern, we think that the reported pressor response to caffeine deserves further study in man.

Since high blood pressure is a well-documented risk factor for the development of cardiovascular disease (9), an acute pressor response to coffee (8) may have consequences for public health. Therefore, many investigators have been looking for a relation between the use of coffee and coronary heart disease. Already in 1963, a prospective study of 1,951 men showed a positive association between coffee consumption and ischemic heart disease (10). Ten years later, the Boston Collaborative Drug Surveillance Program published their results of a multipurpose survey of 12,759 hospitalized patients (11). They observed a 60 and 120 percent increased risk of acute myocardial infarction among those drinking respectively 1-5 and 6 or more cups of coffee per day as compared to non-coffee users. These striking results elicited a stream of epidemiologic reports on this item. However, a lot of retrospective (12-15) and prospective studies (16-22) including the Framingham study failed to ascertain the reported relation between coffee ingestion and coronary heart disease. This discrepancy can be partly explained by differences in the number of variables for which the studies were controlled, for instance: smoking behaviour, alcohol consumption, body-mass index, physical activity and the use of coffee additives. A recent study, which was well controlled for these features, suggests that coffee consumption is indeed a risk factor for coronary artery disease(23).

A possible association between coffee consumption and cardiovascular mortality is not necessarily due to effects of coffee on

blood pressure but could also be the result of a caffeine-induced rise of lipoproteins (24), changes of the electrophysiologic properties of the heart by caffeine (25), or of a direct effect of coffee constituents on pathophysiological mechanisms. Therefore, the consequences of the acute hemodynamic changes after caffeine may be more clearly reflected by epidemiological studies on the relation between the intake of coffee and the height of blood pressure, rather than by studies about the association between coffee and cardiovascular disease. On the former relation, two recent cross-sectional studies were performed by the same investigators on respectively 1,491 Algerian and 6,321 French subjects, and both studies observed a positive association between coffee consumption and blood pressure (26,27).

## AIM OF THE STUDY

In this thesis we will focus on the acute effects of coffee and caffeine on some hemodynamic and humoral parameters. As outlined before, Robertson et al (8) observed that after a 3-week period of caffeine abstention, 250 mg caffeine elicited a pressor response in subjects not used to coffee. Our first question was whether drinking coffee causes hemodynamic and or humoral changes in normotensive habitual coffee users, after a short abstention of caffeine-containing products. Secondly, we tried to find out whether these circulatory effects are the result of the caffeine load, and so similar experiments were performed with decaffeinated coffee (chapter II). After chronic ingestion of caffeine, tolerance has been described with respect to the effects of caffeine on the central nervous system, diuresis, and parotid gland secretion (28,29,30). Recently, this has also been reported for the cardiovascular, both hemodynamic and humoral effects of coffee and caffeine (31,32). Some of the contradictory results in literature concerning the cardiovascular effects of caffeine could be explained by these observations (32,33). In chapter III we study the importance of tolerance with respect to the circulatory effects of drinking coffee in daily life. Since the individual pharmacokinetics of caffeine were supposed to be relevant

for this problem, these were taken into account.

The literature about the hemodynamic effects of drinking coffee mostly refers to normotensive subjects (8,34,35). Some studies were performed in hypertensive patients, but those results were not compared to similar protocols of normotensive subjects (36,37). In chapter VI we report on similar coffee tests in hypertensive and normotensive subjects to find out whether hypertension may change the pressor response to coffee.

Since caffeine increases plasma catecholamines, and especially adrenaline, drinking coffee could be considered as an exogenous stress. Treatment with non-selective β-adrenoceptor blockade with propranolol alters the physiological response to experimental stress unfavourably, whereas this has not been observed during $\beta_1$-selective adrenoceptor blockade with metoprolol (38,39). Therefore it seemed interesting to look for differences in the coffee-induced hemodynamic response after $\beta_1$-selective or non-selective β-adrenoceptor blockade. This subject was analysed in normotensive volunteers, who underwent coffee tests after pre-treatment during one day with placebo, propranolol and metoprolol (chapter IV).

Apart from analysing the acute circulatory effects of coffee and caffeine extensively, it seemed of importance to look for the pharmacological mode of action of caffeine, underlying these effects. Figure 3 schematically presents the most important mechanisms of action, supposed in the literature. Central mechanisms include the stimulation of vagal centers, and of the vasomotor center in the medulla oblongata (40). The other putative modes of action can be subdivided in direct and indirect peripheral actions. The latter include the caffeine-mediated stimulation of the renin-angiotensin-aldosterone system and the sympathoadrenal system (8). The direct mechanisms represent the most relevant possibilities for the action of methylxanthines on the cellular level, including:[1] the antagonism of endogenous adenosine (41); [2] accumulation of intracellular cAMP by inhibition of phosphodiesterase (42) and [3] an increase of transmembrane calcium influx [3a], and changes in intracellular calcium mobilisation [3b and 3c] (6). The numbers [1] to [3a,b&c] refer to figure 3.

Modes of action of caffeine

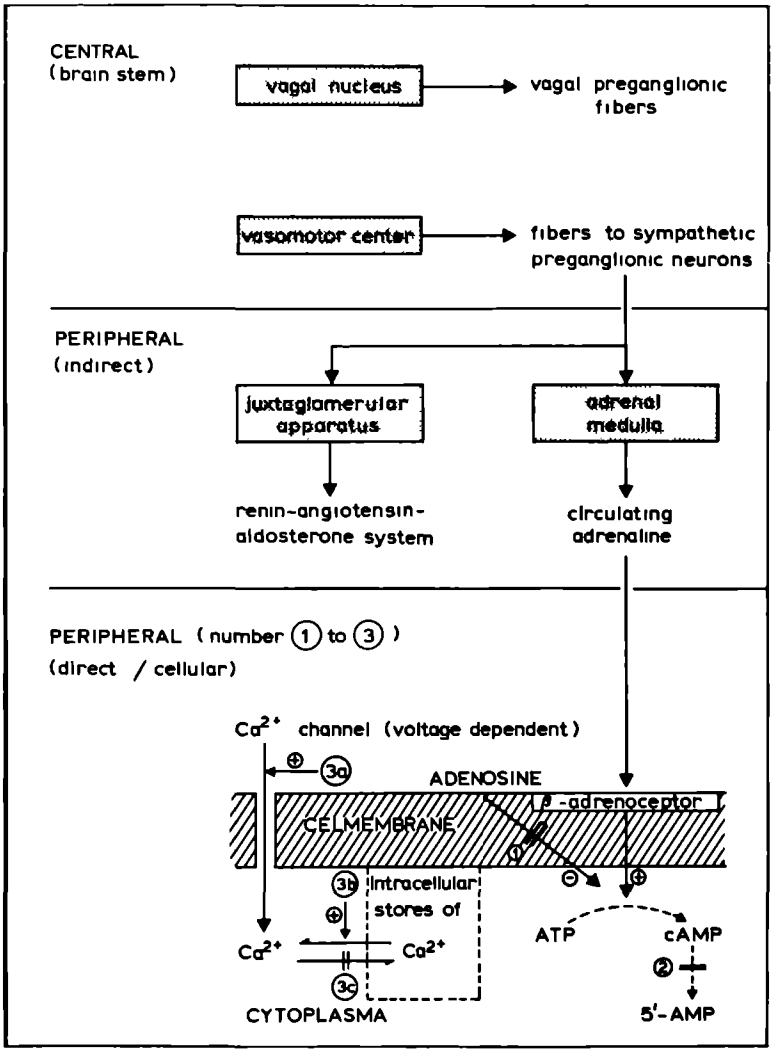



Figure 3: Possible pharmacological modes of action of caffeine with respect to the cardiovascular system

1. antagonism of endogenous adenosine
2. inhibition of phosphodiesterase
3. changes in calcium handling

(+ refers to stimulation, and || or - to inhibition)

The contribution of an increased transmembrane calcium influx to the circulatory effects of drinking coffee was studied in chapter V, using verapamil as a pharmacological tool. In chapter VI the hemodynamic and humoral effects of coffee ingestion were registered, both in healthy normotensive subjects as well as in patients with Cushing's disease, treated by bilateral adrenalectomy and subsequent substitution of corticoids. The comparison between those groups allowed us to analyse the role of adrenaline with respect to the pressor response to coffee. In chapter VII we report on the circulatory response to exogenous adenosine after placebo and after 250 mg caffeine i.v.. This interaction was studied to gain support for the hypothesis that caffeine elevates blood pressure by competitive antagonism of purinergic receptor-mediated vasodilation by endogenous adenosine.

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(British Journal of Clinical Pharmacology 1985; 19: 852-854)

# The cardiovascular effects of regular and decaffeinated coffee

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In a single-blind study the effects of drinking two cups of regular or decaffeinated coffee on blood pressure, heart rate, forearm blood flow and plasma concentrations of caffeine, renin and catecholamines were studied in 12 normotensive subjects Drinking regular coffee led to a rise of blood pressure, a fall of heart rate and an increase of plasma catecholamines Decaffeinated coffee induced a smaller increase of diastolic blood pressure without changing other parameters This study shows that the cardiovascular effects of drinking coffee are mainly the result of its caffeine content.

**Keywords** coffee decaffeinated coffee catecholamines blood pressure

## Introduction

The pharmacological effects of caffeine have been the subject of many recent studies After drinking regular coffee changes of blood pressure heart rate and plasma catecholamines have been reported (Smits *et al* , 1983, Whitsett *et al* , 1984) It is generally accepted that caffeine is the most important pharmacological compound with respect to the circulatory effects of drinking coffee (Eichler, 1976) Only few studies report on the cardiovascular effects of decaffeinated coffee Decaffeinated coffee powder has a very low caffeine content, approximately 0 05% *vs* 1 2–2 0% of regular coffee Dose-response studies on the haemodynamic effects of caffeine only are available in dose ranges equivalent to two to eight cups of coffee (Whitsett *et al* , 1980) but not in the range of low caffeine doses as in decaffeinated coffee Therefore we studied haemodynamic and humoral variables before and after drinking regular and decaffeinated coffee

## Methods

Six men and six women, all healthy and normotensive, gave their informed consent for this study Age, weight, length and quetelet-index (mean ± s d ) of these subjects numbered respectively 25 ± 4 7 years, 68 6 ± 11 8 kg, 179 5 ± 6 0 cm and 21 2 ± 3 3 kg/m$^2$ All persons were used to daily coffee intake and mean daily coffee consumption varied from three to 10 cups of coffee per day In random sequence, all subjects underwent two single-blind tests, one with regular coffee, and one with decaffeinated coffee Percolated regular coffee was automatically prepared with 350 ml water and 24 g of coffee resulting in two cups of coffee containing together about 280 mg caffeine Decaffeinated coffee was prepared in the same way The subjects were asked to abstain from caffeine for 17 h and from smoking for 4 h before the start of each test After arrival at the laboratory a supine rest period of 20 min started, and in the next 20 min systolic and diastolic blood pressure (SBP and DBP by arteriosonde 1225), heart rate (HR by ECG) and forearm blood flow (FBF by venous occlusion plethysmography) were measured each 5 min In eight out of 12 subjects blood was sampled for humoral parameters Afterwards the subjects were asked to drink the coffee within 10 min At 90 min after the start of the test the same periods of rest and measurements were repeated Plasma caffeine concentrations were measured with a reversed phase h p l c method

Plasma catecholamines were determined by a radioenzymatic assay and PRA by a radioimmunoassay All individual haemodynamic measurements were averaged to one mean value respectively before and after the beverage ingestion Haemodynamic and humoral results were analysed by respectively Student's *t*-test and Wilcoxon test for paired observations All results are presented as mean ± s e mean

## Results

Figure 1 shows the mean values of BP, HR and FBF before and after use of coffee and decaffeinated coffee Basal BP in the coffee and decaffeinated coffee test was not significantly different measuring respectively 116 ± 3 1/73 ± 2 4 mm Hg and 115 ± 3 0/70 ± 2 2 mm Hg Mean basal HR also was similar in both tests (60 ± 2 2 beats/min and 62 ± 1 8 beats/min respectively) After coffee there was a significant rise of SBP and DBP of 4 4 ± 1 4% and 11 8 ±

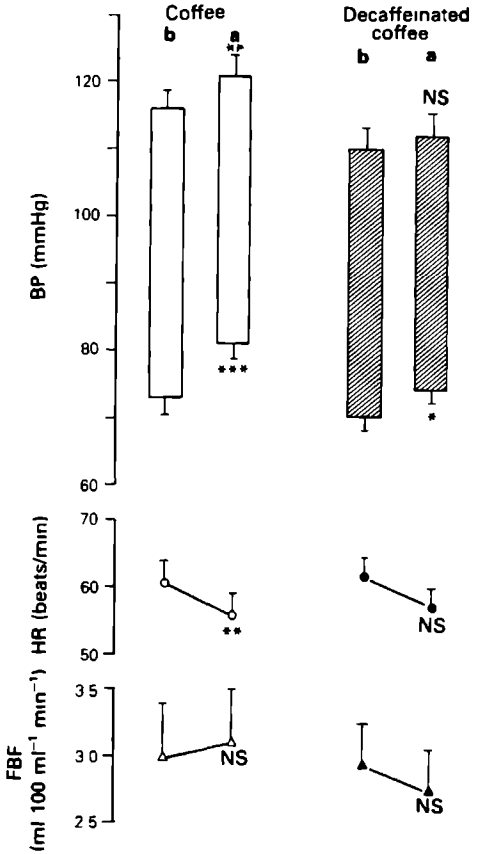


**Figure 1** Blood pressure (BP), heart rate (HR) and forearm blood flow (FBF) before (b) and after (a) the use of regular and decaffeinated coffee (mean ± s e mean of 12 subjects) $^{*}P < 0\ 05$, $^{**}P < 0\ 01$, $^{***}P < 0\ 001$, NS not significant

**Table 1** Plasma concentrations of caffeine (CF), renin (PRA) and (nor)adrenaline (NA, A) before and after ingestion of regular and decaffeinated coffee Mean changes (Δ) of the humoral parameters are also given (mean ± s e mean of eight subjects)

| | *Regular coffee (RC)* | | | *Decaffeinated coffee (DC)* | | | *RC* | | *DC* |
|---|---|---|---|---|---|---|---|---|---|
| | *Before* | | *After* | *Before* | | *After* | Δ | | Δ |
| CF (mg/l) | 0 3 ± 0 1 | *** | 8 8 ± 0 7 | 0 2 ± 0 1 | NS | 0 4 ± 0 1 | 8 5 ± 0 7 | *** | 0 1 ± 0 1 |
| PRA (ng ml$^{-1}$ h$^{-1}$) | 2 49 ± 0 48 | NS | 1 81 ± 0 38 | 2 33 ± 0 54 | NS | 1 85 ± 0 40 | −0 68 ± 0 22 | NS | −0 48 ± 0 20 |
| A (nmol/l) | 0 15 ± 0 02 | ** | 0 38 ± 0 07 | 0 16 ± 0 02 | NS | 0 22 ± 0 04 | 0 23 ± 0 07 | * | 0 07 ± 0 03 |
| NA (nmol/l) | 1 72 ± 0 22 | * | 2 16 ± 0 26 | 1 59 ± 0 14 | NS | 1 69 ± 0 15 | 0 44 ± 0 11 | * | 0 11 ± 0 15 |

$^{*}P < 0\ 05$, $^{**}P < 0\ 01$, $^{***}P < 0\ 0001$, NS not significant

2 5% and HR decreased with 8 4 ± 3 1% After decaffeinated coffee SBP and HR did not alter significantly, but DBP showed a rise of 4 ± 1 4 mm Hg The coffee induced rise of DBP was significantly higher than the increase of DBP after decaffeinated coffee ($P < 0$ 05) In both tests mean FBF remained unchanged

Table 1 summarizes the responses of all humoral variables to the drinking of regular and decaffeinated coffee Basal values of these parameters were the same in both tests In contradistinction to the drinking of decaffeinated coffee, regular coffee gave a significant rise of plasma caffeine concentration Table 1 shows that the coffee induced rises of plasma catecholamines were significantly higher than the changes after decaffeinated coffee In both tests PRA showed an insignificant fall after the beverage ingestion

## Discussion

The relation between caffeine ingestion and blood pressure gains interest from pharmacologists as well as epidemiologists Epidemiological studies report a positive association between blood pressure and coffee consumption (Lang *et al* , 1983) In other studies correlations were analysed between coffee ingestion and morbidity or mortality from coronary heart disease, and most of them observed no significant association (Dawber *et al* , 1974) In pharmacological studies there is also evidence for a positive association between blood pressure and caffeine intake (Smits *et al* , 1983, Whitsett *et al* , 1984) Other studies, however, suggested that after chronic caffeine ingestion the pressor response to coffee disappears (Robertson *et al* , 1981, Ammon *et al* , 1983) In this study we also observed a rise of SBP and DBP after coffee with a caffeine-abstinence of only 17 h In agreement with our results other investigators also observed a decrease of HR after coffee (Whitsett *et al* , 1984)

No epidemiological and only few pharmacological studies report on decaffeinated coffee (Fleish *et al* , 1954, Ammon *et al* , 1983) In both studies decaffeinated coffee did not elevate BP in contrast to regular coffee Our results also indicate that drinking of decaffeinated coffee has almost no haemodynamic effects In the literature no data of radioenzymatic determined plasma catecholamines and of PRA after decaffeinated coffee are available After coffee we observed a rise of plasma adrenaline and to a lesser extent of plasma noradrenaline, whereas PRA showed no alteration These results are in close agreement with a previous report (Smits *et al* , 1983) In our tests decaffeinated coffee had no influence on humoral parameters In spite of the small caffeine content of decaffeinated coffee mean plasma caffeine concentration did not rise significantly

From this study we conclude that drinking regular coffee results in a rise of BP, a fall of HR and an increase of plasma catecholamines Decaffeinated coffee only induces a slight increase of DBP, and so the circulatory effects of regular coffee are mainly brought about by the caffeine load If further studies suggest a causal role for coffee in the development of cardiovascular disease, then the use of decaffeinated coffee would become advisable

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# Circulatory Effects of Coffee in Relation to the Pharmacokinetics of Caffeine

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**Drinking coffee results in an increase in blood pressure (BP) after an interval of caffeine abstinence. During chronic caffeine intake this pressor response disappears and adaptation to the circulatory effects of caffeine develops. This study was designed to determine whether a pressor response to coffee occurs during chronic caffeine intake if low basal plasma caffeine levels are achieved by a period of caffeine abstinence, defined by individual plasma caffeine half-life. In 8 normotensive subjects, circulatory measurements were studied after ingestion of coffee in 2 strengths, decaffeinated coffee and hot water after a caffeine abstinence of 4.5 times individual caffeine half-life. These measurements were compared to the same protocol without intervention. Coffee of both strengths resulted in a similar increase in BP (diastolic BP ± 15%). The coffee-induced increase in forearm blood flow and plasma epinephrine levels were less pronounced. Decaffeinated coffee induced a smaller increase of diastolic BP, and after water, no changes were observed. Additionally, a negative correlation was found between the coffee-induced BP increase and basal plasma caffeine level in a group of 30 normotensive subjects ($r = -0.71$, $p < 0.001$). During chronic caffeine intake, subjects with short plasma caffeine half-life are exposed to a pressor response after drinking coffee, despite the phenomenon of adaptation.**

**(Am J Cardiol 1985;56:958-963)**

Because caffeine and coffee are widely consumed throughout the world, a relation between coffee and blood pressure (BP) would be of clinical interest [1,2] Recent studies have reported a positive association between BP and coffee consumption [3,4] There is also pharmacologic evidence for a BP-increasing effect of caffeine and coffee [5-7] The relevance of these observations to the effect of daily coffee use on BP was questioned by some investigators [8,9] According to these studies complete adaptation or tolerance to the circulatory effects of caffeine develops during chronic caffeine use However, in 1 study there was evidence that cardiovascular reactivity to caffeine was greater in subjects with initial caffeine levels of less than 1 mg/liter than for those with basal plasma caffeine levels of more than 1 mg/liter [8] This means that the development of tolerance to the effects of coffee depends on prior caffeine use and on the individual pharmacokinetics of caffeine In healthy subjects, elimination half-life ($T^1/_2$) of plasma caffeine varies between 1 5 and 9 5 hours [10] To determine whether coffee increases BP during chronic caffeine ingestion, the time of caffeine abstinence before the test must be related to individual pharmacokinetics of caffeine. We studied the circulatory effects of drinking coffee after a period of caffeine abstinence related to individual plasma caffeine $T^1/_2$ in 8 normotensive subjects Hemodynamic and humoral effects of 2 strengths of coffee, and of equal amounts of decaffeinated coffee and water of the same temperature were compared to a similar protocol without intervention In 30 other normotensive subjects, we analyzed the relation between basal plasma caffeine level and the coffee-induced increase in BP

## Methods

Eight normotensive, healthy subjects (5 men, 3 women) gave informed consent for this study, which was approved by the hospital ethical committee The mean age was 23 4 years (range 21 to 25), height 180 4 cm (range 169 to 201) and Quetelet index 21 5 kg/m$^2$ (range 17 9 to 24) All subjects were accustomed to daily coffee ingestion, and mean estimated coffee use ranged from 4 to 9 cups/day Three men were habitual smokers and all women used oral contraceptive drugs

The first part of the study was a pharmacokinetic analysis of all subjects Before and after drinking 2 cups of coffee, blood

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samples were drawn for determination of plasma caffeine concentration After coffee ingestion, blood was sampled every 20 minutes for 2 hours, and afterward another 3 times distributed over about 20 hours From these data, time of plasma peak level (Tm) was registered and the elimination caffeine $T^1/_2$ was calculated As $T^1/_2$ and Tm do not differ within an individual after different doses of oral caffeine, a single measurement of these values was sufficient [10]

After this pilot study every subject took part in 5 tests, which were ordered at random and separated from each other by at least 1 week All tests had the same protocol, different only in the kind of intervention similar amounts of regular coffee, stronger coffee, decaffeinated coffee, hot water and ' no intervention " For the tests with regular, strong and decaffeinated coffee the protocol was single blind, but as a matter of course this could not be realized for the tests with hot water and no intervention Before all tests were performed, the subjects had to abstain from all caffeine containing products for a period of 4 5 half lives At the beginning of this period 200 mg of caffeine were ingested (as tablets) to be sure that abstinence was not longer than 4 5 half lives The subjects were not allowed to smoke for 8 hours before the tests and a light caffeine free breakfast was allowed between 7 30 and 8 00 AM

All tests were performed from 8 15 to 11 15 AM with the subject in the supine position The first 30 minutes served as an equilibration period to reach basal hemodynamic and humoral values In this period an Arteriosonde 1225 (semiautomatic BP monitor) and a mercury strain gauge venous occlusion plethysmograph (forearm blood flow registration) were connected to the subject's left arm Because we only wanted to measure muscle flow, a wrist cuff was inflated during the measurements to block the skin flow of the hand Heart rate was measured by electrocardiogram An antecubital vein of the right arm was cannulated and blood samples were taken for determination of plasma caffeine renin and norepinephrine concentrations just before intervention, at the individual Tm and 120 minutes after intervention After the first 30 minutes of equilibration, systolic and diastolic BP and heart rate were measured every 5 minutes for 30 minutes In between these measurements 4 series of 3 forearm blood flow recordings were made and blood was sampled Subsequently the subjects had to drink 300 ml of a beverage within 10 minutes in the supine position with the aid of a straw (except in the no intervention test) All beverages were prepared using a coffee machine with 300 ml of water and depending on the test, 25 g of coffee (strong coffee) 17 5 g of coffee (regular coffee), 17 5 g of decaffeinated coffee and no coffee (hot water test) Then, systolic and diastolic BPs and heart rate were recorded every 5 minutes for 2 hours, and again a series of 3 forearm blood flow registrations were made in between The protocol of the tests is illustrated in Figure 1

In 30 other normotensive and healthy subjects we also studied the hemodynamic effects of coffee The same protocol as in the regular coffee test was used For these subjects, however, the time of caffeine abstinence was arbitrary and not related to plasma caffeine $T^1/_2$ We used this group to study the relation between basal plasma caffeine levels and pressor responses to coffee In these subjects we did not sample blood for determination of plasma catecholamines or plasma renin activity

Plasma concentrations of caffeine were analyzed with a reversed phase high performance liquid chromatography method [6] Plasma catecholamine levels were measured by a radioenzymatic assay,[11] and plasma renin activity by radioimmunoassay [12]

**Statistical analysis** Hemodynamic variables before intervention were averaged for each subject to 1 basic value, and after intervention to 1 value for every period of 20 minutes Differences between the 20 minute period values and the basic value were averaged for each subject, resulting in 1 mean change over the 2 hour period In the statistical analysis these mean changes induced by strong, regular or decaffeinated coffee or hot water were compared with the results of the no-intervention test by Student $t$ test for paired observations (2 sided) Humoral variables were analyzed by comparing values after intervention with basal values by the paired Wilcoxon test (2 sided) The fractional changes in the 5 tests also were compared with each other Correlation coefficients were calculated according to Pearson Mean arterial pressure was calculated as the sum of diastolic BP and one third of pulse pressure, and forearm vascular resistance was calculated by dividing mean arterial pressure through forearm blood flow Forearm vascular resistance is expressed in arbitrary units All results are presented as mean ± standard error of the mean

## Results

The results of the preliminary pharmacokinetic measurements are shown in Figure 2 Peak plasma caffeine concentrations were reached in 4 subjects in the first, in 1 in the third, in 2 in the fourth and in 1 in the fifth 20 minute period after coffee The mean Tm was 50 ± 12 minutes Calculated $T^1/_2$ ranged from 2 to 8 5 hours (mean 4 2 ± 0 8) The caffeine abstinence period for the 5 tests ranged from 9 to $38^1/_4$ hours In the pilot study the mean peak plasma caffeine level was 4 3 ± 0 6 mg/liter Figure 2 shows that plasma caffeine levels are almost in a steady state during the tests

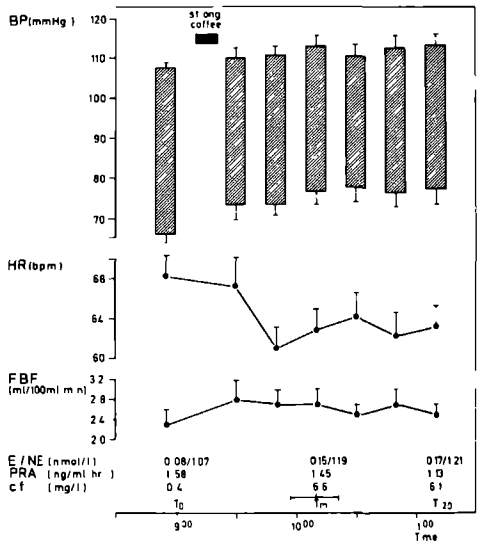


**FIGURE 1** Schedule of measurements in 8 subjects after drinking strong coffee Mean values (± standard error of the mean) of blood pressure (BP) heart rate (HR) and forearm blood flow (FBF) before and for 6 periods of 20 minutes after coffee ingestion are given Plasma concentrations of norepinephrine epinephrine (NE E) renin (PRA) and caffeine (cf) were measured 3 times Tm = time of plasma peak level

**TABLE I Basal Values of all Hemodynamic Parameters in the Five Tests**

| | NI | W | DC | RC | SC |
|---|---|---|---|---|---|
| Systolic blood pressure (mm Hg) | 110 ± 2 | 111 ± 2 | 113 ± 2 | 110 ± 2 | 108 ± 1 |
| Diastolic blood pressure (mm Hg) | 72 ± 2 | 68 ± 3 | 67 ± 2 | 66 ± 3 | 66 ± 2 |
| Mean arterial pressure (mm Hg) | 85 ± 2 | 83 ± 2 | 82 ± 2 | 81 ± 2 | 81 ± 2 |
| Heart rate (beats/min) | 72 ± 3 | 73 ± 3 | 72 ± 3 | 73 ± 3 | 68 ± 2 |
| Forearm blood flow (ml/100 ml·min) | 2.5 ± 0.2 | 2.7 ± 0.3 | 2.7 ± 0.3 | 2.6 ± 0.3 | 2.3 ± 0.3 |
| Forearm vascular resistance (U) | 37 ± 4 | 34 ± 5 | 34 ± 4 | 36 ± 6 | 40 ± 6 |

All values are mean ± standard error of the mean
DC = decaffeinated coffee, NI = no intervention, RC = regular coffee, SC = strong coffee, W = water

In Table I all basal hemodynamic data of the 5 tests are listed, and these values revealed no statistically significant differences. Mean changes over the 2-hour period of systolic and diastolic BPs, heart rate and forearm blood flow in the 5 experimental situations are shown in Figure 3. In the regular and strong coffee tests, the systolic BP increase measured 4 ± 1 and 5 ± 2 mm Hg, respectively; these increases were significantly higher than those in the other tests. The same applied to the increases in diastolic BP of 8 ± 1 and 9 ± 1 mm Hg, respectively, and in mean arterial pressure of 7 ± 1 mm Hg in both tests. Figure 4 shows that the increase in BP was maximal in the last hour. In the regular and strong coffee tests, the percent increase in diastolic BP in the last 20-minute period was 16 ± 3% and 15 ± 4%, respectively. After ingestion of regular coffee, the individual maximal increase in mean arterial pressure ranged from 8 to 19% and after strong coffee from 8 to 15%. There was no relation between the individual increase in mean arterial pressure and the corresponding time of caffeine abstinence. After ingestion of decaffeinated coffee, a smaller increase in diastolic BP was observed, whereas drinking water did not induce any changes. In all tests a decrease in heart rate was observed, and after water, regular coffee and strong coffee, these decreases were greater than those after the no-intervention test ($p < 0.10$); they were 5 ± 1, 7 ± 2 and 5 ± 1 beats/min, respectively. Without intervention, mean heart rate decreased by 2 ± 1 beats/min (Fig. 3). There was a significant difference between the increase in forearm blood flow of 0.3 ± 0.2 ml/100 ml·min after strong coffee intake and the decrease of 0.2 ± 0.2 ml/100 ml·min during the water and decaffeinated coffee test. As a consequence mean forearm vascular resistance decreased 2.1 ± 2.8 U during the strong coffee test, which was different from the increase in forearm vascular resistance of 3.6 ± 2.1 and 3.5 ± 2.1 U after hot water and decaffeinated coffee ($p = 0.03$, $p = 0.07$).

Figure 5 shows all humoral measurements of the 5 tests. Individual basal plasma caffeine levels of these tests were all within the range of less than 0.1 to 2.0 mg/liter, independent of the time of caffeine abstinence ($n = 40$, $r = -0.25$, $p > 0.1$). After ingestion of strong and regular coffee, a significant increase in plasma caffeine levels to 6.6 ± 0.4 and 5.2 ± 0.9 mg/liter was observed, the former being significantly greater than the latter ($p < 0.005$). In the hot-water and no-intervention tests, plasma caffeine concentration showed a small but significant decrease of 0.2 mg/liter at the end of the tests;

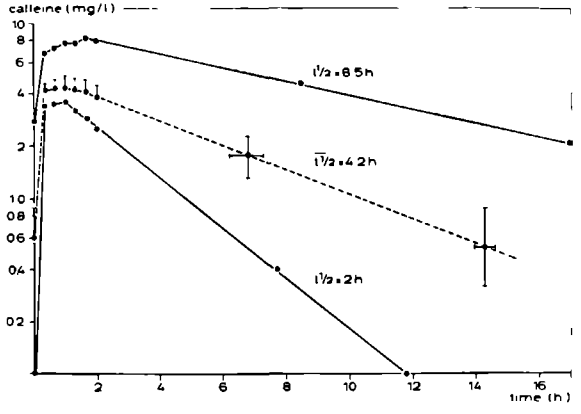


**FIGURE 2.** Course of plasma caffeine levels in subjects after drinking coffee. Mean results (± standard error of the mean) as well as the results of the subjects with the shortest and longest elimination half-life ($t_{1/2}$) of caffeine are given.

after decaffeinated coffee was ingested, no significant change was observed. Table II lists the mean fractional changes of plasma catecholamine levels. Changes in plasma norepinephrine levels were about the same among the 5 tests. Plasma epinephrine levels, however, increased more significantly after consumption of regular and strong coffee than after decaffeinated coffee. Plasma epinephrine levels and plasma renin activity were significantly different during all tests compared with basal values. The percent reduction of plasma renin activity after drinking decaffeinated coffee ($-17 \pm 7\%$), regular coffee ($-19 \pm 7\%$) and strong coffee ($-18 \pm 5\%$) was smaller than after drinking hot water ($-33 \pm 5\%$, $p < 0.10$). In the 4 tests in which a beverage was ingested, there was a significant correlation between the increase in plasma caffeine and the fractional increase in mean arterial pressure ($n = 32$, $r = 0.70$, $p < 0.001$). The fractional increase in plasma epinephrine weakly correlated with changes of plasma caffeine ($n = 32$, $r = 0.36$, $p < 0.05$).

Figure 6 shows the most relevant results of the second part of the study. In the 30 subjects, a strong correlation was observed between basal caffeine level and the increase in mean arterial pressure in the second hour after drinking coffee ([10]log (caffeine) vs mean arterial pressure: $n = 30$, $r = -0.71$, $p < 0.001$). Mean increase in mean arterial pressure measured $7 \pm 1\%$ (range $-1$ to 24%). Because of the arbitrary time of caffeine abstinence, there was also a large range of basal plasma caffeine levels (less than 0.1 to 6.3 mg/liter, mean $1.0 \pm 0.3$).

## Discussion

Under experimental conditions there is clear evidence for a BP-increasing effect of caffeine,[5,7,13,14] but during chronic ingestion of caffeine no cardiovascular response to caffeine or coffee occurred.[8,9] In 1968, Colton et al[15] suggested that this tolerance could partly ex-

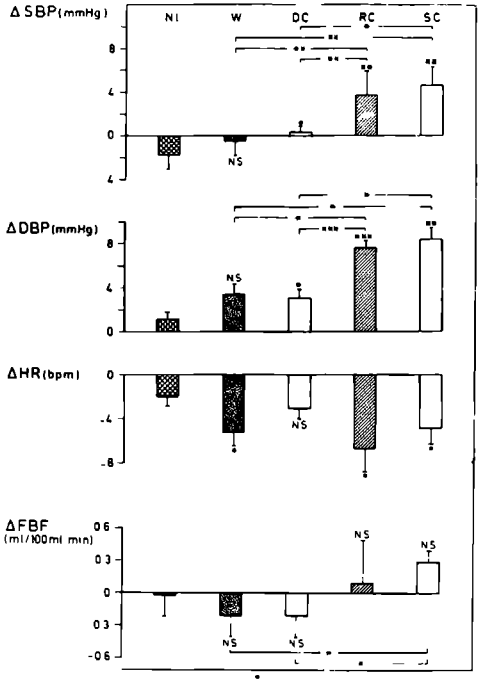


**FIGURE 3.** Mean changes over the 2-hour period of systolic and diastolic blood pressure (SBP, DBP), heart rate (HR) and forearm blood flow (FBF) after no intervention (NI), consumption of water (W), decaffeinated coffee (DC), regular coffee (RC) and strong coffee (SC) (mean ± standard error of the mean) **Asterisks** represent significances with respect to no intervention, unless signed otherwise bpm = beats/min, NS = not significant, * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$, **** $p < 0.001$

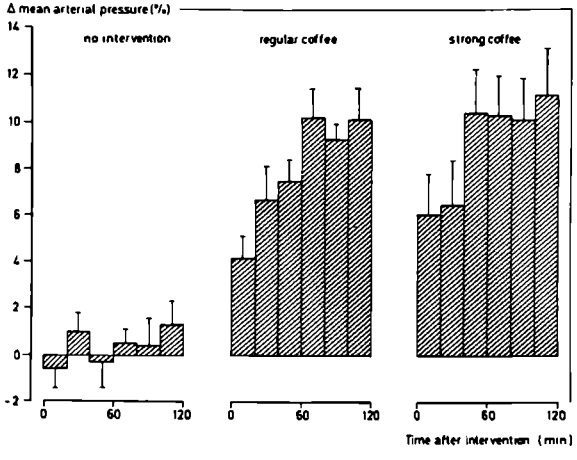


**FIGURE 4.** Fractional changes of mean arterial pressure for every 20-minute period after no intervention and after consumption of regular and strong coffee (mean ± standard error of the mean)

**TABLE II Mean Changes in Plasma Catecholamines in the Five Tests**

| | NI | W | DC | RC | SC |
|---|---|---|---|---|---|
| Epinephrine (%) | 75 ± 33 | 61 ± 41 | 33 ± 10 | 86 ± 14* | 140 ± 47* |
| Norepinephrine (%) | −2 ± 5 | 6 ± 11 | 4 ± 8 | 7 ± 6 | 14 ± 10 |

* $p < 0.05$ vs decaffeinated coffee test
All values are mean ± standard error of the mean.
Abbreviations as in Table I

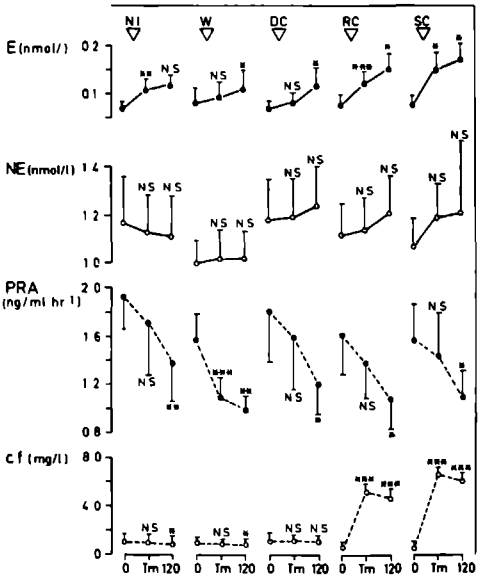


**FIGURE 5.** Mean (± standard error of the mean) values (n = 8) of plasma concentrations of norepinephrine (NE, E), renin (PRA) and caffeine (cf) before, at plasma peak level (Tm) and 120 minutes after no intervention (NI), consumption of water (W), decaffeinated coffee (DC), regular coffee (RC) and strong coffee (SC) **Asterisks** represent significances with respect to basal values NS = not significant; * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$

plain contradictory observations reported with respect to the circulatory effects of caffeine. The evident disparity between the acute effects of caffeine and the results of epidemiologic studies, which show no association between coffee and coronary heart disease,[16–18] also has been explained by the phenomenon of tolerance.[8]

In this study we could affirm the presumption that BP increase after consumption of coffee depends on basal plasma caffeine concentration (Fig. 6). Further, the problem has been evaluated from another point of view by testing the hypothesis, that a significant BP increase will occur when abstinence of caffeine is long enough to reach low basal plasma caffeine levels. In this study we used a caffeine abstinence of 4.5 half-lives, and such periods of abstinence are likely to occur in daily life. The range of half-lives from 2 to 8.5 hours in our subjects is in close agreement with other observations,[10] and this wide range is brought about by several exogenic influences,[19,20–22] as well as by genetically determined interindividual differences.[23] Despite a significant difference between the increase in plasma caffeine levels after ingestion of regular and strong coffee, the responses of BP were similar (Fig. 4). These results agree with the observation of a flat dose-response curve with respect to the BP-increasing effect of drinking 2 to 8 cups of coffee.[24] The observed BP increase after coffee ingestion did not show any correlation with the duration of caffeine abstinence. Consequently, we conclude that drinking coffee leads to an increase in BP after caffeine abstinence for 4.5 half-lives. In a previous study, plasma caffeine levels were measured in 600 consecutive patients; in about 50% of this group, plasma caffeine

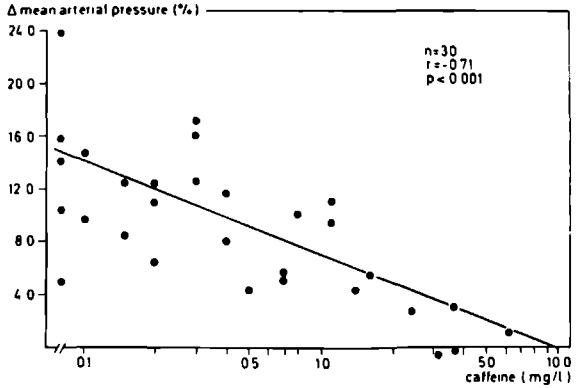


**FIGURE 6.** The relation between basal plasma caffeine concentration and the fractional increase in mean arterial pressure in the second hour after consumption of coffee in 30 normotensive subjects (Δ mean arterial pressure vs $^{10}$log [caffeine])

concentration was less than 2.0 mg/liter.[25] This indicates that drinking coffee may induce an increase in BP in daily life in a considerable proportion of the population. Drinking decaffeinated coffee induced only a small increase in diastolic BP, an observation that agrees with reported data.[26]

In another study, stronger BP increases are reported after a comparable load of coffee drinking.[6] However, in that study caffeine abstinence was longer, also reflected by a lower mean basal plasma caffeine of 0.3 mg/liter. Probably, the lower BP response to coffee in this study can be traced to partial tolerance, which would disappear after longer caffeine abstinence. The complete tolerance in Robertson's study,[8] even after 15 hours of caffeine abstinence, can be explained by the extremely long mean $T^1/_2$ (10 hours) of his subjects, resulting in a mean basal plasma caffeine of 2.3 mg/liter. Ammon et al[9] also observed complete tolerance to coffee, but no plasma caffeine data were available.

Epidemiologic studies have related mean coffee consumption to BP. Because of the results of this study, we believe a more valid conclusion could be drawn if the pharmacokinetics of caffeine were taken into consideration. Additionally, epidemiologists always correct for cigarette smoking because smoking is an independent risk factor in coronary heart disease and because coffee consumption and cigarette smoking are strongly related habits.[16] Because mean $T^1/_2$ of caffeine is shorter in people who smoke,[19] our results indicate that such a correction could lead to underestimation of the relation between BP or coronary heart disease and coffee.

Decreases in heart rate did not reveal clear significant differences between the 5 tests and, therefore, an additional effect of caffeine on the decrease in heart rate could not be proved with these observations, in contrast to other reports.[5,26] The changes in forearm blood flow and forearm vascular resistance illustrate that drinking strong coffee induces a slight vasodilation in the forearm muscle when compared with beverages containing no or a very small amount of caffeine. These data are not conclusive with respect to the effect of coffee on total peripheral resistance, because caffeine could induce opposite effects in blood vessels of other organ systems.

Changes of plasma epinephrine after consumption of coffee were less striking than in former reports.[6,26] This also may be explained by partial tolerance to the effects of coffee. The decrease in plasma renin activity in all tests, including the no-intervention test, suggests that this could be the result of the circadian rhythm of plasma renin activity, because all tests were performed in the morning.[27]

From this study we conclude that drinking coffee results in an increase in BP and a possible vasodilation in forearm muscle. Plasma epinephrine levels tend to increase after coffee, whereas plasma norepinephrine and renin activity do not change. There are no differences when drinking regular or stronger coffee. Drinking water does not result in circulatory changes, whereas drinking decaffeinated coffee induces a small increase in diastolic BP when compared with no intervention. Relevant hemodynamic changes with coffee already occur after caffeine abstinence of 4.5 half-lives. In normotensive subjects there is a strong negative correlation between the coffee-induced BP increase and basal plasma caffeine concentration. The $T^1/_2$ of caffeine shows a large variation, and subjects with short $T^1/_2$ are definitely exposed to pressor responses to coffee, depending on their daily intake.

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# Hemodynamic and humoral effects of coffee after $\beta_1$-selective and nonselective $\beta$-blockade

*Several studies report a substantial rise in plasma catecholamines after caffeine. Epinephrine infusion induces a pressor response after nonselective β-blockade. We studied the hemodynamic and humoral effects of drinking coffee after placebo and after both nonselective (propranolol) and $\beta_1$-selective (metoprolol) blockade in 12 normotensive subjects After placebo, coffee induced a rise in systolic and diastolic blood pressure and a fall in heart rate, whereas forearm blood flow did not change Plasma catecholamines, especially epinephrine (+150%), rose and plasma renin activity, fell after drinking coffee The effects of coffee on blood pressure, forearm blood flow, and all humoral parameters were not altered by pretreatment with propranolol or metoprolol The fall in heart rate after coffee, however, seemed to be greater during propranolol. We conclude that the rise in plasma epinephrine after coffee was too small to reveal differences in reaction in propranolol- and metoprolol-pretreated subjects*

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In other reports from our department, hemodynamic effects of epinephrine infusions after pretreatment with $\beta_1$-selective and nonselective $\beta$-adrenergic blockade have been reported.[16,18,19] After metoprolol, the normal vasodilation after epinephrine was largely maintained, whereas after propranolol, there was a vasoconstrictive or pressor response. This pressor response could be explained by the blockade of $\beta_2$-adrenergic receptors by propranolol, leaving the $\alpha$-adrenergic vasoconstriction caused by epinephrine unopposed. This so-called "unopposed $\alpha$-effect" results in an increase in total peripheral resistance, which is responsible for the pressor response. Possible spontaneously occurring examples of this phenomenon have been reported.[2,21,24] The clinical relevance, however, has not been fully elucidated. Until now, it has not been proved that stresses of daily life can also result in a pressor response during treatment with propranolol.

Since caffeine results in an increase in plasma catecholamines,[25,26,27] drinking coffee can be considered as such a stress. Our aim was to find out whether drinking coffee results in different hemodynamic effects after pretreatment with propranolol and metoprolol.

## Methods

Our subjects were nine male and three female volunteers, ranging in age from 17 to 38 yr,

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*Abbreviations used*

| | |
|---|---|
| BP | Blood pressure |
| DBP | Diastolic blood pressure |
| FBF | Forearm blood flow |
| FVR | Forearm vascular resistance |
| HR | Heart rate |
| MAP | Mean arterial pressure |
| PRA | Plasma renin activity |
| SBP | Systolic blood pressure |

who were normotensive and otherwise healthy All were habitual coffee drinkers (mean = 4 5, range two to eight cups of coffee a day) Lengths and body weights (mean ± SD) of the subjects amounted to 182 5 ± 10 0 cm and 72 7 ± 12 1 kg

Each subject participated in three tests in random order in which they received two cups of coffee after placebo, 240 mg propranolol, and 300 mg metoprolol These doses were given in a double-blind manner and were split up in three tablets, taken 15, 9, and 1 hr before starting each test The three tests were separated from each other by at least 3 days Before each test, the subjects had to abstain from caffeine-containing products for at least 17 hr and from smoking for 10 hr

After arrival at the laboratory, the subjects rested for 20 min in a supine position This period of rest started with the insertion of a catheter in an antecubital vein of the left arm This was followed by the connection of the Arteriosonde and the plethysmograph to the subjects' right arm, which was placed in an arm support 5 to 10 cm above heart level After this initial period, five determinations of blood pressure (BP) and heart rate (HR) were made every 5 min After the first measurement, blood was drawn to determine blood levels of caffeine, plasma renin activity (PRA), and catecholamines Between the following four measurements, three series of five forearm blood flow (FBF) determinations were made After that, the subjects were asked to drink two cups of coffee within 10 min Forty minutes later, exactly the same periods of rest and measurements were repeated The protocol is illustrated in Fig 1 by an example of a coffee test after propranolol

Coffee was prepared according to a standardized method with 350 ml water and 24 gm coffee This resulted in two cups of coffee, each containing 150 ml BP was measured with the Arteriosonde 1225, and HR was calculated from an ECG registration FBF was measured with a mercury strain-gauge venous occlusion plethysmograph Since we wanted to measure only changes in muscle FBF, room temperature was kept between 19° and 20 5° [1]

Samples for determination of plasma caffeine were analyzed with a reversed-phase HPLC method For this determination, a Spectra Physics 3500 B machine was used The column (stainless steel, length 15 cm, internal diameter 4 6 mm) was packed with Lichrosorb RP8, 5-$\mu$ particle size Detection was affected at 270 nm with a UV detector, model SP770 An injection loop of 100 $\mu$l was used The solvent was a mixture of 0 02M sodium acetate and 20% methanol Solvent flow measured 1 2 ml/min The sample was prepared by mixing 100 $\mu$l plasma with 400 $\mu$l perchloric acid, 0 23N The mixture was centrifuged, and 100 $\mu$l of the clear supernatant was injected onto the column Catecholamines were measured by a radioenzymatic assay[17] and PRA by a radioimmunoassay [7] In seven subjects, plasma concentration of propranolol and metoprolol were determined by a gas chromatographic method [9]

The hemodynamic and humoral effects of coffee after propranolol and metoprolol were compared with each other and with the results of the placebo test For each subject, all measurements of BP, HR, and FBF were averaged both before and after coffee Student's t test for paired observations was used Mean arterial pressure (MAP) was calculated as the sum of diastolic blood pressure (DBP) and one third of pulse pressure Forearm vascular resistance (FVR) was calculated by dividing MAP through FBF and expressed in arbitrary units All results are presented as mean ± SE

## Results

Fig 2 shows the values of BP, HR, and FBF before and after use of coffee in the placebo, propranolol, and metoprolol tests Mean basal values of BP and HR after placebo measured 116/69 ± 2/2 mm Hg and 63 ± 3 bpm Both

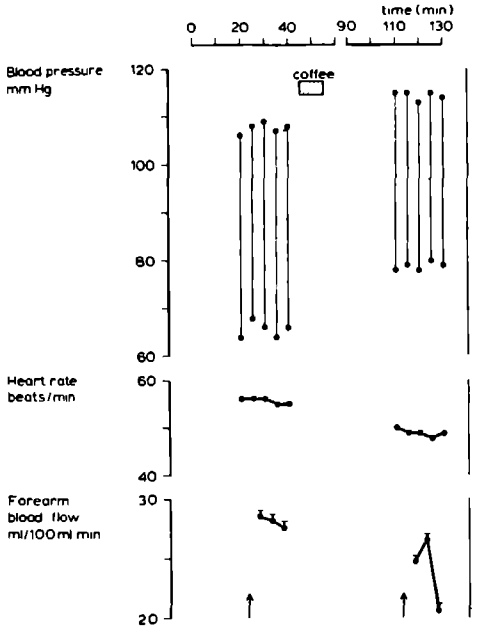


**Fig. 1.** BP, HR, and FBF before and after coffee in one subject after pretreatment with propranolol. Values of FBF are all mean ± SE of five determinations. At the time indicated by the *arrows*, blood was sampled for humoral parameters.

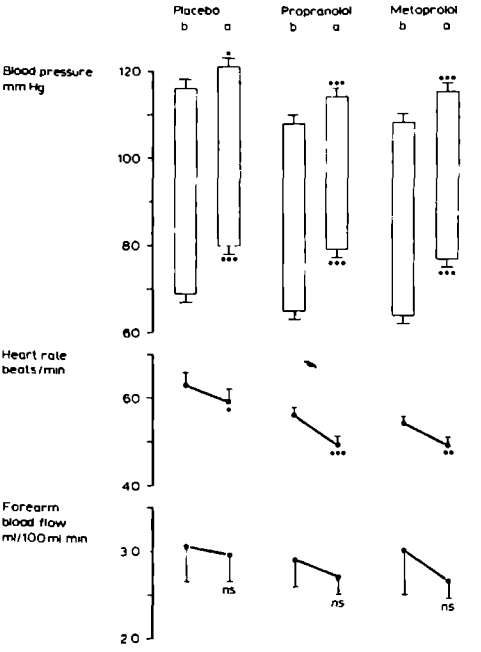


**Fig. 2.** BP, HR, and FBF before *(b)* and after *(a)* the coffee in placebo, propranolol, and metoprolol tests (mean ± SE). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, ns = not significant.

β-blockers reduced BP and HR. After propranolol and metoprolol, basal BP amounted to 108/65 ± 2/1 mm Hg and 108/64 ± 1/1 mm Hg, and HR was 56 ± 1 and 54 ± 1 bpm.

Drinking coffee induced a rise in BP and a fall in HR. The mean percent rise in systolic blood pressure (SBP) after coffee during the placebo, propranolol, and metoprolol test was 4%, 7%, and 7%; those in DBP were 16%, 22%, and 19%. The elevations were all significant but did not differ significantly from each other. After coffee, HR fell in all three tests. The fall in HR of 7 bpm after propranolol was greater than the fall of 4 bpm in both other tests. Table I shows mean values of the changes in BP and HR after coffee in the three tests. Basal FBF after placebo, propranolol, and metoprolol amounted to 3.1 ± 0.4, 2.8 ± 0.3, and 3.0 ± 0.5 ml/100 ml · min, and after coffee these values were not significantly less: 2.9 ± 0.3, 2.4 ± 0.2, and 2.3 ± 0.2. Calculated FVR rose from 31 ± 2.9 to 38 ± 4.6 U in the placebo test, after propranolol from 31 ± 3.5 to 42 ± 4.0 U, and after metoprolol from 32 ± 4.0 to 41 ± 3.5 U. Only in the propranolol test did the elevation in FVR reach statistical significance.

Mean basal plasma concentrations of caffeine were identical in all three tests and amounted to 0.3 μg/ml (range: <0.2 to 1.0 μg/ml). Sixty minutes after the coffee, mean concentrations rose to 8.2 ± 0.8, 7.8 ± 0.5, and 7.9 ± 0.6 μg/ml in the placebo, propranolol, and metoprolol tests (range: 4.9 to 14.1 μg/ml).

The basal PRA after propranolol (1.49 ± 0.36 ng/ml · $hr^{-1}$) was lower than after placebo (2.43 ± 0.50 ng/ml · $hr^{-1}$), whereas basal PRA after metoprolol (1.87 ± 0.51 ng/ml · $hr^{-1}$) was not significantly lower. In all tests, coffee induced a fall in PRA to 1.75 ± 0.24 (placebo), 0.99 ± 0.25 (propranolol), and 1 ± 0.18 ng/ml · $hr^{-1}$ (metoprolol).

Basal plasma epinephrine and norepinephrine were highest after metoprolol and lowest after

**Table I.** *Changes (Δ) in SBP, DBP, MAP, and HR because of coffee after placebo, propranolol, and metoprolol (mean ± SE)*

| | *Placebo* | *P1* | *Propranolol* | *P2* | *Metoprolol* | *P3* |
|---|---|---|---|---|---|---|
| Δ SBP (mm Hg) | 5 ± 1 4 | NS | 7 ± 1 2 | NS | 8 ± 1 2 | NS |
| Δ DBP (mm Hg) | 11 + 2 0 | NS | 14 ± 1 2 | NS | 12 ± 1 4 | NS |
| Δ MAP (mm Hg) | 9 ± 1 4 | NS | 11 ± 1 2 | NS | 11 ± 1 2 | NS |
| Δ HR (beats/min) | −4 ± 1 4 | P < 0 05 | −7 ± 0 9 | P = 0 08 | −4 ± 1 4 | NS |

P1 − placebo vs propranolol P2 − propranolol vs metoprolol P3 − metoprolol vs placebo NS not significant

**Table II.** *Plasma levels of epinephrine and norepinephrine before and after use of coffee in placebo, propranolol, and metoprolol tests (mean ± SE)*

| | *Placebo* | | *Propranolol* | | *Metoprolol* | |
|---|---|---|---|---|---|---|
| | *Before* | *After* | *Before* | *After* | *Before* | *After* |
| E (nmol/l) | 0 15 ± 0 01 | * 0 37 ± 0 08 | 0 17 ± 0 02 | * 0 43 ± 0 09 | 0 21 + 0 04 | † 0 54 ± 0 15 |
| NE (nmol/l) | 1 55 ± 0 18 | † 1 85 ± 0 18 | 1 75 ± 0 16 | ‡ 2 12 ± 0 27 | 1 89 ± 0 37 | ‡ 2 13 + 0 27 |

E − epinephrine NE − norepinephrine
*P < 0 01 †P < 0 02 ‡not significant

placebo but did not differ significantly from each other During placebo, propranolol and metoprolol epinephrine rose after coffee drinking 147%, 153%, and 157% The rise in plasma norepinephrine after coffee ingestion in the placebo test measured only 19% (P < 0 02) Table II shows all data on plasma catecholamines

Mean plasma concentrations of propranolol and metoprolol determined in seven subjects amounted to 289 nmol/l (range 82 to 690 nmol/l) and 703 nmol/l (range 330 to 1150 nmol/l)

### Discussion

Caffeine-containing products such as coffee, tea, cola-flavored drinks, cacao, and chocolate are widely used Thus pharmacologic effects of caffeine and eventual interactions with β-blockade could be of great clinical importance Many organ systems, e g , the gastrointestinal tract, central nervous system, kidneys, and cardiovascular system, are influenced by caffeine [8]

Possible pharmacologic mechanisms for the cardiovascular effects of caffeine are inhibition of the enzyme phosphodiesterase,[4] antagonism of endogenous adenosine,[12] and influence on intracellular $Ca^{2+}$ concentration,[8] all of which can be described as peripheral direct mechanisms The hemodynamic effects of caffeine could be partly based on the increased release of catecholamines and on a rise in PRA [25] Besides the former direct and the latter indirect peripheral mechanisms, central stimulation of vagal centers and of the vasomotor center in the brain stem could be important mechanisms for the cardiovascular effects of caffeine [31]

The literature on the hemodynamic effects of caffeine has many references to an increase in BP [11 13 25 31] In some, however, this effect could not be affirmed [1 28] The effects of caffeine on HR are also controversial [6 14 15 25 29] As far as we know, there is no literature available on the effects of coffee on FBF After infusion of the methylxanthine theophylline, an increase in FBF has been observed [23] A rise in FBF could also be expected after coffee as a result of the direct relaxing effect of caffeine on smooth muscle cells[8] and through epinephrine-mediated $\beta_2$-receptor stimulation In our study, FBF was not changed by coffee Differences in experimental design and tolerance to the effects of caffeine could be responsible for all the contradictions in the literature on the hemodynamic effects of caffeine [6 27] With respect to this tolerance, Robertson et al [27] suggested that abstinence from caffeine for more than 24 hr was required for maximal BP response In our study we measured considerable changes in hemody-

namics after an abstinence period of at least 17 hr Sixty minutes after coffee, we observed an increase in BP and a fall in HR in the placebo test After caffeine, a fall in total peripheral resistance has been reported [15 28] Since we did not observe a fall in FVR in all three tests, whereas DBP showed a rise, the latter being more pronounced than that in SBP, our results indicate that an increase in total peripheral resistance takes place

In our study the rises in plasma epinephrine after coffee always exceeded those in plasma norepinephrine Since we are looking for hemodynamic interactions between propranolol and daily life stresses with a rise in plasma epinephrine, coffee seems a suitable stress stimulus for our study Neither basal plasma catecholamines nor the response of catecholamines to coffee was changed by pretreatment with $\beta$-blockers As could be expected, both propranolol and metoprolol lowered basal PRA [3] After coffee, PRA decreased in all three tests These observations differ from those in other reports,[25 32 33] all of which reported an increase in PRA after methylxanthines Although we do not have an explanation for the observed decrease in PRA, we can nevertheless conclude that it is not likely that, in our study, the effect of coffee on BP was mediated by the renin-angiotensin system

Single-dose studies with the cardioselective $\beta$-antagonists atenolol and metoprolol have revealed an acute hypotensive response in normotensive subjects after both drugs [10 20] After 80 mg propranolol by mouth, Thadani and Parker[30] noted an acute fall in SBP, but according to Buhler,[5] the fall in BP gets through only after several days In our study, BP decreased within 15 hr to identical values after both metoprolol and propranolol The wide range of plasma concentrations of both $\beta$-blockers is in close agreement with other reports[22 30] and is the result of the major first-pass removal of these drugs by the liver With respect to this, there is no evidence for lack of compliance with the $\beta$-blocker pretreatment in our study

With respect to the primary aim of our study, we could not distinguish differences in BP response to coffee during the three tests Reactions of FBF to coffee were also identical throughout the three tests Thus we did not show an "unopposed $\alpha$-effect" after coffee in the propranolol test We have studied[19] the effect of low-dose epinephrine infusion on hemodynamics after selective and nonselective $\beta$-blockade in hypertension At the lowest rate of infusion, which corresponded with a rise in plasma epinephrine of 200% to 400%, we observed significant differences in reaction in propranolol- and metoprolol-treated patients Since, in our study, plasma epinephrine rose 150% to 160% after coffee, the stress stimulus used in our study was likely to be too small to reveal differences in hemodynamics of the propranolol and metoprolol test

During the propranolol test, the fall in HR was stronger than in both other tests This could be the result of the quinidine-like properties of propranolol After in vivo and in vitro experiments with rats, Strubelt[29] concluded that propranolol inhibited the positive chronotropic effect of methylxanthines in rats not only as a result of the $\beta$-receptor–blocking properties of propranolol but also because of its membrane-stabilizing activities Since metoprolol has no membrane-stabilizing activity, this mechanism may have contributed to the greater fall in HR after propranolol

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# Influence of Slow Calcium-Channel Blockade on the Cardiovascular Effects of Coffee

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**Summary.** An increase in blood pressure after coffee and caffeine has recently been reported A possible pharmacological mechanism for this pressor response is a rise in the intracellular calcium concentration, caused by an increase in calcium influx due to a direct effect of caffeine Accordingly, the cardiovascular effects of drinking coffee after placebo and verapamil 3 x 80 mg in 1 day in 10 normotensive volunteers have been examined in a single blind study After placebo, coffee led to an increase in blood pressure (7/14 mm Hg), and a fall in heart rate (−7 beats/min), forearm blood flow did not change Plasma epinephrine rose (257%), plasma norepinephrine did not change and the plasma renin activity fell significantly The haemodynamic and humoral changes after coffee were not altered by pretreatment with verapamil It is concluded that increased transmembrane calcium influx after caffeine does not appear to be an important pharmacological mechanism for the circulatory effects of coffee

**Key words:** caffeine, verapamil, coffee, blood pressure, slow calcium-channel blockade, drug interaction, healthy volunteers, plasma catecholamines, plasma renin activity

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Since caffeine is frequently ingested, its haemodynamic effects and possible interactions with antihypertensive agents are of great importance Although there are many contradictory reports in the literature on the haemodynamic effects of caffeine, recent studies have shown an increase in blood pressure after coffee or caffeine both in normotensive and hypertensive subjects (Freestone and Ramsay 1982, Izzo et al 1983, Smits et al 1983, Whitsett et al 1984) Several pharmacological effects of caffeine might be responsible for the effect (Rall 1980) According to Eichler (1976), one of the most important mechanisms for the circulatory effects of caffeine is a rise in the cytoplasmic calcium (Ca) concentration At least three different explanations for this rise are suggested in the literature, first, increased Ca release from intracellular Ca stores, second, impaired reuptake into the stores (Blayney et al 1978, Hunter et al 1982, Itoh et al 1981, Poledna and Morad 1983), and third, in vitro studies have shown that caffeine may cause increased transmembrane Ca influx (Blinks et al 1972, Kohlhardt et al 1974, Pang 1980)

In order to investigate the role of the latter mechanism in the circulatory effects of caffeine, haemodynamic and humoral changes after coffee have been investigated with and without previous blockade of the transmembrane Ca influx with the Ca slow channel blocker verapamil Besides theoretical interest, there is clinical relevance in question Is the pressor response to the drinking of coffee diminished during treatment with Ca slow-channel blocking agents? The caffeine was administered as a normal coffee beverage since this is most relevant to daily life

## Subjects and Methods

Ten healthy normotensive volunteers (6 men, 4 women) gave informed consent to the study All the subjects were accustomed to drink coffee each day, their mean intake (±SD) was 5 6±2 0 cups of coffee per day (range 2-9) Age, height and body weight (mean±SD) of the group were 24 3±6 1 years, 179 3±9 6 cm and 68 5±9 1 kg, respectively Each subject took part in two coffee tests, one after placebo and one after pretreatment with verapamil (3 x 80 mg) The subjects were instructed to take

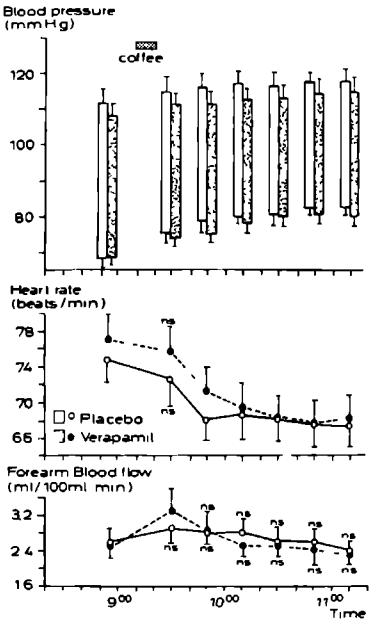


**Fig. 1** BP, HR and FBF before and after coffee in the placebo and verapamil studies (mean ± SEM) All haemodynamic values after coffee are significantly changed, except those marked ns (not significant)

2 tablets of the latter drug in the evening before the test, at 17 00 p m and 23 00 p m , and the third tablet 45 min before starting the coffee test All tests were performed in the morning between 8 15 a m and 11 15 a m The placebo and verapamil studies were separated from each other by at least one week, and the sequence of medication was evenly distributed over the subjects in a single-blind manner Before each test the subjects abstained from all methylxanthine-containing products for at least 24 h, and they were instructed not to smoke on the morning of the test. A light breakfast was allowed between 7 30 a. m and 8 00 a m

The subject remained supine throughout the test. All parameters were measured before and for 2 h after coffee During the initial rest period of 30 min an antecubital vein in the right arm was cannulated for blood sampling. Arteriosonde and plethysmograph were connected to the left arm, which was placed in a support 5 to 10 cm above heart level After the period of rest, blood pressure (BP) and heart rate (HR) were recorded 6 times at 5-min intervals In between four series of three forearm blood flow measurements (FBF) were made, and blood was sampled for determination of basal blood levels of caffeine, plasma renin activity (PRA) and catecholamines The subject was then asked to drink 2 cups of coffee within 10 min, whilst remaining supine Afterwards BP and HR were measured every 5 min for 2 h Series of 3 FBF recordings were made between those measurements Blood was sampled 60 and 120 min after drinking the coffee For measurement of plasma caffeine concentrations an additional sample was taken after 40 min, because some studies have shown peak plasma caffeine at different times (Bonati et al 1982, Robertson et al 1978)

Coffee was prepared with a coffee machine, using 300 ml water and 20 g coffee, giving 2 cups of percolated coffee together containing about 240 mg caffeine BP was measured with an Arteriosonde 1225 and HR was calculated from the ECG FBF was measured using mercury-strain gauge venous occlusion plethysmography As only muscle flow was wanted, the skin flow in the hand was excluded by inflating a wrist cuff during all measurements Plasma caffeine was analyzed by a reversed-phase HPLC method (Smits et al 1983) Catecholamines were measured by a radioenzymatic assay (Hoffman et al 1982), and PRA by radioimmunoassay (Drayer and Benraad 1975)

In each subject the mean values of all haemodynamic parameters before and for each 20-min period after coffee drinking were compared The paired student's t test was employed for statistical analysis of the haemodynamic parameters in both studies Humoral parameters were analyzed by Wilcoxon's paired signed rank test in only 9 subjects, as blood sampling in one subject was incomplete Differences were considered to be statistically significant at P-values of less than 5% (two-tailed) Mean arterial pressure (MAP) was calculated as the sum of diastolic blood pressure (DBP) and one third of pulse pressure Forearm vascular resistance (FVR) was calculated by dividing MAP into FBF and was expressed in arbitrary units The results are presented as mean ± SEM

## Results

Mean values of all haemodynamic parameters in the 20 min periods both for the placebo and verapamil studies are shown in Fig 1. After placebo basal BP and HR were 112 ± 4.0/68 ± 2 4 mm Hg and 75 ± 2 2 beats/min, respectively. Pretreatment with verapamil did not significantly alter the basal values (108 ± 3 3/69 ± 1 9 mm Hg, 77 beats/min), nor was there any difference in basal FBF in either study.

There was a continuous rise in BP following ingestion of the coffee In the placebo and verapamil studies the increase in systolic and diastolic blood pressures (SBP/DBP) 2 h after coffee were, respectively, 7 ± 1 7/14 ± 1 6 mm Hg and 7 ± 1 9/12 ± 1 0 mm Hg The pulse rate decreased after drinking coffee, with a maximal fall of 7 beats/min in the placebo study and 9 beats/min after pretreatment with verapamil The coffee-induced changes in SBP, DBP, MAP and HR were statistically significant in both studies In the verapamil study FBF showed a significant rise in the first 20-min period ($p < 0.05$) The ultimate fall in FBF of 0 2 ml/100 ml min in both studies after coffee was not significant Two hours after coffee, however, the calculated FVR was significantly increased in both the placebo and verapamil studies, by, respectively, 7 2 ± 3 0 and 9 1 ± 3 2 units There were no significant differences in the coffee-induced responses in any haemodynamic parameters between the placebo and verapamil studies

Plasma caffeine levels were similar after pretreatment with placebo and verapamil, the maximal values after 60 min being 5 9 ± 0 5 and 6 1 ± 0 4 mg/l, respectively After drinking coffee, plasma adrenaline rose significantly in both studies, whereas plasma noradrenaline did not change and PRA showed a significant fall (Fig 2) The percentage changes in PRA and plasma catecholamines after drinking coffee in both studies are shown in Table 1 The coffee-induced responses in these humoral parameters were not significantly different in the two studies The basal levels of caffeine and catecholamines, too, were unchanged after verapamil Basal PRA rose from 1 11 ± 0 15 ng Ang I/ml $h^{-1}$ after placebo to 1 84 ± 0 30 ng Ang I/ml $h^{-1}$ after verapamil ($p < 0.05$)

No significant correlation was found between changes in haemodynamic and humoral parameters

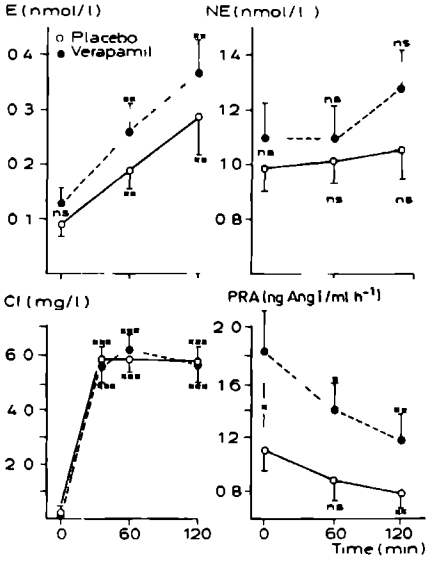


**Fig 2** Plasma levels of adrenaline (E) noradrenaline (NE), caffeine (cf) and PRA before (0) and 40 60 and 120 min after coffee (mean ± SEM) Differences from baseline in the placebo and verapamil studies were statistically tested $*p < 0.05$ $**p < 0.01$ $***p < 0.001$ ns not significant

## Discussion

In the placebo study drinking coffee induced an important rise in BP, notably in DBP The increase was accompanied by a fall in HR and an ultimate rise in calculated FVR, whereas FBF did not change It is generally accepted that these findings should be considered as the result of the caffeine load, as caffeine is the only cardiovascular active drug in coffee (Eichler 1976, Whittset et al 1984) The rise in plasma adrenaline after drinking coffee, as observed here, is in agreement with other observations (Izzo et al 1983, Robertson et al 1978, Smits et al 1983) In vitro studies have suggested that the rise may be the result of a direct stimulant effect of methylxanthines on adrenal release of catecholamines (Poisner 1973) It may also be interpreted as a sign of increased stimulation of the hypothalamo-sympatho-adrenal axis (Robertson et al 1978, Snider and Waldeck 1974) No correlation was found between the coffee-induced changes in plasma adrenaline and systolic or

**Table 1** Percentage changes (%) in plasma levels of adrenaline (A), noradrenaline (NA) and plasma renin activity (PRA) 60 and 120 min after coffee in the placebo and verapamil studies (mean ± SEM)

| Time (min) | Placebo | | Verapamil | |
|---|---|---|---|---|
| | 60 | 120 | 60 | 120 |
| A (%) | 132 ±22 8 | 257 ±58 1 | 128 ±25 3 | 266 ±75 0 |
| NA (%) | 69 ± 9 5 | 92 ± 8 6 | 25 ± 7 4 | 148 ± 8 9 |
| PRA (%) | −18 1 ± 10 5 | −27 3 ± 6 5 | −19 4 ± 6 0 | −33 0 ± 6 8 |

diastolic blood pressure, so the role of the increased level of plasma adrenaline in the haemodynamic effects induced by coffee still remain unclear It was not possible to confirm the increase in PRA after caffeine ingestion reported by others (Robertson et al 1978), but the present results are in close agreement with our previous observations on the effect of drinking coffee (Smits et al 1983) Perhaps an increase in PRA after coffee may occur only after a longer period of abstinence from caffeine, as tolerance to the humoral effects of caffeine has been described (Robertson et al 1981)

One possible explanation for the fall of PRA in both studies is the circadian rhythm of PRA since all tests were performed in the morning (Modlinger et al 1976)

Pretreatment with verapamil did not significantly change basal haemodynamics in the study Muiesan et al (1981) also concluded that verapamil administered acutely did not alter BP or pulse rate in normotensive subjects The basal values of plasma catecholamines did not reveal significant differences after placebo or verapamil The only humoral parameter changed after verapamil was the rise in PRA, probably caused by stimulation of the renin-angiotensin system as a result of peripheral vasodilation (Koch-Weser 1974) The slightly higher basal values of HR and plasma catecholamines in the verapamil study might be a consequence of the vasodilator effect of verapamil The results may indicate that after short-term verapamil administration the balance between the well-known negative chronotropic effect of verapamil and the reflex tachycardia resulting from its vasodilator effect is turned in favour of the latter (Saini 1984)

Verapamil was used here as a slow Ca-channel blocking drug, in the dose of 240 mg over 14 5 h A single dose of 160 mg verapamil orally or 7 5 12,5 mg i v causes vasodilatation in man (Muiesan et al 1981, Vincenzi et al 1976), and as evidence of vasodilation after verapamil was seen in our subjects, it can be assumed that the transmembrane Ca influx was sufficiently blocked in this experiment

Several pharmacological activities of caffeine might be responsible for its circulatory effects The increase in circulating catecholamines after caffeine may induce a rise in intracellular cyclic adenosine monophosphate, and so caffeine might exert a positive inotropic effect This could be enhanced by the caffeine-mediated inhibition of the enzyme phosphodiesterase (Beavo et al 1970) Antagonism of endogenous adenosine (Fredholm 1980) and central mechanisms may also contribute to the cardiovascular effects of caffeine (Thelen 1965, personal communication) As mentioned in the introduction, there is also evidence of an increased intracellular Ca concentration after caffeine in mammalian heart and smooth muscle cells (Blinks et al 1972, Itoh et al 1981) In the present study there were similar haemodynamic and humoral responses to drinking coffee in the placebo and verapamil studies According to the similar time course and height of the plasma caffeine levels in the two studies, the body load and kinetics of caffeine were the same after placebo and verapamil The similarity of the circulatory response to the load in both studies indicates that pretreatment with the slow Ca-channel blocker verapamil had not inhibited the cardiovascular effects of drinking coffee In studies in vitro an increased cytoplasmic Ca has been observed after caffeine, which appeared to be the result of caffeine-induced release of Ca from intracellular stores (Hunter et al 1982, Itoh et al 1981) and impaired Ca re-uptake in those stores (Blayney et al 1978, Poledna and Morad, 1983, Shine and Langer 1971) Since verapamil exerts no effects on intracellular Ca mobilization, the present study was unable to contribute to evaluation of the role of these mechanisms in the circulatory effects of caffeine

It is concluded that the role of calcium in the cardiovascular effects of drinking coffee, if any, may be of intracellular origin and seem not to involve changes in transmembrane calcium influx The contributions of the other pharmacological mechanisms mentioned to the circulatory effects of coffee ingestion have still to be explored

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# CHAPTER VI

## THE ROLE OF EPINEPHRINE IN THE CIRCULATORY EFFECTS OF COFFEE IN MAN

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**SUMMARY**

To assess the contribution of circulating epinephrine to the cardiovascular effects of drinking coffee, we studied the hemodynamic and humoral response to coffee in 10 normotensive, 10 bilaterally adrenalectomised and 10 hypertensive subjects. In the normotensive group drinking coffee exerted a rise in blood pressure (+5.1/+11.5 mmHg), a fall in heart rate (-6.0 bpm), a rise in plasma epinephrine (+257.2%), and no change in plasma norepinephrine. The response to coffee in the hypertensive group was similar or even enhanced. In the adrenalectomised patients the coffee-induced rise in diastolic blood pressure was attenuated (+7.9 mmHg; $P<0.05$), whereas plasma norepinephrine showed a fall (-20.8%) and plasma epinephrine remained undetectable throughout all tests. Additionally, a fall in plasma renin activity after coffee was observed in all 3 groups. We conclude that the pressor response to coffee is not purely due to circulating epinephrine, or to stimulation of the renin-angiotensin-aldosterone system. On the other hand, the coffee-induced increase of plasma epinephrine may increase the pressor response to coffee.

## INTRODUCTION

In previous studies we ascertained that drinking 2 cups of coffee induced considerable changes in blood pressure, heart rate and plasma epinephrine, and that these effects were due to the caffeine load(1,2,3). With respect to the pharmacological basis of these effects there is still much incertitude. In several organ systems the variety of physiologic and biochemical effects of caffeine resemble the effects of sympathomimetic drugs, and therefore it was suggested that the increase of plasma epinephrine after methylxanthines should be responsible for its circulatory effects(4). As caffeine and coffee have been reported respectively to raise(5) and to lower plasma renin activity(1), the importance of the renin-angiotensin-aldosterone system with respect to the effect of coffee on blood pressure also remains unclear.

Our first aim of this study was to find out what is the role of increased levels of plasma epinephrine in the circulatory effects of coffee and therefore we analysed the hemodynamic and humoral response to coffee in patients, who were adrenalectomised bilaterally. Additionally, we were interested in the plasma renin activity before and after coffee in this group. To answer these questions we performed coffee tests in adrenalectomised patients as well as in normotensive healthy subjects. Since mean blood pressure is higher in adrenalectomised patients similar coffee tests were performed in hypertensive subjects also.

## PATIENTS AND METHODS

Ten normotensive subjects, 10 patients with Cushing's disease who had been treated previously by bilateral adrenalectomy and 10 hypertensive patients gave their informed consent for this study, which was approved by the ethical committee of the hospital. All healthy volunteers were used to daily coffee ingestion, with a mean intake of 5.6±0.6 cups of coffee per day. In the hypertensive and adrenalectomised group, all patients but one of each group were habitual coffee users, but the mean intake of coffee

in the 3 groups did not differ significantly. The time between bilateral adrenalectomy and the coffee tests averaged 53.0 ± 26.3 months (range 0.5 - 252) and all adrenalectomised patients were substituted with cortisone (9x), or prednisone (1x) and 9-α-fluorocortisol (10x). From all hypertensive patients 2 had renovascular hypertension, whereas the others were suffering from essential hypertension, and none of them had medication. Table I gives some other relevant characteristics of the 3 groups.

After a period of caffeine abstinence of at least 24 hr all subjects participated in a coffee test. All tests were performed in the morning from 8.15 - 11.15 hour. A light caffeine-free breakfast was allowed between 7.30 and 8.00 am. Smoking was not allowed in the morning of the test. Throughout the whole test the subjects remained in the supine position. In an initial equilibration period of 30 minutes an antecubital vein of the right arm was cannulated for blood sampling. The left arm was placed in an arm support 5 to 10 cm above heart level, and this arm was used for blood pressure monitoring by an Arteriosonde 1225, and for measuring forearm blood flow by strain-gauge venous occlusion plethysmography. Heart rate was measured by ECG. After equilibration systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) were measured every 5 minutes for 6 times. Meanwhile 4 series of 3 forearm blood flow registrations (FBF) were made and blood was sampled for the determination of basal concentrations of caffeine, plasma renin activity (PRA), catecholamines, and in the hypertensive group also plasma aldosterone. After the basal measurements the subjects were asked to drink 2 cups of regular coffee within 10 minutes in the supine position with the aid of a straw. Subsequently, SBP, DBP and HR were registered each 5 minutes for 2 hours, and meanwhile again series of 3 FBF registrations were made. Blood was sampled again at 60 and 120 minutes after the ingestion of coffee.

Coffee was prepared with a coffee machine using 300 ml of water and 20 grams coffee, and this resulted in 2 cups of coffee containing together about 240 mg caffeine. Plasma caffeine concentrations were analysed with a reversed-phase HPLC-method(1), plasma catecholamines by radioenzymatic assay(6) and PRA by radioimmunoassay(7). In this study no tests with placebo or

**Table I:** Some relevant characteristics of the 3 groups of 10 subjects (Mean ± SE, range between brackets).

| | NORMOTENSIVES | ADRENALECTOMISED | HYPERTENSIVES |
|---|---|---|---|
| Sex (M/F) | 6/4 | 1/9 | 3/7 |
| Age (years) | 24.3 ± 1.9(19-37)* | 36.9 ± 4.0(19-56) | 39.0 ± 4.3(18-56) |
| Length (cm) | 179 ± 3(168-201)* | 167 ± 4(144-184) | 168 ± 2(158-179) |
| Weight (kg) | 68.5 ± 2.9(54.4-85.0) | 60.3 ± 4.4(42.0-75.1) | 66.3 ± 3.3(53.0-84.0) |
| Quetelet-index ($kg/m^2$) | 21.3 ± 0.5(19.3-24.3) | 21.4 ± 0.8(17.8-25.4) | 23.4 ± 0.8(19.0-27.7)** |
| Endogenous Creatinine Clearance (ml/min) | - | - | 104 ± 7(82-155) |
| Plasma-sodium (mmol/l) | - | 142.3 ± 0.6(140-145) | 140.6 ± 0.7(138-142) |
| Plasma-potassium (mmol/l) | - | 3.6 ± 0.1(3.1-4.0) | 4.1 ± 0.1(3.7-4.6) |
| Plasma cortisol (µmol/l) | - | 0.26 ± 0.06(<0.02-0.50) | - |

* $P<0.05$ vs adrenalectomised/hypertensive

** $P<0.05$ vs normotensive

decaffeinated coffee were performed, firstly because we previously studied the circulatory effects of coffee in a placebo-controlled manner(3), and secondly because the aim of this study was only to compare the response to coffee in 3 different groups.

To evaluate the hemodynamic coffee-induced changes for each group, variables were averaged for each 20 minute period after coffee and compared to mean basal values with Student's t-test for paired observations. For comparing the changes after coffee in the 3 different groups, the mean change over the complete 2-hour period after coffee was calculated, and these values were compared with each other by Student's t-test for unpaired observations. Humoral parameters were analysed in the same way with Wilcoxon's 2 sample test and with Wilcoxon's paired rank test. Differences were considered to be statistically significant at P-values of less than 0.05 (2-sided). Correlation coefficients were calculated according to Pearson. Mean arterial pressure (MAP) was calculated as the sum of DBP and one third of pulse pressure. Forearm vascular resistance (FVR) was calculated by dividing MAP through FBF and was expressed in arbitrary units (U). All results are presented as mean ± SE, unless indicated otherwise.

## RESULTS

Table I shows that mean age in the normotensive group was lower, and mean length higher than in both other groups. In the hypertensive patients Quetelet-index was higher when compared to the normotensive group. Table II summarizes the basal values of all hemodynamic and humoral parameters. As expected mean basal blood pressure of the hypertensive patients was significantly higher than of both other groups. Between the normotensive and adrenalectomised subjects there were no significant differences in mean SBP and MAP. Basal DBP, however, was higher in the adrenalectomised patients. Mean basal values of HR and FVR revealed no significant differences between the 3 groups, whereas basal FBF appeared to be higher in the hypertensive patients.

**Table II:** Mean basal values (±SE) of all hemodynamic and humoral parameters of the 3 groups of 10 subjects

| | NORMOTENSIVE | P1 | ADRENALECTOMISED | P2 | HYPERTENSIVE | P3 |
|---|---|---|---|---|---|---|
| HEMODYNAMIC | | | | | | |
| Systolic blood pressure (mmHg) | 111.6±4.0 | ns | 116.5±5.7 | P<0.01 | 150.3±6.9 | P<0.001 |
| Diastolic blood pressure (mmHg) | 68.3±2.4 | P<0.05 | 78.4±3.8 | P<0.01 | 99.6±4.7 | P<0.001 |
| Mean arterial pressure (mmHg) | 82.8±2.7 | ns | 91.1±4.0 | P<0.01 | 116.5±5.3 | P<0.001 |
| Heart rate (bpm) | 74.7±2.2 | ns | 76.6±2.4 | ns | 75.9±3.3 | ns |
| Forearm blood flow (ml/100 ml.min) | 2.6±0.3 | ns | 2.5±0.2 | P<0.05 | 3.6±0.4 | P=0.07 |
| Forearm vascular resistance (U) | 34.8±3.4 | ns | 39.7±3.7 | ns | 37.3±5.1 | ns |
| HUMORAL | | | | | | |
| Caffeine (mg/l) | 0.2 ±0.04 | ns | 0.1±0.1 | ns | ND (< 0.1) | ns |
| Epinephrine (nmol/l) | 0.09±0.02 | P<0.01 | ND(<0.05) | P=0.0002 | 0.13±0.03 | ns |
| Norepinephrine (nmol/l) | 0.99±0.08 | ns | 2.03±0.30 | P<0.05 | 1.19±0.12 | ns |
| Plasma renin activity ($ng/ml.hr^{-1}$) | 1.11±0.15 | ns | 1.44±0.49 | ns | 1.95±0.70 | ns |

P1= normotensive vs adrenalectomised; P2= adrenalectomised vs hypertensive; P3= normotensive vs hypertensive
ns= not significant; ND= not detectable

Figure 1 presents the mean values of SBP, DBP, HR and FBF before and for all 20-minute periods after coffee of the 3 groups. In the normotensive subjects coffee induced a rise in SBP from 111.6±4.0 to 118.3±4.0 mmHg (P<0.01), and in DBP from 68.3±2.4 to 82.6±2.1 mmHg (P<0.0001) in the last 20-minute period. This corresponds with a percentual rise in DBP of 21.5±2.8%. MAP rose from 82.8±2.7 to 94.5±2.4 mmHg after coffee (P<0.001). Mean HR showed a fall from 74.7±2.2 to 67.4±2.3 bpm (P<0.001). Drinking coffee did not result in FBF-changes in the normotensive subjects. After an initial insignificant fall, mean FVR showed a small rise of 7.2±3.0 U in the last 20-minute period (P<0.05).

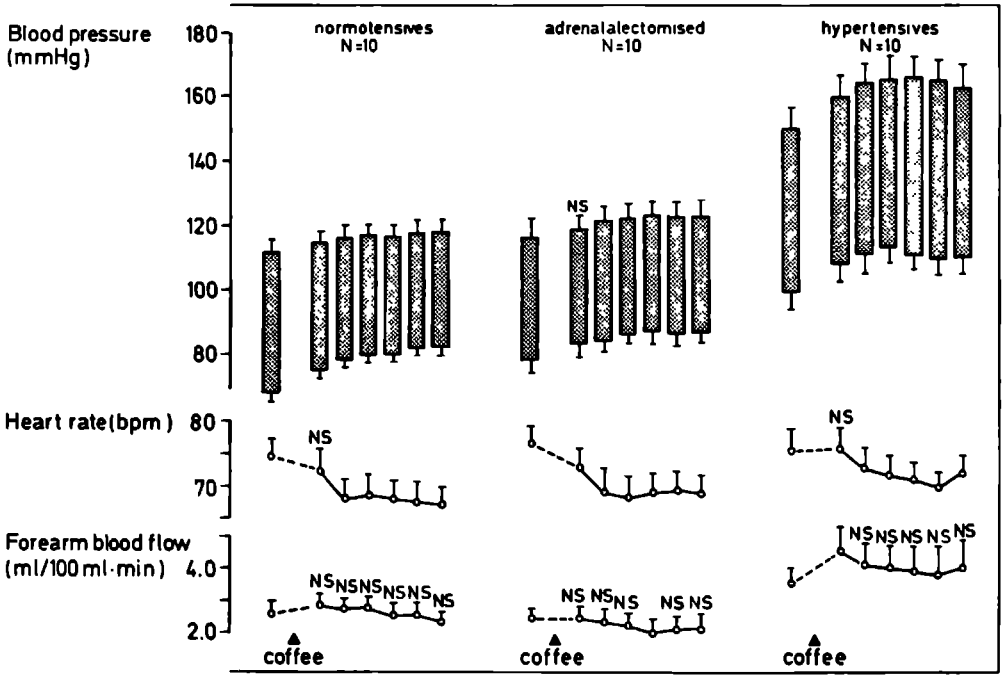


Figure 1: Mean (±SE) values of blood pressure, heart rate and forearm blood flow before and for each 20-minute period after coffee in the normotensive, adrenalectomised and hypertensive subjects. All values after coffee were significantly different from baseline values, unless signed with NS (not significant).

In the adrenalectomised patients SBP and DBP also were increased after coffee with respectively 6.5±1.4 and 9.2±1.6 mmHg ($P<0.01$ and $P<0.001$). Mean HR decreased after coffee with a maximum in the 3rd 20-minute period (-7.9±1.8 bpm; $P<0.01$). Mean FBF remained almost unchanged, with only a slight fall of -0.3±0.2 ml/100 ml.min ($P=0.07$). From 20 minutes after coffee to the end of the test mean FVR was increased when compared to basal values ($P<0.05$).

The hypertensive subjects also showed an increase in blood pressure after coffee. MAP rose from 116.5±5.3 to a maximum of 131.0±5.7 mmHg in the 3rd 20-minute period after coffee ($P<0.001$). HR fell from 20 minutes after coffee to the end of the test with a maximum of -5.7±1.4 bpm ($P<0.01$). Drinking coffee initially raised FBF from 3.6±0.4 to 4.6±0.7 ml/100 ml.min ($0.05<P<0.1$) but afterwards FBF ranged from 3.9±0.8 to 4.2±0.6 ml/100 ml.min. being not significantly different from baseline values. FVR firstly showed a fall from 37.3±5.1 to 32.9±5.2 U ($P=0.09$) and ultimately a small but not significant rise to 40.0±4.5 U.

Figure 2 shows the mean hemodynamic changes over the entire 2-hour period after coffee in the 3 groups. In the hypertensive patients the rise in SBP and MAP was larger than in both other groups. As a result of the higher basal values of blood pressure in the hypertensive group, the fractional changes in SBP and MAP showed no significant differences in the 3 groups. Mean rise of DBP of 7.9±1.1 mmHg in the adrenalectomised group was significantly smaller than in the normotensive (11.5±1.0 mmHg; $P<0.05$) and in the hypertensive subjects (11.3±1.2 mmHg; $P<0.05$). There were no differences in the coffee-induced changes of HR and FBF between the 3 groups. However, the rise in calculated FVR in the adrenalectomised patients of 11.4±3.4 U was greater than the rise in both other groups (Fig. 2).

Mean basal values of plasma caffeine, catecholamines and PRA are summarized in Table II. Individual basal plasma caffeine ranged from <0.1 to 0.6 mg/l. There were no significant differences in mean basal plasma caffeine between the 3 groups. As expected, plasma epinephrine was below the level of detection in all adrenalectomised patients (<0.05 nmol/l). Basal plasma

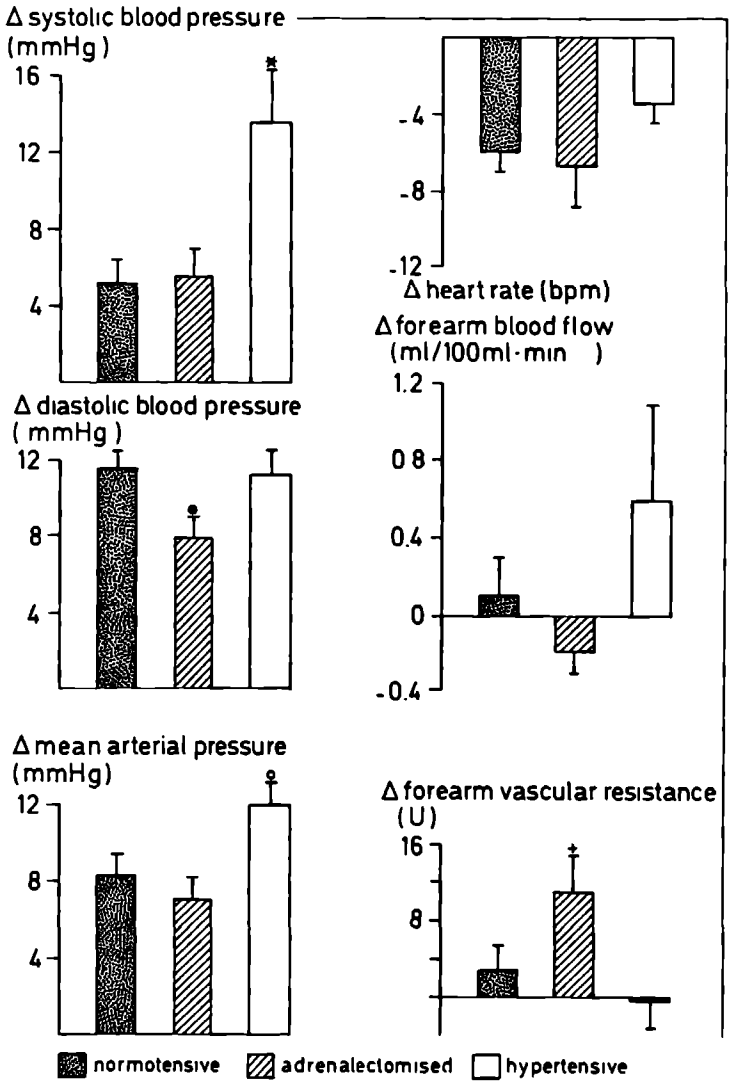


Figure 2: Mean (±SE) changes of all hemodynamic parameters over the entire 2-hour period after coffee in the normotensive, adrenalectomised and hypertensive group.

* P<0.01 vs normotensive, P<0.05 vs adrenalectomised

● P<0.05 vs both other groups

o P<0.01 vs adrenalectomised, P<0.05 vs normotensive

+ P<0.05 vs hypertensive, P=0.06 vs normotensive

catecholamines revealed no differences between normotensive and hypertensive subjects. In the adrenalectomised patients plasma norepinephrine was significantly higher than in the hypertensive group. We did not observe differences in baseline PRA between the 3 groups.

Figure 3 shows mean values of plasma caffeine, catecholamines and PRA before and after coffee. In the normotensive and adrenalectomised subjects mean plasma caffeine was maximal 60 min after coffee, and in the hypertensive group 120 minutes after coffee. Peak plasma levels were similar and measured 5.9±0.5, 5.8±0.5 and 6.2±0.3 mg/l respectively. In normotensive, adrenalectomised and hypertensive subjects mean PRA showed a fall of respectively -27.3±6.5, -14.1±4.7 and -8.7±6.0%, which only reached significance in the normotensive and adrenalectomised subjects. The changes of PRA were statistically not different between the 3 groups. In the hypertensive subjects mean basal plasma aldosterone numbered 6.3 ± 1.9 ng/100 ml, and remained unchanged after coffee. Plasma epinephrine did not reach detectable levels after coffee in the adrenalectomised patients, whereas in both other groups a significant rise was observed. The mean maximal rise of plasma epinephrine of 257.2±58.1% in the normotensive group was not significantly different from the rise of 115.1±21.4% in the hypertensives. In the normotensive and hypertensive subjects plasma norepinephrine hardly changed after coffee whereas a significant decrease was observed in the adrenalectomised group. This latter fall of -20.8±7.7% was significantly different from the rise of 2.9±8.6% in the hypertensive group ($P<0.05$).
There were no significant correlations between changes of humoral parameters and hemodynamic changes.

## DISCUSSION

Several years after the observation that the urinary excretion of catecholamines was increased by methylxanthines in man(8,9), valid laboratory methods became available to ascertain increased plasma catecholamines (especially epinephrine) after caffeine and coffee(1,5). This rise in plasma epinephrine could be the result

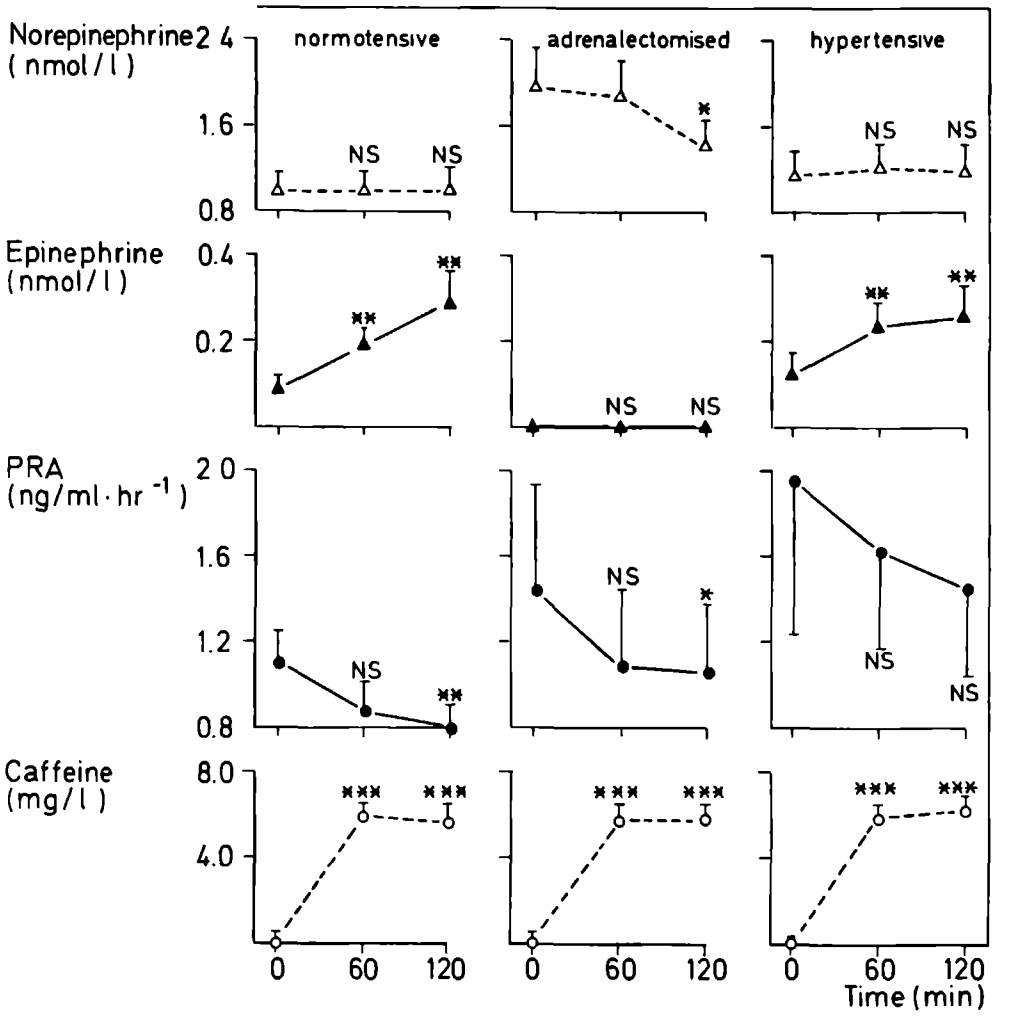


Figure 3: Mean (±SE) plasma concentrations of caffeine, PRA and catecholamines before (0) and 60 and 120 minutes after coffee in normotensive, adrenalectomised and hypertensive subjects

*P<0.05; **P<0.01; ***P<0.001; NS= not significant

of a direct effect of methylxanthines on the adrenal gland(10,11) or of the increased stimulation of sympathetic nerves to the adrenal medulla(12). Recent reports show that drinking coffee induces a rise in blood pressure(1,2,3) but until now the role of increased plasma epinephrine in the circulatory effects of caffeine is not clear.

In this study we analysed the hemodynamic and humoral effects of drinking coffee in 10 adrenalectomised patients, in 10 normotensive subjects and in 10 hypertensive subjects. The observations in normotensive subjects closely agree with former reports (1,2,3). In the adrenalectomised patients coffee elevated blood pressure, but the rise in DBP was attenuated when compared to both other groups, whereas the increase of plasma caffeine was the same. The higher age of the adrenalectomised groups could not account for this difference because the circulatory response to coffee increases with age(13). It may be assumed that there were no differences in the water- and sodium balance between the 3 groups, firstly because there were no differences in basal PRA and secondly because in the adrenalectomised patients plasma sodium, potassium and cortisol all were within the normal range (Table I).

It is interesting to hypothesize that the smaller DBP-rise in the adrenalectomised group is the result of the lack of circulating epinephrine. With respect to this, another striking observation was the fall of plasma norepinephrine in the adrenalectomised patients, whereas in the other groups no change was observed, and in comparable studies even a small rise of plasma norepinephrine has been reported(1,2,5). Indeed, a decline in plasma norepinephrine would be the expected passive response of the sympathoadrenal system to an extrinsic pressor stimulus. Consequently, our data may suggest that drinking coffee results in a pressor response without mediation of the sympathoadrenal system (adrenalectomised group), but that this pressor response may be enhanced by caffeine-induced circulating epinephrine (normotensive and hypertensive group). The physiologic substrate for this observation could be the stimulation of presynaptic $\beta_2$-receptors by epinephrine(14). The phenomenon of increased sympathetic tone as a result of circulating epinephrine in rats has already been

suggested by Majewski et al(15). The observation that bilateral adrenal demedullation of hypertensive rats attenuated the pressor response to sympathetic nerve stimulation also partly supports this hypothesis(16).

A recent article of Onrot et al(17) reported about the circulatory effects of caffeine in autonomic failure. In that study no statistical comparison with healthy subjects was performed, but the results indicate that the pressor effect to caffeine is not primarily due to elevations in sympathoadrenal activity. However, in autonomic failure both adrenergic and noradrenergic mechanisms are partially blunted and so the possible role of circulating epinephrine on an intact autonomic nervous system can not be studied.

In the adrenalectomised patients coffee induced a rise in FVR whereas this was not observed in the other groups (Figure 2). This may be the expression of an altered balance between the $\beta_2$-mediated vasodilation in the forearm muscle by epinephrine after coffee, the direct action of caffeine on smooth muscle cells(18) and an altered sympathetic tone of the forearm vessels.

In former reports(1,2,3) and in this study drinking coffee induced a fall in PRA, whereas Robertson et al observed an increase in PRA after 250 mg caffeine(5). We have no clear explanation for those contradictory results, but our and other recent findings(17) suggest that the rise in blood pressure after coffee is not mediated by the renin-angiotensin-aldosterone system.

As suggested in a former study(19) our results indicate that the pressor response to coffee seemed elevated in hypertensive patients when compared to normotensive subjects. The significant higher age of the hypertensive patients may contribute to this phenomenon(13). Apart from that, it must be realised that fractional rises in blood pressure after coffee were broadly the same in normo- and hypertensive subjects. However, our observations and those from recent literature(20,21) show that the pressor response to coffee in hypertensive patients resembles or even surpasses the effects in normotensive subjects and this may emphasize that the circulatory effects of coffee may have epidemiological, clinical and therapeutic consequences for the problem of high blood pressure.

In conclusion, drinking coffee exerts a rise in blood pressure, a fall in heart rate, and a rise in plasma epinephrine in normotensive as well as in hypertensive subjects. In the adrenalectomised group coffee also induced a pressor response, but the rise in DBP was attenuated and plasma norepinephrine fell significantly, whereas plasma epinephrine remained undetectable throughout the tests. We suggest that the rise in blood pressure after coffee is not the result of an increase in circulating epinephrine. However, the latter may exaggerate the pressor response to coffee, by an epinephrine-mediated increase in sympathetic tone. Further, our data indicate that the rise in blood pressure after coffee is not mediated by the renin-angiotensin-aldosterone system. Until now, the pharmacological mechanism of the circulatory effects of caffeine in man remains unclear, and we think this item deserves further studies in man.

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# CHAPTER VII

## EVIDENCE FOR AN ANTAGONISM BETWEEN CAFFEINE AND ADENOSINE IN THE HUMAN CARDIOVASCULAR SYSTEM.

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**SUMMARY**

A randomized, double-blind and placebo-controlled study was performed in 10 normotensive male subjects to analyse a possible antagonism between caffeine and adenosine with respect to their effects on the cardiovascular system in man. Caffeine, 250 mg intravenously, increased blood pressure with 9/12 mm Hg, and resulted in a fall in heart rate of 3 bpm. Plasma epinephrine rose with 114% after caffeine. Adenosine, in an increasing dose of 0.04-0.16 mg/kg/min induced an increase in systolic blood pressure (17 mm Hg) and heart rate (33 bpm), a moderate fall in diastolic blood pressure (-4 mm Hg), and no change in mean arterial pressure. Forearm blood flow, skin temperature and transcutaneous oxygen tension were lowered at the highest adenosine infusion rates. Adenosine induced a strong rise of plasma (nor)epinephrine (resp. 227.2% and 215.9%). The fractional changes in systolic blood pressure, heart rate, plasma catecholamines, plasma renin activity and aldosterone, supposed to be induced by adenosine-mediated regional vasodilation, all were significantly reduced after previous administration of caffeine. Our results indicate an interaction between caffeine and adenosine in man, supporting the hypothesis that caffeine exerts its circulatory effects by competitive antagonism of endogenous adenosine.

## INTRODUCTION

Caffeine and other methylated xanthines have been reported to affect many different organ systems (1). Previously, we have shown relevant effects of drinking coffee on the cardiovascular system (2,3). According to these results and the literature, the most striking caffeine-induced circulatory changes are the rise in blood pressure, due to an increased vascular resistance, and a fall in heart rate (2-5). In addition, caffeine elevates plasma epinephrine, and to a lesser extent, plasma norepinephrine (2,3, 5). The pharmacological basis of these effects still has not been fully elucidated. From some reports, however, there is evidence that the caffeine-induced effects may be due to antagonism of endogenous adenosine (6). In both in-vitro and in-vivo studies the antagonism between adenosine and caffeine has been observed at caffeine concentrations which are likely to occur in daily life (6), whereas much higher concentrations are needed to demonstrate other possible pharmacological modes of action of caffeine, such as inhibition of the enzym phosphodiesterase (7), or changes of intracellular calcium concentration (1). In laboratory animals adenosine behaves as a potent vasodilating agent in cerebral, intestinal and coronary circulation (8,9,10), whereas renal vascular resistance increases during adenosine infusion (11). In man, the circulatory effects of adenosine have hardly been studied, whereas these effects and the interaction with caffeine could provide interesting results with respect to the concept of human purinergic cardiovascular receptors. Firstly, a caffeine-induced inhibition of vasodilating effects of endogenous adenosine would explain the well-documented pressor response to the drinking of coffee. Additionally, adenosine increases coronary blood flow and may be involved in several physiological and pathophysiological processes of the cardiovascular system (12,13,14,15). Consequently, the hemodynamic effects of adenosine and its putative inhibition by caffeine, a drug daily ingested by a lot of people, could be of theoretical and clinical importance. Therefore, we performed a randomized, double-blind and placebo-controlled study to find out whether some circulatory effects of exogenous adenosine are changed by prior caffeine administration.

## SUBJECTS AND METHODS

After approvement of the local hospital ethical committee 10 healthy normotensive male volunteers were selected and gave their written informed consent for this study. The mean (± SD) (and range) of age, height, weight and Quetelet-index of the subjects numbered respectively 26.3±6.2 years (20-42), 184.7±6.4 cm (177-197), 73.7±8.6 kg (62-86) and 21.6±2.6 kg/$m^2$ (18.4-25.5). The subjects were used to daily caffeine intake and mean (± SD) coffee use was 3.3±2.2 cups of coffee per day (range 1-6.5 cups/day).

To be sure that intravenous administration of caffeine exerts similar effects as the oral ingestion of coffee in previous studies (2,3), we firstly performed a "caffeine-test", with registration of hemodynamic and humoral parameters before and after caffeine i.v.. Subsequently, the subjects took part in 2 "adenosine-tests" in a randomized order. In those tests adenosine was infused after previous double-blind administration of caffeine or placebo. The schedule of measurements of the caffeine-test and the 2 adenosine-tests was the same, and all tests were performed in the morning from 9.00 to 11.20 hour. The subjects were asked to refrain from smoking the morning before the test, and from caffeine-containing products for at least 24 hours before the start of each test. A light caffeine-free breakfast was allowed one hour before entering the laboratory.

Each test started with an equilibration period of 30 minutes and the subjects remained in the supine position from the beginning to the end of the test. During equilibration an Arteriosonde 1225 (semi-automatic blood pressure monitoring) and a strain-gauge venous occlusion plethysmograph were connected to the subjects left arm for monitoring blood pressure and forearm blood flow. Chest electrodes were connected to calculate heart rate by ECG. On the right hand, skin temperature was measured with a thermocouple(index finger), and transcutaneous oxygen tension was measured by a Tacomette(middle finger). In the meantime an antecubital vein of the left and right arm was cannulated for sampling and drug infusion, respectively.

After equilibration basal hemodynamic values were registered during 10 minutes: 5x systolic and diastolic blood pressure (SBP, DBP), 5x heart rate (HR), 4x forearm blood flow (FBF) and 3x skin temperature and transcutaneous oxygen tension (ST, $T_cpO_2$). At the same time blood was sampled for determination of plasma concentrations of caffeine, catecholamines, renin activity (PRA), aldosterone, potassium and adenosine with its degradation products inosine and hypoxanthine. Next, caffeine (250 mg caffeine-sodium benzoate in 20 ml glucose 5%) was infused during the caffeine-test in 10 minutes, and in the adenosine-tests placebo or caffeine was infused. Subsequently, a 10 minute-period of hemodynamic registrations was performed and blood was sampled for all humoral variables. From 60 to 120 minutes after the start of the adenosine-tests, adenosine was continuously infused with rates of 0.04, 0.08, 0.12 and 0.16 mg/kg/min, each lasting 15 minutes. The last 10 minutes of every dose, again a series of hemodynamic parameters were registered. The adenosine solution (10 mg/ml in sodium chloride 0.9%) was proved to be stable, with unchanged concentrations after 2 weeks of storage. The 3rd sample for all humoral variables was taken at the end of the highest adenosine infusion rate, 120 minutes after the start of the test. After finishing the infusion, recovery of all hemodynamic variables was monitored for another 15 minutes. In the caffeine-test the same registrations were made, but no adenosine was infused. Figure 1 illustrates the protocol of the tests.

Plasma caffeine concentration was determined with a HPLC-method (2). For determination of plasma adenosine, inosine and hypoxanthine a special sampling procedure was used to prevent rapid loss of adenosine from plasma. Two ml of venous blood was mixed with 2 ml of a prepared cooled saline solution. This solution contained 20 µM dipyridamol to inhibit adenosine uptake into blood cells (16), 10 µM deoxycoformicine to block adenosine deaminase in plasma (17) and 2 µg/ml of indomethacin to prevent nucleotide release from thrombocytes during centrifugation (18). This mixture was immediately centrifuged at 3000 rpm for 10 minutes, and then the supernatant was frozen at -20° C. The concentration of adenosine, inosine and hypoxanthine in the mixture were determined with a HPLC-method (19). Because the

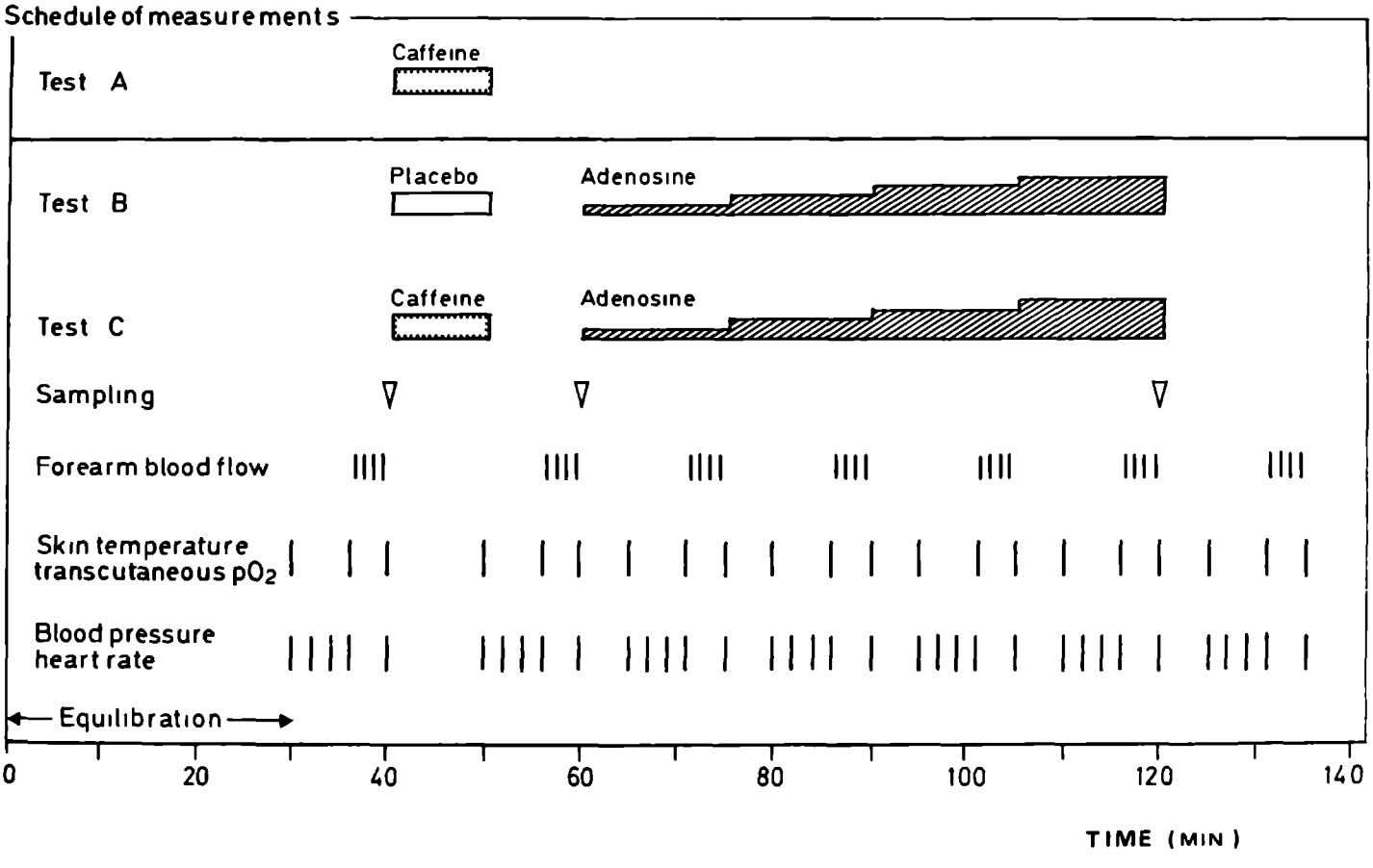


Figure 1: Schedule of measurements of the caffeine-test (test A) and the 2 adenosine-tests (test B&C)

the blood samples were diluted, we adjusted for the packed cell volume. Plasma catecholamines were measured by a radioenzymatic assay (20), and PRA (21) and aldosterone (22) by radioimmunoassay. Potassium concentration was determined with an automatic flame fotometer (corning type 460).

Statistical analysis

All hemodynamic parameters were averaged for every period of 10 minutes to one mean value. Mean arterial pressure (MAP) was calculated from these values as the sum of DBP and 1/3rd of pulse pressure. Forearm vascular resistance (FVR) was calculated by dividing MAP through FBF and presented in arbitrary units (U).In the 2 tests where caffeine or adenosine was administered as the only drug, the circulatory effects of that drug were demonstrated by comparing post-intervention values to basal values. To study the interaction between caffeine and adenosine, we compared the means of all adenosine-induced fractional changes after placebo and after caffeine with each other, using the post-caffeine (or -placebo) values as basal values. All hemodynamic parameters were analyzed by paired Student-t-test, and humoral parameters by paired Wilcoxon-test. Differences were considered to be statistically significant at P-values of less than 0.05 (2-sided). Correlation coefficients were calculated according to Pearson. All results are presented as mean ± standard error of the mean (SEM), unless indicated otherwise.

## RESULTS

The ultimate calculations were performed in 9 subjects, because basal plasma caffeine concentration of 1 subject was too high (resp. 3.0 and 4.2 mg/l), indicating that the instructions with respect to caffeine abstinence were not followed.

The circulatory effects of caffeine alone

Figure 2 shows the hemodynamic results of single caffeine-

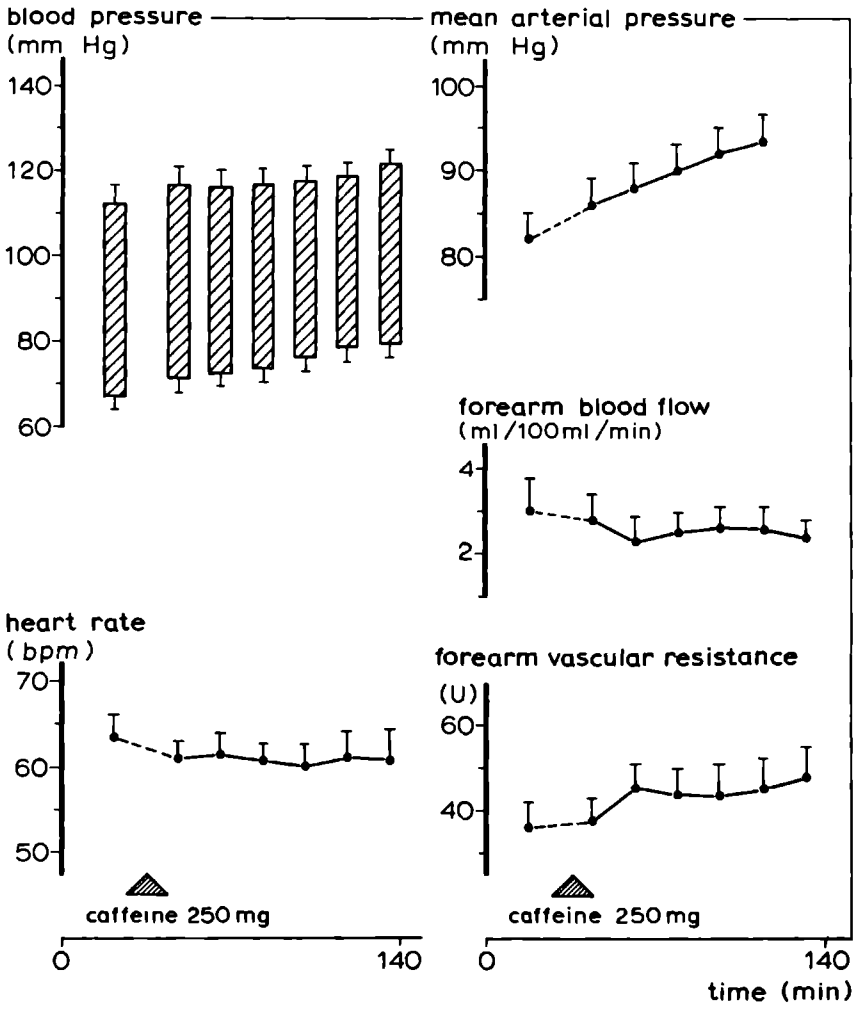


Figure 2: Mean values (±SEM) of hemodynamic parameters before and after the intravenous infusion of 250 mg caffeine in 10 minutes.

infusion. SBP rose from 112.0±4.5 to ultimately 121.2±4.0 mm Hg ($P<0.05$), DBP from 67.1±3.1 to 79.4±3.0 mm Hg ($P<0.001$), and MAP from 82.0±3.2 to 93.4±3.2 mm Hg ($P<0.001$). HR slightly decreased from 63.4±2.5 to 60.1±2.7 bpm ($P<0.05$). FBF and calculated FVR hardly changed after caffeine. Plasma caffeine rose from 0.9 ± 0.1 to 7.0 ± 0.3 mg/l immediately after infusion of caffeine, and decreased to 5.2±0.2 mg/l at the end. Plasma epinephrine increased significantly with 114.2±19.7% ($P<0.01$), whereas norepinephrine remained unchanged. PRA showed a fall of 44.9±7.3% ($P<0.01$), and no changes in plasma potassium, aldosterone, adenosine or its degradation products were found after caffeine infusion.

## The circulatory effects of adenosine alone

Figure 3 shows the response of blood pressure and HR to adenosine after placebo and after caffeine. Adenosine induced an increase in pulse pressure. During the highest infusion rate, SBP rose from 108.0±4.3 to 125.8±5.7 mm Hg ($P<0.001$), whereas DBP fell from 67.6±2.7 to 63.2±2.7 mm Hg ($0.05<P<0.10$). Adenosine infusion did not induce changes in MAP. A strong rise in HR from 61.2±1.6 to 94.0±5.6 bpm occurred ($P<0.001$). The fractional rises in SBP and HR correlated significantly ($r=0.71$, $P<0.025$). After finishing adenosine infusion, pulse pressure decreased again, and HR also returned to basal values within 15 minutes. Figure 4 shows some peripheral blood flow parameters before, during and after adenosine, preceded by administration of placebo or caffeine. During the highest infusion rate FBF was decreased, and calculated FVR was increased ($P<0.05$ ). Skin temperature fell from 34.3±0.5 to 32.2±0.7°C ($P<0.05$), and $T_cpO_2$ initially showed an increase and at the highest rate a fall to about basal values. After the end of adenosine infusion, FBF, FVR and ST recovered rapidly.

Table I shows the changes of humoral variables in the 2 adenosine-tests. During the infusion rate of 0.16 mg/kg/min. an increase in plasma adenosine was not observed, but the degradation products inosine and hypoxanthine both showed a significant rise.

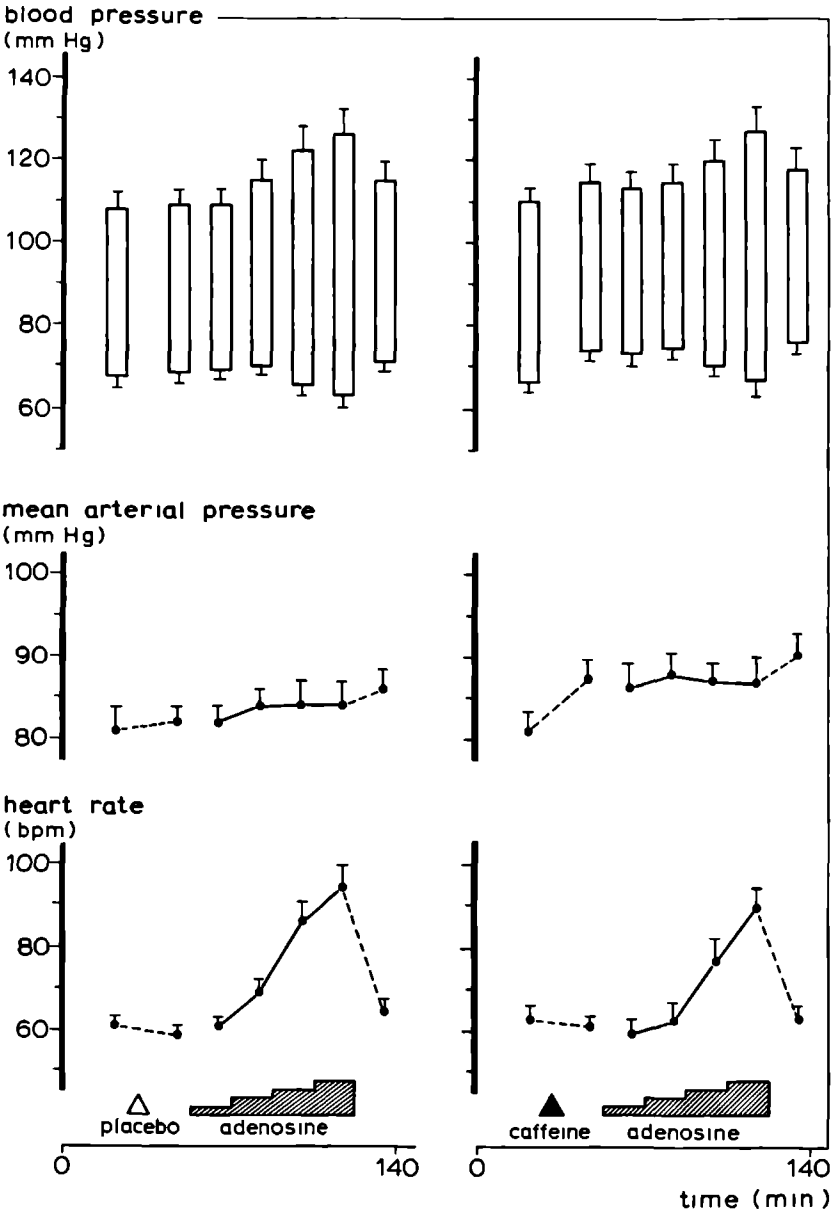


Figure 3: Mean values (±SEM) of blood pressure and heart rate before, during and after continuous infusion of adenosine (0.04-0.16 mg/kg/min) after previous administration of placebo or caffeine (250 mg i.v.).

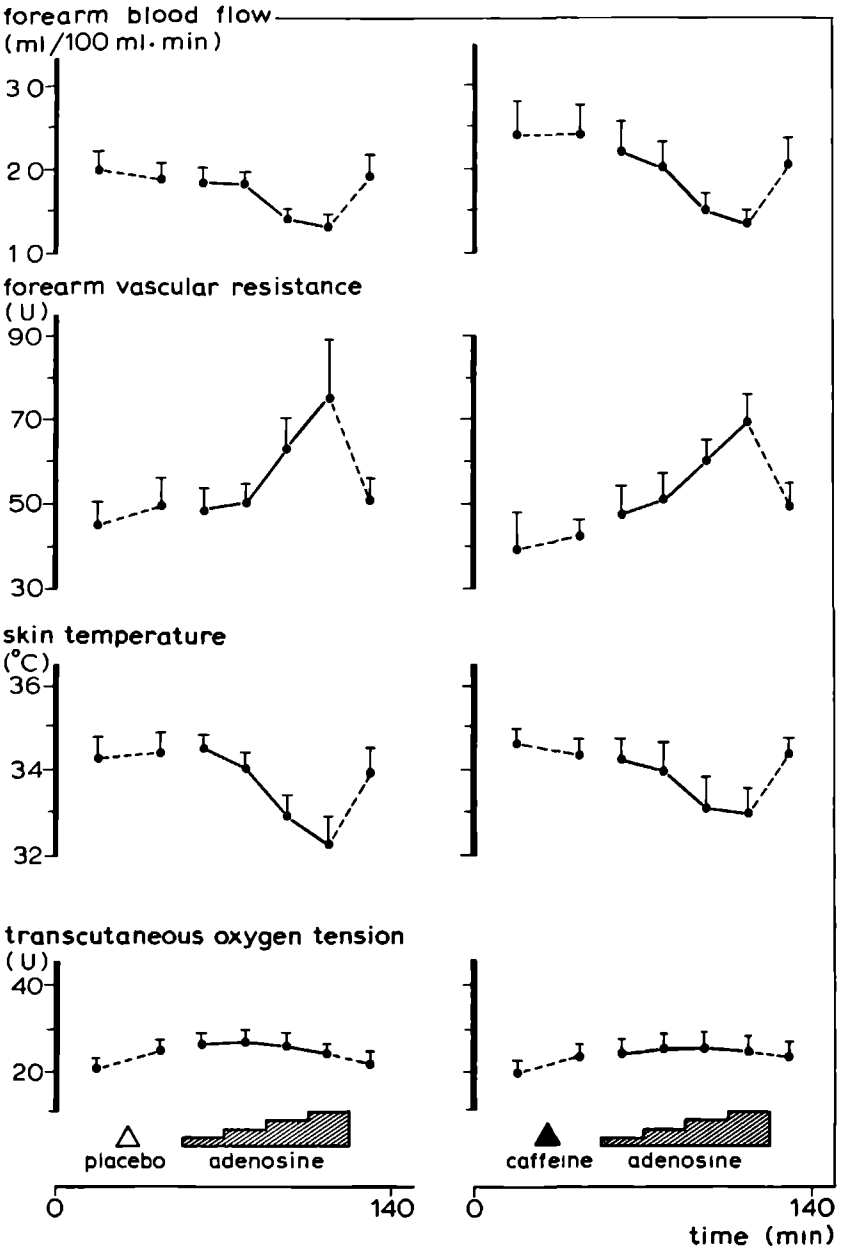


Figure 4: Mean values (±SEM) of peripheral blood flow parameters before, during and after continuous infusion of adenosine (0.04-0.16 mg/kg/min) after previous administration of placebo or caffeine (250 mg).

**Table I:** Mean values (±SEM) of all humoral parameters before and during continuous infusion of adenosine after previous administration of placebo or caffeine.

| | PLACEBO | | ADENOSINE | PLACEBO | | ADENOSINE |
|---|---|---|---|---|---|---|
| | before | after | during | before | after | during |
| CAFFEINE | 0.2±00 | 0.2±00 | 0.1±00 | 0.1±0.1 | 5.2±0.6*** | 4.0±0.4*** |
| NOREPINEPHRINE (nmol/l) | 0.65±0.07 | 0.69±0.08 | 2.03±0.26** | 0.84±0.08 | 0.94±0.10 | 1.73±0.25** |
| EPINEPHRINE (nmol/l) | 0.13±0.04 | 0.12±0.03 | 0.32±0.05** | 0.12±0.03 | 0.21±0.05* | 0.29±0.06** |
| PRA ($ng/ml.hr^{-1}$) | 1.40±0.28 | 1.34±0.26 | 1.21±0.19 | 2.08±0.27 | 1.71±0.20 | 1.03±0.12* |
| ALDOSTERONE (ng/100 ml) | 5.2±1.0 | 4.9±0.8 | 6.6±1.6 | 9.7±1.3 | 7.0±1.2* | 6.1±1.0** |
| POTASSIUM (mmol/l) | 4.0±0.1 | 4.0±0.1 | 4.2±0.1 | 4.0±0.1 | 4.1±0.1 | 4.2±0.1 |
| ADENOSINE (µmol/l) | 1.28±0.52 | 1.03±0.34 | 1.40±0.45 | 0.65±0.17 | 0.66±0.19 | 1.28±0.40 |
| INOSINE (µmol/l) | 0.16±0.01 | 0.17±0.02 | 1.83±0.48** | 0.15±0.00 | 0.17±0.01 | 2.54±0.49** |
| HYPOXANTHINE (µmol/l) | 0.39±0.07 | 0.44±0.13 | 6.31±0.79** | 0.75±0.14 | 0.49±0.08 | 7.26±0.55** |

*P < 0.05, **P < 0.01, ***P < 0.001 vs values before placebo or caffeine

As a matter of course plasma caffeine remained low throughout this test. Plasma epinephrine and norepinephrine showed increments of respectively 215.9±43.8% and 227.2±64.6%. No significant correlations were found between the rise of catecholamines and hemodynamic changes. Plasma aldosterone and plasma potassium did not change significantly, when compared to basal values. During the 2 highest infusion rates of adenosine all subjects had some of the following symptoms: flushing, palpitations, nausea, and a discomfort in the head, the neck, the chest and the abdomen.

The circulatory effects of adenosine after caffeine

The basal values of all hemodynamic and humoral parameters were not significantly different in the 2 adenosine-tests, with the exception of basal PRA (table I). Figure 3 and 4 present that the hemodynamic responses to adenosine infusion show a more or less similar pattern after previous placebo or caffeine administration. However, figure 5 shows differences between the adenosine-induced fractional changes in blood pressure and HR during each infusion rate after placebo and caffeine. After caffeine the adenosine-induced rise in SBP and HR are significantly lower when compared to placebo and for these parameters the dose-response curve of adenosine is shifted to the right by caffeine. No differences were found with respect to DBP and MAP. Figure 6 shows adenosine-induced fractional changes after placebo and caffeine for all peripheral blood flow parameters. The percentual fall of $T_cpO_2$ during the highest infusion rates of adenosine was significantly reduced after previous infusion of caffeine. Changes of FBF, calculated FVR and ST due to adenosine were not altered by caffeine.

Changes of plasma adenosine, inosine and hypoxanthine during infusion of adenosine were not significantly altered by caffeine (table I). The mean rise of plasma caffeine in the caffeine-adenosine-test was similar as in the caffeine-test. Figure 7 presents the fractional changes due to adenosine of catecholamines, PRA and aldosterone after placebo and caffeine. The adenosine-induced rise in catecholamines was significantly

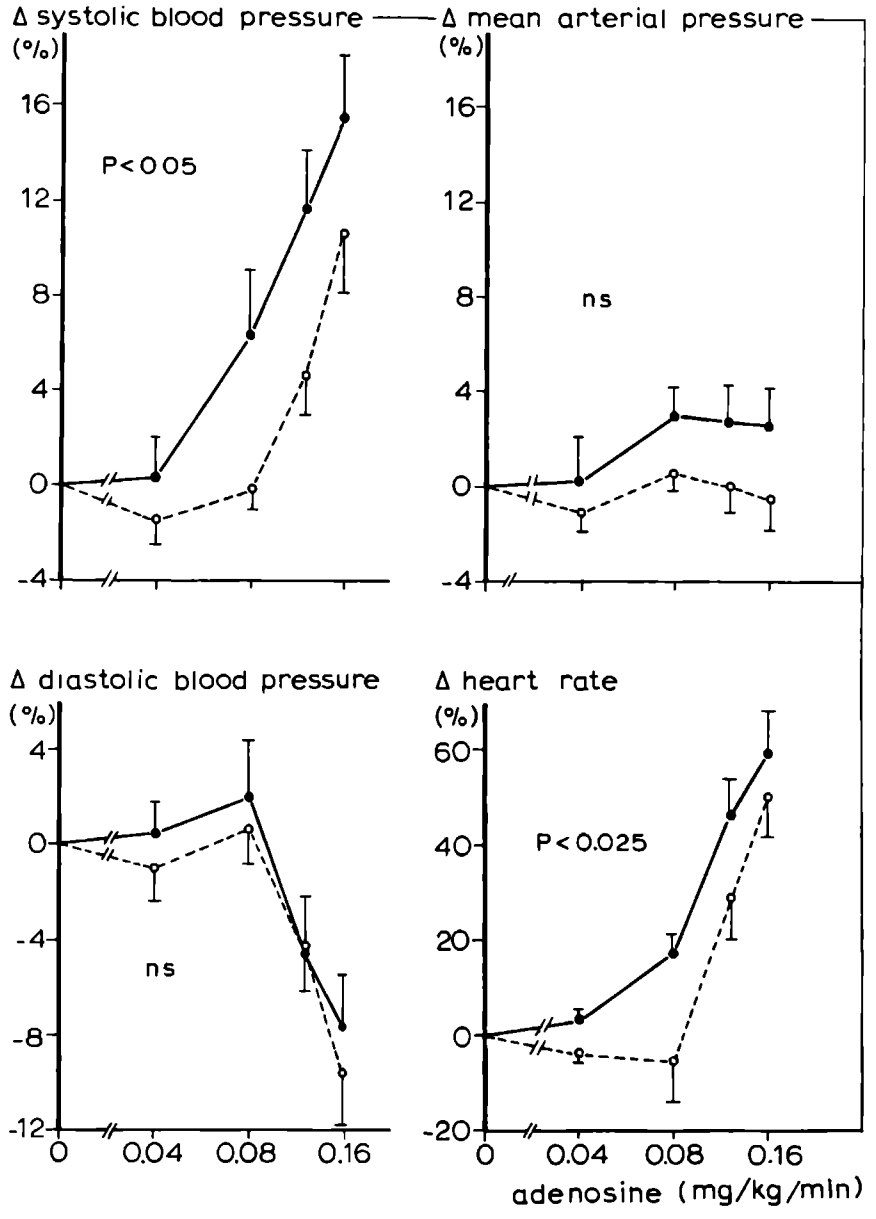


Figure 5: Mean fractional adenosine-induced changes (±SEM) in blood pressure and heart rate after placebo (solid lines) or 250 mg caffeine (dotted lines) for each adenosine infusion rate (0.04-0.16 mg/kg/min).

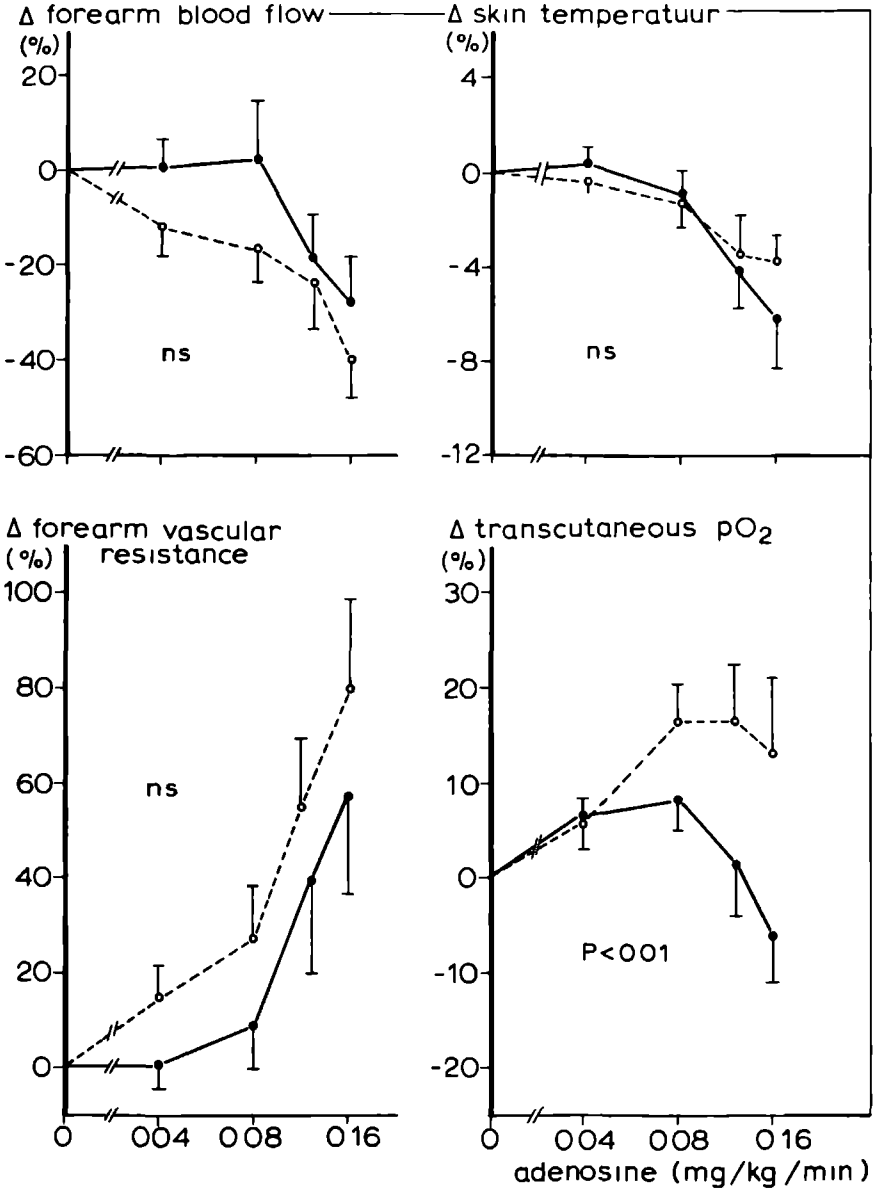


Figure 6: Mean fractional adenosine-induced changes (±SEM) in peripheral blood flow parameters after placebo (solid lines) or 250 mg caffeine (dotted lines) for each adenosine infusion rate (0.04-0.16 mg/kg/min).

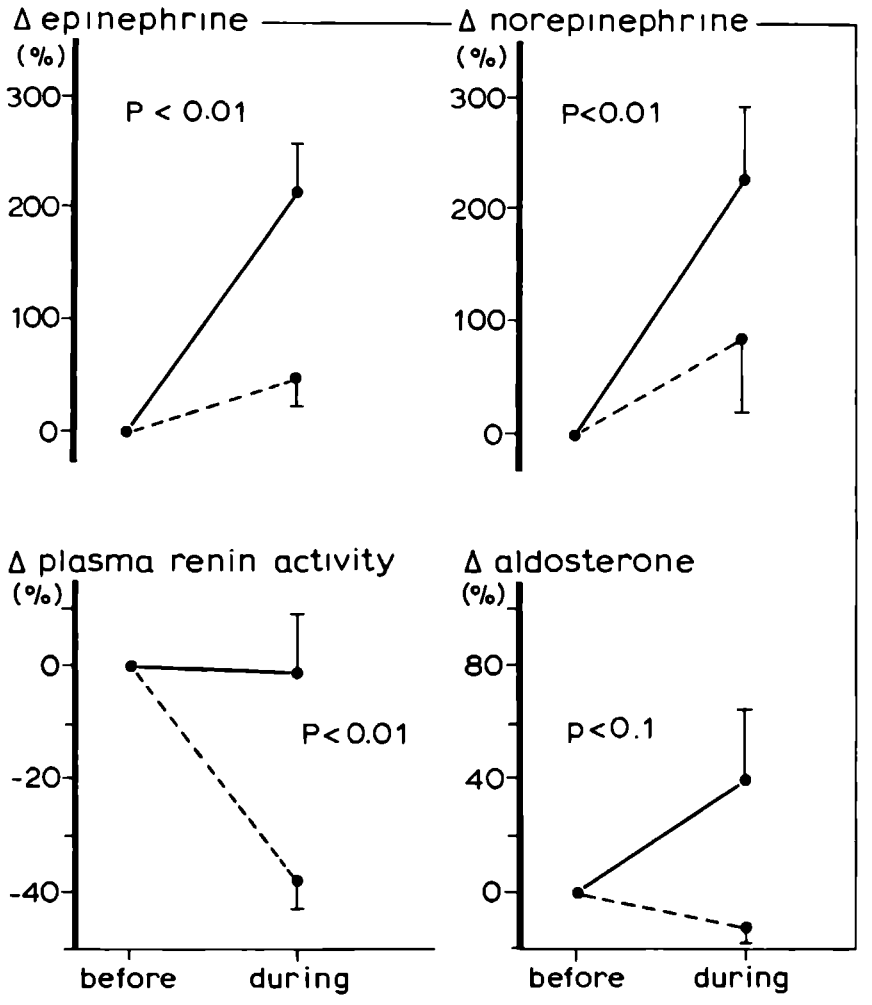


Figure 7: Mean fractional adenosine-induced changes (±SEM) in plasma concentrations of catecholamines, renin activity and aldosterone after placebo (solid lines) or 250 mg caffeine (dotted lines).

attenuated by caffeine. Moreover, caffeine altered the response of PRA and of aldosterone to continuous infusion of adenosine.

## DISCUSSION

This study indicates that the circulatory effects of adenosine are partly inhibited by caffeine, and until now this never has been reported in man. The dosage of caffeine used (250 mg) is equivalent to 2 or 3 cups of coffee, and our present results of single caffeine infusion closely agree with the rise of blood pressure and plasma epinephrine as has been observed after oral intake of coffee or caffeine (3,5,23). The pressor response to caffeine has been reported to be the result of an increase of total peripheral resistance (4). We hardly perceived a fall of FBF after caffeine, and according to the literature both caffeine and theophylline even increase FBF slightly (3,24). Consequently, the suggested vasoconstriction after caffeine seems not to be located in the forearm muscle.

In the present study a complex hemodynamic response occurred during continuous infusion of adenosine. In literature only one report deals with these effects, and a strong fall of mean blood pressure (-43%), with only a moderate increase of heart rate (+16%) was observed (25). However, those subjects were anesthetized with the use of several drugs, and consequently the normal cardiovascular reflex mechanisms may have been blunted. The same applies to a report on adenosine infusion in anesthetized dogs (8). In our study no premedication was used and we observed a pronounced tachycardia (+60.2±8.9%), with only a slight fall in diastolic blood pressure (-7.7±2.4%) and no change in mean blood pressure during the highest adenosine infusion rate. This hemodynamic response and the rise in plasma catecholamines indicate a stimulation of the sympathoadrenal system. Since adenosine itself even inhibits adrenergic neurotransmitter release (12,26), we think this must be caused by a cardiovascular reflex reaction to adenosine-induced regional vasodilation. Our results are insufficient to localize this vasodilation, but in-vivo studies suggest that this is most evident in the splanchnic vascular bed (27).

During the highest adenosine infusion rates the parameters of peripheral blood flow showed a fall, suggesting local vasoconstriction in the forearm muscle and the skin (28,29). Apparently, infusion of adenosine in man may elicit opposite responses in different vascular beds. Currently, 2 kinds of purinergic $P_1$-receptors are sensitive to adenosine, one leading to reduced and the other to enhanced cAMP accumulation, respectively $A_1$- and $A_2$-adenosine receptors (12,30). This may be the pharmacological ground for opposite responses to adenosine as well as caffeine in different tissues. Otherwise, the rise of catecholamines during adenosine-infusion could be another explanation for the vasoconstriction in forearm muscle and skin, via α-adrenoceptor-mediated vasoconstriction.

No significant increase of plasma adenosine concentration could be demonstrated in our venous samples. The plasma half-life of adenosine has been reported to be less than 10 seconds, and since the adenosine degradation products inosine and hypoxanthine are hemodynamically inactive (12), we must assume that increased concentrations of adenosine have circulated in the arterial system and were broken down by adenosine deaminase or taken up by blood cells before entering the venous system. Indeed, we observed significant rises of both inosine and hypoxanthine after infusion of adenosine (table I).

The primary aim of this study was to look for antagonism of exogenous adenosine and caffeine in man. Because of the assumed compensatory stimulation of the sympathoadrenal system mean blood pressure failed to decrease after adenosine, and so the antagonism between caffeine and adenosine cannot be demonstrated by showing a reduction of adenosine-induced hypotension after caffeine as was found in rats (31). However, caffeine significantly diminished the signs of compensatory reflex mechanisms, indicating a reduced adenosine-induced regional vasodilation. For systolic blood pressure and heart rate the dose-response curve of adenosine was shifted to the right after caffeine and this fits with the concept of a competitive antagonism between caffeine and adenosine on putative cardiovascular purinergic receptors. Being aware of the spontaneous fall of PRA during experiments in the morning hours (3), the effects of adenosine infusion on PRA and

aldosterone after placebo and caffeine may agree with the interpretation that caffeine reduced the stimulation of the renin-angiotensin-aldosterone system caused by adenosine-mediated local vasodilation.

This study shows evidence for antagonism between caffeine, in concentrations likely to occur in daily life, and exogenous adenosine with respect to the cardiovascular system in man. If this interaction also holds for endogenous adenosine such an antagonism could explain the pressor response to coffee and caffeine. Since adenosine is a strong coronary vasodilator (8,32), the hemodynamic antagonism between caffeine and endogenous adenosine would also imply a vasoconstricting effect of caffeine on human coronary arteries. Additionally, adenosine has been reported to play a physiological role in control of the heart during stress via presynaptic inhibition of neurotransmitter-release (12,26), and this may also be blunted by caffeine. Throughout the world caffeine is widely consumed, and in the USA coffee consumption accounts for nearly 80% of total caffeine intake (33). Therefore the effects of caffeine on blood pressure, and the hypothetical coronary vasoconstriction and impaired cardiac stress tolerance after caffeine could all form pathophysiological substratee for the repeatedly suggested (34) and recently affirmed (35) epidemiological association between coffee consumption and cardiovascular morbidity or mortality. Electrophysiological effects of caffeine (36), and its effects on blood lipids (37) could also contribute to this association. On the other hand, caffeine ingestion could theoretically exert beneficial effects, since for example the sick-sinus syndrome, and the post-prandial depressor response in autonomic failure both could be adenosine-mediated (13,15). Indeed, caffeine 250 mg daily, has recently been reported to attenuate the postprandial fall of blood pressure in autonomic failure (38). Because of these hypothetical clinical consequences of caffeine ingestion, we think that further human studies on caffeine and adenosine have to be performed to asses both the harmfull and beneficial effects of caffeine in the management of cardiovascular disease.

In conclusion, infusion of adenosine in man exerts a complex hemodynamic response with an increase in SBP and HR, a moderate

fall in DBP and signs of vasoconstriction in forearm muscle and skin. According to changes of catecholamines, PRA and aldosterone the sympathoadrenal system and to a lesser extent the renin-angiotensin-aldosterone system seemed to be stimulated during adenosine infusion. We have demonstrated that these compensatory mechanisms to a presumed adenosine-mediated regional vasodilation, were significantly reduced after previous administration of caffeine. These results indicate an antagonism between caffeine and adenosine in man, affirming the hypothesis that caffeine exerts its circulatory effects by competition with endogenous adenosine on purinergic cardiovascular receptors. Furthermore, this finding implies that the daily habit of drinking coffee could influence several physiological and pathophysiological adenosine-mediated processes of the cardiovascular system.

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## GENERAL DISCUSSION AND CONCLUSIONS

There are many contradictions in the literature concerning the consequences of drinking coffee for the cardiovascular system. In pharmacological studies caffeine has been reported to elevate, to lower and not to alter blood pressure, and the same contradictions exist with respect to the effects of caffeine on heart rate (1-5). From an epidemiological point of view, a positive association between blood pressure and coffee consumption has been reported recently (6,7). However, most of the epidemiological studies have focussed on the relation between coffee ingestion and morbidity or mortality from coronary heart disease. Although there is still no unanimity, the majority of these reports do not support a significant association between coffee and coronary heart disease (8,9).

In chapter II we observed a rise in blood pressure, a fall in heart rate and a rise in plasma catecholamines (especially adrenaline) after coffee, whereas decaffeinated coffee only induced a small rise in diastolic blood pressure. The results of the coffee tests after placebo pretreatment in the other studies (chapter IV and V) confirm this caffeine-mediated pressor effect of drinking coffee. The most striking effect was the rise in diastolic blood pressure, amounting up to 20% in the 2$^{nd}$ hour after drinking coffee. The results of chapter II, IV and V were obtained after a caffeine abstinence of at least 18-24 hours. Although such caffeine abstentions may occur, the majority of coffee users probably do not reach such periods of caffeine abstinence in daily life. Indeed, the observation of tolerance or adaptation to the circulatory effects of caffeine ingestion after chronic caffeine intake, suggests that drinking coffee will not elevate blood pressure in daily life (10,11). This tolerance may partly explain all contradictory results concerning the cardiovascular effects of coffee and caffeine (10,12). In chapter III we ascertained that the rise in blood pressure after coffee correlates negatively with basal plasma caffeine concentration.

Consequently, the pressor response to coffee is related to prior caffeine use and to individual pharmacokinetic properties. These findings suggest that despite the phenomenon of tolerance, drinking coffee may result in relevant rises of blood pressure during daily life in a considerable fraction of the population.

It has to be emphasized that we could not demonstrate principal differences in the cardiovascular response to coffee between normotensive and hypertensive subjects (chapter VI). Since the decrease of blood pressure during most antihypertensive regimens averages 10-20% (13), the observed coffee-induced rise in blood pressure could nullify the results of treatment. Furthermore, the pressor response to coffee seemed not to be diminished by antihypertensive agents like propranolol, metoprolol or verapamil (chapter IV and V), nor by chronic diuretic treatment (14). Clinicians dealing with the problem of high blood pressure should be aware of these findings because the pressor response to coffee may interfere with the interpretation of blood pressure measurements and results of treatment.

In our studies coffee induced a 2 to 3-fold rise of plasma adrenaline, and a small or even no rise of noradrenaline. Although adrenaline may be regarded as a $\beta_2$-adrenoceptor mediated vasodilator, it may be changed into an unopposed $\alpha$-adrenoceptor mediated vasoconstrictor during non-selective $\beta$-blockade, whereas this has not been found after $\beta_1$-selective-adrenoceptor-blockade (15). Consequently, pretreatment with propranolol may increase the pressor response to coffee. However, according to the results in chapter IV propranolol does not change the coffee-induced response of blood pressure and forearm blood flow when compared to placebo or metoprolol pretreatment. Houben et al. ascertained that plasma adrenaline had to rise up to 200-400% before non-selective $\beta$-blockade altered the vasodilatory response to adrenaline in a vasoconstrictory one (15). In the experiments of chapter IV drinking coffee raised plasma adrenaline with 160%, and so the stress-stimulus was likely to be too small to reveal differences in hemodynamics between the propranolol-, and metoprololtests. Indeed, after longer caffeine abstention, we observed rises in plasma adrenaline up to 260% (chapter V). Theoretically, propranolol could have increased the coffee-

induced pressor response in this group of subjects. Nevertheless, as such long caffeine abstinences ( >24 hours) are not likely to occur in daily life, we have found no evidence for the conclusion that treatment with $\beta_1$-selective blockers should be preferred over non-selective β-blockade in patients with hypertension or angina pectoris, who habitually use coffee.

In figure 3 of chapter I, some suggested modes of action of caffeine with respect to its circulatory effects are summarized. The results of coffee tests in adrenalectomised patients indicate that drinking coffee elevates blood pressure independently of plasma adrenaline, but that the coffee-induced rise in circulating adrenaline may facilitate the pressor response to coffee in healthy subjects (chapter VI). Furthermore, our data failed to demonstrate an important role of the renin-angiotensin-aldosterone system in the circulatory effects of coffee. In chapter V we have described coffee tests in normotensive subjects with and without pretreatment with the calcium slow-channel blocker verapamil. We conclude that the role of calcium in the cardiovascular effects of drinking coffee, if any, should be of intracellular origin but appeared not to concern changes of transmembrane calcium influx. This thesis does not comprise data with respect to the inhibition of the enzyme phosphodiesterase by caffeine. In vitro such an inhibition only occurs at caffeine concentrations, which are 10 times higher than those reached after drinking coffee (16) and so this mode of action seems unlikely to be of importance with respect to our findings.

In all recent reports on the effects of caffeine in man the antagonism of endogenous adenosine is mentioned as the mode of action most likely to be involved. However, those suggestions are all based on in-vitro studies (17) or on experiments in animals (18), but no human studies have been performed. In chapter VII we have shown that the circulatory effects of exogenous adenosine in man were attenuated after previous administration of caffeine. This observation may indicate that caffeine indeed exerts its circulatory effects by antagonizing the vasodilatory effects of endogenous adenosine.

In conclusion, drinking coffee exerts a pressor response in normotensive as well as hypertensive subjects, combined with a

moderate fall in heart rate. The extent of the pressor response appears to depend on basal plasma caffeine level and thus on both, prior caffeine use and individual pharmacokinetics of caffeine. Further, drinking coffee exerts a rise of plasma adrenaline. Despite increased levels of circulating adrenaline after coffee, we observed no harmful fortification of the coffee-induced pressor response during non-selective β-blockade with propranolol.

The circulatory effects of caffeine are not mediated by the sympathoadrenal system or the renin-angiotensin-aldosterone system. In addition, the increase in transmembrane calcium influx appeared to be of no relevance for the circulatory effects of drinking coffee. Finally, we have observed an interaction of caffeine and exogenous adenosine in normotensive volunteers, supporting the hypothesis that caffeine may bring about its circulatory effects via an antagonism of endogenous adenosine. Since adenosine has been reported to be involved in several physiological and pathophysiological processes (19,20,21), the antagonism as shown in our study could be of importance with respect to developments in clinical pharmacological research on caffeine and other methylxanthines.

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# SAMENVATTING

In onze samenleving wordt coffeïne op grote schaal gebruikt. De voornaamste bron vormt het dagelijks kopje koffie, maar coffeïne bevindt zich ook in thee, coca cola, cacao, chocolade en sommige pijnstillende middelen. Eén kopje koffie bevat gemiddeld ongeveer 90 mg coffeïne, maar dit kan, afhankelijk van de bereidingswijze, variëren van 30 tot 180 mg. Het verband tussen het drinken van koffie en de hoogte van de bloeddruk vormt al lang een dankbaar onderwerp voor zowel epidemiologische als farmacologische studies. De resultaten van laatstgenoemde studies over de effecten van koffie en coffeïne op het hart- en vaatstelsel zijn erg controversieel. Zo zijn er in verschillende proefopstellingen zowel stijgingen als dalingen van bloeddruk en hartfrequentie waargenomen na inname van coffeïne. Op epidemiologisch gebied gelden dezelfde tegenstrijdigheden. In enkele bevolkingsstudies is een relatie gevonden tussen koffiegebruik en de hoogte van de bloeddruk. Ook is in verschillende studies een verband tussen koffieconsumptie en het voorkomen van en de sterfte aan hart- en vaatziekten vastgesteld, maar andere onderzoekers ontkennen dit weer. Theoretisch kan het gebruik van koffie tenminste op een drietal manieren in een verhoogde sterfte aan hart- en vaatziekten resulteren: 1) coffeïne leidt tot een verhoging van de bloeddruk en/of van het lipoproteïnegehalte van het bloed, beide bekende risicofactoren voor het ontstaan van hart- en vaatziekten; 2) coffeïne veroorzaakt veranderingen van electrofysiologische eigenschappen van het hart (ritmestoornissen); 3) coffeïne of andere bestanddelen van koffie kunnen een direct effect hebben op al dan niet bekende pathofysiologische mechanismen van hart- en vaatziekten.

In dit proefschrift hebben wij ons beperkt tot farmacologische studies naar de effecten van koffie en coffeïne op de bloeddruk, de hartfrequentie, de spierdoorbloeding en op een aantal humorale, circulatoire parameters. De vraagstelling was enerzijds in hoeverre deze parameters worden beïnvloed door coffeïne en anderzijds wat het farmacologisch werkingsmechanisme van coffeïne is met betrekking tot deze veranderingen.

In hoofdstuk II werden de hemodynamische en humorale effecten van het drinken van koffie vergeleken met die van coffeïnevrije koffie. Na een coffeïneonthouding van 17 uur verhoogde het drinken van koffie de bloeddruk (diastolisch sterker dan systolisch), terwijl de hartfrequentie licht daalde. Tevens werd een stijging waargenomen van de concentraties van catecholaminen in het plasma (met name van het adrenaline). Coffeïnevrije koffie gaf geen hemodynamische of humorale veranderingen, met uitzondering van een geringe stijging van de diastolische bloeddruk. Deze resultaten geven aan dat de effecten van het drinken van koffie op bloeddruk, hartfrequentie en plasmacatecholaminen toegeschreven kunnen worden aan de farmacologisch actieve stof coffeïne.

Eerder hebben andere onderzoekers aangetoond dat bij chronisch gebruik een aantal effecten van coffeïne verminderen of zelfs verdwijnen, met andere woorden er treedt gewenning op. Het is nu de vraag of bij regelmatig coffeïnegebruik, zoals in het dagelijkse leven gebruikelijk is, het drinken van koffie nog aantoonbare circulatoire effecten geeft. Hiertoe werden in hoofdstuk III de cardiovasculaire effecten van koffie gemeten na een relatief korte periode van coffeïneonthouding. Aangezien de snelheid waarmee coffeïne uit het bloed verdwijnt van mens tot mens sterk verschilt, werd de duur van de coffeïneonthouding afhankelijk gesteld van de tevoren voor ieder individu bepaalde verdwijningssnelheid.

Acht gezonde vrijwilligers, die deelnamen aan het eerste deel van dit onderzoek, varieerden inderdaad sterk in de eliminatie halfwaardetijd voor coffeïne, en wel van 2 tot 8.5 uur. Hierbij bleek dat het drinken van 2 koppen koffie na een coffeïneonthouding van 4 maal de coffeïnehalfwaardetijd nog resulteerde in een stijging van de bloeddruk (diastolisch tot 20%). Dit effect werd niet waargenomen wanneer in een identieke proefopstelling coffeïnevrije koffie, warm water of geheel niets werd toegediend. In een tweede deel van dit onderzoek werd in een groep van 30 vrijwilligers, na een willekeurige periode van coffeïneonthouding, een negatieve correlatie gevonden tussen de procentuele bloeddrukstijging na koffie en de basale plasmacoffeineconcentratie. De bloeddrukstijging na het drinken van koffie is dus zowel afhankelijk van het voorafgaand coffeïne

gebruik als van de individuele farmacokinetiek voor coffeïne. Wij hebben aannemelijk kunnen maken dat ondanks het beschreven adaptatiefenomeen, het dagelijks drinken van koffie voor een deel van de bevolking aanleiding kan geven tot een belangrijke stijging van de bloeddruk.

De resultaten van hoofdstuk VI laten onder meer zien dat de cardiovasculaire effecten van het drinken van koffie bij hypertensiepatiënten even uitgesproken zijn als bij gezonde vrijwilligers. Bovendien wijzen eigen gegevens en die uit de literatuur erop dat de bloeddrukstijging na coffeïne niet verminderd wordt door het gebruik van bloeddrukverlagende medicamenten zoals propranolol en metoprolol (hoofdstuk IV), verapamil (hoofdstuk V) en chloorthalidon. Voor artsen die betrokken zijn bij de behandeling van hypertensie kunnen deze resultaten van belang zijn bij de interpretatie van bloeddrukmetingen en van resultaten van therapie, te meer omdat de bloeddrukstijging na koffiegebruik in dezelfde orde van grootte ligt als de gemiddelde daling tijdens chronische antihypertensieve therapie. Onze gegevens kunnen tevens een gedeeltelijke verklaring vormen voor de vele tegenstrijdigheden in epidemiologisch onderzoek naar het verband tussen coffeïnegebruik enerzijds, en de hoogte van de bloeddruk en het optreden van hart- en vaatziekten anderzijds.

Het drinken van koffie geeft een stijging van plasmacatecholaminen en met name van het adrenalinegehalte (stress-hormoon). Uit vorig onderzoek van onze afdeling (proefschriften van C. van Herwaarden en van H. Houben) is bekend dat behandeling van hypertensie met zogenaamde niet-selectieve β-blokkers in combinatie met verhoogde adrenaline-spiegels ("stress") kan leiden tot een ongunstige bloeddrukstijging, terwijl dit niet optreedt na behandeling met $\beta_1$-selectieve blokkers. Bij de door coffeïne geïnduceerde stijging van adrenaline konden wij deze ongunstige veranderingen niet waarnemen bij proefpersonen die koffie dronken na kortdurende voorbehandeling met de niet-selectieve β-blokker propranolol. De bloeddrukeffecten waren gelijk aan die na een placebo of na de $\beta_1$-selectieve blokker metoprolol. Gezien deze bevindingen zijn $\beta_1$-selectieve blokkerende middelen dan ook niet zonder meer te verkiezen boven niet-selectieve β-blokkers bij de behandeling van patiënten met hypertensie of angina pectoris, die regelmatig koffie drinken.

In figuur 3 van hoofdstuk I wordt een aantal mogelijke farmacologische werkingsmechanismen van coffeïne opgesomd, die in de loop der jaren in de literatuur zijn genoemd. De meerderheid van deze voorgestelde mechanismen vloeit voort uit resultaten van in-vitro studies of van dierexperimenten en met betrekking tot de cardiovasculaire effecten van coffeïne bij de mens zijn deze mechanismen dan ook nog louter hypothetisch. Verschillende onderzoekers hebben de circulatoire effecten van coffeïne toegeschreven aan een directe invloed op belangrijke bloeddrukregulerende systemen, zoals het autonome (sympathische) zenuwstelsel en het renine-angiotensine-aldosteron systeem. De resultaten van de koffietoediening bij gezonde vrijwilligers (hoofdstuk II t/m V) en bij patiënten die geen adrenaline meer produceren vanwege een doorgemaakte bijnieroperatie (bilaterale adrenalectomie, hoofdstuk VI) tonen aan dat de hemodynamische effecten van het drinken van koffie niet primair een gevolg kunnen zijn van een stimulatie van een van beide genoemde systemen. In hoofdstuk V worden de circulatoire effecten van koffie bestudeerd na voorbehandeling met de calciuminstroomblokker verapamil. De veranderingen van de bloeddruk, de hartfrequentie en de plasmacatecholaminen na koffiegebruik werden niet gewijzigd door voorafgaande toediening van verapamil. Dit maakt een directe invloed van coffeïne op de calciuminflux over de celmembraan eveneens tot een minder waarschijnlijk werkingsmechanisme. De invloed van coffeïne op de intracellulaire verschuivingen van calcium (zie figuur 3 van hoofdstuk I) is niet als zodanig bestudeerd, en hierover kan dan ook geen uitsluitsel worden gegeven. Dit geldt eveneens voor de weergegeven centrale werkingsmechanismen.

De laatste jaren komen steeds meer dierexperimentele gegevens ter beschikking die erop wijzen dat coffeïne en verwante stoffen zoals theophylline hun effect sorteren via antagonisme van de endogene vaatverwijdende stof adenosine. Met betrekking tot de hemodynamische effecten van coffeïne bij de mens was dit antagonisme tot op heden niet bestudeerd. In hoofdstuk VII is de interactie tussen coffeine en exogeen toegediend adenosine bij gezonde vrijwilligers bestudeerd. De hemodynamische en humorale effecten van adenosine bleken geremd te kunnen worden door voorafgaande intraveneuze toediening van coffeïne. Deze resultaten

geven steun aan de hypothese dat het drinken van koffie bloeddrukverhogend werkt via remming van de endogene vaatverwijder adenosine. Aangezien de laatste jaren blijkt dat adenosine waarschijnlijk betrokken is bij een aantal fysiologische en pathofysiologische processen van het hart- en vaatstelsel, kan dit antagonisme tussen coffeïne en adenosine bij de mens van belang zijn bij ontwikkelingen op het gebied van de cardiovasculaire farmacotherapie.

# WOORDEN VAN DANK

Allen die hebben bijgedragen aan het tot stand komen van dit proefschrift wil ik bij deze hartelijk danken. Op de eerste plaats geldt dit voor alle proefpersonen en patiënten die bereid waren deel te nemen aan de verschillende tests. In het kader van een wetenschappelijke stage heeft Paul Boekema, met assistentie van Joeke Reijenga, een belangrijke bijdrage geleverd aan de inhoud van hoofdstuk VII. De vele plasmaconcentraties van coffeïne werden steeds nauwgezet bepaald door Ita Baars op het laboratorium voor Klinische Farmacie (hoofd: Dr. T. Vree). De plasmaspiegels van catecholaminen, renine en aldosteron werden respectievelijk bepaald door Jacques Willemsen, Miekie Thissen-Janssen en Angeline van Geel op het laboratorium voor Chemische en Experimentele Endocrinologie (hoofd: Prof. Dr. Th. Benraad). De bepalingen van adenosine-, inosine- en hypoxanthineconcentraties in het bloed werden verricht door John van Baal en Ronney de Abreu op het laboratorium voor Pediatrie (hoofd: Dr. P. van Munster). Alle tekeningen in dit proefschrift werden zorgvuldig vervaardigd door Cees Nicolasen van de afdeling Medische Illustratie, en gefotografeerd door de medewerkers van de afdeling Medische Fotografie. Ten slotte wil ik Anky Verweijen en Ineke ten Have hartelijk danken voor het met zorg uittypen van de verschillende hoofdstukken en artikelen.

# CURRICULUM VITAE

De schrijver van dit proefschrift werd op 23 juni 1957 geboren te Etten en Leur. In 1975 behaalde hij het diploma Atheneum-B aan het Jacob-Roelandslyceum te Boxtel. Aansluitend studeerde hij een jaar Biologie (faculteit der Wis- & Natuurwetenschappen) aan de Universiteit te Nijmegen. In 1976 begon hij met zijn studie in de Geneeskunde aan dezelfde Universiteit, waar hij in 1981 het doctoraalexamen en in 1983 het artsexamen aflegde. Sinds september 1983 is hij in opleiding tot internist op de afdeling Inwendige Geneeskunde van het Sint Radboud ziekenhuis te Nijmegen (hoofd: Prof. Dr. A. van 't Laar).
Hij is getrouwd met Liesbet Korebrits. Zij hebben een zoon, Loek.

# STELLINGEN

I

De stijging van de bloeddruk en die van het plasma-adrenalinegehalte na het drinken van koffie zijn voornamelijk het gevolg van de farmacologisch actieve stof coffeïne.

(dit proefschrift)

II

De hemodynamische en humorale reactie op intraveneuze infusie van adenosine kan geremd worden door coffeïne. Dit steunt de hypothese dat de cardiovasculaire effecten van coffeïne tenminste gedeeltelijk berusten op antagonisme van endogeen adenosine.

(dit proefschrift)

III

De bloeddrukstijging na het drinken van koffie is geringer naarmate het coffeïnegehalte in het bloed vóór het drinken van koffie hoger is. De grootte van deze bloeddrukstijging is dus afhankelijk van voorafgaand coffeïnegebruik en van de individuele halfwaardetijd voor coffeïne.

(dit proefschrift)

IV

De circulatoire effecten van coffeïne worden niet primair veroorzaakt door een stimulatie van het sympathische zenuwstelsel, het bijniermerg of het renine-angiotensine-aldosteron systeem.

(dit proefschrift)

V

Bij een recidief van acute leukemie blijkt de duur van de eerste complete remissie een prognostische betekenis te hebben voor het bereiken van een tweede complete remissie.

(P. Smits, L. Schoots, B. de Pauw et al. Prognostic factors in adult patients with acute leukemia at first relapse. Aangeboden voor publicatie.)

VI

Neurohypofysaire diabetes insipidus kan een vroeg symptoom zijn van leukemie.

(eigen waarneming)

VII

Medicamenteuze behandeling van lichte hypertensie verlaagt de incidentie van cerebrovasculaire accidenten.

(Medical research council working party. MRC trial of mild hypertension: principal results. Br.Med.J. 1985; 291: 97-104)

VIII

Bij patiënten met asthma bronchiale is de bronchusverwijdende werking van enprofylline 3 tot 5 maal sterker dan die van theophylline. Aangezien enprofylline in vitro veel minder in staat is om de effecten van adenosine te antagoneren dan theophylline, is het dan ook onwaarschijnlijk dat laatstgenoemd mechanisme bijdraagt aan de anti-asthma effecten van xanthinederivaten.

(Laursen et al. Intravenous administration of enprofylline to asthmatic patients. Eur.J.Clin.Pharmacol. 1983; 24: 323-327)

IX

Het star vasthouden aan het verrichten van lichamelijk onderzoek vanuit de rechterzijde van de patient is in de literatuur over fysische diagnostiek onvoldoende onderbouwd, en kan ongemakkelijk zijn voor arts en patient. Het verdient dan ook overweging om medisch studenten wat dit betreft zowel links- als rechtshandig op te leiden.

(Akgün S. Left may be right, too. N.Eng.J.Med.1986; 314: 994)

X

De verminderde sympathicusactiviteit na β-adrenoceptorblokkerende stoffen is niet altijd alleen het gevolg van een competitieve binding van de β-blokker aan de β-adrenerge receptor, maar kan ook berusten op een vermindering van het aantal β-adrenerge receptoren.

(De Blasie et al. Reduction of beta-adrenergic receptors by tertatolol: an additional mechanism for beta-adrenergic blockade.Clin.Pharm.&Ther.1986; 39: 245-254)

XI

Bij bejaarden met diabetes mellitus is het voorschrijven van een dieet in het algemeen niet zinvol, en vaak zelfs schadelijk.

XII

Ook voor koffie lijkt te gelden: "what is true about nutrition is not really sensational, and what is sensational about nutrition is not really true".

(naar Victor Herbert)

Nijmegen, 1986

Paul Smits