Non-Pharmacological Methods of Blood Pressure Reduction in Elderly Hypertensives Evaluated by 24-Hour Ambulatory BP Monitoring

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CONTENTS

Abstract

This Thesis examines the effects of non-pharmacological methods on lowering blood pressure and the potential mechanisms for their action in elderly hypertensive and normotensive persons. Changes in blood pressure following these interventions were evaluated by conventional clinic blood pressure measurements and 24-hour ambulatory blood pressure monitoring. The reproducibility of individual 24-hour ambulatory blood pressure measurements in elderly subjects was shown to be greater than clinic measurements, enabling smaller blood pressure changes to be detected in a given number of subjects; other advantages are the ability to assess blood pressure changes over the 24 hour period and the lack of observer bias and placebo effect.

Moderate restriction of dietary sodium intake (from 174 to 95 mmol/24 hour) resulted in a fall in clinic systolic blood pressure only, while a moderate increase in potassium intake using diet supplements produced falls in clinic systolic and diastolic blood pressure and also in 24-hour ambulatory systolic blood pressure. Sustained caffeine use was found to have no significant effect on the clinic or ambulatory blood pressure levels. The substitution of non-pharmacological methods including reduction of weight and sodium intake and increases in dietary potassium intake following withdrawal of anti-hypertensive drug therapy in elderly hypertensive patients with controlled blood pressure allowed 20% of such patients to remain normotensive off medication for over 1 year. The main limitations on the replacement of anti-hypertensive drugs with non-pharmacological therapies was the high prevalence of poorly controlled blood pressure levels in currently treated elderly hypertensives.

The routine use of non-pharmacological methods by general practitioners to lower high blood pressure in elderly hypertensive patients was found to be limited, only a minority use such methods as first line treatment.

In conclusion, significant reductions in blood pressure with certain non-pharmacological methods have been observed in some elderly hypertensive persons.

However it appears that non-pharmacological therapy will need to be combined with drug therapy to achieve satisfactory blood pressure control in many elderly hypertensive subjects.

Acknowledgement

I would like to thank all the volunteers and doctors who have participated in these studies, without whom this work would not have been possible. I would also like to thank my colleagues, particularly Professor C.M Castleden, who have given me advice and time to pursue these studies. My greatest thanks must go to my supervisor Professor John Potter without whom this work would not have begun; he has given me encouragement, enthusiasm and invaluable advice throughout all of these studies.

I must also thank Sue Gilbert who has typed this thesis and made innumerable alterations without a word of complaint.

Study Declaration

The work described in this thesis was undertaken by the candidate over a 4 year period while working as a Research Fellow at the University of Leicester, Department of Medicine for the Elderly at Leicester General Hospital and as Senior Registrar in Integrated Medicine at Leicester General Hospital and the Leicester Royal Infirmary. The final manuscript was prepared during the authors present appointment as Senior Lecturer in Medicine for the Elderly, University of Leicester. This work was supported by a grant from the British Heart Foundation on the basis of a protocol submitted for research into non-pharmacological methods of blood pressure reduction in elderly hypertensive persons.

The studies reported in this thesis were carried out by the author who undertook the majority of the work with the assistance of those mentioned below.

Validation of the Spacelabs 90207 BP Monitor in Elderly Subjects

I am indebted to Dr P Iqbal who undertook with me the simultaneous recording of conventional blood pressure measurement require for proper validation of the BP monitor. Inception and organisation of the study, recruitment of subjects and analysis of the data were carried out by the author.

Reproducibility of Ambulatory BP and Clinic BP Measurement in Elderly Hypertensive Subjects

The organisation of the study, recruitment of subjects, measurement of clinic and 24-hour ambulatory blood pressure measurements and data analysis were the full responsibility of the author.

Effects of Moderate Sodium Restriction on Clinic and 24-hour ABP in Elderly Hypertensive Subjects

I am indebted to Dr Wood of Ciba Geigy Pharmaceuticals for supplying the sodium tablets and matching placebo and the Pharmacy Department at the Leicester General Hospital for organising randomisation and packaging. Miss F Robson and N Henry of the Dietitics Department at the Leicester General Hospital who gave dietary advice and analysed the food diaries. Assay of aldosterone was carried out by Miss Ruth Elliott, assay of plasma renin activity was carried out by the author. The organisation of the study and all clinical measurements were the responsibility of the author.

Effect of Potassium Supplementation on Blood Pressure in Elderly Hypertensive Subjects

The organisation and running of the study was the sole responsibility of the author. However, I am indebted to the Pharmacy Department at the Leicester Royal Infirmary for preparing the potassium elixir and placebo and to the Pharmacy Department at the Leicester General Hospital for organising the randomisation. All clinical measurements and assay of plasma renin activity were carried out by the author.

The Effect of Chronic Caffeine Ingestion on Blood Pressure in Elderly Subjects

I am indebted to Drs Ghandi and Haigh for help with recruitment of subjects for this study. I am also indebted to Dr I A Macdonald (Queens University Hospital, Nottingham) for performing the catecholamine and caffeine assays. Clinical measurements, assays for plasma renin activity, analysis of the data were carried out by the author.

The Effect of Anti-Hypertensive Drug Withdrawal on Substitution with Non-Pharmacological Therapy in Elderly Subjects

The recruitment and follow-up of subjects, clinical measurements and collection of blood and urine samples were the sole responsibility of the author. I am indebted to Mrs J Baldwin for carrying out the echocardiography to assess LV mass. Miss S Ward-Close entered the data into the database of a personal computer, but data analysis was carried out by the author.

The Use of Non-Pharmacological Therapy in the Treatment of Elderly Hypertensive Patients in General Practice

This study was organised by the author who designed the questionnaire, arranged for its distribution and analysed the data. I am indebted to Dr G Harper who helped with the construction of the database and data entry.

Abbreviations

ABP	Ambulatory blood pressure
BHS	British Hypertension Society
BMI	Body mass index
BP	Blood pressure
Cr	Creatinine
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
JNCV	The first report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure.
K	Potassium
MAC	Mean arm circumference
Na	Sodium
PRA	Plasma renin activity
SBP	Systolic blood pressure
SD	Standard deviation
SDD	Standard deviation of the difference
W : H	Waist to hip ratio
WHO/ISH	World Health Organisation/International Society of Hypertension

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CHAPTER 1

INTRODUCTION

1.1 EPIDEMIOLOGY OF HYPERTENSION

Changes in Blood Pressure with Age

In most Western populations blood pressure (BP) rises with age, but in primitive or unacculturated societies this age related rise is greatly reduced or absent (1,2).

Cross-sectional studies

Cross-sectional studies from the United Kingdom (3), Belgium (4), USA (5,6) and many other Westernised populations (7) as well as the world-wide Intersalt project (8) have shown an age-related rise in BP, systolic BP (SBP) increasing by 5-10 mmHg and diastolic (DBP) by 5-6 mmHg from age 40-70 years. In young females SBP levels are lower than in males but the rate of increase is greater in females so that after middle age they have on average higher SBP levels than men. In the young, average DBP is lower in females but increases at a faster rate than in men so that after age 50 years DBP levels are higher in women. Diastolic blood pressure peaks at about age 55 in men and age 60 in women and then declines.

Longitudinal studies

Longitudinal studies of the Framingham cohort show an almost linear rise in SBP with age for both men and women (6). In young women SBP levels are initially lower than those in men but then converge at about age 60 years and continue to rise together. In contrast DBP levels rise only modestly with age until age 55-65 years and then decline. Diastolic BP trends for men and women are similar except that levels remain consistently about 5 mmHg higher in men.

The gender differences in BP between cross-sectional and longitudinal studies may be explained by selected mortality, that is a higher mortality rate occurring in those with higher BP, especially in males, resulting in an under representation of these persons in the older age groups of cross-sectional studies. However both study methods show a progressive rise in SBP with age and a decline in DBP after age 60-65 which probably reflect age related arterial changes.

24 hour ambulatory blood pressure and age

When the relationship between BP and age is examined in cross-sectional studies using ambulatory BP monitoring most studies report a much less pronounced increase in SBP with advancing age compared to conventional blood pressure measurements (9-13). This may reflect an age related increase in the alerting reaction to the observer so that the true effect of ageing on usual blood pressure is less pronounced or may be related to underestimation of high BP by the BP monitors (14), though the latter seems unlikely (see below).

Pathophysiology of age related BP changes

The pulsatile blood flow from the left ventricle is cushioned by the normally distensible aorta allowing blood to be propelled forward during diastole, thereby producing an almost continuous flow. Pressure is also maintained in diastole by pressure wave reflection from the resistance vessels. With ageing there is dilatation of the aorta and major arteries and increased wall thickness (15). The arterial media shows degeneration of elastic fibres and an increase in collagen and ground substance which leads to an increase in arterial stiffness and loss of compliance in large and small arteries and arterioles (16). These changes produce (a) a loss of the cushioning function of the aorta causing an increase in systolic and decrease in diastolic pressure, (b) increased arterial pulse wave velocity causing early return of reflected waves further increasing systolic pressure and (c) an increased load on the left ventricle.

What factors lead to these arterial changes is unclear, but they may not be an inevitable part of ageing, at least to the extent seen in Westernised cultures as no or little BP rise with age is seen in many unacculturated societies (1,2).

Definition of Hypertension

Any definition of hypertension is arbitrary, BP being a continuous variable with no clear cut off point for defining a sudden change in risk. Prospective epidemiological studies show that both SBP and DBP exhibit a smooth curvilinear relationship between level of BP and risk (17,18). Hypertension has therefore been defined as the level of arterial pressure at which the benefits of intervention exceed those of inaction (19).

Prevalence of Hypertension

Estimates for the prevalence of hypertension derived from the second National Health and Nutrition Examination Survey (NHANES) in the United States for each gender

and race at various ages is shown in table 1.1 (20). Hypertension was defined on the average of three BP measurements ≥ 160 mmHg or DBP ≥ 95 mmHg obtained at a single visit, or current use of antihypertensive medication. The prevalence of hypertension can be seen to increase markedly with age, particularly in females and even more so for black females.

	Males		Females	
Age	**White**	**Black**	**White**	**Black**
18-24	2.9	2.4	0.9	3.2
25-34	8.9	13.3	3.7	7.3
35-44	12.1	23.8	8.9	26.9
45-54	26.2	26.0	21.6	58.3
55-64	31.3	46.4	34.4	60.1
65-74	37.5	42.9	48.3	72.8

Table 1.1. Prevalence (%) of hypertension by age, gender and race among adult residents of the US studied between 1976-1980 (ref 20).

In the Framingham Study the prevalence of definite hypertension (defined as SBP >160 mmHg and/or DBP >95 mmHg or on anti-hypertensive treatment) for the age range 65-94 years was 39% for men and 48% for women (21). Similar figures have been obtained in the UK; a large general practice screening study of 10,732 persons aged 60-79 years found 44% had an SBP ≥160 mmHg and/or a DBP ≥90 mmHg (22). When BP is re-measured on further examinations higher values tend to fall and estimates of definite sustained hypertension are therefore lower, values of about 13% for men and 16% for women over the age of 65 years have been suggested (23).

The rise with age in SBP is greater than that for DBP and isolated systolic hypertension (ISH, defined as SBP >160 mmHg and DBP <90-95 mmHg) accounts for more than half the cases of hypertension in males and two-thirds in females over the age of 65 years (18). The results of a recent meta-analysis of 12 studies assessing the prevalence of ISH in the general population shows a dramatic increase in prevalence with age (24). After repeated BP measurements the prevalence of ISH in those over 60 years decreases from 14.1% to 9.5% (24) and on ambulatory BP recordings an even greater decline in prevalence is found (25,26).

Risks of Hypertension

Cardiovascular disease (CVD) is the most common cause of mortality in persons over 65 years of age. Taylor et al (27) found up to 55% of all deaths in this age group were due to CVD while the next largest group, cancer deaths, accounted for 22% of total mortality. A strong and direct relation between increasing levels of SBP and DBP and risk of all cause and CV mortality has been consistently demonstrated in middle-aged populations (28,29).

Data from the 30 year follow-up of the Framingham Study (see table 1.2) show that the absolute risk of CVD increases with age at all levels of SBP, the rates being substantially greater in men than women. There are similar risk associations with age for DBP although less marked in women.

	35-64 y		65-94 y			35-64 y		65-94 y	
SBP	**M**	**F**	**M**	**F**	**DBP**	**M**	**F**	**M**	**F**
74-119	10	4	20	14	**20-74**	12	6	32	25
120-139	12	6	26	23	**75-84**	12	6	32	23
140-159	21	11	39	25	**85-94**	19	10	41	33
160-179	31	13	61	27	**95-104**	25	13	70	23
180-300	40	23	86	48	**105-160**	39	22	94	44

Table 1.2. Age adjusted annual rate/1000 incidence of cardiovascular disease according to SBP and DBP in the Framingham Study (45).

However, as discussed below, some reports in elderly populations have shown a more complex relationship between BP and mortality depending on the sex, age group and presence or abscence of co-existing diseases (27,30).

Total Mortality and BP in the Elderly

The first formal study of the associations between mortality and blood pressure was the 1925 Blood Pressure Study using insurance company data which revealed that even modest elevations of blood pressure were associated with increased mortality (31). The 1979 Blood Pressure Study, again using insurance data, demonstrated a positive and independent relationship between mortality, SBP and DBP for both sexes and in all age groups studied (32). Overall mortality rates obtained from the Framingham data were more than doubled for those aged over 65 years with definite hypertension compared to an age

and sex matched normotensive group (18). Taylor et al (27) as part of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) studied all persons over the age of 65 years in 3 US populations and divided them into 3 BP strata; lowest: < 130/< 75 mmHg, middle: 130-159/75-89 mmHg, highest: ≥ 160/≥ 90 mmHg; all-cause mortality was greatest in the lowest compared to middle BP stratum at 2 years of follow-up. However this effect diminished after 5 years of follow-up such that there was no statistically significant association between SBP or DBP strata and odds from death from all causes relative to the lower BP stratum. Langer et al (30) reported on a 10 year follow-up of men and women ≥ 65 years. In women in all age groups and in men < 75 years increasing DBP was associated with increasing mortality. For men ≥ 75 years mortality decreased with increasing DBP, there was no clear relationship between SBP and survival. In an 11 year follow-up of a 70 year old population, Landahl et al (33) found the highest mortality in those with the highest BP (for men : > 190/105 mmHg; women > 200/105 mmHg); mortality was 30% higher among the men and 50-60% higher among the women in this group compared to the low BP group.
Other studies have also shown no relationship between survival in men and women over 70 years (34) or a very weak relationship (35).

Sorenson and Hilden (36) found no correlation between BP and mortality in 75, 80 and 85 year old citizens of Copenhagen after 3 years of follow-up; although it is unclear what confounding effect from co-existing mortality had on these results. Agner (37) reported that higher SBP in 70 year old women was significantly and in men non-significantly associated with excess total mortality after 10 years. High DBP had no association with total mortality. Lindholm (38) using a 13 year follow-up period in persons ≥ 70 years found increased mortality at higher SBP and DBP levels particularly during the second half of the follow-up period.

Other studies have reported U or J shaped relationships between BP and mortality including the European Working Party on Hypertension in the Elderly (EWPHE) study (39), Coope et al (40), and the Systolic Hypertension in the Elderly Program (SHEP) pilot study (41). In the EWPHE study subjects in the placebo group had a U shaped relation between total mortality and DBP but a linear relation with SBP; in the active treatment group mortality showed a U shaped relation with SBP and an inverse association with DBP. Patients in the lowest thirds of SBP and DBP were characterised by decreases in body weight and haemoglobin concentration suggesting that co-existing morbidity accounted for the lower BP and mortality (39). Coope et al (40) using the initial screening BP in their study of 60-79 year old men and women also found that if subjects with serious associated

diseases were excluded the increased mortality at low BP's disappeared. In a Chinese population of mostly women aged > 70 years a U-shaped association between BP and mortality was also found after 40 months of observation (42).

In a population of very elderly subjects (≥ 85 years) Mattila et al (43) reported an inverse association between BP and mortality (41). Survival was greatest in those with SBP > 160 mmHg and DBP > 90 mmHg.

In summary, for elderly populations up to the age of 75-80 years a higher mortality at lower than average BP levels is largely explained by the effect of co-existing disease affecting both BP and mortality. The majority of studies in this age group show either strong evidence of a higher mortality at higher BP levels or a weak positive association. In very elderly subjects, older than 80-85 years, the relationship between BP and total mortality is less clear.

Cardiovascular Disease

The linear relationship between CVD mortality and morbidity is well established in young and middle-aged populations (44). In older populations many but not all studies report a similar relationship.

Framingham study data (45) have shown increases in CVD morbidity and mortality with increasing SBP and DBP for both young and elderly men and women although there is a much weaker relationship between DBP and CVD risk particularly in older women (see table 1.2). The absolute risk for CV complications is substantially higher in older than younger subjects for a given BP level. For both sexes and over the age range 35-94 years the risk of CVD mortality and morbidity is 2-3 times greater in subjects with definite hypertension (BP ≥ 160/95 mmHg) compared to normotensives (BP < 140/90 mmHg) with an intermediate risk level for borderline hypertensives. Age-adjusted incidence rates for CV morbidity and mortality indicate the absolute risk is 2-3 times higher in older than younger subjects for both men and women, although the risk is on average higher in men irrespective of age. These increased risks are seen for coronary heart disease, strokes, cardiac failure and peripheral arterial disease. The risk for example of developing congestive heart failure is closely associated with hypertension, being six times greater in hypertensive than normotensive subjects, the absolute risk increasing with age (46). However when the Framingham data are analysed using the age bands 65-74 and 75-84 years results show a positive relationship between SBP and DBP and coronary heart disease (CHD) mortality in the former age group but a weakening of the association between SBP and CHD mortality in the 75-84 year group and no predictive effect at all of DBP for CHD

mortality (47). Hypertension, after age, was also the main predisposing factor for stroke, particularly cerebral infarction, for all age groups from 45-74 years in the Framingham study (48).

Hypertensive subjects in the Chicago Stroke Study aged 65-74 years showed a significant increased incidence of stroke, the three year incidence in those with SBP $>$ 179 mmHg being three times greater than in those with SBP $<$ 130 mmHg (49).

In the EPESE study (27) of over 10,000 elderly persons in 3 communities in North America, for those aged 65-79 years the 5 year risk of CV death was greatest in the highest SBP stratum in all 3 sites, but reached statistical significance in only one. Using SBP measurements taken 9 years prior to the beginning of the main study revealed that persons with SBP in the middle and highest strata had a greater risk of CV mortality compared with those in the lowest SBP strata. Overall no relationship between DBP and CV mortality was seen.

Agner (37) reported that high SBP but not DBP in both sexes at age 70 was associated with excess CVD morbidity during the following decade while high SBP was independently predictive of CVD mortality in women only. In the Bronx Longitudinal Aging Study of 488 subjects aged 75-85 years at entry, subjects with hypertension (defined as BP$>$ 140/90 mmHg) had a significantly higher incidence of CV morbidity and mortality compared to normotensives after 8 years of follow-up (50).

Ueda et al (51) in a 20 year prospective Japanese population survey found higher BP in patients aged over 60 was also associated with increased CVD mortality. Patients with diastolic hypertension (defined as DBP $\geq$ 100 mmHg) had an increased relative risk (RR) of cerebral haemorrhage and infarction of 3.4 and 1.5 respectively and those with systolic hypertension (defined as SBP $\geq$ 160 mmHg) had an RR for cerebral infarction of 3.7 and myocardial infarction of 6.7 compared to normotensives. Langer et al (30) found the usual positive but weak association between BP and CV mortality in women but not men over 75 years of age.

Summary

A meta-analysis of prospective observational studies of individuals aged 25-84 years found a positive and almost linear relationship between usual DBP levels and the risk of stroke and coronary heart disease with no evidence of a threshold effect with DBP levels down to 75 mmHg (17). A 5 mmHg increase in usual DBP was associated with a 34% increase in stroke and a 21% increase in coronary heart disease risk.

When the elderly are studied in greater detail, overall there is evidence of a positive relationship between SBP and CV mortality in men up to the age of 75 years and in women up to 85 years. The relationship between DBP and CV mortality appears weaker or absent in subjects greater than 70 years of age. However it is unclear to what degree the relationship between BP and CV mortality is weakened by the inclusion in studies of persons with conditions that are responsible for producing a low BP and increased mortality. It is possible that BP levels, particularly systolic pressures, in healthy very elderly persons remain a risk factor for CVD morbidity and mortality.

Risks of Isolated Systolic Hypertension

Although both systolic and diastolic pressures predict cardiovascular risk in the elderly, the relationship is much stronger for SBP than DBP (52). A study of Dutch Civil Servants aged 40-65 years at entry and followed-up for 25 years showed total mortality for men with ISH to be more than twice that for normotensive subjects (53). Similar results were obtained from the Framingham cohort aged 45-74 years in a 20 year follow up where a two-fold increase in total mortality for men and women with ISH compared to normotensives was found, most of this excess being due to cardiovascular disease (54). Results from several other studies suggest mortality from cardiovascular disease is between 5-7 times higher in subjects with ISH compared to normotensives (55). Garland (56) found males over 60 years with ISH had an excess risk of death from stroke (relative risk 4.0) and the Chicago stroke study found a 2.5 times greater incidence of stroke in those with ISH compared to normotensives (49). Colandrea et al (57) in a group of 72 subjects of mean age 69 years with ISH, found CV mortality increased by seven fold compared to normotensive subjects.

In conclusion studies following middle aged subjects into old age and shorter term studies in the elderly have shown a positive relationship between isolated increases in SBP and total and CV mortality.

Benefits of Anti-hypertensive Therapy

The benefits of treating very high BP manifest as malignant hypertension have been known for over half a century. In 1939 Keith et al (58) showed that without treatment 80% of patients with malignant hypertension were dead within a year of diagnosis. Dustan et al (59) in 1958 found that reducing BP in malignant hypertensives resulted in at least 50% surviving three years, similar results were soon reported by other workers (60,61). The value of treating less severe levels of hypertension in the early 1960's was less clear. In

Table 1.3 **Randomised controlled intervention studies of anti-hypertensive drug therapy in middle aged persons**

Study	ref	Treatment	Age Range	Entry BP (mmHg)		
Veteran Administration Study I (1967) II (1970)	 63 64	HCTZ ± Reserpine Hydralazine v placebo	49*	 DBP 115-129 DBP 90-114	Study I in moderate-severe HT rapidly revealed benefit of active treatment in CV events. Study II in mild-moderate HT only showed benefit in those with DBP > 104 mmHg.	In VAII 81 subjects recruited aged 60-75 years. Treatment produced significant 54% reduction in all CV events mainly due to reductions in LV failure.
Hypertension Detection and Follow-Up Programme (1979)	65	SC v RC not placebo controlled	30-69	DBP ≥ 90	SC reduced CV mortality by 17% compared to normal RC.	1204 subjects aged 60-69 yeras in SC group had a significant reduction in strokes compared to RC group.
Australian National BP Study (1980)	66	Chlorothiazide ± Methyldopa/betablocker v placebo	30-69	DBP 95-110 DBP < 200	Active treatment significantly reduced overall trial end points and CV deaths.	582 subjects aged 60-69 years had a significant 39% reduction in end points (ischaemic heart disease and stroke).
Oslo Study (1980)	67	HCTZ ± Methyldopa/propranolol v placebo	40-49	SBP 150-179 DBP < 110	In 785 men aged 40-49 years active treatment reduced cerebrovascular but not coronary events.	
Medical Research Council Treatment Trial for Mild Hypertension (1985)	68	BFZ or propranolol v placebo	35-64	DBP 90-109	After 5 years of follow-up significant reduction in stroke but not coronary events was reported in men and women aged 35-64 years.	Women gained no benefit from treatment and bendrofluazide was better at preventing stokes than propranolol.
International Prospective Primary Prevention Study in Hypertension (1985)	69	Oxprenolol v non-betablocker	40-64	DBP 100-125	6357 men and women aged 40-64 had no overall reduction in stroke or myocardial infarction with a β-blocker compared to non-β-blocker (mainly diuretic)	In non-smokers, β-blocker reduced cardiac events compared to non β-blocker treatment.

* Median Age; HCTZ Hydrochlorothiazide; BFZ Bendrofluazide; SC Stepped Care; RC Referred Care

1963 Leishman (62) reported on the effect of treatment with either ganglion blocking drugs or guanethidine versus no treatment in over 300 patients with DBP ≥ 120 mmHg and noted that treatment reduced the probability of dying within 5 years in those with initial DBP ≥ 130 mmHg by a third to one-sixth of that found in untreated patients. None of those treated with initial DBP 120-129 mmHg had died within three years of follow up, whilst up to one-third of the untreated group had died. He noted the reduction in mortality was largely due to a reduction in stroke and renal failure.

Randomised Intervention Trials of Pharmacological Therapy

It is not the objective of this thesis to describe in detail the effects of anti-hypertensive therapy in younger age groups, only a brief summary is given.
In the last 25 years several randomised clinical intervention trials of anti-hypertensive agents have reported on the effect of BP reduction on cardiovascular disease morbidity and mortality in mild to moderate hypertension. However, it is only in the last decade that trials specifically including older subjects (≥ 60 years) have reported; until then the only data available were from subgroup analyses of larger studies in mostly middle-aged persons which were not directly aimed at the elderly group and therefore based on small numbers. These trials (summarised in table 1.3) showed that anti-hypertensive treatment, even in subjects with mild hypertension, reduced the risk of stroke, although the reduction in CHD events was less dramatic and not found in all trials. An overview of 17 randomised trials (70) in which DBP was on average reduced by 5-6 mmHg for 2-3 years showed that stroke risk was reduced significantly by 38% (95% confidence interval [CI] 31-45%) and CHD risk by 16% (CI 8-23%). The benefits of anti-hypertensive therapy were seen to be greatest in those sub-groups at highest risk, ie, the elderly, those with higher BPs, other cardiovascular risk factors and also in males.

Randomised Intervention Trials Of Pharmacological Therapy In Elderly Subjects

A brief description of the seven trials carried out in hypertensive patients over the age of 60 years is given below and summarised in table 1.4.

1 Treatment of mild hypertension in the aged (Kuramoto et al (71), 1981).

This study enrolled 91 patients with the mean age of 76 years who were randomised to either placebo or thiazide diuretic treatment. After four years of follow-up, and only when eight placebo group patients who were withdrawn from the study as their blood pressure exceeded 200/110 mmHg were included in the analysis of fatal and non-fatal

cardiovascular events, was there a statistically significant benefit seen with active treatment which reduced BP by 5/2 mmHg compared to placebo.

2 *Randomised Control Trial of Methyldopa (Sprackling et al (72), 1981)*

This open trial enrolled 120 subjects with a mean age of 80 years and a diastolic blood pressure >100 mmHg into an untreated or Methyldopa treated group. Treatment reduced BP by 12/4 mmHg at 6 months, subjects were followed-up for up to 90 months. Anti-hypertensive treatment did not significantly decrease mortality or non-fatal cardiovascular events, although this is perhaps not surprising in view of the small number of subjects recruited.

3 *The European Working Party in Hypertension in the Elderly (EWPHE) Trial (Amery et al (73), 1985)*

840 patients aged over 60 years (mean age 72 years, range 60-80+ years) were entered if sitting SBP was between 160 and 239 mmHg and DBP 90-119 mmHg. Subjects initially received hydrochlorothiazide plus triamterene or matching placebo in a double-blind randomised fashion. After three years BP fell in the active treatment group from 183/101 mmHg to 149/85 mmHg and placebo group BP fell from 182/101 mmHg to 172/94 mmHg a net difference of 23/9 mmHg between groups.. After a 4½ year follow-up period the actively treated group showed a significant reduction in cardiovascular mortality (-27%, $p = 0.04$), mainly due to a 60% reduction in deaths from myocardial infarction, but a non-significant reduction in overall mortality (-9%, $p = 0.41$) and cerebrovascular deaths (-32%, $p = 0.16$). Cardiovascular mortality rose with increasing baseline SBP but not DBP. The main benefits of active treatment were seen in patients under 80 years of age, but were independent of sex and cardiovascular complications at randomisation. However, as most patients were recruited from hospital out-patient clinics, results may not be applicable to the elderly population in general.

4 *Trial of Treatment of Hypertension in Elderly Patients in Primary Care (Coope et al (74), 1986)*

In this trial Coope and Warrender randomised 884 patients drawn from general practice aged 60-79 years with SBP ≥ 170 mmHg or DBP ≥ 105 mmHg on two occasions to either treatment (atenolol ± bendrofluazide) or an observation group. During the 4½ years of follow-up there was an average BP difference of 18/11 mmHg between the groups. Those actively treated had a significant reduction in numbers of fatal and total strokes, but

not myocardial infarction, although there was a trend to lower total and cardiovascular mortality, but this did not reach statistical significance.

5 The Systolic Hypertension in the Elderly Project (SHEP (75), 1991)

This was the first trial to test the efficacy of anti-hypertensive drug treatment on clinical end points for persons with ISH. Subjects over 60 years of age with ISH (SBP ≥ 160 mmHg and DBP ≤ 90 mmHg) were entered into a double-blind randomised trial of Chlorthalidone 12.5 mg daily or placebo. Of the 447,921 screened persons, just over 1% were recruited. The 5 year mean reduction in BP in the treated versus placebo group was 12/4 mmHg. On an intention-to-treat basis active treatment reduced the incidence of stroke by 36% although the benefit of treatment may be even greater than suggested, as 35% of the placebo group received anti-hypertensive drugs during the trial. Treatment was equally effective in those over or under 80 years of age. Fatal and non-fatal cardiovascular events were reduced by 32% in the active treatment group with a 5 year absolute benefit of 55 events per 1,000 participants. Total coronary heart disease events were reduced by 25% but total cardiovascular mortality was not significantly affected, in contrast to the EWPHE Study where it was significantly reduced by 38%.

6 The Swedish Trial in Old Patients with Hypertension (Dahlof et al (76), 1991)

1,627 patients aged 70-84 years with SBP < 180 mmHg and DBP between 90-105 mmHg were randomised to treatment with a beta-blocker and/or thiazide diuretic or placebo group. After four years the mean difference in BP between the active and placebo groups was 27/10 mmHg with a mean duration of follow-up of 25 months. The actively treated group showed significant reductions in cardiovascular and total mortality (-43%), stroke events (-46%) and cardiovascular events (-40%) but no significant reductions in myocardial infarction (-13%) or sudden death (-50%). It was estimated that 14 elderly hypertensive patients would need treatment for five years to prevent one stroke and one death.

7 The Medical Research Council Trial of Treatment of Hypertension in Older Adults (MRC Working Party (77), 1992)

This trial enrolled 4,396 patients aged 65-74 years with SBP between 160-204 mmHg and DBP < 115 mmHg. They were randomised to atenolol 50 mg daily, hydrochlorothiazide 25 mg or 50 mg plus amiloride 2.5 mg or 5 mg or to placebo and followed-up for an average of 5.8 years. Blood pressure in the active treated group fell by

15/6 mmHg compared to the placebo group. Actively treated subjects had a 25% reduction in stroke but those treated with beta-blockers showed no significant reduction in fatal stroke or total coronary events, or in all cardiovascular events or death. It was also found that the reduction in strokes in the actively treated subjects was confined to non-smokers.

Summary

In a meta-analysis of all the trials specifically involving elderly subjects with combined systolic and diastolic hypertension Thijs et al (78) reported that pharmacological antihypertensive treatment reduces cardiovascular mortality by 22% (95% confidence interval, 10-32%) which was due to a significant reduction of 33% (9-50%) in cerebrovascular mortality and a significant reduction of 26% (9-40%) in coronary mortality. All cause mortality was not significantly reduced (-9%, -18-1%). The incidence of fatal and non-fatal cardiovascular events combined decreased significantly in all trials, except for the elderly cohort in the Australian Therapeutic Trial in Mild Hypertension (66). It was also noted that the higher the DBP at randomisation, the greater the effect of pharmacological treatment.

Table 1.4

Randomised controlled intervention studies of anti-hypertensive drug therapy in elderly persons

Trial	Ref	Total No.	Initial Treatment	Mean Age or range (years)	Follow-up (years)	Entry BP (mmHg)	BP reduction (mmHg)	Outcome
Treatment of Mild Hypertension in the Aged (1981)	71	91	Thiazide v Placebo	76	4	≤200/≤110	5/2	Decrease in fatal and non-fatal CV events (when 8 withdrawn placebo patients included in analysis)
Randomised Controlled Trial of Methyldopa (1981)	72	120	Methyldopa v No treatment	80	up to 7.5	DBP > 100	12/4	No significant decrease in mortality or non-fatal CV events (small trial)
European Working Party Hypertension in the Elderly (1985)	73	840	Thiazide v Placebo	72	4½	SBP 160-239 DBP 90-119	21/7	CV Mortality ↓27%, p < 0.05 Cardiac mortality ↓ 38% p < 0.05 Severe CCF ↓63% (-85 to -10%) Main benefit in those < 80 years
Hypertension in Elderly Patients in Primary Care (1986)	74	884	Atenolol ± BFZ v No treatment	60-79	4½	> 170/ > 105	16/10	All strokes ↓58% (35 to 96%) MI not affected
Systolic Hypertension in Elderly (1991)	75	4736	Thiazide v Placebo	> 60	5	> 160/ < 90	14/4	Stroke ↓36%. All CV events ↓ 32%. Total mortality ↓13% (NS)
Swedish Trial in Old Patients with Hypertension (1991)	76	1627	β-Blocker v Thiazide v Placebo	70-84	2	< 180/90-105	22/9	All stroke ↓46% p < 0.01 CV event ↓40% p < 0.01 CV & total mortality ↓43% < 0.01
Medical Research Council Trial of Treatment in Older Adults (1992)	77	4396	β-Blocker v Thiazide v Placebo	65-74	5-8	160-204/ < 115	16/7	Stroke ↓25% (3-42%) Coronary events ↓19% (-2 to 36%) All CV events ↓17% (2-29%) Benefit mainly due to diuretics

1.2 TREATMENT OF HIGH BP

Historical Background

The first attempts at reducing high BP involved dietary manipulation. In 1904 Ambard and Beaujard (79) reported that low sodium chloride (NaCl) diets reduced BP in patients with high BP, levels incresing again when their dietary NaCl intake was increased. In the early 1940's Kempner using a rice fruit diet also lowered high BP, an effect which depended on severe sodium restriction to levels of 10-30 mmols/day (80).

The anti-malarial agent Pentaquine, first used in 1947, was efficient at lowering high BP but was too toxic for general use (81). In the late 1940s the ganglion blocking agent tetra-ethyl-ammonium was investigated but required parenteral administration and had a very short duration of action (82). Hexamethonium a more potent and longer lasting ganglion blocker investigated in 1950 lowered high BP dramatically but caused marked orthostatic hypotension and it also required parenteral administration (83). In the early 1950's Hydralazine, a vasodilator, was introduced and was a major improvement over the ganglion blocking agents (84). However, at the doses initially used it too was toxic and produced serious side effects in high doses (85). In lower doses, and in combination with other agents, Hydralazine is still occasionally used today.

Modern Anti-hypertensive Drugs

The major advance in anti-hypertensive treatment came with the development of the orally administered diuretic, chlorothiazide, in 1957 (86,87). To this day thiazide diuretics remain one of the main effective treatments for control of hypertension and in low doses their side-effects are greatly reduced making them well tolerated, particularly as they need only be taken once daily (88).

Adverse Effects Of Anti-Hypertensive Drugs In Elderly Patients

Although, as reported in section 1.5, pharmacological reduction of high BP in the elderly reduces cerebrovascular morbidity and mortality these agents are not without side-effects. Each class of anti-hypertensive drug has recognised side-effects and cautions or contra-indications to its use. Even when appropriately prescribed such treatment can still result in adverse effects as assessed using reports on a symptoms check list, withdrawal from treatment rates or changes in quality of life. Adverse drug induced metabolic effects are of disputed significance and may or may not lead to symptoms or adversely affect

prognosis (89,90). In younger patients anti-hypertensive drug withdrawal rates (due to side-effects) in large trials have been reported at 15-30% (91,92), in addition when long-term antihypertensive treatment is stopped the prevalence rate of symptoms declines significantly (93). Although various side-effects of such drugs have been reported in the elderly (94), the prevalence of adverse side-effects may be no greater than in younger patients (92); indeed there is no clear evidence that the elderly are more likely to suffer side-effects of appropriately used anti-hypertensive drug therapy than younger subjects (95). However, in general the incidence of adverse drug reactions increases with age, this is mainly due to altered pharmacodynamics and pharmacokinetics as well as multiple prescribing and the effect of illness rather than the effect of age per se (96).

Adverse Metabolic Effects of Anti-hypertensive Drug Therapy in the Elderly

The majority of anti-hypertensive drug trials in the elderly have used either thiazide diuretic and beta-blocker based regimes, which have lead largely to only minor metabolic disturbances.

Comparison of the actively treated group in the SHEP Study (chlorthalidone supplemented in a minority of subjects with a beta-blocker, atenolol) with the placebo group (75) showed a greater incidence of hypokalaemia (3.9% v 0.8%) hyponatraemia (4.1% v 1.3%) hyperuricaemia (5.3% v 1.3%) and hypercholesterolaemia (13.2% v 11%) in the treated v placebo groups respectively.

A similar prevalence of metabolic changes has been reported in other trials in the elderly. Impaired glucose tolerance in the MRC in Older Adults Trial (77) led more frequently to drug withdrawal in the thiazide diuretic (6.9/1000 patient/years) and Atenolol (5.8/1000 patient/years) compared to placebo treated patients (2.7/1000 patient/years). In the EWPHE Study (73), in which a potassium sparing diuretic combination was the initial treatment, there was an excess of nine cases per 1,000 patients of diabetes compared to placebo.

Perry et al (97) compared atenolol, enalapril or isradipine taken for 22 weeks in elderly women aged 60-80 years. Atenolol caused significant decreases in HDL-cholesterol and increases in triglcerides; isradipine therapy was associated with a non-significant decrease in LDL-cholesterol and an increase in HDL-cholesterol while enalapril had little effect on lipids other than a small increase in triglycerides.

The significance of such drug induced metabolic changes is not always clear, but they may lead on to symptomatic problems e.g. raised urate levels causing gout and

hyponatraemia causing confusion, or they may adversely affect the cardio-vascular (CV) risk profile e.g. the effects of hypercholesterolaemia and diabetes (89, 90).

Adverse Symptomatic Effects of Anti-Hypertensive Drug Therapy

Symptoms reported during treatment in six clinical trials conducted in the elderly will be considered.

Swedish Trial in Old Patients

This trial used three different beta-blockers, metoprolol, atenolol and pindolol, and hydrochlorothiazide plus amiloride (76). Significant differences in the excess prevalence of symptoms compared to placebo were reported for beta-blockers only, with dry mouth occurring in 12%, and cold hands and feet in 14% of patients taking atenolol and muscle discomfort and cramps in 22% of subjects taking pindolol. Symptoms of tiredness, depression, disturbed sleep, dizziness, shortness of breath and swollen ankles were not significantly different between active treatment groups and placebo.

Subjective side-effects led to treatment discontinuation in 7.1% of actively treated subjects and 5.8% of placebo treated subjects, a non-significant difference.

Systolic Hypertension in the Elderly Program.

This trial used low dose chlorthalidone supplemented in a minority of subjects with a beta-blocker (atenolol) if required (75). Thirteen percent of subjects assigned to active medication stopped this because of side effects compared with 7% of patients on placebo. There were more complaints in the treated versus placebo group of cold or numb hands (13.6% vs 9.8%), ankle swelling (19.5 vs 15.6%), trouble with memory/concentration (26.4% vs 20.4%) and falls and faints (13% vs 10%). Overall there was a greater prevalence of 'any specified problem' (91.8% vs 86.4%) and 'any specified problem characterised as intolerable' (28.1% vs 20.8%) in the active treated versus placebo group respectively.

Medical Research Council Trial of Treatment of Hypertension in Older Adults

This trial used hydrochlorothiazide plus amiloride or beta-blocker (Atenolol) or placebo (77). Withdrawal rates for symptomatic side-effects are shown in table 1.5.

Over five years the diuretic group had 160 (14.8%) withdrawals for major side-effects compared to 333 (30.2%) withdrawals in the beta-blocker group and 82 (3.7%) in the placebo group.

	HCTZ	Placebo	Atenolol
Gout	4.4*	0.1	0.0
Skin Disorders	3.9*	1.1	-
Muscle Cramps	5.2*	0.1	1.0
Nausea	7.4*	1.1	-
Dizziness	7.4*	1.2	10.6*
Raynaud's	0.6	0.3	11.3*
Dyspnoea	0.8	1.1	22.9*
Lethargy	4.1	2.0	19.1*
Nausea	-	1.1	4.1*
Headache	2.5	1.1	7.2*

* $p < 0.05$

Table 1.5. Patient withdrawals/1,000 patient years for selected symptoms in subjects recruited to the MRC Trial of Treatment of Hypertension in Older Adults

Treatment of Hypertension in Elderly Patients in Primary Care

This open trial used atenolol and bendrofluazide without a placebo control group making an unbiased assessment of treatment side-effects difficult (74). However about a quarter of patients were unable to tolerate atenolol becuse of side-effects, principally fatigue, weakness and breathlessness on exertion. There was also an excess of gout in the treatment group, presumably from the diuretic treatment. Over 80% of subjects in each group were also given self-administered symptom questionnaires. No difference in the level of complaints of perceived symptoms was seen between treated and observed groups, although the background level of symptoms was high.

European Working Party on High Blood Pressure in the Elderly Trial

In this trial adverse treatment effects were assessed in 840 patients randomly assigned to either triamterine plus hydrochlorothiazide with the addition of methyldopa in one third of patients or placebo (73). In every 1000 patients treated for 1 year there was an excess over placebo of 4 cases of gout, 124 with a dry mouth and 71 complaining of diarrhoea.

Symptoms of dry mouth and diarrhoea were more often reported in those patients also taking methyldopa in addition to the diuretic (98).

More treated than placebo patients (14 v 7) stopped medication because of side-effects - gastric pain, gout, dizziness and lethargy.

Newer anti-hypertensive drugs

An angiotensin converting enzyme inhibitor enalapril, a calcium antagonist isradipine and the beta-blocker atenolol were compared over 22 weeks by Perry et al (97) in 315 women aged 60-80 years. Anti-hypertensive efficacy was similar for all drugs as were drop-out rates because of adverse symptoms: atenolol 16%, mostly due to slow pulse but also lower respiratory symptoms; enalapril 13%, primarily for cough, also abominal symptoms and constipation and isradipine 11%, due mainly to complaints of dizziness and flushing. Overall, complaints of cough occurred in 26% of enalapril treated patients and peripheral oedema in 15% taking isradipine.

Effects on Quality of Life

In addition to recognised side-effects, anti-hypertensive drug therapy may affect persons in more subtle ways, such as overall well-being and functioning which can be considered as part of the quality of life (QOL). There have however been few studies on the effect of anti-hypertensive therapy on QOL in older hypertensives. The diagnoses and starting of anti-hypertensive treatment in the US Health and Nutrition Examination Survey of persons aged 18-74 years was associated with a reduction of scores in the general wellbeing questionnaire (99).

In the SHEP study diuretic treatment had no significant effect on cognitive function or depression (75). Bird et al (100) and Goldstein et al (101) also reported no adverse effects of diuretics on cognitive or behavioural function in older subjects. However in the Treatment of Mild Hypertension Study (TOMHS) involving patients aged 45-69 years, 17% of men on chlorthalidone reported problems obtaining and maintaining an erection compared to 7% in the placebo group (102). Testa et al (103) reported that in men aged 55-79 years captopril and enalapril had no adverse effect on QOL measures in those with a low QOL score at baseline where as in those with a higher baseline QOL, enalapril but not captopril caused a deterioration. In older women Applegate et al (104) found no difference in QOL measures between those treated with enalapril, atenolol or slow-release diltiazem. In younger patients other workers have found no adverse effects on QOL from captopril (105). An adverse effect of nifedipine on cognitive function(106) and of B-blockers on

memory performance has been reported (107,108). However in the TOMH Study drugs from 5 different classes, a B-blockers, an angiotensin converting enzyme inhibitor, a calcium antagonist, a thiazide diuretic and an alpha-blocker were not associated with a decline in global QOL measures (102). In fact there was an improvement in overall QOL measures for participants given acebutolol and chlorthalidone compared to patients on placebo. In this study all patients were given non-pharmacological advice so drug treatment plus advice was compared to non-pharmacological advice only. In middle-aged patients calcium channel blockers have been associated with greater withdrawal rates and deterioration in cognitive function compared to atenolol and cilazapril (109), although this has been seen mainly with the dihydropyridine type of calcium channel blocker such as nifedipine, rather than verapamil (106).

Summary

Of the selected elderly patients entered into clinical trials, anti-hypertensive drug treatment was generally well tolerated although it was still associated with more side effects, withdrawals and metabolic abnormalities than occurred in the placebo groups. Because of entry criteria into clinical trials, recruited subjects are not necessarily representative of the index population and are likely to be less frail, on fewer other medications and more motivated. There is the potential for a greater incidence of adverse drug effects in the wider population of elderly persons who would be likely to receive treatment in usual clinical practice. (96)

1.3 NON-PHARMACOLOGICAL METHODS OF BP REDUCTION

1.3.1 Sodium Restriction

The relation between sodium intake and BP levels has been thoroughly investigated by several different methods including (a) experimental animal studies, (which will not be considered further), (b) epidemiological studies, and (c) intervention studies. Evidence regarding the sodium-BP relationship from the latter two types of study, with particular emphasis on age related aspects, will be outlined below.

Epidemiological Studies

These can be divided into (1) between population studies, (2) within population studies and (3) migration studies. They all suffer to a varying extent from similar methodological problems; the measurement and variability of usual dietary sodium intakes and BP levels and other confounding variables. Sodium intake can be estimated from (in increasing order of reliability) personal recall of food consumption over a 24 hour period or longer; dietary history records, food diaries maintained at the time of food ingestion over varying periods of time, estimation of urinary sodium excretion and the most reliable, preparation of duplicate meals (110).

Measurements of urinary sodium excretion potentially represent a satisfactory estimate of dietary intake as in a steady state situation 95% or more of ingested sodium is excreted in the urine over a 24 hour period (110). In practise however there are problems with the completeness of urine collections and the wide variability within individuals in the amount of sodium ingested and hence excreted. Depending on the degree of variability, in middle-aged persons, several 24 h collections (estimated at approximately 9-14) will be needed to reliably characterise any given individuals usual sodium intake (111), however in the elderly two consecutive 24 h urine collections may be sufficient (112,153).

The effect of variability in both casual BP measurements and estimation of sodium intake, particularly within population studies where true differences in sodium intake between persons are swamped by large day to day variations within persons, is to underestimate the relationship between dietary sodium intake and BP. On correcting for this regression dilution bias, the Intersalt Study (113) found the relationship between sodium excretion and BP was strengthened. Other confounding factors often not adjusted

for which will obscure the relationship between sodium and BP, especially between population studies are social, geographic and environmental influences.

Between Population Studies

Dahl in 1960 first described a positive, near linear association between dietary sodium intake and BP across five populations (114). He noted that hypertension was uncommon in populations with sodium intakes less than 70-80 mmols/24 h. Froment et al (115) using published data from 28 populations found the regression slope for 50 year old men showed a 10 mmHg rise in SBP for each 100 mmol/day increase in sodium intake; it was also estimated that for each 100 mmol/day increase in sodium intake the SBP would rise an additional 7.7 mmHg over 30 years. However, the analysis was strongly influenced by 9 isolated populations with low-average sodium intakes and it is probable that they differed from the remainder in many ways other than in sodium intake.

Over 20 non-industrialised low salt consuming populations with no or little hypertension have been described (2). For the majority of unacculturated societies with a low incidence of hypertension and low salt intake the latter was not the only difference from industrialised societies with a high prevalence of hypertension. These more primitive societies generally have a higher consumption of potassium (116), fibre and vegetarian diets (117) and a reduced intake a saturated fat (118) and alcohol (116); they also tend to be leaner, more physically active and do not gain weight with age - all factors which may to a varying extent reduce BP (2). In addition the cultural and psychological factors within such societies are quite different from those operating in industrialised ones.

The above studies have been criticised because of methodological problems, particularly inaccurate and non standardised estimates of sodium intake and BP measurement (119). To overcome these criticisms the Intersalt Study was established and reported in 1988 (116).

The Intersalt Study included 10,079 men and women aged 20-59 years with data collected from approximately 200 persons in each of 52 centres in 32 countries. Four centres with unacculturated populations consumed $<$ 61 mmols/day of sodium and had low BP and almost no hypertension or increase in BP with age, confirming findings in earlier studies of similar populations (120). However, as noted above, factors other than a low salt intake may contribute to these findings i.e. a high intake of potassium, low body mass and increased alcohol consumption. When data from all 52 centres are considered for a between population analysis, a significant positive correlation is found between median

sodium excretion and median SBP level when adjusted for age, sex, body mass index and alcohol intake but not when the four low salt centres are excluded. The tendency to increasing BP with age was positively associated with sodium intake when all 52 centres were included and also when the four low salt centres were excluded. The value for the slope of SBP with age was 0.34 mmHg/100 mmols sodium/year, ie, a decrease in SBP by 10 mmHg from age 25 to 55 years if sodium intake is reduced by 100 mmols/day.

Law et al (121) examined the association between sodium intake and BP from published studies of 24 communities (excluding the Intersalt Study) and performed separate analysis for each ten year age group. They confirmed that BP varies with sodium intake with no evidence of a threshold effect and also that the association is stronger for older persons and those with higher BPs. At age 20-29 years for example a 100 mmol/day change in sodium intake is associated with an average change in SBP of 5 mmHg, whilst at age 60-69 years the average SBP difference is 10 mmHg for the same change in sodium intake.

Within Population Studies

Single population studies have the advantage over interpopulation studies of greater cultural and genetic homogeneity. However, the range of average or usual sodium intake is not as great as that in cross population studies, but the day to day variation about this mean is large. In American men the intra-individual standard deviation of 24 hour sodium intake was reported as 58 mmols/24 hours, larger than the inter-person standard deviation of 32 mmols/24 hours (122). Therefore, the use of single 24 hour urine collections to estimate the sodium intake when plotted against BP will tend to underestimate the strength of the relationship by 20% to 50% of the true value. Many within population studies correlating individuals BP and sodium intake have therefore failed to confirm a significant relationship.

In the Framingham population Dawber et al (123) reported a greater sodium excretion, as judged by 24 hour urine collections, was associated with a higher prevalence of hypertension. Significant positive correlations of dietary sodium intake with BP have also been reported from Belgium (124), North Kashmir (125) and Southern California (126).

Other reports (127) have not confirmed a significant relationship between sodium intake and BP. Langford and Watson (128) studying 104 black females found no significant correlation between BP and salt intake despite using multiple measurements of both parameters to reduce variability. In the west of Scotland, Beevers et al (129) found no

difference between the sodium excretion of 92 normotensive and 110 hypertensive persons and no correlation between BP and urinary sodium excretion in either group of subjects; the high levels of sodium excretion and high prevalence of hypertension in the region were however commented on. More recently the Scottish Heart Health Study in 7,354 men and women found independent effects of body mass, alcohol, pulse rate and potassium on BP, but not of 24 hour urinary sodium excretion (130).

Instead of 24 hour urine collections some studies have estimated sodium intake from spot urine samples, a less satisfactory method than 24 hour collections. Using this method six of eight population studies reported significant sodium - BP correlations (131-138).

Overnight urine collections have also been used in place of 24-hour urine collections and 7 (139-144a) of 8 studies using this method have reported significant positive correlations with BP (139-145). However, overnight urine collections cannot be used to assess the association between dietary sodium intake and blood pressure as the agreement between daytime and overnight urinary sodium and potassium excretion is poor (144a). Also night-time sodium excretion may reflect pressure natriuresis, indeed hypertensive subjects have been shown to have a reversal of the usual diurnal pattern, excreting more sodium at night than during the day (145a).

Within population analysis from the Intersalt Study found a significant positive association between 24 hour urinary sodium excretion and the sodium :potassium ratio (116). When adjusted for body mass index, alcohol consumption and potassium excretion, in addition to age and sex, 33 centres showed positive correlations of sodium excretion with SBP although in only 8 were these significant and none were significant for DBP. A pooled, corrected correlation coefficient adjusted for the above five confounding variables and adjusted for reliability of their estimates, suggested that a 100 mmol/day decrease in sodium intake would result in a significant 3.1 mmHg fall in SBP and a non-significant 0.14 mmHg fall in DBP (146). For a decrease in the sodium : potassium ratio of 2, SBP was estimated to fall by 3.7 mmHg and DBP by 1.0 mmHg. The effect of changes in sodium intake on BP were considered to be largely independent of and in addition to any changes in body mass index (147). The relationship between sodium and SBP was also noted to be stronger for older than younger adults.

Two recent overviews of within population studies reported significant positive associations between sodium intake and BP. That of Elliott (148) included 14 studies, (excluding the Intersalt Study), and estimated from the pooled regression coefficient corrected for reliability that a 100 mmol/day reduction in sodium intake would result in SBP lower by 3.7 mmHg and a DBP lower by 2.0 mmHg. In women the regression slope

was steeper than in men, giving a 4.8 mmHg change in SBP for a 100 mmol/day change in sodium intake.

Law et al also included 14 within population studies in their analysis (121). Regression slopes of SBP on sodium intake were significant in only 6 studies but collectively they were highly significant ($p < 0.001$); results for DBP were similar.

Studies in Elderly Populations

There have been few studies examining the relationship between sodium intake and or excretion and BP in elderly populations. Khaw and Barrett-Connor (126) in a group of 584 men and 718 women aged 30-79 years described a positive association in men but not women between intake of sodium estimated from a 24 h dietary recall and SBP and DBP and also a positive association in both sexes between SBP and DBP and the sodium:potassium ratio. The strength of the relationship increased with age such that in those > 65 years BP decreased 3.7/3.2 mmHg for each unit decrease in the sodium:potassium ratio. In a later study of a similar cohort aged 40-89 years using casual urine samples to estimate sodium excretion the positive relationship between BP and sodium was confirmed (149). Adjusting for age and BMI, the sodium:creatinine ratio in men correlated with systolic and diastolic BP ($r=0.13$ and 0.08, respectively) and in women with only the SBP ($r=0.20$) In men and women the correlation was stronger between both SBP and DBP and the sodium:potassium ratio. There was a 3-4 mmHg fall in SBP and 1 mmHg fall in DBP per unit decrease in the sodium : potassium ratio.
In a Belgian study of 510 men and women with a mean age of 71 years, SBP was significantly and independently related to 24 hour urinary sodium excretion, a finding confirmed when 366 survivors were re-examined after 5 years (150). It was estimated that for each 100mol/24 hour decrease in sodium excretion, SBP would fall by 4-5 mmHg. In a further Belgian study of 53 men and 110 women > 75 years, 24 hour urinary sodium excretion was not related to BP, but being on a low salt diet was correlated with a lower DBP (151).

A London study of 58 subjects aged 41-87 y using 24 h urine collections found, after correcting for reliability, (from within person variability of sodium excretion) the SBP - sodium regression slope was 10.6 mmHg per 100 mmols sodium (152).

However, not all studies in older persons have demonstrated associations between sodium intake and BP. In 425 elderly Chinese persons no significant correlation between BP and casual urinary sodium:creatinine or sodium:potassium ratios was found (153).

Also, from the NHANES1 data Harlan et al (154) could find no significant relationship between dietary sodium intake or the sodium:potassium ratio (estimated from 24 hour dietary recall and 3 month food frequency records) and either SBP or DBP in subjects aged 55-74 years.

Migration Studies

These studies which have the advantage of comparing groups with similar genetic backgrounds and more definable changes in environmental factors report that on migration to a westernised environment BP usually rises (155-157). For example compared to living on Polynesian atolls migration to New Zealand resulted in BP elevations, in all age groups, of 7-8 mmHg for men and about half this amount for women (156). Migrants were found to have increases in sodium intake, decreases in potassium intake and an overall increase in body mass. There is also the less easily definable effect of urbanisation in general on the migrants whilst their counterparts continued with their traditional island life.
It is unclear which of the many factors that change following migration are responsible for the increase in BP although it is likely to be a combination of several factors, not all operating to the same extent in all subjects.

Summary

There are major methodological problems in assessing the relationship between sodium intake and BP because the large degree of intra-individual variability of both parameters makes estimations of usual levels difficult. In addition any relationship is confounded by numerous other factors affecting BP levels. Despite these difficulties, analysis of many studies from within and between populations and migrant groups involving mostly young and middle-aged persons suggests a positive relationship between sodium intake and BP levels.

However there are few data available on the relationship between sodium intake or excretion and BP in older persons. There has been no large study conducted using 24 h urinary electrolyte excretion and multiple BP measurements in the elderly. Of those studies that have been conducted there is evidence that the relationship between sodium and BP is at least as strong in older as in younger persons.

Intervention Trials Examining the Effect of Changes in Sodium Intake on BP

Early Studies with Severe Sodium Restriction

The studies of Allen in 1922 (158) and Kempner in 1948 (80) showed that severe sodium restriction could lower BP and decrease morbidity in severe hypertensives. Studies by Grollman et al (159) in 1945, Watkins et al (160) and Murphy (161) in 1950 also confirmed the hypotensive effect of severe sodium restriction in essential hypertensives. Such diets were however unpalatable and compliance with them poor, such that they were not used routinely in hypertensive patients. Effective anti-hypertensive drugs became available soon after the benefits of severe sodium reduction were shown and dietary therapy went out of fashion.

Studies on Moderate Sodium Restriction

Since the 1970's with the realisation that treating mild to moderate hypertension is beneficial in middle-aged persons, but exposes a large number of people to pharmacological treatment, interest in non-pharmacological methods, and in particular moderate sodium restriction, grew. Studies of varying size and duration and trial design with varying degrees of sodium restriction were carried out in normotensive and hypertensive subjects, either with or without other (intentional) dietary interventions or in combination with anti-hypertensive drug treatment.

Studies of Moderate Sodium Restriction in Normotensive Persons

(i) Studies of sodium restriction in middle-aged normotensive adults

There have been over 20 studies of sodium restriction in normotensive adults, however, only some of them have had a satisfactory design including randomisation to sodium restriction or control group, freedom from confounding by other interventions and use of moderate sodium restriction. Six trials meeting these criteria; four using a cross-over design (162-165) with 371 subjects and two parallel group trials (166, 167) with 389 subjects were considered in a meta-analysis by Cutler et al (168) and are shown in table 1.6. Four trials were of one month duration or less (162, 164 [2 studies], 166), one of two months (163) and the other of 36 months duration (167). Reductions in sodium excretion varied from 16 to 170 mmols/day. All trials except one {The Hypertension Prevention Trial (167) in which sodium intake was reduced by only 16 mmol/24 hour and SBP rose 0.1 mmHg} reported lower SBP with sodium reduction although these mean decreases were

Table 1.6

Randomised Studies of Sodium Restriction in Normotensive Subjects

Study	Ref	Year	n	Mean Age	Duration of Na Restriction (wks)	Urinary Na change (mmol/24hr)	BP Change	
							SBP	DBP
Crossover Studies								
Skrabal	162	1981	20	33	2	-170	-2.7	-3.0
Cooper	163	1984	113	16	3.4	-69	-0.6	-1.4
Watt	164	1985	35	-	-	-74	-1.4	+1.2
Watt	164	1985	31	23	4	-60	-0.5	+1.4
Myers	165	1989	172	37	2	-130	-3.5*	-1.9*
Mascioli (SNaP)	171	1991	48	52	4	-61	-3.6*	-2.3*
Parallel Studies								
Puska	166	1983	19	-	2	-117	-1.5	-1.1
HPT	167	1990	196	39	156	-16	+0.1	+0.2
TOHP	170	1993	327	43	78	-61	-2.1*	-1.2*
Elderly Studies								
Cobiac	173	1992	51	67	4	-74	-2.8*	-0.7
Nestel	172	1993	32	65	6	-65	M: -0.8 F: - 6.1*	-0.5 -1.9*

n = number on salt restriction
* $p < 0.05$

very modest, ranging from 0.6 - 3.5 mmHg. The DBP in four of the reported trials declined and in three increased following sodium restriction. Only one trial, that by Myers (165) reported a statistically significant decrease in SBP and DBP. Overall for all six trials SBP decreased significantly by approximately 1-2 mmHg and DBP by 1 mmHg.

Law et al (169) carried out a meta-analysis of 21 sodium restriction trials in normotensive subjects and concluded sodium restriction did lower BP in these subjects. It was estimated that in persons over 50 years a 50 mmol/24 hour long-term reduction in sodium intake would reduce BP by approximately 5/2 mmHg. The modest and often non-significant changes of these individual trials could be explained by the young age of subjects enrolled (the response of BP to salt restriction probably increases with age) and short duration (four weeks or less in 16 out of 21 trials).

Two more recent studies not considered in the above overviews are the Trials of Hypertension Prevention (TOHP) and the Study of Sodium and Blood Pressure (SNaP). In the TOHP (170) sodium restriction in subjects aged 30-54 years had a greater hypotensive effect on SBP in women than men (-4.4 v -1.2 mmHg respectively). For all subjects it was estimated that a 100 mmol/24 hour reduction in sodium intake would lead to a fall in SBP of 1.4 mmHg and in DBP of 0.9 mmHg. Using a greater degree of sodium restriction the SNaP study (171) in subjects aged 30-59 years also found a significant fall in SBP of 3.6 mmHg and DBP of 2.3 mmHg.

(ii) Studies of sodium restriction in normotensive elderly subjects

There have been two randomised studies of moderate sodium restriction conducted in the elderly, both summarised in table 1.6. Nestel et al (172) found a greater hypotensive effect of sodium restriction in women than in men for both SBP and DBP. After adjustment for sodium chloride intake, SBP in women was 6.1 mmHg lower ($p < 0.001$) on the low sodium intake but only 0.8 mmHg (NS) lower in men. In women DBP was 1.9 mmHg lower ($p < 0.001$) and in men a non-significant 0.5 mmHg lower on the low sodium intake. In both sexes and for both SBP and DBP there was a significant relationship between changes in urinary sodium excretion and changes in BP. The waist : hip ratio exerted a major influence on BP responses to sodium in women. Women in the lowest quartile for waist : hip ratio showed the most significant change in SBP and DBP for the change in sodium, (7.1 and 2.7 mmHg respectively). The waist : hip ratio was not a significant predictor of BP in men although it remained the strongest predictor of salt responsiveness in women after adjustment for other co-variates.

Cobiac et al (173) assigned subjects to one of four matched treatment groups while they continued on a low sodium diet (LSD); (a) 80 mmol/day sodium supplement + sunflower oil capsules, (b) matching placebo tablets + sunflower oil capsules, (c) placebo sodium tablets + fish oil capsules or (d) 80 mmol sodium supplement + fish oil capsules. At the end of each four week treatment phase there was no significant change in BP from baseline in groups taking either oil with a normal sodium diet (NSD). Those subjects on LSD with either oil showed significant reductions in SBP but only the fish oil + LSD significantly lowered DBP. Comparing LSD + sunflower oil group with NSD + sunflower oil group revealed a modest but significant reduction in SBP for the former group (-5.2 ± 1.0 vs -2.4 ± 1.0 mmHg, $p < 0.05$).

Summary

Moderate sodium chloride restriction in normotensive young and old persons has been shown to produce either no or a modest reduction in BP. There may be important sex differences in the BP response to sodium restriction with women showing a greater hypotensive effect.

Studies on Sodium Loading

(i) In Normotensive Subjects

Many studies have reported that increasing sodium intake so that urinary excretion increased to over 300 mmols/day in normotensive adults resulted in no significant change in BP (174-179). Luft et al (180) in normotensive adults found no effect on BP of increasing sodium intake from 10 to 600 mmols/24 h, but at 1200 mmols/24 h there were significant BP rises in white subjects and in black subjects at 800 mmols/day. Overack et al (181) found no effect on BP after one week of low salt (20 mmols/day) and high salt (300 mmols/day) intake in young normotensives.

Overall young normotensive subjects appear very resistant to any pressor effect of sodium chloride loading even at high doses, at least in the short term. No such similar studies have been conducted in elderly normotensive subjects.

(ii) In Hypertensive Subjects

In two studies, increasing sodium intake from normal levels to high intakes of 250-300 mmols/day resulted in no change in average BP (182,183). Dustan and Kirk (184) using intravenous saline loading in hypertensives noted increases in BP in some subjects

only. Although many studies show no overall change in BP with salt loading there is a great individual variability in response with a proportion showing significant BP rises.

(C) Studies on Moderate Sodium Restriction in Young and Middle Aged Hypertensive Subjects.

These trials aim to produce moderate sodium restriction to levels in the range of 70-100 mmols of sodium per day. For various reasons the findings from these trials are not uniform, some reporting significant BP falls and others no effect from the reduced sodium intake. Data on these trials are summarised in table 1.7.

(i) Short-term studies using clinic BP measurements

The first controlled trial was reported by Parijs et al (185) in 1973. Twenty-two middle aged male and female hypertensive subjects entered a 4 week cross-over design trial of a regular diet plus placebo and a moderate sodium reduction diet plus placebo group. The initial assignment was randomised but the sodium reduction diet was not blinded. Despite a reduction in sodium excretion of 98 mmols/24 hours to 93 mmols/24 hours there was no significant change in BP which was 9/6 mmHg lower on the placebo low sodium diet compared to the placebo regular diet.

One of the major problems in trial methodology had been the non-blinded nature of the sodium restriction groups which was addressed by MacGregor's group.

In 1982 MacGregor (186) implemented the study design proposed by Parijs et al (185) which was of a randomised double blind cross over design. In this all patients restrict their sodium intake whilst receiving either slow sodium or placebo tablets in a randomised double blind fashion and then cross-over to the alternative period. Clearly one advantage of this design was that subjects act as their own controls and are managed in an identical way so that in theory the only difference between the periods are the changes in sodium intake. Using this design McGregor et al (186) reduced sodium excretion by 50% to 83mmol/24h and noted a significant fall in BP of 10/5 mmHg. A year later Watt et al (187) used a similar design reducing sodium excretion by 39% to 87 mmol/24h, however no significant BP change was found. The difference in results between these trials may be due to the lower baseline BP and sodium intake and smaller percentage reduction in sodium excretion seen in the trial of Watt et al. In a later study McGregor et al (182) randomised subjects in a similar fashion to approximately 50, 100 or 200 mmol/24h sodium intake and reported a linear relationship between the level of salt intake and BP, those with the lowest intake having the lowest BP.

Table 1.7 **Controlled trials on the efficacy of sodium chloride restriction in hypertension**

Date	Study	ref	Design	Age Mean (Range)	n[a]	Duration	Baseline		Change		Sodium (mmol/day)		
							SBP	DBP	SBP	DBP	Initial	Final	Change
1973	Parijs et al	185	x	41	17	4 Weeks	147	98	-9.1	-5.8	191	93	-98
1978	Morgan et al	201	p	60	31	2 years	160	97	-2.0	-7.3*	191	157	-34
1980	Longworth et al	192	p	45 (15-64)	82	10 days	121[b]			-1.7[b]	197	70	-127
1982	MacGregor et al	186	x	49 (30-66)	19	4 weeks	156	98	10	5	191	83	-108
1983	Watt et al	187	x	52 (36-64)	18	4 weeks	136	82	0.5	-0.3	143	87	-56
1983	Silman et al	198	p	55 (50-64)	12	1 year	165	98	-8.7[c]	6.3[c]	151	117	-34
1983	Puska et al	190	p	- (30-50)	34	6 weeks	139	90	-0.7[d]	+0.8	192	77	-115
1984	Richards et al	195	x	40 (19-52)	12	4-6 weeks	137	86[e]	-4.0	-3.0	180	80	-100
1987	Erwteman et al	189	p	46 (20-70)	44	4 weeks	143	94	2.7	2.5	130	72	-58
1987	Grobbee et al	191	x	22 (18-28)	40	18 weeks	141	76	-0.8	-0.8	129	57	-72
1989	Dodson et al[f]	206	p	62	17	12 weeks	180	91	-13.0*	-1.8	199	137	-62
1989	McGregor et al	188	x	57	20	4 weeks	155	95	8	4	108	49	59
1989	McGregor et al	188	x	57	20	4 weeks	163	100	8	5	190	108	82
1989	Australian NHMRC	193	p	59	103	8 weeks	155	95	-4.8*	-2.8	142	90	-52
1989	Australian NHMRC	207	x	59	88	8 weeks	154	95	3.6*	2.1*	156	90	66
1992	Fagerberg et al	208		51	30	9 weeks	147	85	-8.6	-5.5	195	96	-99
1992	Benetos et al	194	x	42 (22-55)	20	4 weeks	154	96	**-6.5	-3.7**	163	85	-78
1993	Zoccali et al	197	x	47 (30-65)	14	1 week	147	95	-9*	-2	146	43	-103
			x	47 (30-65)	14	1 week	138[g]	88[g]	-11*	-4*	146	43	-103

[a] n represents the number of subjects who underwent salt restriction. In parallel group design studies (p), the overall number included is of course greater. (x) Cross-Over Study

[b] Mean arterial pressure

[c] Taken as difference between salt restricted and non-salt restricted groups

[d] Change from baseline at end of study

[e] Intra-arterial

[f] subjects, non-insulin dependent diabetes

[g] mean 24 hr ambulatory BP

* $p < 0.05$, ** $p < 0.01$

Other investigators (189-191) found no significant changes in BP despite reporting significant reductions in sodium excretion for at least 4 weeks although in one study (192) the duration was of 10 days only.

In both the Australian Dietary Salt Study (193) and that by Benetos et al (194), significant falls in BP were recorded following sodium restriction, which increased with increasing age

A summary of the studies of moderate sodium restriction is shown in table 1.7.

(ii) ***Short term studies assessed by 24 Hr ambulatory BP monitoring***

Three studies have reported the effect of dietary sodium chloride on 24 h BP levels. Richards et al (195) investigated the effect of a 4 week low sodium diet and a potassium supplemented diet compared to a controlled diet in 12 young mild hypertensives using intra-arterial and clinic BP measurements. Despite a fall in urinary sodium excretion of 100 mmols/day there was no significant fall in clinic BP or in 24 hr intra-arterial BP. Night-time (midnight to 0900 hrs) BP levels were however lower on the low sodium diet by 5.3/4.3 mmHg, ($p = 0.07$). Changes in plasma renin activity (PRA) were found to correlate with changes in intra-arterial BP. Patients with the greatest increase in PRA on sodium restriction showed little change or a rise in BP while those whose PRA did not change or fell, had a fall in BP. This was thought to suggest the possibility that stimulation of renin release may limit or overcome the hypotensive effect of sodium reduction. A postulated explanation of the greater nocturnal fall in BP was the reduction in BP variability during sleep and the reduced activity of the renin-angiotensin system at night.

In a study of 7 days severe sodium restriction (from 250 mmols/day to 10 mmols/day) in 15 young hypertensive subjects, Moore et al (196) found a significant fall in clinic but not in 24 hour ABP. However, nocturnal BP during the low sodium diet was significantly lowered (4 ± 2 mmHg, $p < 0.05$). The greater hypotensive effect of sodium restriction during sleep was again attributed to a reduction in compensatory mechanisms (presumably the renin-angiotensin system).

Zoccali et al (197) reported on the effect of 1 week periods of low (sodium excretion:43 mmol/24h), habitual (146 mmol/24h) and high (212 mmol/24h) sodium intakes on mean 24h ambulatory BP in 14 middle aged hypertensives. Mean 24h SBP and DBP were significantly lower on the low compared to habitual intake (-11 and -4 mmHg, $p<0.01$, respectively); DBP was significantly lower on the habitual intake compared to the high intake (-4mmHg, $p<0.01$) but not SBP (-5 mmHg). Clinic SBP was also significantly lower on the low compared to habitual intake (-9 mmHg, $p<0.01$) but there were no

significant changes between habitual and high intakes. Overall this study showed increasing ambulatory BP levels with increasing sodium intake.

(iii) Long term trials of sodium restriction

Four studies in excess of nine months will be described. Silman et al (198) randomised 16 patients to a control group and 12 patients to low sodium diet who after 12 months reduced their sodium excretion from 151 to 117 mmol/24h; however the accompanying fall in BP of 8.7/6.3 mmHg was not significant.
Morgan et al (199) in a parallel group study lasting 2 years reported a significant fall in DBP of 7.3 mmHg in 31 subjects aged over 50 years randomised to the sodium reduced diet (sodium excretion decreased from 191 to 157 mmol/24h) whilst no change in BP was seen in the control group.

In the 1989 study of MacGregor et al (188), 19 subjects continued on a sodium restricted intake of 50 mmols/day for one year and maintained the same reduced BP as seen after one month sodium restriction when compared to BP levels on diets containing 100 and 200 mmols/day sodium chloride.

Omvik and Lund-Johansen (200) studied 19 men aged 16-51 years with mild hypertension on a low sodium diet for nine months using intra-arterial BP measurements in addition to clinic measurements. Sodium excretion fell by 75 mmols/24 hours from a mean baseline level of 209 mmols/24 hours. There was no control group, but as intra-arterial BP measurements are either little, or not at all, affected by the placebo effect they may represent a true change induced by the intervention. Intra-arterial BP levels fell significantly but modestly at the end of nine months by 4.2/2.9 mmHg supine and 6.8/4.7 mmHg sitting.

Studies of sodium restriction in older hypertensive subjects

The two year study of Morgan et al (199) described above and reporting a significant fall in DBP did include subjects over the age of 50 years but the age range was not given. The same group also reported on 49 subjects aged 48-78 years with mild diastolic hypertension (201). Sodium intake was reduced from 190 to 150 mmols/day and after three years there was a significant fall reported in SBP from 155 to144 mmHg and DBP from 102 to 94 mmHg compared with an untreated control group. However, the study was open and not placebo controlled. In addition three patients in the sodium restricted group whom BP increased were started on drug therapy.

Palmer et al (202) studied a group of 7 normotensive and borderline hypertensive long stay residents of a care facility with a mean age of 85 years. This was a randomised, placebo controlled, double-blind crossover trial of a high sodium (175 mmols/day) and low sodium (43 mmols/day) intake for 4 weeks each, following which DBP was significantly reduced from 79 ± 4 to 70 ± 4 mmHg but not SBP. 24 h urine collections were not made to confirm changes in sodium intake and the small number of subjects increased the chance of a type II statistical error.

The effect of a reduced sodium and increased potassium and magnesium intake for 24 weeks on BP in 48 'mildly hypertensive' persons (mean BP 158/90 mmHg), aged 55-75 y (mean 67 y) compared to a control group of 49 persons was studied by Geleijnse et al (203). Between week 8 and 24 there was a significant net reduction in clinic SBP of 7.6 mmHg (CI 4.0-11.2 mmHg) and in DBP of 3.3 mmHg (0.8-5.8 mmHg). Sodium excretion was 38 mmol/24h and potassium 17 mmol/24h higher in the diet group. Although the sodium reduction was modest the combination with increased potassium and magnesium may have a synergistic effect on lowering BP. The relatively large hypotensive effect is also suprising since baseline blood pressures were low, many of the subjects would be classified as normotensive (BP < 160/90 mmHg).

There have so far been no well controlled and unconfounded studies of moderate sodium restriction in a group of elderly hypertensive subjects.

Community studies of sodium restriction

Staessen et al (204) attempted sodium reduction in one Belgium town through mass media techniques and used another town as a control. After 5 years the net reduction in 24h urinary sodium excretion was greater in women than men and greater in older (50 to >60 years) than younger persons. Even in these groups sodium excretion was reduced by only 25mmol/24h and no reduction in BP was seen compared to the control town.

In contrast Forte et al (205) in Portugal compared the effect of sodium restriction using a health education programme with three simple messages in 800 adults from two matched rural communities, one receiving the advice, the other acting as control. In the intervention community BP fell significantly by 3.6/5.0 mmHg at the end of one year and 5.0/5.1 mmHg at 2 years whilst in the control community DBP remained stable and a slight rise in SBP occurred. In these communities sodium intake was high at over 350 mmols/day and at the end of the intervention period fell to 200 mmols/day.

Summary of sodium restriction trials in hypertensive subjects

A summary of the controlled trials of moderate sodium restriction in hypertensive subjects is shown in table 1.7. In Cutlers (168) overview of sodium restriction trials in hypertensive subjects, 18 randomised trials free of confounding interventions were included. Eight were crossover trials enrolling 221 subjects with a treatment period of between 1-2 months and a net reduction in sodium excretion of 56-105 mmols/day. All 8 trials reported lower SBP during sodium restriction and 7 with lower DBP, although only 4 of the SBP and 3 of the DBP differences were significant. Twelve trials were of parallel design with 652 subjects and a median follow-up time of 3 months, range 1.5 - 24 months; median reduction in sodium excretion was 65 mmols/24 hrs, range 27 - 171 mmols/24 hrs. Blood pressure changes in the low sodium intake groups were all in a negative (lower) direction except for two studies; the reductions were significant in six studies for SBP and nine for DBP. The overall SBP reduction for all trials was 4.0 ± 1.2 mmHg and 2.5 ± 0.7 mmHg for DBP (mean $\pm$ 95% confidence interval).

In the meta-analysis conducted by Law et al (169) 57 trials in hypertensive subjects and 21 in normotensive persons were considered. They concluded that in salt restriction trials that lasted five weeks or longer the reductions in BP were similar to those predicted from between population analysis of observational data. Observed reductions were below predicted values in trials lasting four weeks or less, suggesting a longer time was needed to attain the full effect of sodium restriction. The analysis confirmed that salt restriction lowers BP to an extent that increases with age and with initial BP. It was calculated that for a hypertensive person aged over 50 years a 50 mmol/24 hr reduction in sodium intake would reduce SBP by 7 mmHg and DBP by 3.5 mmHg.

A further overview of sodium restriction trials (209) and other studies not considered by them (194) also suggest that older rather than younger subjects have a greater hypotensive response to sodium restriction. Despite this there have been only 3 studies conducted in elderly persons none of which have been satisfactory because of their open and uncontrolled design (201), small numbers (202) or confounding by changes in other electrolytes (203).

Problems with sodium restriction studies

The variability of the BP response to salt restriction in the numerous studies is probably a reflection of the differences in study design as well as the patients recruited. Potential problems in interpreting the various intervention studies may be related to the following.

Study Design: Due to the placebo effect and regression to the mean, ie, a fall in clinic BP without any specific hypotensive intervention, a control group is essential to demonstrate the true effect of the intervention. The most satisfactory, sensitive and specific design is a double-blind, randomised, cross-over trial when subjects are exposed to intervention and control periods in a random sequence. Sources of variation other than the intervention can be minimised as subjects act as their own controls. The trial design pioneered by MacGregor et al (186) for sodium restriction studies successfully overcame these problems. In parallel group design studies there is a greater chance that factors besides sodium intake will vary between groups e.g. changes in other dietary constituents, weight, exercise and alcohol intake.

Study duration: There is a great variation in the duration of trials from 5-10 days to more than a year although the majority lasted approximately one month. As suggested by Law et al (169) trials of sodium restriction lasting less than four weeks may not show the full potential effect of sodium restriction on BP.

Level of sodium intake and degree of sodium reduction: The level of sodium intake during low sodium diet periods varied considerably from 20 mmols/day to 117 mmols/day (as judged by 24h urinary sodium excretion) and the change in sodium intake (control phase minus low sodium diet) varied from less than 30 mmols/day to over 170 mmols/day. The baseline sodium intake in the various studies also varied widely from about 200 to 130 mmol/24h or less. The baseline intake and level to which sodium is reduced may be of relevance if a threshold level of sodium intake exists above which changes in sodium have little effect on BP and below which some patients will respond by lowering BP.

Type of anion associated with sodium: Animal and human studies have shown that although sodium chloride can increase BP other sodium salts, such as sodium bicarbonate, citrate and phosphate do not (210,216). Non-chloride salts of sodium have been found to cause similar degrees of sodium and water retention and suppression of plasma renin

activity as sodium chloride, but less volume expansion and urinary calcium excretion (212). The effects of sodium chloride appear to be specific to this molecule.

Subject variability: Subjects recruited to studies vary in many other respects than just their level of sodium intake e.g. sex, race, age, body fat and general diet. Older subjects may demonstrate a greater hypotensive effect to a given degree of sodium restriction than the young (169). Subjects with high initial BP levels are statistically more likely to show a greater fall in BP than those with lower BP levels (217). The effect of age and initial BP levels on response to a low sodium intake may also act through the renin-angiotensin system (RAS). In these older subjects with higher BP levels the RAS is relatively suppressed compared to young subjects and those with lower BP levels (218), hence a greater stimulating effect on the RAS for a given change in sodium intake may occur in the latter group, thereby eliminating any BP fall triggered by the low sodium diet (219).

Statistical power: The statistical power to detect changes in BP have been limited in many studies by the small number of subjects recruited and the variability in casual BP measurements. Very few studies have recorded a power calculation to determine the number of subjects required to show a given difference in BP at a given significance level. For example for a cross over study to detect a change in SBP between two treatment periods of 5 mmHg with a power of 90% at the 5% significance level and assuming standard deviation of the difference of clinic SBP of 14 mmHg, 78 subjects would be required. Of all the unconfounded randomised studies listed in Table 1.7 only one (207) was of sufficient size to demonstrate this difference.

HETEROGENEITY OF BP RESPONSE TO SODIUM RESTRICTION: SALT SENSITIVITY

Although average changes in BP levels of groups of subjects undergoing sodium restriction are only modest, this conceals a wide variation in individual responses. For example Richards et al (195) found no overall significant change in BP on reducing sodium intake, but 7 of the 12 subjects had lower intra-arterial DBP than control by 1.6 - 20 mmHg. These heterogeneous responses to sodium restriction have been explained by some on the basis of sodium sensitivity and resistance (220,221). Sodium sensitivity has been variously defined as a sodium related change in mean BP of $>10\%$ (220) or >10mmHg (214), or >3 mmHg (222) or any increase in DBP with increasing salt intake (223) usually after severe sodium restriction (approximately 10 mmols/24 hours) and sodium loading (250-300 mmols/day). Many factors have been proposed that determine, or are related to salt sensitivity eg, age (224), sex , race (225), the renin-angiotensin system (226) and many others (227-229).

There has however been no clear bi-modal response to changes in sodium intake, defining responders and non-responders depends on arbitrary cut off points on a normal distribution curve (230). On repeated BP measurement without any specific intervention, due to variability and random error, some subjects will have high and others low BP levels compared to initial values. It is unclear at present to what extent there are two groups of responders and non-responders to changes in sodium intake and how much physiological significance is being attached to random variation. Repeated intervention in selected subgroups of either responders or non-responders would help clarify the situation. Sharma et al (231) have reported good reproducibility of salt-sensitivity in 15 normotensive subjects. Weinberger and Fineberg (232) studied the reproducibility of salt sensitivity in 28 normotensive and hypertensive subjects over a period of one year; 4 subjects changed category from either salt sensitive to salt resistant and 6 changed from either salt resistant to salt sensitive to indeterminate category, ie, 10 out of 28 subjects changed their status, overall not a high level of reproducibility!

Effect of age on salt sensitivity

Several investigators have considered older age to be associated with a greater degree of salt sensitivity (224). As previously noted observational studies have found a stronger association between sodium intake and BP at older ages. Both Grobbee and Hofman (209)

and Law et al (169) conducting meta-analysis of salt restriction trials have also reported a greater fall in BP with sodium restriction for older than younger subjects. Weinberger's group found salt sensitivity of BP to increase significantly with increasing age and to a greater extent in hypertensive than normotensive subjects (223).

The physiological basis for the increased sodium sensitivity with increasing age has been related to the concomitant age related change in plasma renin activity and renal function. Circulating plasma renin diminishes with increasing age (234, 235) and renin responsiveness, for example to a low sodium intake is blunted resulting in an incomplete compensatory response and hence a hypotensive effect. The ability to increase and decrease sodium excretion with age is also diminished (236). Older subjects are slower to excrete sodium loads than those younger (237). A tendency to sodium retention may be secondary to age related declines in renal dopamine (238) and vasodilatory prostaglandins (239). Increased sympathetic nervous system activity in older subjects, suggested by higher urinary noradrenaline levels may indicate increased renal sympathetic nerve activity leading to increased sodium retention (240,241).

Race, obesity and electrolytes

Like older subjects, black persons appear to have a greater frequency of salt-sensitivity compared to the general population and may also have delayed excretion of a sodium load (242) and a greater decline in renal function with age than white persons (243). There is some evidence to suggest obese hypertensives have a greater frequency of salt sensitivity than lean hypertensives (241,245). Elderly normotensive women with the lowest waist : hip ratio, i.e. a gynaecoid distribution of fat, independent of body mass index, had the greatest sensitivity to the hypotensive effect of a moderate reduction in sodium intake (172). Deficiencies in both potassium and calcium intakes have been linked with an increased frequency of salt sensitivity (246), both ions are also linked with sodium excretion, increased sodium excretion being accompanied by increased potassium and calcium excretion (247).

Conclusions

Although the concept of salt sensitivity is not universally accepted there is a marked heterogeneity in BP responses to variations in sodium intake between individuals. The limited data available suggests that subjects who are older, more obese or with a gynaecoid distribution of fat and have higher BP levels have a greater hypotensive response to sodium restriction.

Adverse effects of low sodium diets

There are few data on the adverse effects of sodium restriction, that which are available often relates to severe degrees of sodium restriction (< 50 mmols/day) which may not apply when more moderate degrees of sodium restriction are practised (50-100 mmols/day). The following points have been raised:

Increase in BP with sodium restriction

As previously mentioned there is a heterogenous response to salt restriction in both normotensive and hypertensive subjects probably resulting from poor reproducibility of the measurements as well as inter-individual variation.

That the variation in BP (including BP elevations) on moderate sodium restriction is largely due to chance variation is supported by the results of the Australian salt restriction study (193). In this study there was considerable variation in responses to sodium restriction with increases in DBP of up to 20 mmHg and decreases of 12 mmHg in the control group.

Effect on circulatory responses

There is the potential in the elderly whose kidneys may be less efficient at conserving sodium and water (248), that a low sodium diet, particularly in combination with diuretic therapy could lead to dehydration and orthostatic hypotension (249). It has also been demonstrated that in middle-aged persons with poor orthostatic tolerance that a sodium supplement of 80 mmol/24h leads to an improvement, suggesting that in some elderly hypertensive patients with, or prone to, orthostatic hypotension the condition could be exacerbated with a low sodium diet (250). However, there is no evidence that in healthy man moderate sodium restriction has any harmful effects on the cardiovascular system.

Metabolic effects

Reported adverse changes in blood lipid levels with severe sodium restriction (251-253) probably reflect transient haemoconcentration and have not been seen in other studies (254) and those using moderate sodium restriction (255). Insulin resistance and impairment of glucose tolerance has been noted during severe sodium restriction (251, 256, 257) although the mechanisms underlying these changes is unclear, the stimulation of the sympathetic nervous system or the renin angiotensin system has been suggested (251).

Effect on intake of other nutrients

In Britain approximately 32% of total sodium intake comes from cereals and 24% from meats (258). It has been claimed that large reductions in sodium intake may reduce the intake of fibre, minerals and vitamins (259), in fact moderate sodium restriction has been reported to result in no change in the intake of other electrolytes or vitamins, although total calories, fat and iron intake did decrease (260).

Quality of life

It cannot also be assumed that the effects on quality of life (QOL) of using low salt diets in hypertensive subjects will necessarily be more favourable than the use of anti-hypertensive medications. Difficulties with adhering to low salt diets when eating out may cause difficulties and lead to a degree of stress when high sodium containing foods cannot be avoided. In the TOMH Study (102), QOL scores were poorer in the placebo group who were given non-pharmacological advice , which included sodium restriction compared to those also given anti-hypertensive drug treatment. Although the Trials of Anti-hypertensive Intervention and Management reported increased fatigue with the use of a moderate sodium restricted diet (261) this was not seen in the Trials of Hypertension Prevention study (262), in fact psychological general well being scores were higher in the intervention group (reducing sodium to approximately 100 mmols/day) after 18 months than at baseline or in the control group.

In summary there is no evidence that moderate sodium restriction to approximately 70-100 mmols/day has an adverse effect on health (263).

FEASIBILITY OF LONG TERM MODERATE SODIUM RESTRICTION

Moderate sodium restriction, either alone or in combination with other non-pharmacological methods has been evaluated for its hypotensive effect in normotensive and hypertensive subjects in nine studies, involving over 1700 participants followed up for a minimum period of one year and extending to five years in some studies (102, 262, 264-269). None of these studies involved elderly persons, the majority recruited subjects between the ages of 30-59 years although in the TOMHS study (102) the upper age range was 69 years. All studies were randomised and controlled in design and dietary intervention aimed for a sodium intake of 70-80 mmols/day. The intervention programmes typically included an initial phase of intensive education lasting 2-6 months which provided group or individual counselling sessions or a combination of these, information on the sodium content of foods, behavioural approaches towards dietary change, food purchasing and preparation. Motivation was enhanced by follow-up visits at 1-3 month intervals and completion of food diaries and 24 h urine collections for feedback on sodium intake. After 12 months, reductions in sodium excretion of between 13-55%, average 34%, were achieved.

The degree of dietary sodium reduction that could be achieved with a simpler educational or counselling programme is less clear. As the majority of ingested sodium comes from processed food a major change in eating habits would be required by many people if a reduction of 30-40% in sodium intake is to be achieved. An Italian study of newly diagnosed middle aged hypertensives (mean age 44 years) concluded that long term low sodium diets using simple dietary instructions were not feasible (270).
In a New Zealand study to test the feasibility of salt restriction in a community, only 42% of 191 subjects aged below 64 years invited to participate in the study took up the offer (271). The sodium restriction programme provided information on low sodium foods, advice on cooking methods and salt poor bread, but there were no intensive counselling sessions. After eight months sodium excretion was significantly reduced from 156 to 88 mmols/day in men and from 117 to 74 mmols/day in women whilst no change occurred in the control group; however 26% of the low sodium and 5% from the control group dropped out. Of those on the low sodium diet 66 % found it tolerable and 17% considered it 'good'. It was commented that for significant reductions in sodium intake to be achieved food manufacturers would need to provide low salt foods.

Opportunities for sodium restriction in elderly subjects

There have been few studies assessing sodium intake or excretion in older persons, in Belgium levels of sodium excretion of 161-188 mmol/24 h in men and 124-160 mmol/24 h in women > 60 y have been reported (152). In the only U.K. study that included elderly subjects, Elliot et al (153) in London found mean urinary sodium excretion of 190 mmol/24 h in men and 142 mmol/24 h in women aged 41-87 y. If these values are typical of elderly persons sodium excretion they suggest significant opportunities for moderate sodium restriction to 80-100 mmol/24 h. However it is unclear to what extent an older population would adopt a low sodium diet and how good long-term compliance would be. Results from a Belgium community study (204) suggested older compared to younger persons had greater reductions in sodium excretion, even so, this amounted to a reduction of only 25 mmol/24 h. Retired persons may have a more stable home life and a greater control over their dietary intake compared to working people who may be obliged to take many of their meals in restaurants, this probably explains their previously noted lower within-person variation in sodium excretion compared to younger persons (112,153). It is therefore probable that motivated older persons, particularly those with hypertension, could more easily adopt a low sodium diet compared to younger working people. If moderate sodium restriction is shown to lower high BP in older persons there will be a need for studies to test the feasibility of such diets in this population.

1.3.2 THE RELATIONSHIP BETWEEN POTASSIUM AND BP

Introduction

There are epidemiological, experimental and clinical studies that suggest BP is related to dietary potassium intake, although this has not been confirmed in all studies. Addison in 1928 (273) was one of the earliest workers to comment on a link between potassium and BP concluding that '...one has forced on one the concept that the prevalence of arterial hypertension on this continent is in large part due to a potash (potassium) poor diet and an excessive use of salt ..'. In 1931 Priddle alluded to the use of potassium in control of high BP when he stated ' .. it will be necessary for all cases with well established hypertension to continue indefinitely with their diet regulations and in many, the high intake of potassium as well' (274). Since then there have been many studies examining the relationship between potassium and BP.

Epidemiological Studies

These studies suffer from the same problems as outlined in the epidemiological studies of sodium and BP, namely the large degree of variability in casual BP measurements and the difficulties in estimating usual electrolyte intake. There also exists the problem of confounding variables, particularly the relation between sodium and potassium. Potassium occurs in large amounts in meat, fruit and green vegetables, foods low in sodium content. Conversely high sodium containing foods are mainly convenience, manufactured products and tend to be low in potassium. In unacculturated societies who do not add salt to food and have a high intake of fruit and vegetables - a high potassium, low sodium diet is common (2). In Western countries more affluent persons may consume high sodium and potassium diets, while those of more limited means may have a greater intake of high sodium foods but a reduced intake of fruit and vegetables leading to a high sodium, low potassium diet (7). There is therefore a tendency for an inverse relationship between sodium and potassium in individual food stuffs and diet in general. Other dietary confounding variables are likely to be the greater fibre and vitamin intake in high potassium fruit and vegetable diets.

The first epidemiological study relating dietary potassium intake to BP by Sasaki et al (275,276), noted that two villages in Northern Japan with similar salt intakes had different average BP levels; the inhabitants of the village where BPs were lower having a greater potassium intake. To examine the role of dietary potassium intake, hypertensive persons were given 8-10 apples to eat daily and a significant BP fall was noted!

Within Population Studies

Studies showing a significant relationship between BP and potassium intake.

Walker et al (277) studied 574 normotensive and hypertensive subjects, those with DBP > 90 mmHg had lower urinary potassium excretion and lower a urinary potassium : creatinine ratio than subjects with DBP < 90 mmHg. In the entire group there was a significant negative correlation (r = -0.23) between DBP and 24 h urinary potassium excretion but no significant relationship of DBP with urinary sodium excretion. Staessen et al (278) measuring 24 h urinary potassium excretion also reported a significant inverse association with SBP (r = -0.11) in a random sample of Belgian men.
Kihara (279) studied spot urine samples of over 1,000 inhabitants of a Japanese rural village over 30 years of age and found a significant positive correlation of the urinary sodium : potassium ratio with SBP and DBP and a negative correlation of the potassium:creatinine ratio with BP in males but not in females.

Khaw and Rose (280) studying a West Indies population also reported that a lower urinary potassium excretion was related to a higher BP (SBP, r = -0.14; DBP, r = -0.20; $p < 0.05$). The Scottish Heart Health Study (130) in persons aged 40-59 showed there was a consistent negative correlation between potassium excretion with BP even after adjustment for other confounding factors, ie, age, body mass index, urinary sodium excretion and alcohol consumption.

The within-population analysis of the Intersalt Study (116) reported a significant inverse relationship between SBP and 24 h urinary potassium excretions and a positive relationship with the sodium : potassium ratio, both of which increased in strength with increasing age. For women aged 40-59 years a 40 mmol/day increase in potassium intake was estimated to reduce SBP by 2.2 mmHg and for men by 1.6 mmHg.

Studies conducted in elderly persons

Khaw and Barrett-Connor (281) using the 24 hour dietary recall method studied 685 predominantly white males and females aged 20-79 years and reported that in men, age adjusted SBP and DBP negatively correlated with potassium consumption from fruit and vegetables (SBP reduced by 1.7 mmHg for a 10 mmol increase in potassium) and with total potassium intake, while in females only SBP correlated negatively with potassium intake; these relationships were similar over the whole age range studied. The same investigators in 1988 reported on further subjects aged 30-79 years (584 males and 718 females) in the

same population and found age adjusted DBP correlated negatively with potassium intake in both males and females (282). There was however a stronger positive correlation between the sodium : potassium ratio and BP which increased in strength with increasing age for men although no age effect was seen in women. In a later report (283) involving a greater number of subjects from the same population, aged 40-89 years, but using casual urine specimens, the significant correlation between the potassium:creatinine ratio and DBP and the stronger relationship (increasing with age) between the sodium:potassiuum ratio and both SBP and DBP was confirmed.

Using the National Health and Nutrition Evaluation Survey data of persons aged 18-74, both Frisancho et al (284) and McCarron et al (285) found significant inverse associations between potassium intake and BP.

Studies on plasma potassium and BP

Within populations several investigators have reported that a lower plasma potassium concentration is related to a higher BP. Lever et al (286) and Berreta-Piccolo (287) examined the relationship between BP and plasma exchangeable and total body potassium in essential hypertensives not on drug therapy and found significant negative correlations of all measures of body potassium with SBP and DBP. Bulpitt et al (288) studying London Civil Servants also reported a significant negative correlation between plasma potassium concentration and DBP in over 2,000 men and with SBP and DBP in over 2,000 women; similar results were reported by Ljungman (290).

Studies reporting no significant association between potassium and BP.

Not all studies have reported a significant correlation between potassium intake (measured as urinary potassium excretion) and BP or significant differences in potassium excretion between normotensive and hypertensive groups (129, 291-299). These findings may be related to the previously discussed difficulty in establishing usual dietary potassium intake, the variability of casual BP measurements and the effect of confounding variables, in addition in one study (299) almost one half of the hypertensive group were on anti-hypertensive medication which may have affected electrolyte excretion and its relation to BP.

Between population studies

Although the Intersalt Study (116) found (after adjusting for age, sex, body mass index and alcohol consumption) a significant positive correlation between the urinary sodium : potassium ratio and SBP and DBP and a negative association between potassium excretion and SBP for all individuals; no consistent relationship between potassium and BP was found in cross-centre analysis. The sodium : potassium ratio was positively related to both the slope of BP with age and the prevalence of hypertension for all 52 centres, but not when the four low salt centres were excluded.

Racial differences in potassium intake and its relation to BP

Grimm et al (300) in Georgia, USA, found sodium intake and excretion was significantly higher in white than in black persons (intake: 186± 64 mmol/day vs 136 ± 14 mmol/day, respectively) whilst potassium intake and excretion was significantly lower in the black population (intake: 54±2.2 mmols/day vs 23 ± 2.2 mmol/day). The black men and women had higher BPs than the white population. Other studies have confirmed a lower potassium intake and excretion in black compared to white subjects (301).

Conclusions of epidemiological studies

The majority of epidemiological studies have shown a negative correlation between potassium intake and BP and a positive relationship between the sodium: potassium ratio and BP levels. Again few studies have examined the potassium-BP relationship in older populations, of those that have there is some evidence of a stronger inverse relationship at older ages.

Intervention studies of potassium intake on BP

(a) Potassium Depletion Studies

Perera in 1953 (302) reported that in 4 hypertensive patients who were given a low potassium and sodium diet, BP fell by 15/8 mmHg although there was no control group. In contrast Krishna et al (303) found no significant change in BP in subjects consuming a low sodium (35 mmols/day) and low potassium (10 mmols/day) diet compared to when taking a 'normal' potassium intake of 90 mmols/day. Sodium balance was positive during low potassium but negative during 90 mmol/day potassium intake. In addition the low potassium diet blunted the urinary sodium excretion of an isotonic saline infusion. However, the same group in a randomised cross-over study in ten normotensive men aged 20-40 years maintaining their normal sodium intake, but either a low potassium (10 mmols/day) or normal potassium (90 mmols/day) intake for nine days each, reported a significant increase in SBP of 6 mmHg and DBP of 4 mmHg on the low potassium intake (304). During the low potassium phase, plasma potassium levels fell, plasma aldosterone levels were suppressed and a positive sodium balance occurred, but with no change in plasma renin activity, arginine vasopressin and catecholamine levels. There was however no correlation between the amount of sodium retained and the degree of BP elevation. Following infusion of 2 litres of normal saline BP rose significantly when subjects were on the low potassium phase but was unchanged whilst on the normal potassium diet, suggesting the higher potassium intake protected against salt induced hypertension.

Lawton et al (305) evaluated the effect of a low potassium diet on BP in ten normotensive men (mean age 24 years) and 11 borderline hypertensive men (mean age 25 years). A low potassium (30 mmols/day), high sodium (400 mmols/day) and a high potassium (100 mmols/day), high sodium (400 mmols/day) diet were each taken for six days in a randomised cross-over fashion. On the low potassium phase daytime ambulatory SBP increased significantly in both normotensive and borderline hypertensive groups by 7 and 10 mmHg respectively. Plasma renin activity was suppressed, body weight increased and haematocrit levels lower whilst on the low potassium diet suggesting an increase in plasma volume. Iimura et al (306) in a study of potassium restriction and loading in 20 hypertensive patients found no significant change in BP during the ten days of potassium restriction (mean arterial pressure 111 ± 3 mmHg) compared to the control period (mean arterial pressure 114 ± 3 mmHg). However, urinary potassium excretion was only

Table 1.8

Summary of Randomised Trials of Potassium Supplementation in Normotensive Subjects

Trial	Ref	Design	t	n	Age	Dose	Control	Active	SBP	DBP	Δ SBP	Δ DBP
Skrabal	162	X	14	20	21-25	120	71	115	125	73	-1.7	-4.5
Khaw	309	X	14	20	21-35	64	78	130	116	72	-1.1	-2.4*
Zoccali	310	S	5	10	20-29	100	59	161	117	71	-4.0	-2.0
Weissberg	308	S	7	20	19-29	96	83	178	123	61	-4.4	-0.1
Barden	307	X	28	43	18-55	80	50	125	114	70	0	0
Miller	311	S	28	64	42*	66	59	82	113	73	+0.4	+0.8
Mullen	312	X	14	24	-[a]	75	77	100	117	69	0	+3.0

Control = 24 h urinary K excretion (mmol/l) in control group
Active = 24 h urinary K excretion (mmol/l) in potassium group
Age = range (* = mean)
SBP and DBP = baseline BP (mmHg)
ΔSBP and ΔDBP = change in BP (active - control)
[a] age not given

X = Cross over study
S = Sequential study
n = number on K supplements
t = Trial duration in days
Dose = dose of K given (mmol/24 h)
* $p < 0.05$

modestly reduced on the potassium restricted phase by 5 to 35 mmols/day. Urinary sodium excretion and plasma renin activity decreased and plasma volume increased.

Conclusion

In man a low potassium intake in the short term (up to 10 days) leads to an increase in BP with evidence of sodium retention and volume expansion.

(b) Effect of potassium supplementation on BP

Only in the last 15 years have well designed clinical trials examining the effect of potassium supplementation on BP been conducted in normotensive and hypertensive subjects. However none of these studies have included elderly subjects.

Effect of potassium supplementation on BP in normotensive subjects

A summary of the eight randomised studies of potassium supplementation in normotensive subjects (162,307-312) is shown in table 1.8. When studies are considered separately there is little evidence for a hypotensive effect of potassium on BP in normotensive subjects. In only one (162) of 8 studies was a significant reduction in DBP reported while no studies have reported a significant change in SBP. However, all studies have been of short duration, four weeks or less, and many have resulted in only small increases in urinary potassium excretion, despite supplements of over 60 mmols/day being given, suggesting poor compliance with treatment in some studies. This probably reflects what is likely to happen at best in usual clinical practice, particularly if dietary means are used to supply additional potassium. However, there are no studies on the long term effects of modest increases in potassium intake on BP in normotensive subjects.

Effect of potassium supplementation on BP in hypertensive subjects

Following Addison's report in 1928 (273) on the hypotensive effect of potassium salts in hypertensive patients there were few studies taking this observation further until half a century later. In 1978 Morino (313) in an open study described the natriuresis and significant fall in BP following one week of a 200 mmol/day potassium chloride supplement in hypertensive patients. Further uncontrolled studies by Overlack et al (314) suggested that potassium supplementation of 200 mmol/24h for 1 week did not lower BP in young hypertensives but 100 mmol/24h for 8 weeks did.

Controlled studies

A summary of the randomised controlled studies of potassium supplementation in hypertensive persons is included in table 1.9. These studies were mainly of a short duration (< 8 weeks) except in those by Siani et al (321) and Obel (325) where the duration of potassium supplementation was 15 and 16 weeks respectively.

Effect of potassium supplementation with a high sodium intake

Morgan (328) gave 8 mildly hypertensive patients, sensitive to sodium, in a randomised cross-over fashion, either placebo or 70 mmols/day sodium chloride supplement which caused BP to rise by 19/14 mmHg or sodium bicarbonate which resulted in a BP rise of 12/5 mmHg or sodium chloride 70 mmols/day plus potassium chloride 70 mmols/day when BP rose by 9/6 mmHg, significantly less than during the sodium chloride supplement alone. Fujuita and Ando (329) studied 23 young males with sodium sensitive borderline hypertension who took 180 mmols/24 h of sodium supplement; 11 subjects also took 96 mmols/day potassium chloride. After one week BP increased significantly in the high sodium only group, but did not change in the 11 taking the additional potassium supplement. Tabuchi et al (330) found a potassium supplement of 96 mmols/day decreased BP in 10 hypertensive patients on a high sodium diet of 300 mmols/day. Those that had the greatest increase in BP whilst on the high sodium diet had the greatest decrease with the addition of potassium.

Effect of potassium supplementation with a low sodium intake

As shown in table 1.9, Smith et al (317) reported a potassium supplement given to hypertensive subjects on a low sodium intake had no effect on supine BP levels, Grimm et al (324) also concluded that supplemental potassium chloride did not affect BP levels or reduce the need for anti-hypertensive treatment in hypertensive men on a sodium restricted diet. In contrast Grobbee et al (323) did find a modest hypotensive effect of potassium supplementation on a background of a low sodium intake.

Effect on BP of potassium supplementation combined with anti-hypertensive drug therapy

Whether an increase in potassium intake could further reduce BP in hypertensive patients on anti-hypertensive drug therapy has been investigated in two studies. Kaplan et al (318) considered whether the decrease in potassium caused by diuretics might effect their anti-hypertensive efficacy. Sixteen hypertensives with diuretic induced hypokalaemia completed a 66 week randomised double-blind cross-over trial comparing 60 mmols/day

Table 1.9

Summary of Randomised Trials of Potassium Supplementation in Hypertensive Subjects (i) Trial Design

Date	Trial	ref	Country	Type	Design	Duration (Days)	No. of Participants	Age (years)	(range)	Sex (M:F)	Race (W:B)	Dose (mmol/day)	Formulation
1981	Iimura et al	306	Jpn	O	X	10	20	39		11:9		100	diet
1982	MacGregor et al	315	UK	DB	X	28	23	45	(26-66)	12:11	18:5	60	KCl
1983	Smith et al	316	UK	O	S	12	10	56		6:4	6:4	96	KCl
1983	Overlack et al	314	FRG	O	S	56	16	29		13:3		100	KCl
1984	Richards et al	195	NZ	DB	X	28-42	12	-	(19-52)			140	KCl
1985	Smith et al	317	UK	DB	X	28	20	53	(30-66)	11:9	18:2	64	KCl
1985	Kaplan et al	318	USA	DB	X	42	16	49	(35-66)	6:10	3:13	60	KCl
1985	Zoccali et al	319	UK	DB	X	14	19	38	(26-53)	10:9	19:0	100	KCl (92%)
1986	Matlou et al	320	UK	SB	X	42	32	51	(34-62)	0:32	0:32	65	KCl
1987	Siani et al	321	It	DB	P	105	19 + 18	45	(21-61)	23:14	37:0	48	KCl
1987	Svetkey et al	322	USA	DB	P	56	47 + 54	51		75:26	89:12	120	KCl
1987	Grobbee et al	323	Neth	DB	X	42	40	24	(18-28)	34:6		72	KCl
1988	Grimm et al	324	USA	DB	P	84	150 + 148	58		298:0		96	KCl
1989	Obel	325	Ken	DB	P	112	24 + 24	41	(23-56)	21:27	0:48	64	KCl
1990	Patki	326	India	DB	X	112	37	50		8:29	-	60	KCl
1991	Valdes	327	Chile	DB	X	28	24	50		13:11	-	64	KCl

O Open Study
OB Double-Blind Study
X Cross-Over Study
P Parallel Group Study
S Sequential study

Table 1.9 (cont.)

Potassium Supplementation in Hypertensives (ii) changes in blood pressure

		Supine				Standing				BP Changes			
		Control		Active		Control		Active		Supine		Standing	
Date	Trial	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
1981	Iimura et al	144.5	92.6	133.4	87.4					-11.1*	-4.5*		
1982	MacGregor et al	155.0	99.0	148.0	95.0	155.0	105.0	147.0	105.0	-7.0*	-4.0*	-8.0*	0
1983	Smith et al	156.0	93.0	147.0	91.0	153.0	101.0	141.0	96.0	-9.0*	-2.0	-12.0*	-5.0*
1983	Overlack et al	152.0	98.0	135.0	88.0					-10.0*	-8.0*		
1984	Richards et al	149.9	92.4	148.0	91.4	151.7	102.3	148.7	100.4	-1.9	-1.0	-3.0	-1.9
1985	Smith et al	162.0	103.0	160.0	103.0	160.0	111.0	160.0	110.0	-2.0	0	0	-1.0
1985	Kaplan et al	133.2	97.7	127.6	91.9					-5.6	-5.8*		
1985	Zoccali et al	147.0	92.0	146.0	89.0	147.0	99.0	146.0	99.0	-1.0	-3.0	-1.0	0
1986	Matlou et al	151.0	103.0	144.0	100.0					-7.0*	-3.0*		
1987	Siani et al	145.8	92.5	131.8	82.0	145.9	98.5	134.8	91.1	-14.0*	-10.5*	-11.1*	-7.4*
1987	Svetkey et al	142.0	92.4	141.1	91.1					-0.9	-1.3		
1987	Grobbee et al	135.7	72.5	133.2	71.9					-2.5	-0.6		
1988	Grimm et al	121.8	79.5	121.6	80.1					-0.2	+0.6		
1989	Obel	172.0	100.0	133.0	83.0	168.0	102.0	130.0	84.0	-39.0*	-17.0*	-38.0*	-18.0*
1990	Patki	155.7	97.6	143.6	84.5	156.4	98.1	143.2	84.9	-12.1*	-13.1*	-13.2*	-13.2*
1991	Valdes	145	92.0	138.0	89.0	143.0	98.0	138.0	94.0	-6.3*	-4.1*	-5.0*	-4.0*

* $p < 0.05$

potassium chloride vs matching placebo. Compared to placebo mean supine BP decreased significantly from 109±2 mmHg to 104±2 mmHg during potassium supplementation.

Siani et al (331) considered the effect of an increase in potassium intake from foods rather than supplements to control BP in a group of pharmacologically treated hypertensives and hence reduce their need for anti-hypertensive medication in a long term study. 47 patients with well controlled hypertension completed a one year follow-up after being randomly assigned to a high potassium group (n = 28) or usual diet group (n = 26). An increase in urinary potassium excretion to levels of approximately 75 mmols/day were achieved in the potassium group and 55 mmols/day in the usual diet group. These levels were maintained throughout the 12 month study period. No change in body weight or urinary sodium excretion was reported over this time. If BP levels remained below 160/95 mmHg drug therapy was reduced in a step-wise fashion. After one year there was a significantly greater reduction in drugs taken relative to baseline in the potassium group compared to usual diet group (percentage reduction: 76% vs 40% respectively, $p < 0.001$). In addition, at the end of the study the number of symptoms reported was significantly lower in the potassium group than in the usual diet group.

Conclusions

The majority of published studies examining the effect of potassium supplementation on BP in hypertensive patients have reported a significant hypotensive effect. Of 16 studies listed in table 1.9, ten (63%) reported a significant fall in BP and the remainder a non-significant BP reduction following potassium supplementation.

In a meta-analysis of 13 potassium supplementation studies in hypertensive persons conducted between 1981 and 1989, Cappuccio and MacGregor (332) estimated potassium supplementation reduced supine SBP by 8.2 mmHg (95% CI, 7.3-9.1 mmHg) and DBP by 4.5 mmHg (95% CI, 3.8-5.2 mmHg). The average potassium supplement given was 86 mmols/day for 39 days to subjects with a mean age of 40 years and mean BP of 140/87 mmHg. The degree of BP reduction achieved was not related to the difference in urinary potassium levels between groups. Rather than use potassium supplements as in clinical trials, the wider use of increased potassium intake will rely on increased potassium from the diet.

The relationship, if any, between the hypotensive effect of potassium supplements and sodium intake is not entirely clear, there is some evidence of a greater hypotensive response to increased potassium intake on the background of a high level of sodium intake.

Epidemiological studies also suggest that the relation between BP and the sodium : potassium ratio is stronger than for either sodium or potassium levels alone (333,116).

All studies to date have been conducted in young or middle aged subjects; from table 1.9 it can be seen that no person over the age of 66 years was included in any study. In addition all studies except one have relied on clinic BP measurements which show large intra-individual degrees of variability limiting their ability to show true differences in BP following an intervention. Richards et al (195) did use 24 h intra-arterial BP monitoring but this was performed in subjects whilst confined to hospital. These results in younger subjects cannot simply be extrapolated to elderly hypertensives who may demonstrate different responses to potassium supplementation, in view of age-related pathophysiological changes in the cardiovascular system (15,16). In addition, as Svetky and Klotman have stated (333), 'SBP decreased by 10 mmHg or more in 34% of subjects taking supplemental potassium in one study and in 61% in another; because of the high prevalence of isolated systolic hypertension in the elderly this subgroup might be particularly susceptible to the effect of potassium on SBP'. The lack of data in the elderly highlights the need to study the effect of dietary potassium manipulation on BP in this age group where the prevalence of hypertension is high and dietary potassium intake tends to be low (334).

1.3.3 CAFFEINE AND BLOOD PRESSURE

Introduction

Whether caffeine, and coffee consumption in particular, has adverse effects on cardiovascular disease, blood pressure and heart rate has been under discussion for several decades. The interest is relevant as beverages containing caffeine (coffee, tea, chocolate and cola drinks) are consumed in vast amounts throughout the world. As early as the 1930s coffee was reported to influence resting cardiovascular activity. Horst et al (335) in 1934 noted BP rises in some normotensive subjects several weeks following coffee versus decaffeinated coffee consumption. In 1939 Gilliland and Nelson (336) found coffee compared to a control drink maximally increased BP by 6/4 mmHg approximately 2 hours after ingestion in young caffeine naive subjects. Other work at this time suggested that tolerance developed to the acute effects of caffeine with prolonged consumption (337). Following this many, but not all studies, have reported a positive association between coffee intake and cardiovascular disease. The situation with regard to the effect of coffee consumption on blood pressure is also unclear.

Epidemiology

Caffeine and coronary heart disease

Epidemiological studies provide conflicting evidence regarding the relationship between caffeine, usually in the form of coffee drinking, and coronary heart disease (CHD). LaCroix et al (338) reported in men aged 19-45 years followed-up for 25 years a dose response association of coffee consumption with CHD resulting in a 2 to 3 fold increase in risk of CHD among heavy drinkers. Other workers have also reported a strong association between coffee consumption and myocardial infarction (MI) in young adults; Rosenberg et al (336) considered men under 55 years who drank $>$ 5 cups/day increased their risk of MI 2 fold and Tverdal et al (340) found in 35-54 year olds the risk of death from CHD increased 2.2 in men and 5.1 in women for those drinking $\geq$ 9 cups/day compared to $\leq$ 1 per day. In a 5 year longitudinal study Klatsky et al (341) found a weak association between coffee use and MI; this was present in persons younger than and older than 65 years. In contrast Grobbee et al (342) found no association between coffee or caffeine consumption and risk of CHD or stroke in men aged 40-75 years followed-up for 2 years;

this short follow-up period may have been insufficient to reveal any underlying associations. Other prospective studies have also reported no association between coffee and CHD (343-345). A meta-analysis of 11 prospective studies found no association between coffee consumption and CHD (346). In a more recent overview of 8 case control studies and 15 cohort studies, Kawachi et al (347) concluded that the cohort data suggested little excess risk of CHD although the case control data did suggest an increased risk of CHD in a subgroup of people who acutely increased their coffee intake. The relationship between coffee consumption and CHD or MI in elderly persons also remains unclear, few studies have included subjects > 65 years; of those that have some suggest a positive association (341) and others none (342).

The mechanism for the increased CHD risk, if any, between coffee and heart disease is unclear. Coffee drinking has been reported to increase serum total cholesterol and LDL cholesterol (348-350) or to have no association (351, 352), although the effect of coffee may be independent of (341) or in addition to any increases in serum cholesterol levels (340). Given the apparent lack of association between tea consumption, which also contains caffeine (usually lower amounts per cup than coffee), and the risk of MI (341, 353, 354), the role of caffeine rather than other substances contained in coffee remains unclear. A further mechanism through which coffee or caffeine consumption could influence CHD is through effects on BP.

Caffeine And Blood Pressure

Epidemiological studies have also reported no consistent effect of coffee drinking on blood pressure, a brief description of the studies conducted to date is given below.

Studies reporting a positive association between caffeine and BP

Lang et al (355) in 6,665 persons aged 18-60 years found a positive association between coffee consumption and systolic, but not diastolic, BP after controlling for age, sex, BMI, alcohol, tobacco consumption and socio-economic group. The effect however was quite modest ranging from 125.6/79.8 mmHg for non coffee drinkers to 128.1/80.6 mmHg for the highest coffee consuming group. Birkett and Logan (356) found in adults over age 17 years an even more modest positive relation between total caffeine consumption and DBP (an increase of < 1 mmHg) but no association with SBP. Burke et al (357) in a study of 60-87 year olds found coffee drinking was positively related to SBP in treated hypertensive females and to DBP in treated hypertensive men and women but not to BP in

untreated groups. Shirlow et al (358) in persons aged 20-70 years found that caffeine consumption only within 3 hours prior to BP recordings was associated with higher SBP and DBP compared to those with no caffeine intake. When average caffeine consumption per day was considered and after adjusting for time since caffeine ingestion there was no association.

Studies reporting an absent or an inverse association

Salvaggio et al (359) found in 9,601 subjects aged 18-65 years an inverse relationship between habitual coffee consumption and BP levels after correction for age, BMI, smoking and alcohol consumption. Periti et al (360) also reported an inverse association between coffee consumption and blood pressure in 500 Italian subjects aged 18-62 years. Bertrand et al (361) found the prevalence of hypertension in subjects drinking > 4 cups of coffee/day was less than expected. Klatsky et al (362) have reported no significant relationship between coffee intake and BP levels in adults over a wide age range including subjects over 60 years. Dawber et al (363) on examining the Framingham study data also found no relationship between coffee consumption and blood pressure, although adjustments were only made for age. In younger persons aged 18-30 years Lewis et al (364) found no association between caffeine intake and BP or lipoproteins after adjusting for multiple confounding factors e.g. physical activity, age and alcohol use.

Deficiencies of studies

Some of the discrepancies between studies may be due not only to acknowledged confounding by factors such as weight, smoking and alcohol consumption, but by the intake of other caffeine containing beverages and the method of coffee preparation. Most of the studies do not account for tea consumption or cola drinks which contain caffeine. Whether coffee is boiled or filtered may also be of relevance with regard to its effect on BP (365). Few studies have included persons over the age of 65 years, of those that have two showed a modest positive relationship (357, 358) and one no association between either caffeine or coffee ingestion and BP (362).

Intervention studies

Acute Effect Of Caffeine Intake On BP

Acute effects of caffeine in young normotensives

In 1978 Robertson et al (366) conducted a double-blind randomised cross-over study of the effect of a single dose of oral caffeine on BP and other cardiovascular parameters. Caffeine (250 mg) or placebo was administered to 9 young normotensive subjects who had no caffeine consumption in the previous three weeks. BP rose 14/10 mmHg one hour after caffeine ingestion with concomitant increases in plasma renin activity and plasma adrenaline and noradrenaline levels. Casiglia et al (367) gave two cups of expresso coffee (equivalent to 200 mg of caffeine), 200 mg caffeine solution, placebo or decaffeinated coffee to 15 non-coffee drinkers aged 24-30 years. 24-hours after regular coffee and caffeine ingestion BP increased although not significantly by 3-5/4-6 mmHg and a strong positive correlation was seen between plasma caffeine and BP levels 90 and 120 minutes after ingestion. After placebo or decaffeinated coffee a small reduction in BP was seen. In addition no effect on heart rate was seen although peripheral resistance increased after coffee and caffeine consumption. Pincomb et al (368) also found increases in BP in men aged 20-35 years after caffeine administration (equivalent to 2-3 cups of coffee) following abstention lasting 30 hours; systemic vascular resistance was also found to increase significantly. Smits et al (369) reported increases in SBP of 5 mmHg and DBP of 7 mmHg and a fall in heart rate following coffee drinking after a period of 1-2 days abstention. They also noted a greater BP increase after coffee consumption in subjects with lower basal plasma caffeine levels. In a later study Smits et al (370) reported elevations in SBP and DBP, compared to placebo, of 6.3 mmHg and 8.0 mmHg, respectively after a single infusion of 250 mg of caffeine. In combination with nicotine the BP rise was enhanced. Other investigators (371,372) have also reported increases in BP of up to 11/9 mmHg compared to placebo, following ingestion of 300 mg of caffeine in caffeine naive subjects.

Acute effect of caffeine in older normotensive subjects

Increases in BP with caffeine ingestion following a period of abstention have also been seen in older normotensive subjects. Izzo et al (373) studied 12 young subjects and 8 with a mean age of 62 years (although only one was > 65 y) following ingestion of 250 mg of caffeine. Older subjects had greater increases in BP than younger subjects and caffeine non-users had greater BP rises than caffeine users regardless of age. In 8 subjects aged 67-

82 years, Haigh et al (374) found 250 mg of caffeine given after 48 hours of abstention significantly increased SBP by 12 mmHg and DBP by 7 mmHg. After only a 12 hour period of caffeine abstention the pressor effect was greatly attenuated. Conrad et al (375) infused caffeine into 10 men of mean age 72 years who had abstained from caffeine for 72 hours prior to infusions and noted BP increases of up to 16/7 mmHg; however no placebo control was used.

Effect of caffeine on ambulatory BP in normotensive persons

Jeong and Dimsdale (376) in a double-blind cross-over study examined the effect of coffee or decaffeinated coffee on work time BP in 12 subjects aged 29-59 years. No caffeine was taken from the evening prior to the study day until breakfast when the study drink was consumed and BP monitoring carried out. Ambulatory BP monitoring during work following coffee drinking demonstrated increases in BP of 4/4 mmHg which were maintained for the six hour monitoring period. Myers and Reeves (377) in a controlled study also found caffeine (400 mg/day) in 25 subjects aged 21-43 years, who had abstained from caffeine for 3 weeks, increased ambulatory BP on the first day of caffeine ingestion by 3/3 mmHg although values returned to normal by the 3rd day. No changes in manual sphygmomanometer readings were seen throughout the study. As part of a more sophisticated cross-over, randomised, placebo controlled study, James (378) examined the effect of 1 day of caffeine, equivalent to 1-1.5 cups of coffee thrice daily, on 24 h ambulatory BP following 6 days of caffeine abstention in subjects with a mean age of 23 y. Although BP levels peaked shortly after ingestion at 7.7/6.8 mmHg compared to placebo, mean 24 h BP was significantly increased by 3.8/3.6 mmHg. In summary the above studies suggest that there is a consistent increase in ambulatory SBP and DBP of 3-4 mmHg over a 6 to 24 h period on the first day of caffeine consumption following a brief period of abstention.

Effect of caffeine on the BP response to mental stress and exercise

Pincomb et al (379) have shown that acute caffeine administration in normotensive persons elevates BP during psychomotor tasks and also enhances abnormal BP responses during exercise as well as at rest. Lovallo et al (380) also reported that in normotensive men at a high risk of hypertension, the combination of psychomotor tasks and caffeine consumption enhanced BP levels and also lead to high levels of cortisol production. France and Ditto (381) also reported that the effects of occupational stress on BP were enhanced by

caffeine while Jeong and Dimsdale (376) found the pressor effect of mental arithmetic was enhanced following caffeine consumption.

Acute effects of caffeine on BP in young hypertensive persons

Freestone and Ramsey (382) in middle-aged untreated and diuretic treated mild hypertensives have reported that drinking coffee containing approximately 200 mg of caffeine raises BP by up to 10/7 mmHg for one to two hours. Smits et al (383) found one hour after ingestion of two cups of coffee (240 mg caffeine) following a 24-hour period of abstinence that mean arterial pressure increased in hypertensives (mean age 39 y) by 11 mmHg compared to 8 mmHg in normotensives (mean age 24 y) although the percentage increase from baseline was similar in both groups. A fall in heart rate and a rise in plasma adrenaline levels were seen in both normotensive and hypertensive groups. Sung et al (384) in 30 men aged 30-45 years, reported that a single dose of caffeine equivalent of two to three cups of coffee elevated SBP and DBP in hypertensive and normotensive subjects for a period of at least three hours. The hypertensive group maintained greater caffeine induced DBP and vascular resistance than the normotensive group.

Acute effect of caffeine in older hypertensive subjects

Potter et al (385) found 250 mg of caffeine administered 48 hours after caffeine abstention in hypertensive subjects with a mean age of 75 years produced only a mild BP rise. The maximum increases occurred at the time of peak caffeine levels, 30-60 minutes after caffeine ingestion. Compared to baseline, SBP and DBP were not significantly higher but compared to placebo there was a significant overall increase in supine SBP of 10 mmHg and in DBP of 6.8 mmHg. No significant changes occurred in plasma catecholamines or renin activity between placebo or caffeine phases. When caffeine was taken regularly followed by 12 hours of abstention a 250 mg capsule of caffeine produced no pressor effect.

Effects of prolonged caffeine administration on blood pressure

1. In normotensive persons assessed by clinic BP measurements

Robertson et al (386) in subjects aged 18-52 years found an increase in SBP of 10 mmHg on day 1 after 250 mg of caffeine but by day 4 BP had returned to baseline levels. Denaro et al (387) gave normotensive subjects aged 19-55 years, placebo, low dose or high dose caffeine (equivalent to 6-11 cups of coffee per day) for 5 days during which complete tolerance to the pressor effect of caffeine developed. However it was concluded that only

partial tolerance to effects on the sympathetic nervous system as judged by plasma noradrenaline levels, had developed during this time whilst on the high dose caffeine intake. On switching from 4 weeks of decaffeinated coffee to regular coffee (4 cups/day), Ammon et al (388) noted a small increase in BP during the first few days after which levels returned to baseline. In a parallel group study of 4-6 cups of boiled coffee, filtered coffee or no coffee for nine weeks in normotensive persons aged 18-33 years, Bak and Grobbee (389) found SBP to be 3.4 mmHg higher in those subjects who continued drinking coffee suggesting complete tolerance to this amount of caffeine does not occur.

2. In normotensives assessed by ambulatory BP monitoring

As previously noted Myers and Reeves (377) found an increase in BP in 25 normotensive caffeine naive subjects one day after 400 mg of caffeine, however, after three days of caffeine, ambulatory BP values returned to baseline.

Superko et al (390) divided 150 coffee drinking middle-aged normotensive men into 3 groups: 1) to continue drinking coffee, 2) to drink decaffeinated coffee and 3) to stop drinking coffee. After 2 months there were no changes in resting BP between groups but daytime ambulatory SBP and DBP was significantly reduced by 3-5 mmHg and 2-3 mmHg respectively on switching to decaffeinated or no coffee. This suggests complete tolerance to caffeine does not occur despite prolonged consumption and such elevations of BP are not evident during resting measurements.

In a double-blind cross-over trial, van Dusseldorp et al (391) gave 45 normotensive persons aged 25-45 years 5 cups of decaffeinated coffee for 6 weeks or 5 cups of regular coffee for 6 weeks. BP was measured at home by the subjects using an automatic device, taking 5 readings one day per week. Throughout the study mean SBP remained 1.5 mmHg and mean DBP 1.0 mmHg higher during regular coffee consumption also suggesting complete tolerance does not occur.

In the study of James (378), taking caffeine equivalent to 1-1.5 cups thrice daily after 6 previous days of caffeine consumption produced post-ingestion BP peaks of 6.0/5.2 mmHg and increases in 24 h BP of 1.8/1.5 mmHg compared to placebo. These BP rises were lower than those occurring after acute caffeine administration again suggesting some but not complete tolerance occurs on chronic caffeine consumption. In addition, within 24 h of ceasing consumption of caffeine following 6 days of use, BP fell to, or a little below, those obtained after 6 days of placebo.

Although not supported by the work of Myers and Reeves (377), the latter three studies (390,391,378) suggest that in normotensive persons regular caffeine consumption

equivalent to 4-6 cups per day can produce a small sustained elevation of BP and that any tolerance to caffeine's acute effects on BP are incomplete.

3. In hypertensive subjects assessed by clinic BP measurements

Robertson et al (392) gave caffeine (250 mg thrice daily) to 9 young (age 20-44 y) mild hypertensives after 3 days on placebo. SBP rose within 15 minutes of first ingesting caffeine by 5.4 mmHg with no change in DBP; this BP rise was maintained during the first day of caffeine administration. After the first day no significant BP increase occurred, although BP levels remained non-significantly higher during the 7 days of caffeine intake, returning to baseline levels on switching to placebo. In addition no change in catecholamines or plasma renin activity was seen between placebo and caffeine periods. These results suggest the development of almost complete tolerance to the pressor effect (measured in the clinic) of caffeine occur within 1-2 days, a similar duration to that seen in normotensive persons.

4. In hypertensive subjects assessed by ambulatory BP monitoring

MacDonald et al (393) studied 50 middle aged patients with untreated mild hypertension in a randomised cross-over trial of four consecutive two week regimens of either normal diet, caffeine free diet, caffeine free diet plus decaffeinated coffee or with caffeinated coffee. There was no difference in mean 24-hour BP between regimens, suggesting no long term pressor effect of caffeine in mild hypertensives.
Eggersten et al (394) studied 23 treated (mainly with beta-blockers) male hypertensives aged 28-74 years (mean 56 y) in a double-blind placebo controlled cross-over trial of two weeks caffeine free diet or two weeks regular caffeine use. No difference in mean 24-hour, day or night-time BP, heart rate or plasma renin activity was seen between either regimen. Again in a predominantly middle-aged group of hypertensive persons chronic caffeine administration had no detectable effect on BP. However no studies of prolonged caffeine administration in elderly hypertensives have been carried out to assess the effect on BP.

Mechanisms of the pressor effect of caffeine

The mechanisms of the acute pressor effect of caffeine remain unclear. Increases in systemic vascular resistance and decreases in baroreceptor sensitivity have been reported following caffeine administration in some (367) but not all studies (395). No consistent changes have been reported in sympatho-adrenomedullary activity and the renin-angiotensin

system. Although plasma adrenaline levels increase on consumption of caffeine (396), BP increases have occurred following ingestion of caffeine in adrenolectomised subjects (397). Clearly factors other than adrenaline release are involved in the pressor response to caffeine. Caffeine is an antagonist to the effects of adenosine (398) which has vasodilating properties and also inhibits renin secretion and sympathetic activity; such inhibition of adenosine action could lead to increases in total peripheral resistance. Caffeine can also exert a positive inotropic effect on cardiac muscle by inhibiting phosphodiesterase activity and increasing intracellular calcium although this has not been confirmed (368).

Summary

There is evidence in both normotensive and hypertensive persons that initially on ingesting caffeine following a period of at least 12 hours without caffeine a pressor effect is achieved. However this pressor effect is not fully maintained suggesting almost complete tolerance to the effects of caffeine develops within 2-3 days. At present work on the effect of chronic caffeine ingestion on BP in hypertensives is incomplete; no studies have adequately been conducted in older hypertensive subjects. In one of the few epidemiological studies addressing the relationship between coffee and BP in older persons, Burke et al (357) did find coffee drinking was positively related to BP levels in treated hypertensives. The effect of chronic caffeine consumption in older hypertensive persons needs to be further investigated.

1.3.4 OTHER NON-PHARMACOLOGICAL METHODS TO LOWER BP

Effect of weight reduction on BP levels

Epidemiological studies

In the Community Hypertension Evaluation Clinical Study (CHECS) in which 1 million Americans were screened, the prevalence of hypertension in those reported as being overweight was 50-300% higher than in those who reported normal or low body weight (399). Other studies have confirmed this association (400,401).
Several longitudinal studies have shown that being overweight increases the risk of developing hypertension (402-404) and body mass index at initial screening is positively and strongly related to the development of hypertension (405, 406). In addition to weight at baseline, weight gain appears to exert an even stronger risk for the development of hypertension (407).

Effect of age on the weight-BP relationship

There is evidence that with increasing age the weight-BP relationship is attenuated. In the NHANES II Study the relative risk of hypertension in overweight subjects aged 20-45 years was 5.6 compared to 1.98 in those 45-75 years old (401). The Tecumseh study (408) also found increasing age weakened the association between SBP and weight. However, data from the Chicago Heart Association Detection Project in Industry (409) suggested obesity had an amplifying effect on the age-BP relationship. Also in the very elderly (> 80 y) the relationship between body weight and mortality overall is less clear (410), data suggest that the lowest mortality occurs at a higher BMI in older persons (411).

Body Fat Distribution

The waist circumference : hip circumference ratio (W:H) has a stronger relationship to the development of hypertension (412) and a stronger relationship with BP levels than does body mass index or relative weight (413). A high W:H ratio reflects abdominal fat predominance and is seen characteristically in males while females tend to have a low W:H ratio and more gluteal fat.

Studies on the effect of weight reduction on BP levels

Effect of weight loss in hypertensive persons

MacMahon et al (414) found weight loss of 7.4 kg in young overweight hypertensive persons lowered BP by 6/7 mmHg . Haynes et al (415) in a similar randomised trial found no significant effects of weight reduction on BP levels although in this study mean BP levels were barely hypertensive (135/90 mmHg) and weight loss was 4.1 kg. In TAIM trial (416) of persons aged 30-65 years who were 110% to 160% of ideal weight, subjects who lost ≥ 4.5 kg had a DBP fall of 11.6 mmHg whilst those losing < 2.25 kg had a DBP fall of 7 mmHg. Scherrer et al (417) found that in mildly hypertensive patients who lost 8.5 kg in weight after 10 weeks on a hypocaloric diet average 24 h BP fell by 14/5 mmHg and clinic BP by 16/11 mmHg. Similar results were reported by Das Gupta et al (418) in both hypertensive and normotensive persons after weight loss.

These studies suggest weight loss can, independently of other variables, in particular the level of sodium intake, lower BP.

Studies of weight reduction in older persons

Applegate et al (419) assessed the effect on BP of weight reduction, sodium restriction and increased physical activity in overweight 60-85 year olds with mild hypertension. After six months weight decreased significantly in the intervention group by 2.1 kg, less than half that aimed for, and exercise time increased but sodium excretion showed no significant change between intervention and control group. These changes resulted in a net BP fall of 4.2/4.9 mmHg in the intervention group.

Feasibility of weight loss

Not only intensive weight loss programmes but also the use of routine dietetic services can result in weight reduction in a significant number of overweight persons, although use of a diet sheet and advice only are less effective (420).

Conclusions

Staessen et al (421) analysed four adequately controlled studies and concluded that a 1 kg fall in weight was associated with a 1.6/1.3 mmHg fall in BP. There have been no controlled studies in overweight elderly hypertensive or normotensive persons on the effect of weight loss alone on BP levels. However, the multiple intervention study of Applegate in the elderly suggests weight loss is an effective measure in this group.

Calcium and BP

Many epidemiological studies including both cross-sectional (422-428) and longitudinal studies (405, 406) but not all (429) have confirmed an inverse association between calcium intake, most frequently recorded in the form of milk and BP. Whether this relationship is specific for calcium intake or is more generally related to calcium containing foods, e.g. dairy products, is uncertain. However no consistent effect of calcium supplements on blood pressure has been seen in either young or old normotensive or hypertensive subjects (430-443). Grobbee and Wall-Manning (444) reviewing 22 calcium supplementation studies considered the effect on BP to be limited but could be of benefit in some hypertensives with evidence of calcium deficiency. In an overview of 15 calcium supplementation trials Cappuccio (445) found that there was no significant change in supine BP in normotensive or hypertensive subjects, but a modest 1.6 mmHg fall in standing SBP in hypertensive subjects given calcium. The wide confidence intervals indicated heterogeneity of response and supported the idea that some individuals might respond to calcium supplements with a fall in BP. They concluded that it was inappropriate to recommend calcium supplements in the treatment of hypertension.

Magnesium and BP

Levels of dietary magnesium intake and urinary magnesium excretion have been inversely associated with BP levels in most (405, 406, 446-448) but not all studies (435). However because of the high degree of intercorrelation between nutrients it is difficult to separate the effect of magnesium from that of other variables (447). Using erythrocyte magnesium levels, Petersen et al (449) found an inverse relationship with BP in 73 elderly persons.

In hypertensive subjects with no evidence of magnesium deficiency many studies have shown no effect on BP (450-454) although some have (455-457). Several studies of magnesium supplementation carried out in hypertensive patients on thiazide diuretics where a state of magnesium deficiency may be precipitated (582) have reported significant reductions in BP (459-461) although this was not confirmed by Henderson et al (462). There have however been no studies assessing the effect of oral magnesium supplementation on BP in elderly patients.

Vegetarian diets and BP

Vegetarian compared to omnivorous diets appear to lower BP levels (463-467), but the effect is not clearly related to specific changes in protein, fibre or fat intake (468). Changes in body weight and sodium excretion have been similar on both diets although potassium excretion has been greater in vegetarians. It is likely that complex dietary changes involving increased intake of fibre from fruits and vegetables, a reduced saturated fat intake with increased polyunsaturated fats and probably other nutrient changes from fruit, vegetables and cereals including an increased intake of potassium and other less clearly defined nutrient effects are required in combination to produce the BP lowering effect of vegetarian diets (469). Again there have been no studies of vegetarian diets specifically in elderly hypertensive persons although fish oil supplements in this age group were found to have no effect on BP (468).

Exercise and BP

Observational studies have suggested that aerobic type exercise, or rather the lack of it, is associated with hypertension (470-472) even in older subjects (473) and is also a risk factor for both the development of hypertension (474) and cardiovascular disease (475). In elderly normotensive persons significant decreases in BP following aerobic training have been reported (476, 477) although Cunningham et al (478) found no significant fall in BP after 12 months of training .

Fagard et al (479) concluded that in normotensives BP was reduced by 4/4 mmHg and in hypertensives by 11/6 mmHg while a recent meta-analysis of randomised controlled trials in hypertensives of mean age 52 y (range 29-72y) concluded aerobic exercise would reduce BP by 7/6 mmHg (480). From the limited studies available in the elderly the hypotensive effect of exercise appears to be as great in older hypertensives as in those younger (481). In addition there is evidence that low intensity training may be as beneficial as high intensity training for lowering BP levels and it also has the advantage that it can be started immediately and the beneficial effects accrue rapidly (482, 483).

Alcohol and BP

Epidemiology

The great majority of epidemiological studies have shown a positive relationship between alcohol consumption and BP in middle aged (484-492) and elderly subjects (490). Whether the relationship is strictly linear or occurs above a threshold level of alcohol intake is less clear (490,491). The relationship has also been reported in some studies to be stronger at older ages (490,492). In subjects aged 60-87 years, Burke et al (493) found alcohol intake was positively associated with SBP in men and women.

Reductions of moderate or heavy alcohol intake can lower BP in both normotensive (494-496) and hypertensive subjects (497, 498). There have been no well controlled and randomised studies of the effect of alcohol restriction in elderly hypertensive subjects. Given the continuing relationship between alcohol and blood pressure in the elderly reported in epidemiological studies there is no reason to believe that this manoeuvre would not lead to a reduction in blood pressure in older subjects.

Relaxation and stress management

Muscle relaxation had been demonstrated to reduce BP levels over 50 years ago (499). Since then many stress management techniques have been tested including biofeedback, relaxation therapy using behavioural and cognitive strategies, muscle relaxation, yoga and transcendental meditation. It is unclear whether a persistent BP reduction is produced or merely a transient fall produced by a conditioned response to the presence of the therapist; different therapists have been found to obtained different results when using similar treatment regimens in comparable groups of patients (500).

Variable results of behavioural therapy on BP have been reported (500) and a recent review of cognitive behavioural strategies for hypertension considered them ineffective (501). Long term reductions in BP following short term relaxation programmes have been found (502, 503) but although casual BP has been decreased, average 24-h BP levels have not changed following therapy suggesting that such techniques reduce only the pressor or white coat response to BP measurements by a health professional and do not lead to a reduction in BP overall (504, 505).

Smoking and BP

Smoking increases the risks from hypertension by two-threefold (506) although the mechanisms involved are unclear. Smokers tend to drink more alcohol (507) eat less fruit and fresh vegetables (508) and weigh less than non-smokers (509). Stopping smoking reduces the risk of coronary heart disease close to that of life long non-smokers within approximately two years (510). The relative risks from smoking declines with age but because cardiovascular disease is more common in the old, the absolute risk is greater (511).

Acutely smoking leads to increased sympathetic activity, tachycardia and increased BP levels (512) which may be potentiated by the consumption of coffee (513). Chronically smokers have lower BP or similar BP levels to non-smokers (507). However, Groppelli et al (514) reported that heavy smoking (2 cigarettes/hour) leads to a persistent rise in BP, the pressor effect of one cigarette lasting considerably longer than the smoking time. Daytime ambulatory BP was persistently higher on smoking than non-smoking days. Similar findings were reported by Mann et al (515) who matched hypertensive smokers and non-smokers with regard to clinic BP. However the daytime ambulatory SBP was significantly higher in the smokers, an effect more marked in subjects over the age of 50 y. For these older subjects, smokers had daytime ambulatory SBP 11 mmHg higher than non-smokers. Stopping smoking is associated with weight gain and little, if any, increase in BP (516).

Although smoking does not increase clinic BP levels it may increase daytime BP levels when measured away from the clinic and it greatly increases the risks of high BP which can be reduced within a short time of smoking cessation.

1.3.5 COMPARISON AND COMBINATIONS OF NON-PHARMACOLOGICAL INTERVENTIONS ON BLOOD PRESSURE

As with drug treatment many, but not all, non-pharmacological therapies may interact synergistically. In addition some therapies may be more effective at lowering BP than others.

Studies in young hypertensives

The trials of anti-hypertensive intervention and management (517) randomised 787 middle aged subjects to receive placebo, chlorthalidone or atenolol combined with the usual, a weight loss or a low sodium/high potassium diet. In the placebo treated subjects the weight loss group had a significantly lower DBP of 2.5 mmHg compared to the usual diet group. In the low sodium, high potassium group, no significant DBP difference was seen although the net reduction in urinary sodium excretion was modest at 26 mmols/24 hours and net increase in potassium excretion was only 12 mmols/24 hours.
Kostis et al (518) compared the effect of non-pharmacological therapy, propranolol or placebo on BP and other variables in a 12 week study of 79 hypertensives. Non-pharmacological therapy consisted of a reduced calorie, low salt diet, low intensity exercise and muscle relaxation. Compared to placebo the BP fall in the non-pharmacological group was 7.5/7.9 mmHg and in the propranolol group 7.3/9.4 mmHg, only the DBP fall was significantly different. The DBP fall in the non-pharmacological group was significantly related to the degree of fitness and weight loss. Although BP reductions were similar in non-pharmacological and propranolol groups, only the non-pharmacological group showed a reduced body mass index, lower total and LDL cholesterol and an increase in exercise tolerance. Improvements in quality of life and in particularly sexual function was seen in the non-pharmacological group.

Little et al (519) compared a combination of low sodium, low fat, high fibre diet with the individual components in treated hypertensives. For single interventions BP was not significantly reduced. However, the combination group demonstrated significant reductions in BP of 11.6/7.3 mmHg. It was thought weight loss was largely responsible for this result as the combined group had the greatest reduction in weight.

Jula et al (520) compared non-pharmacological intervention - low sodium, increased potassium, low saturated fat and weight loss - with a control group in 91 middle-aged untreated mild hypertensives. Compared to the control group, after one year BP fell significantly by 8.2/5.8 mmHg in men and 9.5/5.6 mmHg in women in the non-

pharmacological intervention group. Significant reductions in LDL cholesterol were also seen in the intervention group.

In the Treatment of Mild Hypertension Study (102) non-pharmacological advice i.e. weight, sodium and alcohol restriction and increased physical exercise was given to all of six groups taking either a placebo or one of five anti-hypertensive drugs. After 4 y of follow-up BP reductions were significantly greater in the drug treatment groups compared to non-pharmacological intervention alone (15.9/12.3 mmHg vs 9.1/8.6 mmHg, respectively) and the former group also had lower rates of cardiovascular events. Echocardiographic left ventricular mass was reduced to a similar degree in all groups, but ECG left ventricular hypertrophy was not reduced in the group receiving non-pharmacological intervention only. Quality of life scores were no better in the non-pharmacological group compared with the drug treated groups.

Studies in older hypertensives

Only one study of multiple non-pharmacological interventions has been carried out in the elderly, that of Applegate et al (419) who assessed the hypotensive effect of such interventions against a control group in 47 mild hypertensives aged 60-85 years. Intervention consisted of weight reduction, sodium reduction and increased physical activity; after six months compared to the control group weight fell 2.1 kgs and sodium excretion fell non-significantly by 21 mmols/24 hours and reported physical activity time tripled. BP fell significantly by 4.2/4.9 mmHg in the intervention group.

Summary

These studies suggest multiple non-pharmacological interventions can lower blood pressure in normotensive persons by a small degree and reduce or delay the progression to hypertension. In hypertensive persons such methods can lead to significant reductions in BP levels. Reductions in excess weight appear to be the one intervention that is most consistently related to a hypotensive effect.

1.3.6 SUMMARY OF NON-PHARMACOLOGICAL THERAPIES IN ELDERLY HYPERTENSIVE SUBJECTS

In elderly subjects hypertension remains a cardiovascular risk factor, the absolute risk of such an event being greater than that in a younger person with the same BP level and risk profile. The benefits from pharmacologically reducing high BP in elderly hypertensives has previously been noted (table 1.4), again with a reduction in absolute risk being greater in older than younger subjects. The benefits from such anti-hypertensive therapy also accrue rapidly, within 1-5 years of lowering BP. Despite these demonstrated benefits and the greater prevalence of hypertension in older persons it is surprising that only a minority of the studies on non-pharmacological therapy have been conducted in elderly subjects; indeed many non-pharmacological interventions have undergone no formal testing in the elderly, those that have are summarised below and in table 1.10.

Conclusions

The effect of moderate sodium restriction in elderly hypertensive subjects is unclear as the study of Morgan et al (201) was uncontrolled and the degree of sodium restriction was limited. Palmer et al (202) studied only a small number of subjects, only some of whom had hypertension. Calcium supplementation and fish oil had no significant effects on BP levels although low intensity exercise was reported in two studies to lower BP in elderly hypertensives (482,483). Weight reduction has only been studied when combined with other non-pharmacological therapies in elderly hypertensives.

There have been no studies in elderly hypertensive subjects to examine the individual effects on BP of weight loss, potassium supplementation, alcohol restriction, vegetarian diets or relaxation therapy and no well controlled studies of sodium restriction. This is despite evidence from epidemiological studies and extrapolation from studies in younger subjects that some interventions such as sodium and alcohol restriction may have greater hypotensive effects in elderly compared to younger persons

Table 1.10

Summary of studies of non-pharmacological methods in older normotensive and hypertensive subjects

Intervention	Author	Ref	Age	Change in SBP	Change in DBP
		Normotensives			
Sodium Restriction	Nestel	172	60-79	(m) 6.1 (f) NS	1.9 NS
	Cobiac	173	60-80	2.8	NS
Exercise	DeVries	476	52-88	4	3
	Cunningham	478	54-88	NS	NS
	Barrie	477	55-78	20	NS
Alcohol	Schnall	496	70-74	19	10
		Hypertensives			
Sodium Restriction	Morgan	201	48-78	11	8
	Plamer	202	85	NS	9
↓Na↑K	Geleijnse	203	55-75	7.6	3.3
Calcium supplementation	Galloe	440	42-75	NS	NS
	Morris	441	50-80	NS	NS
	Takagi	442	65-86	13.6	5.0
	Kynast-Gales	417	46-75	NS	NS
Fish Oil	Margolin	468	60-80	NS	NS
Exercise	Hagberg	482	60-69	20	11
	Seals	483	50-74	10	7
↓Na ↓ Wt ↑ Exercise	Applegate	419	60-85	4.2	4.9

NS, not significant
where a value is given, this is significant.
m, male
f, female

1.4 USE OF NON-PHARMACOLOGICAL METHODS FOLLOWING ANTI-HYPERTENSIVE DRUG WITHDRAWAL

Introduction

Reduction or complete withdrawal of anti-hypertensive drug treatment has been considered since shortly after the widespread introduction of such therapy. Page and Dustan (521) writing in 1962 hypothesised that in hypertensives, if lowered BP levels were maintained for long enough a resetting of the controlling mechanisms could occur such that continuing treatment may not be necessary. More recently evidence of at least partial reversal of structural vascular changes following anti-hypertensive treatment has been reported, adding support for the premise of Page and Dustans hypothesis (522-524).

As reviewed in Section 1.3 various non-pharmacological methods, particularly reduction of excess weight and alcohol intake and an increase in aerobic exercise, have been shown to reduce BP in hypertensive subjects. The application of such methods to hypertensive persons on anti-hypertensive drug therapy may lower BP levels sufficiently to make pharmacological treatment unnecessary providing such methods are continued following drug withdrawal. A shift in emphasis or reliance on tablet taking towards life-style changes may provide benefits in addition to those associated purely with BP reduction. It could be hypothesised that in persons with mild hypertension, substitution of non-pharmacological interventions for drug therapy would not only lower BP levels but also other cardiovascular risk factors and hence potentially be more beneficial than continuing drug treatment alone (525).

Further reasons for considering anti-hypertensive drug withdrawal are the cost of drug therapy, concern with the 'medicalisation' of a large proportion of the population and the adverse effects of such drugs. Metabolic side effects of long term anti-hypertensive therapy are often minor and of disputed relevance (526). Thiazide diuretics for example can lower serum potassium levels, increase serum uric acid, cholesterol and fasting blood glucose levels - all of which normalise rapidly after stopping treatment (527, 528). In addition the majority of symptoms patients complain of whilst on treatment are significantly reduced following withdrawal (529).

National hypertension guidelines (530) including those of the British Hypertension Society (BHS) (531) suggest the reduction or withdrawal of anti-hypertensive therapy whilst continuing with non-pharmacological measures in those with well controlled BP levels. However, there have been few studies assessing these proposals and none which have been carried out in elderly hypertensive subjects.

Studies of anti-hypertensive drug treatment withdrawal without non-pharmacological intervention

Uncontrolled trials

The first report of such a study was in 1956 by Perry and Schroeder (532), who in a later study (533) observed prolonged remission of hypertension in 16 (5%) of 316 patients after discontinuation of drug treatment. Page and Dustan in 1962 (521) withdrew all treatment from 27 previously severe hypertensives. In 18, the BP rose, requiring re-institution of treatment but in the other 9 (33%) BP levels remained satisfactory without treatment for between 6 months and 5 years; in a further study of 60 patients (534) two remained normotensive off treatment for at least 8 years.

Following these initial studies, many other uncontrolled and controlled studies have been performed in mostly middle-aged hypertensive persons. These trials (summarised in table 1.11) suggest approximately 25-35% (range 0 to 75%) of controlled hypertensives can remain of drug therapy for at least 1 year.

Studies in elderly hypertensives

Hanssen et al (549) withdrew anti-hypertensive therapy in 169 patients aged over 50 years; 51 (30%) rapidly became hypertensive. Of the remaining 118, 105 were over 60 years of age (mean age 75 years) and had DBP $<$ 110 mmHg three weeks after withdrawal and were re-examined after one year. At this time 43 (41%) had DBP $<$ 110 mmHg and were untreated while 16 (15%) developed BP levels requiring treatment (DBP $\geq$ 110 mmHg); 34 (32%) started treatment for angina or congestive cardiac failure, but DBP did not exceed 110 mmHg.

Lernfelt (550) found 8 (32%) of 25 hypertensive 70 year olds remained normotensive four years after drug withdrawal.

Ekbom et al (551) studied 333 patients aged 70 to 84 years being withdrawn from treatment for possible inclusion in the STOP-Hypertension Trial. Those patients whose SBP on three occasions was 180-230 mmHg with DBP $\geq$ 90 mmHg or who had DBP between 105-120 mmHg were randomised into the STOP Hypertension Trial. Those not meeting these criteria were observed for a period of up to five years; 22% of patients died during this time but the mortality in those without treatment was lower than that in the general population. During the first year, 60% of patients had their medication restarted, after five years 20% remained off anti-hypertensive therapy. However, 37% of patients returning to treatment did so for reasons other than hypertension - oedema, heart failure,

anxiety, headache, angina and many who were unwilling to continue without anti-hypertensive therapy. Factors suggesting successful withdrawal were initial BP control on monotherapy and low BP before withdrawal.

Studies using non-pharmacological intervention

Fernadez et al (536) reported on 24 patients with well controlled hypertension (BP < 140/95 mmHg) for an average of two years whilst on treatment. Patients were instructed with the help of a dietician to reduce their sodium intake to < 100 mmols/24 hours. All 24 patients withdrawn from therapy remained normotensive (BP < 145/95 mmHg) for 48 weeks. In 6 (25%) BP increased to levels requiring drug treatment between 48 and 60 weeks, but even then the medication required was less than previously administered prior to withdrawal.

Two controlled studies, described below, have evaluated the effect of treatment withdrawal either alone or with non-pharmacological intervention, on BP levels and compared these with a control group continuing on treatment.

Langford et al (547) screened patients who had completed the step-care arm of the Hypertension Detection Follow-Up Programme Study for inclusion into the Dietary Intervention Study of Hypertension (DISH). Of 865 patients screened 584 were eligible for inclusion - average DBP < 95 mmHg, last two DBP readings < 90 mmHg and SBP never above 180 mmHg whilst on treatment. These patients were stratified into overweight (>120% of ideal weight) or normal weight and then randomised into one of four groups (i) continue treatment (ii) stop treatment plus no advice (iii) stop treatment plus low sodium high potassium diet (iv) stop treatment plus weight reduction. Treatment was restarted if DBP averaged 95-99 mmHg on three occasions within the three month period, if two DBP readings were between 100-104 mmHg or if DBP was ≥105 mmHg at any one time.

After 56 weeks the overweight group had a 5% reduction in weight and the sodium reduction group reduced their sodium excretion by 44-59 mmols/24 hours. After 56 weeks, 48% of the dietary advice group had returned to treatment compared with 60% in the withdrawal plus no advice group. The greatest success rate for maintenance of treatment withdrawal was 78% in the non-overweight mild hypertensives with sodium restriction and 72% in overweight mild hypertensives with weight loss. In conclusion weight loss and sodium restriction doubled the success of drug withdrawal.

Using a similar population and BP criteria for treatment withdrawal as the HDFP study, Stamler et al (548) in the Hypertension Control Programme randomised 189 patients to (i) stop treatment plus non-pharmacological intervention, (ii) stop treatment plus no

intervention (iii) continue treatment without non-pharmacological intervention. After four years group 1 had a reduction in weight of 1.8 kg, in sodium excretion of 60 mmols/24 hours and in alcohol intake of 12.5 g/day. Groups 2 and 3 had an increase in weight of 4.5 kg, an increase or no change in sodium excretion and less of a reduction in alcohol intake compared to group 1. After 1 year 69% of group 1 continued without treatment compared to 50% in group 2 and after three years these figures were 42% vs 16% respectively. After 4 years 39% in group 1 were without treatment while only 5% in group 2 remained normotensive.

Weinberger et al (552) in an uncontrolled study observed that patients on anti-hypertensive treatment who were able to reduce their sodium intake to ≤ 80 mmols/day for 6 months were significantly more likely to reduce their medication, compared to those who were less compliant with sodium restriction.

Overall potential for drug withdrawal

Two studies have considered the potential for drug withdrawal in a defined population of hypertensives. In a general practice study, Van Kruijsdijk (553) found 18% of 2120 patients met criteria for treatment withdrawal, which included no history of cardiovascular disease, single or low dose double medication, age < 70 years and DBP < 95 mmHg. 27% of eligible patients refused to enter the study leaving 13% of the total group who were withdrawn from treatment. After one year, of those withdrawn from treatment 48% had a DBP < 95 mmHg.

A further study with a defined population was reported by Alderman (539). Of 196 middle aged store workers with hypertension, 88 (44%) met criteria for withdrawal i.e. pre-treatment BP > 160/95 mmHg and subsequently on anti-hypertensive treatment for a minimum of six months, no angina or oedema, BP on treatment < 140/85 mmHg if less than 65 years or < 150/90 mmHg if ≥ 65 years. 22 patients could not be regularly monitored, leaving 66 (34%) actually withdrawn from treatment and 63 who were followed up for at least one year. 44 patients (22%) remained off therapy for at least one year, eight required treatment for elevated BP and 11 for other reasons. In patients off treatment BP rose slightly after one year, but for those followed up to two years no further increase in BP levels were seen. There were no cardiovascular deaths in the drug free group during two years of follow-up.

These two studies suggest between 13 and 34% of unselected hypertensive persons can be considered for a trial of treatment withdrawal

Factors influencing the return to hypertension.

Age: No consistent effect of age on the success of treatment withdrawal is evident.

Gender: No consistent effect of gender has been reported although the large controlled MRC Trial (546) found men reverted to hypertension more rapidly than women.

Pre-Treatment BP level: Most studies have reported a lower pre-treatment BP level is associated with longer maintenance of normotension. In the Hypertension Control Programme (548) and the VA Trial (544) a lower DBP, and in the MRC Trial (546) a lower SBP in men on stopping bendrofluazide was associated with a greater success of withdrawal. However, pre-treatment BP level in the study of Ekbom et al (551) was not associated with maintenance of normotension.

Pre-Withdrawal BP level: Levinson et al (537) and Ekbom et al (551) found however that lower on treatment BP levels were associated with the maintenance of normotension.

Duration and type of treatment: Most studies have required anti-hypertensive therapy to have been taken regularly for over one year before withdrawal. Although Page and Dunstan (521) found greater success of normotension in those treated for over two years compared to less than two years, subject numbers were small and no consistent duration effect has been reported in other trials including that of Ekbom et al (551) in elderly patients. No consistent effect of treatment time has been reported.

Body weight: Stamler et al (548) found that being overweight at baseline predicted an earlier return to hypertension, while Langford et al (547) found weight loss was associated with a high success rate, weight at baseline was not a predictor.

Left ventricular hypertrophy: Fagerberg et al (540) found pre-withdrawal left ventricular mass was greater in those who rapidly returned to hypertension compared to those whose BP increased more slowly. However, Levenson et al (537) found no difference in ECG diagnosed left ventricular hypertrophy between those reverting or not reverting to hypertension.

Effect of treatment withdrawal on biochemical parameters

Return of biochemical parameters altered by drug treatment to normal levels has been reported in several studies. Stamler et al (548) reported a 0.6 mmol/l rise in serum potassium and a decrease in the prevalence of hypokalaemia from approximately 30% at

baseline to approximately 5% following drug withdrawal. Increases in serum potassium levels have been reported by Finnerty et al (528), the VA Trial (544) and in the MRC study (546). These studies also reported falls of 11% to 40% in serum uric acid levels on withdrawal of mainly diuretic based treatment. Withdrawal of drugs and institution of non-pharmacological advice, particularly weight loss can lead to a reduction in serum cholesterol levels (548).

Effect of treatment withdrawal on morbidity and mortality

Only the trial of Ekbom et al (551) has considered this. Perhaps due to selection of healthy patients and their removal for anti-hypertensive drug treatment if BP rose above certain criteria, the untreated group had a lower risk of cardiovascular events than the treatment group and lower mortality rate than the general Swedish population. Anti-hypertensive therapy withdrawal therefore appears safe, at least in selected patients.

Mechanisms involved in maintenance of normotension following treatment withdrawal.

Resetting of baroreceptor

This was first proposed by Page and Dustan (521) in 1962, it was suggested that after a period of normotension the carotid baroreceptor was reset at a new lower level and would react to an increase in BP by lowering it. Carretta et al (554) found baroreceptor sensitivity was affected by anti-hypertensive therapy. During the period of diuretic treatment when BP was lowered baroreceptor sensitivity was increased, but decreased on drug withdrawal when BP increased. Baroreceptor sensitivity during treatment was correlated with the time during which patients remained normotensive after stopping therapy.

There have been no further studies examining baroreceptor function following anti-hypertensive treatment withdrawal and their role in the maintenance of normotension is unclear.

Regression of vascular changes

Hypertension is believed to cause vascular wall remodelling with an increase in the wall:lumen ratio and left ventricular hypertrophy and these in turn may contribute to the maintenance of hypertension (555). A period of normotension induced by drugs can lead to a regression of these changes - at least partially (524). Following drug withdrawal it is

hypothesised that normotension will persist because of normalisation of the structural changes. However, the initial stimulus to hypertension may persist leading to an elevated BP and the redevelopment of vascular and ventricular hypertrophy. This possibility is suggested by the report from Fagerberg et al (540) in which a lower left ventricular mass was correlated with a longer period of normotension following treatment withdrawal; however, all subjects eventually returned to hypertension. In contrast Levinson et al (537) found no difference in ECG left ventricular hypertrophy between those reverting and not reverting to hypertension. Jennings et al (556) reported that in 7 patients normotensive on treatment the cardiac index and peripheral resistance increased during the first week off therapy with further increases in cardiac index over the next ten weeks being responsible for the redevelopment of hypertension in all subjects.

BP variability

The variability of BP and the tendency for BP to rise when taken by a doctor and fall on repeated readings (as will be discussed in section 1.5) may be responsible for some conversions of 'hypertension' to normotension. Initially, if on recording a high BP reading, further BP checks are not made before instituting anti-hypertensive drug therapy an incorrect diagnosis of hypertension may be made. Subsequent BP readings due to regression to the mean and familiarity with the procedure, may show a normal BP either on or off drug therapy.

Summary

Studies of anti-hypertensive drug withdrawal are summarised in table 1.11. These studies suggest that withdrawal of anti-hypertensive treatment with maintenance of normotension for periods in excess of one year is possible in a minority of selected hypertensives. From the limited data available the substitution of non-pharmacological intervention can more than double the chance of success. In these selected patients cardiovascular morbidity and mortality does not appear higher during the period off treatment than in the general population. Age does not appear to affect the chance of successful treatment withdrawal such that older patients are as likely to remain normotensive off treatment as younger patients. However the effect of substituting non-pharmacological interventions for drug therapy has not been examined in the elderly.

Table 1.11

Results of anti-hypertensive withdrawal studies

Study	ref	n	Age	BP Criteria for Normotension	Follow-Up (months)	% Normotensive off drugs
Thurm	535	69	57	<90	10-42	23
Fernandez	536	24	42	<140/95	11	75
Levinson	537	24	*	<90	12	21
Finnerty	528	59	50	<85	57	61
Boyle	538	20	51	<100	31	10
Alderman	539	66	56	<160/95	36	23
Fagerberg	540	32	49	<170/105	33	0
Dannenberg	541	95	60	<160/95	48	12
Mitchell	542	103	52	<90	12	37
Aylett	543	9	54	<100	24	89
VA†	544	60	52	<95	18	15
Maland †	545	62	30-70+	<90	12	74
MRC †	546	650	35-64	<90	24	45-55
Langford †	547	415	56	<95	13	35-60
Stamler †	548	136	55	<90	48	5-39
Ekbom	551	333	70-84	-	60	20

Table 1.11. Results of anti-hypertensive withdrawal studies in middle aged subjects (n = number of subjects withdrawn from treatment) age is mean age or range; * age not available, † controlled studies.

1.5 BLOOD PRESSURE MEASUREMENT AND AMBULATORY BLOOD PRESSURE MONITORING

Historical background

The discovery of the circulation of the blood and measurement of blood pressure.

Although for many thousands of years the medical literature has made reference to abnormalities of the pulse and their presumed clinical significance, the scientific foundation for the study of blood pressure (BP) was not established until the work of William Harvey (1578-1657) on the circulation of the blood (557). Further progress awaited the introduction of a method of BP measurement. As part of his investigations into the properties and control of the circulation Steven Hales (1677-1761) was the first to develop this and in 1733 in the second volume of Statical Essays, Containing Haemastatics he gave the first description of an invasive method of BP measurement (558). Following Poiseuille's mercury manometer of 1828 which still required direct arterial access, Vierodt in 1854 designed an instrument to measure arterial pressure indirectly in man. However, Marey of Paris in 1863 introduced a more practical instrument which was modified by Mohammed working in Guy's Hospital who applied the technique to the study of human disease for the first time and in 1874 described the association between high BP and acute nephritis. Despite various modifications this sphygmographic instrument remained unsatisfactory due to inaccuracies and uncertain performance.

The prototype of the modern mercury sphygmomanometer stems from the work of Riva-Rocci in 1896. He placed a cuff around the upper arm, inflating it with air until the pressure was sufficient to obliterate the pulse; on releasing the air gradually while observing the pressure on a manometer and palpating the pulse he was able to record the SBP. In 1901 Janeway described the occurrence of sounds during deflation of the cuff, but it was left to Korotkoff (1874-1920) in 1905, a Russian military surgeon, to relate these sounds to the systolic and diastolic BP. Since this time, although the equipment has been modified to improve accuracy, the technique of indirect manual BP measurement is essentially unchanged.

Modern measurement of BP

To standardise the technique for BP measurement using the mercury syphgmomanometer the American Heart Association and the Cardiac Society of Great Britain and Ireland in 1939 issued joint recommendations which have been updated at

intervals (559). If adhered to reliable BP determinations are possible. However, in practice the full recommendations are rarely followed and which together with poor maintenance of equipment can lead to errors in BP measurement.

Oscillometric techniques to measure BP

This technique allows for the automatic determination of BP; on deflation of the arm cuff oscillations begin at approximately SBP, are maximal at mean intra-arterial pressure and continue below DBP. SBP and DBP can only be estimated from empirically derived algorithms. On evaluation, devices using the oscillometric principle have shown excellent agreement with intra-arterial measurements (560,561).

Automatic ambulatory BP measurement

Both intra-arterial and indirect BP recording systems have been developed for ambulatory use but the usefulness of the former in practice is limited because of the invasive nature of the technique. Its main use is as a research tool rather than for clinical use (562).

Non-invasive ambulatory BP recording

Nearly all of these devices require a conventional BP cuff to be worn and use the Korotkoff sound method or oscillometry to measure the BP. The first machine to be developed, the Remler M 2000 in the early 1960's by Hinman and Sokolow (563), was bulky and required manual inflation of the cuff, but provided very useful data. Modern machines are fully automatic, compact and light weight and many show an acceptable degree of accuracy when static readings are compared to the mercury sphygmomanometer or intra-arterial readings (564, 565). However, when assessed under 'ambulatory conditions' ie, during daily activities and exercise, the monitors in general perform less well (565). In effect, as the advice often given to patients is to hold the arm still during a BP measurement, the BP determinations are a series of intermittent static recordings over 24 hours. There are reports of an increased frequency of failed readings and unsatisfactory recordings in elderly and obese subjects, although the number of studies conducted in elderly subjects has been very limited (566).

Data handling

Non-invasive BP monitors can be programmed to take readings as frequently as every 5 minutes but for whole day monitoring a maximum frequency of 15-20 minutes is

more acceptable to patients. Up to 100 readings over a 24 hour period can therefore be produced and downloaded from the monitors memory into a personal computer. Such raw data have been analysed by several methods all of which take into account atypical values or outliers which may represent either true readings or artefacts. A large number of artefactual readings relative to the number of true readings will have a disproportionate effect on measures of BP centrality and variability. Algorithms have been incorporated into monitor software and can be varied by the user to remove readings that are physiologically implausible, eg, SBP $<$ 70 or $>$ 280 mmHg; DBP $<$ 30 or $>$ 150 mmHg or pulse pressure $>$ 150 or $<$ 20 mmHg. Further manual editing of data to remove BP values dissimilar from the bulk of readings may introduce substantial bias.

Summary statistics

Mean and Median Level of BP: This is the most widely used method; the mean of varying time periods can be used, eg, 24 hours, day and night periods. As BP values are usually approximately normally distributed (slightly skewed towards higher levels) use of the mean in most analysis is statistically satisfactory.

BP Load: This is expressed as the percentage of BP readings above a threshold level. Although this method has been successfully used to correlate ambulatory measurements with target organ damage (567, 568), it suffers from several problems. The choice of the threshold value is arbitrary, outlying BP values will have a disproportionate effect and if the number of recorded BP measurements above the threshold level is small, the variance of the estimated load will be high.

Area Under the Curve: This is the area under the curve when BP is plotted against time and gives a measure of the overall BP load of a subject. It is however influenced by both the mean level and variability of BP.

Use of ambulatory BP monitoring in evaluating anti-hypertensive treatment

Ambulatory BP monitoring (ABPM) offers several advantages over conventional clinic based sphygmomanometer measurements in the assessment of interventions on BP levels. Conventional clinic measurements have certain limitations: (a) poor reproducibility from one occasion to another (569), (b) unrepresentative of BP levels away from the clinic (570) and (c) vulnerability to observer bias (571). BP can be measured away from the clinic by using self BP recording (either manually or by using a semi-automatic device) or by fully automatic BPM. Self BP monitoring requires adequate patient education and compliance and cannot give data over the 24 h period.

Advantages of Fully Automatic Ambulatory BP Monitoring

Better representation of 'usual' BP levels

In subjects diagnosed hypertensive on clinic BP readings, measurements taken away from the clinic, either by self monitoring or ABPM and expressed as the mean 24 h or daytime values, BP is often found to be significantly lower. This was first reported by Ayman and Goldshine in 1940 where differences of up to 70/36 mmHg were found in hypertensives between clinic and home BP - differences that persisted for many months of observation (572). Subjects hypertensive in the clinic, but with normal BP away from the clinic have been termed 'white coat hypertensives' (573). It is thought that this alerting reaction begins before attending the clinic, declines after leaving the clinic and is greater when BP is measured by a doctor than a nurse (574). The term 'white coat hypertensive' should be reserved for subjects who have sustained clinic BP elevations, but normal BP away from the clinic. It is common for BPs to be high when a person is first seen, but then to fall on repeated visits. A further problem, emphasising the arbitrary definition of 'white coat hypertension', is the upper level of ambulatory BP levels taken away from the clinic that are considered normal. Some investigators have used the 90th percentile of daytime BP readings (575), others SBP and DBP 10 mmHg higher than daytime ambulatory BPs (576) and some have selected a value considered borderline on clinic BP levels, eg, 140/90 mmHg (577). Whatever criteria are used, in subjects with mild hypertension the prevalence of 'white coat hypertension' has been reported as between 20-40% in several studies (578, 579) and up to 42% in elderly patients with isolated systolic hypertension (580). However at present all large outcome trials on the treatment of hypertension are based on clinic not ABPM measurements, for this reason only clinic BP values have been used for the diagnosis of hypertension in this thesis.

Reduction of placebo effect

The placebo effect has been defined as 'any effect attributable to a pill, potion or procedure, that is not related to its pharmacodynamic or specific properties' (581). Many studies, but not all, have reported the administration of a placebo to be accompanied by a fall in recorded clinic BP (582-584). Much of this BP reduction, particularly in those with initially elevated BP levels, can be explained by regression to the mean and perhaps some to habituation to the measuring procedure with a reduction of anxiety on repeated clinic visits. Studies comparing the effects of placebo on clinic and ambulatory BP have reported significant decreases in clinic BP but no significant change in ambulatory BP levels (585,

586). These results suggest placebo treatment affects the clinic alerting reaction but has no effect on BP levels when this alerting reaction has settled away from the clinic.

Effects of BP variability

When clinic BP measurements are repeated on different occasions the BP level, particularly in subjects with high pressures, tends to fall. Watson et al (587) reported SBP and DBP to fall 5.8 and 4.0 mmHg respectively in mild hypertensives over the first three visits, each a week apart, but with no consistent change between visits 4 and 12. The between visit variation calculated as the standard deviation of the differences (SDD) was 10 mmHg for systolic and 7 mmHg for diastolic pressure. The tendency for an initially high BP to fall with time is largely a result of regression to the mean and familiarity with the procedure of BP measurement.

The circumstances in which clinic BP measurements are taken can be highly controlled and replicated on successive occasions. In contrast when measuring over a 24 hour or daytime period there is less chance of controlling the environment and hence a greater likelihood of considerable variation in a persons activities from one occasion to another. Mental and physical activity account for much of the BP variation throughout the day (588); if these and environmental stimuli are minimised the BP profile throughout the day becomes relatively flat with a fall of about 20% during sleep (589,590). In addition BP variability also increases with age, probably as a result of impaired baroreceptor sensitivity and is greater in hypertensive than normotensive subjects (591).

The effect of such sources of variation on the reproducibility of ambulatory BP measured on two occasions has been investigated by several groups, mainly in young or middle aged hypertensive subjects. Surprisingly of 12 studies repeating ambulatory BP monitoring over periods ranging from one day to six months (592-603) only one study reported any significant difference in mean ABP levels between the two occasions; this was after a six month interval when SBP fell by 4 mmHg on the second recording, but no change in DBP was seen (603). In older subjects with isolated systolic hypertension aged 60-99 y, falls in clinic BP over 1 month of 3/2 mmHg and over 1 year of 7/1 mmHg occurred whilst the falls in 24 h ABPM were much smaller at 1/0 mmHg and 2/1 mmHg respectively (604, 605).

The variability or reproducibility of BP over time, measured as the standard deviation of the differences (SDD) is also usually lower when measured by 24 h ABPM compared to clinic readings. For middle-aged hypertensives the SDD for clinic versus 24h ABPM, respectively, have been reported as 16/9 v 7/5 mmHg and 17/10 v 9.8/4.7 mmHg

(606) and in older hypertensives with ISH 19/7 v 9.5/5.5 mmHg over 4 weeks (604) and in a larger group over 1 year 16/7 v 11/8 mmHg (605). These latter two studies in elderly subjects with ISH were carried out at multiple centres using many different investigators and ABPM devices. It is unclear how far these results can be generalised to an elderly mixed group of hypertensives studied under more controlled conditions and using one model of ABP monitor until further studies are undertaken.

The degree of BP reproducibility or SDD will influence the sample size required in a study to show a given treatment effect. The sample size is related to the square of the SDD, hence even small changes will produce substantial effects. The data available so far suggest that a given BP difference could be detected with fewer subjects or a smaller treatment effect could be seen with same number whist retaining the same power of a cross-over study if 24 h ABPM rather than clinic BP measurements were used. Further studies are required in elderly hypertensive subjects to determine the SDD of repeated BP measurements in order to carry out such power calculations that are relevant to this group.

Duration of treatment effect

To determine the duration of effect of an intervention, repeated conventional clinic BP measurements could be made, although this is inconvenient to participating subjects. Ambulatory BP monitoring offers a much more satisfactory alternative and will also provide data on BP control during the day and during sleep (607).

Summary

Fully automatic ambulatory BP monitoring offers several advantages over clinic BP measurements, chiefly through the ability to take a large number of readings away from the clinic and also to take readings throughout the 24 hour period. Although these advantages have been realised in younger subjects, few studies using such techniques have been conducted in older subjects and none have evaluated the reproducibility of such recordings or validated ambulatory devices using the oscillometric principle in an elderly population.

AIMS OF THE STUDIES

This introduction has summarised work relating to non-pharmacological methods to lower BP in general with particular emphasis on the effects of sodium restriction, potassium supplementation and caffeine use. The paucity, or in some cases the total lack, of data on the effect of non-pharmacological methods to lower BP in elderly subjects (> 65 years) has been highlighted. The higher prevalence of hypertension and greater risk of cardiovascular disease in older than younger subjects demands that the efficacy of various non-pharmacological methods are tested in the elderly population. Because of age related pathophysiological changes in the renal and cardiovascular systems that can affect BP, merely extrapolating from studies in younger subjects to those older may not be appropriate. In addition due to the great degree of BP variation there are difficulties in detecting small but clinically significant BP changes that might be produced by such non-pharmacological intervention. The advantages of multiple BP measurements taken by 24-h ABPM compared to clinic BP measurements has been discussed, but again there are little data on the use of such BP monitoring techniques in elderly persons.

The studies conducted for this Thesis aim to address some of these unresolved issues. In Chapters 2 and 3 the validation and reproducibility of 24-h ABPM in elderly subjects is addressed. Chapters 4 and 5 are concerned with the effects of moderate sodium restriction and potassium supplementation respectively on clinic and 24-h BP levels and the renin-angiotension aldosterone system in elderly hypertensive persons. Chapter 6 deals with the effect of regular caffeine consumption on clinic and 24-h BP and catecholamines in elderly normotensive and hypertensive subjects. Substitution of multiple non-pharmacological methods for anti-hypertensive drug therapy in well controlled elderly hypertensives and the potential for such intervention is dealt with in Chapter 7. The current management by general practitioners of hypertension in elderly persons with particular regard to the use of non-pharmacological therapy is considered in chapter 8.

The above studies described in this Thesis will hopefully add to the limited body of knowledge on the efficacy and potential of non-pharmacological methods to lower BP in elderly persons.

CHAPTER 2

VALIDATION OF THE SPACELABS 90207 BLOOD PRESSURE MONITOR IN ELDERLY SUBJECTS

Summary

Objective

To validate static BP readings obtained with the SpaceLabs 90207 blood pressure monitor (SL 90207 BPM) against a mercury sphygmomanometer in elderly subjects.

Methods

85 normotensive and hypertensive subjects (SBP range: 100-230 mmHg, DBP: 58-123 mmHg) aged 63-85 y had 3 sets of BP measurements taken in the supine position by 2 observers using one of three SL 90207 BP monitors and a standard mercury sphygmomanometer using the same arm sequential measurement technique. Subjects age, mean arm circumference (MAC), waist:hip ratio and body mass index were recorded.

Results

For the average of 85 sets of readings there was an under-estimate by the SL90207 of (mean ± SD) 4.8±8.7 mmHg for SBP and 0.2±5.4 mmHg for DBP in comparison to the standard readings. According to the BHS grading criteria the SL 90207 BPM achieved a grade 'C' for SBP and a grade 'A' for DBP. However inter-device SBP differences just failed the American Association for the Advancement of Medical Instrumentation (AAMI) limits of acceptance but these were met for DBP differences. When subjects with SBP ≥ 200 mmHg were excluded from analysis the AAMI criteria were met. Absolute SBP differences between the two methods were correlated with MAC ($r=0.35$, $p=0.003$), level of SBP ($r=0.34$, $p=0.002$) and body weight ($r=0.26$, $p=0.03$). On multiple regression analysis MAC and the SBP level remained significant predictors of SBP differences between the two devices. DBP differences were related only to the average DBP level ($r=0.23$, $p=0.04$).

Conclusions

In elderly subjects with a wide range of DBP levels and with SBP $<$ 200 mmHg, measurements taken with the SL90207 BPM have an acceptable degree of agreement with readings obtained with a mercury syphgmomanometer under static conditions. Discrepancies between devices in SBP measurement are greatest in those elderly subjects with a large MAC and high SBP level.

Introduction

Protocols for evaluating non-invasive ambulatory BP monitoring devices have been produced by the BHS (608) and the Association for the Advancement of Medical Instrumentation (AAMI) (609). The SpaceLabs 90207 BP monitor (SL 90207 BPM) using the oscillometric principle has been evaluated under static and ambulatory conditions according to both protocols and found to be satisfactory (610). However, at higher BP levels the accuracy compared to a standard mercury sphygmomanometer decreased, with a tendency for the monitor to under estimate high BP levels (611). According to both validation protocols 85 subjects are required to be tested, this however includes subjects with a wide age and BP range, such that in general the number of elderly subjects with high BP's tested has been small. Two groups of investigators have validated auscultatory ambulatory BP monitors in older subjects, Miller et al (612) found a discrepancy with increasing age, whilst Clarke et al (613) found acceptable accuracy when measured in the elderly. A report recently published on the validation of the SL 90207 has included elderly subjects but used a validation technique different from that recommended by the BHS; it concluded that measurement error increased with age and BP level (14). The validation of the SL 90207 is of relevance to this thesis, in which interventions affecting BP levels in elderly hypertensive subjects were assessed by both clinic and 24 h ABPM, using the SL 90207 BPM.

The most satisfactory and accurate method for determining the accuracy of BP monitors at rest is to perform same arm simultaneous measurements obtained using a T-connector allowing the cuff to be connected to both the ambulatory BP monitor and a standard mercury sphygmomanometer. However, the SL 90207 BP monitor has a rapid deflation rate (8 mmHg/second), the pressure of which also falls in series of irregular steps with occasional re-inflations of the bladder, this makes same arm simultaneous recording of BP with a standard mercury sphygmomanometer difficult. To overcome this Atkins et al (614) have shown that a same arm sequential measurement technique is as accurate as simultaneous measurements in the same arm. This recommendation has been incorporated into the BHS validation protocol. In addition it is recommended by both protocols that two observers take BP readings, simultaneously in the AAMI protocol, although this is not stipulated as a requirement of the BHS protocol.

Included amongst the special groups that both protocols recommend automatic BP monitors are tested in are the elderly, a group in which ABPM may become widely used due to the high prevalence of hypertension, concerns over white coat hypertension and the widespread

use of anti-hypertensive drug therapy in this age group. A validation study of the SL 90207 BPM has not previously been carried out exclusively in elderly subjects according to the BHS protocol.

Hypothesis

The hypothesis is that validation of the SL 90207 BPM in elderly subjects falls within the criteria of acceptability as defined by the BHS and AAMI protocol.

Specific objectives

1 To compare BP measurements obtained with the SL 90207 BPM with those from a mercury sphygmomanometer in elderly normotensive and hypertensive persons.

2 To determine the effect of age, BP level, body mass index, mean arm circumference and the waist : hip ratio on BP differences between the devices.

Methods

Subjects

85 subjects (44 female) aged > 60 years, hypertensive (both treated and untreated) and normotensive to provide a wide range of BP levels, were recruited from medical out-patients and the hypertension clinic. Subjects were also selected to provide a wide range of body mass index (BMI) and mean arm circumferences (MAC). Subjects with cardiac arrhythmia's e.g. atrial fibrillation were excluded.

Procedures

Height and weight without shoes and in light clothing, were recorded. Mean arm circumference was measured midway from the tip of the acromium to the olecranon; waist measurements were taken at the level of the umbilicus and hip measurements at the level of the anterior superior iliac spines. the average of two measurements were recorded and the waist : hip ratio calculated.

Validation procedure

After subjects had rested for 5 minutes in the supine position, BP was measured using a recently serviced and calibrated standard mercury sphygmomanometer placed on a trolley adjacent to the examination couch. The height of the couch was adjusted so that the heart, upper arm and sphygmomanometer were at the same height. The mercury sphygmomanometer was deflated at 2 mmHg/second and Korotkoff sounds I and V were defined as SBP and DBP levels respectively. For arms with a circumference greater than 32 cm a large adult cuff with a bladder length of 36 cm was used. Following this initial measurement, the cuff was removed and a similar size cuff attached to the SL 90207 BPM (Redmond, Washington, USA) was applied and a BP measurement was initiated by the

monitor, then the cuff of the standard mercury sphygmomanometer was re-applied and a second BP measurement was taken. This procedure was carried out three times in all subjects. On each test occasion one of three SL 90207 BP monitors, which had been in use for $>$ 1 year was selected at random.

Measurements were taken by two observers (MDF and PI), one third of subjects were studied by each observer independently and the remaining third by both observers simultaneously using a stethescope with two pairs of ear pieces. Mercury sphygmomanometer BP measurements during simultaneous recording were noted independently by each observer. To reduce bias from knowledge of the BP measurement taken by the SL90207 BPM the display panel was obscured. The stored readings were recovered from the monitor after the test was completed. If the SL 90207 BPM audibly signalled a failed reading a further measurement was triggered.

Analysis

All data regarding age, anthropometric and BP measurements were entered into a personal computer using the Minitab statistical package.

The BP data was analysed according to the method suggested by the BHS protocol for evaluation of automatic BP devices (608) except that for measurements taken simultaneously by two observers the average of the readings was used rather than the recording nearest to that obtained by the test device. The second measurement, that recorded by the SL 90207 BPM, was compared with the first and third measurements made by the observer. If the SL 90207 derived BP lies between the first and third pressures, the difference is taken to be zero; otherwise the nearer of the two readings is subtracted from the SL 90207 BPM value to give the difference. The average inter-device BP differences from the three sets of measurements for each subject were calculated; according to the BHS protocol, the percentage of BP differences falling within the limits given in table 2.4 allow grading of the monitors performance. Comparisons between devices can also be inspected by constructing a Bland-Altman plot (615) where the inter-device BP difference from each set of BP readings is plotted against the average of the mercury manometer and SL90207 BP levels and the limits of agreement ($\pm$ 2 standard deviations) between both BP measuring devices can be drawn. These plots also allow the differences in BP recorded by each method to be compared at various BP levels. The AAMI limits of acceptable accuracy are a mean BP difference of $\pm$5 mmHg with a standard deviation of 8 mmHg (609).

For the validation study to be considered acceptable the AAMI protocol stipulates that 95% of simultaneously recorded BP measurements taken by the two observers should agree to within ± 10 mmHg and 85% to within ± 5 mmHg.

To explore any association between inter-device BP discrepancies and other variables, the BP differences were represented as absolute values i.e. irrespective of their sign and Pearsons correlation coefficient was calculated. To establish if the continuous variables were normally distributed plots of data were visually inspected.

Results

All subjects completed the validation procedure satisfactorily and tolerated the repeated BP measurements with no adverse effects. The SL 90207 BPM failed to record BP measurements instead displaying an error code, to produce on average 0.6 errors / true recording (range 0-4 errors / BP recording). Error codes given by the monitor software revealed the reasons for failed readings to be: 'cuff not pumped above SBP' in 64% of failed events, 'movement artefact or arrhythmia' in 32% and 'loosely applied cuff' in 4% of events.

Inter-observer agreement

The mean BP levels and inter-observer differences for the 133 BP measurements made simultaneously by both observers are shown in table 2.1. Over 93% of SBP and DBP recordings agreed to within 5 mmHg and over 99% agreed to within 10 mmHg, achieving the criteria for inter-observer agreement set out by the AAMI.

	Observer		% Difference	
	PI	MF	≤5 mmHg	≤ 10 mmHg
SBP (mmHg)	178	178	98	100
DBP(mmHg)	96	95	93	99

Table 2.1. Mean BP for 2 observers (PI and MF) taking 133 simultaneous BP readings and the percentage of BP differences between observers agreeing to within 5 mmHg and 10 mmHg.

Validation study

The validation procedure was carried out in 85 patients, 44 female, whose characteristics are shown below in table 2.2.

	Mean ± SD	Range
Age (years)	71 ± 7	60 - 88
Supine SBP (mmHg)	174 ± 30	100 - 233
Supine DBP (mmHg)	92 ± 14	58 - 123
BMI (kg/m^2)	27.0 ± 5.1	16.9 -47.2
W : H	0.89 ± 0.08	0.77 - 1.13
MAC (cm)	28.2 ± 3.8	20.0 - 36.0

Table 2.2. Characteristics of the 85 patients studied in the validation procedure.
BMI, Body mass index, W : H, waist : hip ratio, MAC, Mean arm circumference.

The average of the 3 sets of BP recordings in 85 subjects i.e. a total of 255 comparisons, for the first, the SL 90207 BPM and the second sphygmomanometer BP readings and the sum of the mean differences are shown in table 2.3. Overall the SL 90207 underestimated SBP by 4.8 ± 8.7 mmHg, within acceptable limits for the mean SBP difference but just outside the standard deviation limits of acceptable performance given by the AAMI; however both these criteria were met for the recording of DBP.

Reading	Device	Mean SBP ± SD (mmHg)	Mean DBP ± SD (mmHg)
1	Standard	173 ± 31	91 ± 15
2	SL 90207 BPM	166 ± 28	90 ± 15
3	Standard	171 ± 31	90 ± 14
Difference		-4.8 ± 8.7	-0.2 ± 5.4

Table 2.3. Mean (± SD) SBP and DBP level of the 3 sets of readings for the first standard BP reading, the SL 90207 BPM and the second standard BP reading. The difference is that between the SL 90207 BPM and the closest standard BP reading.

Bland-Altman plots and the limits of agreement between all 255 sets of BP measurements taken with both devices for SBP and DBP are shown in figure 2.1. With increasing SBP and DBP levels a greater variability in inter-device BP differences is seen.

BHS Grading

The BHS grading criteria and the percentage of SL 90207 BPM readings agreeing within 5, 10 and 15 mmHg of the standard mercury manometer are shown in table 2.4. A grade 'C' is achieved for SBP measurements and grade 'A' for DBP.

Difference between standard and test device (mmHg)			
BHS Grade	**≤ 5**	**≤ 10**	**≤15**
A	80	90	95
B	65	85	95
C	45	75	90
D		Worse than C	
	Spacelabs 90207 BPM		
% SBP readings	56	75	91
% DBP readings	80	92	98

Table 2.4. Upper panel: BHS grading criteria for difference between standard and test device. The percentage of BP readings that must fall within the given limits to achieve the specified grade.
Lower panel: The percentage of BP readings taken with the SL 90207 BPM compared to a standard mercury sphygmomanometer that fall within the given limits.

Associations between sphygmomanometer - SL 90207 BPM differences and other variables

Discrepancies in SBP measurements correlated with MAC ($r = 0.35$, $p = 0.003$), the average SBP level ($r = 0.34$, $p = 0.002$), body weight ($r = 0.26$, $p = 0.03$) and inversely with age ($r = -0.25$, $p = 0.04$). On multiple regression analysis, entering the above variables into the equation, only the MAC and average SBP level remained significant predictors, explaining 21% of the variation in SBP differences between the two

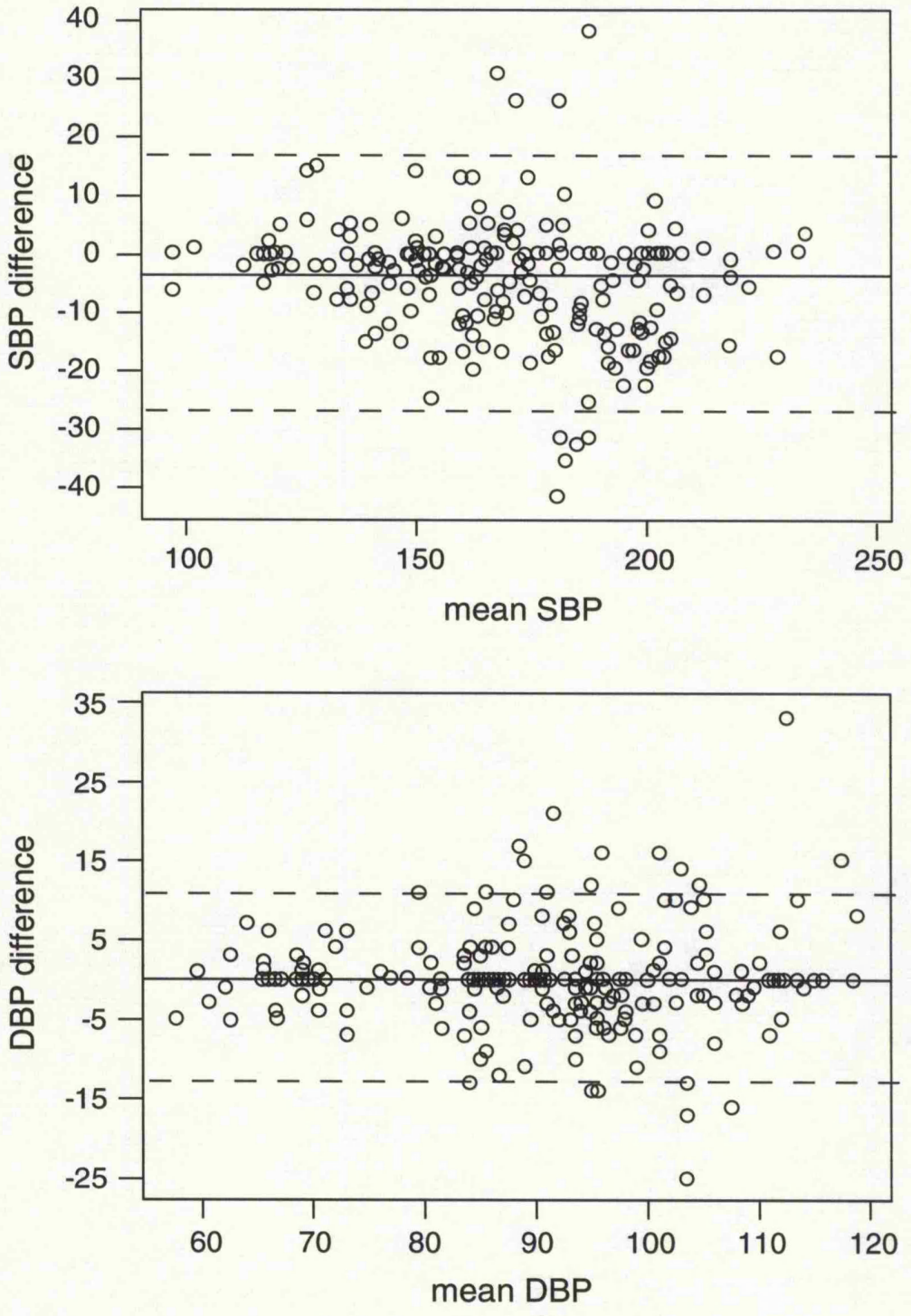


Figure 2.1 *Upper panel:* plot of SBP differences (SL90207-Hg sphygmomamometer) versus mean SBP level.

Lower panel: plot of DBP differences versus mean DBP level.

devices. DBP differences were correlated only weakly with the average DBP level ($r = 0.23$, $p = 0.04$)

When the 23 subjects with SBP levels ≥ 200 mmHg are excluded from analysis the sum of SBP differences between both devices is reduced to -2.8±7.5 mmHg, within the limits of acceptance given by the AAMI for automatic sphygmomanometers; although grading according to the BHS protocol remained unchanged.

Discussion

The Spacelabs 90207 BP monitor has been found to have an acceptable degree of accuracy, as defined by the BHS grading system, compared to a mercury sphygmomanometer in measuring SBP and DBP over a wide BP range in elderly subjects. According to the criteria of the AAMI, SBP differences between the SL 90207 BP monitor and a mercury sphygmomanometer were outside the given acceptable limits although DBP recording was satisfactory. With increasing SBP level and MAC there was a tendency for the SL 90207 BP monitor to underestimate SBP compared to the mercury sphygmomanometer. Disparity in DBP measurements was only weakly influenced by the level of DBP over the range studied and variation in MAC and other variables exerted no significant influence.

When subjects with the highest SBP levels i.e. those with the greatest BP discrepancies between devices, were excluded from analysis, recording of SBP by the SL 90207 BPM was satisfactory according to the AAMI criteria.

Comparison with other studies using the SL 90207 BPM

O'Brien et al (610) have evaluated the SpaceLabs monitor in subjects aged from 15-80 years and found it to be of acceptable accuracy, achieving a BHS Grade B for both SBP and DBP. The same investigators later reported on the accuracy of the SL 90207 BPM and five others according to BP levels (611). At low and medium BP levels a Grade B was achieved for SBP and DBP, but at levels > 160/100 mmHg accuracy was reduced and a C Grade was awarded. The authors stated that when accuracy of measurement is required across the whole BP range the SL 90207 BPM and one other BP monitor could be recommended. A recent report on subjects aged 17-94 y but which included 47 elderly subjects found the SL 90207 to have mean BP differences from a mercury sphygmomanometer of 2.8 mmHg for SBP and 3.9 mmHg for DBP (14). However it just failed to pass the AAMI criteria because of the high variability in differences of SBP

measurements. SBP discrepancies were correlated with SBP level, pulse pressure and age and DBP errors with pulse pressure, DBP level and gender. Overall there was a tendency to over-estimate low SBP and under-estimate high SBP levels. This study varied methodologically from the present study in a number of important ways: a random zero sphygmomanometer was used which tends to slightly under-estimate BP levels compared to the standard device (616), a simultaneous opposite arm comparison was used and persons with an arm circumference greater than 32 cm were not studied. In addition because an opposite arm comparison was made, subjects with inter-arm differences $>$ 5 mmHg, a not infrequent finding in the elderly (617), were excluded and also the method of calculating inter-device BP differences varied from that used in the present study. Despite the different methodology the magnitude of the BP errors and the tendency to under-estimate high SBP levels was similar to the findings reported in the present study.

Gropelli et al (514) evaluated the SL 90207 and an earlier model, the SL 90202, at rest and in ambulatory conditions using a comparison with intra-arterial measurements. In 19 subjects aged between 17-60 years at rest there was close agreement for SBP but an over estimation by the SpaceLabs monitors of DBP by 9 mmHg. In 9 subjects undergoing ambulatory testing, the group average 24 h SBP levels for both methods were almost identical although the SpaceLabs monitor average 24-h DBP levels were 14 mmHg higher than intra-arterial measurements. However, the SpaceLabs monitors were able to faithfully reflect directional hour to hour changes in intra-arterial BP and were considered suitable for assessing 24 h BP profiles quantitatively and qualitatively.

Comparison with other ABPM devices

Miller et al (612) assessed an ambulatory BP monitor (the Suntech Accutracker II) which used the Korotkoff sounds detection method in subjects aged from 23-91 years. Simultaneous BP measurements with a standard mercury sphygmomanometer were made. The BP monitors readings were 5.6/6.3 mmHg lower than the average auscultatory BP measurements, differences greater than those recorded with oscillometric devices. Discrepancies were associated with increasing age and SBP; for each yearly increase of age the SBP discrepancy increased by 0.15 mmHg. Clarke et al (613) carried out an evaluation of another automatic ambulatory auscultatory device (the TM2420) in persons aged 60-94 years with a wide BP range. Compared to a random zero sphygmomanometer the BP monitor over estimated BP by a mean of 4.4 $\pm$ 6.7/4.8 $\pm$ 5.5 mmHg; no effect of BP level on the BP discrepancy was seen.

Conclusion

In elderly subjects the SpaceLabs 90207 BP monitor demonstrated an acceptable level of agreement with a mercury sphygmomanometer over a wide range of DBP levels and also for SBP levels < 200mmHg. On criteria given by the BHS the monitor can be considered satisfactory, achieving a grade "C" for SBP and Grade "A" for DBP measurements. Although the monitor demonstrated acceptable performance for DBP on the AAMI criteria, standards for the variability of inter-device differences in SBP measurements were not met. However when subjects with the highest SBP were excluded from analysis the criteria for satisfactory performance from both organisations were met. With increasing SBP levels and in subjects with a large MAC there was a wider variation in BP differences and a tendency for the SL 90207 BPM to underestimate SBP. In subjects demonstrating high SBP levels and a large arm circumference it is particularly important prior to using the SL 90207 BPM to ascertain the level of agreement between BP's taken by this device and a mercury sphygmomanometer.

CHAPTER 3

REPRODUCIBILITY OF AMBULATORY AND CLINIC BLOOD PRESSURE MEASUREMENTS IN ELDERLY HYPERTENSIVE SUBJECTS

Summary

Objective

To compare the reproducibility of clinic and 24 h ambulatory BP measurements in elderly hypertensive subjects.

Methods

Twenty-two untreated elderly hypertensives of mean age 76 years (range 66-86y) with a clinic SBP > 160 mmHg and/or DBP > 95 mmHg underwent three clinic supine BP measurements followed by 24h non-invasive ambulatory BP monitoring (ABPM). The SpaceLabs 90207 monitor programmed to take readings at 20 minute intervals during daytime (07:00-22:00 h) and every 30 minutes at night-time (22:00-07:00 h) was used. Measurements were repeated during a second visit at a median interval of 10 weeks (range 1-10 months).

Results

The standard deviation of the differences (SDD) between visits, a measure of the reproducibility, was significantly better for mean 24h BP measurements than for clinic BP measurements, (SBP: 6.3 v 17.4 mmHg, $p < 0.001$; DBP: 4.8 v 7.0 mmHg, respectively $p < 0.05$). With daytime defined as 10:00-19:59 h the SDD between visits was 12.4 mmHg for SBP and 8.3 mmHg for DBP, but with daytime defined as 07:00-21:59 h, the SDD fell to 6.0 mmHg for SBP and 4.8 mmHg for DBP, values similar to those obtained with full 24 h BP monitoring. There was no difference in night-time BP reproducibility whether defined as 00:00-05:59 h or 22:00-06:59 h.
Daytime ambulatory SBP levels were 20 mmHg (95% CI 14-27 mmHg, $p<0.001$) lower than clinic SBP although DBP values were similar.

Conclusions

Both 24 h and daytime ABP monitoring significantly improve the reproducibility of BP measurements compared with the mean of 3 clinic BP readings in elderly hypertensive subjects. Increasing the number of daytime BP readings by 50%, from 30 to 45 reduced the variability of BP measurements by 50%.

Introduction

Interventions such as non-pharmacological methods for lowering high BP may result in modest but clinically significant falls in BP, which may not be realised because of the large inherent degree of BP variability whether measured several times on one occasion or when BP is repeated on two or more occasions (587).

Even at rest a substantial degree of BP variability can occur, in the short term through respiratory variations and Mayer waves, on a daily basis through diurnal BP variations and in the longer term through seasonal effects (618). Added to this inherent or background BP variability is that occurring due to physical and mental activity and the effects of environmental variations such as in temperature and food intake.

Variability in BP measured between occasions can be expressed as an absolute measure by using the standard deviation of the differences (SDD) or variability can be related to the level of BP using the coefficient of variation (CV) which is the SDD expressed as a percentage of the average BP level. If the reproducibility of BP measurements is affected by the BP level this will be taken into account by the CV but not by the SDD. The reproducibility or level of agreement between individual mean BP measurements taken on two occasions can also be analysed by plotting the BP differences against the mean BP level as described by Bland and Altman (615). This allows visual inspection of the data and calculation of the limits of agreement.

The greater the BP variability measured on two occasions or the poorer its reproducibility, the greater the number of subjects required in a clinical trial to show a given difference in BP. The variability in BP measurements between two occasions, expressed either as the SDD or the CV can be reduced by taking multiple clinic measurements under controlled circumstances. With frequent BP measurements (20-60 per day) several studies have shown that the reproducibility of mean daytime and 24 hour BP levels is considerably increased compared with clinic readings in younger subjects (597, 606, 607, 619) and in a group of elderly subjects with isolated systolic hypertension (604). This latter study suffered from methodological problems including the use of several observers with different types of 24 h BP monitors.

There are other potential advantages of 24 h ABPM over clinic measurements as discussed in Section 1.5; absence of the white coat effect, observer bias and digit preference, attenuation of the placebo effect and the ability to evaluate BP levels throughout the day and night.

Hypothesis

The hypothesis is that intra-individual BP reproducibility over periods of many weeks assessed using 24 h ABPM is superior to that assessed by using the mean of 3 clinic BP measurements.

Specific Objectives

These are to determine:

(1) the degree of BP reproducibility measured as the SDD and CV.
(2) the limits of agreement for repeated clinic and 24h ABPM measurements.
(3) the effect of visit interval, mean BP level and age on BP reproducibility, and
(4) to examine BP reproducibility during daytime and night-time as defined by two different time periods.

Subjects and methods

Subjects

22 untreated white hypertensive subjects (7 female) with a mean age of 76 years, range 66-86 years, were recruited from out-patient clinics and general practitioners lists. 19 subjects had previously taken anti-hypertensive treatment which had been stopped at least eight weeks prior to the study, three were newly diagnosed and untreated hypertensives.

Inclusion Criteria

Subjects with hypertension defined as clinic SBP $>$ 160 mmHg and/or DBP $>$95 mmHg in the supine position after the following procedure. Three BP measurements were taken on each of 3 occasions, two weeks apart after subjects had emptied their bladder and rested supine for 5 minutes. All BP measurements were carried out in the same quiet, warm clinic room by the same investigator (MDF) with a Hawksley random zero sphygmomanometer using Korotkoff phase V for DBP and a cuff deflation rate of 2-3 mm/sec. The sphygmomanometer was placed on a trolley at heart level and a cuff of the appropriate size was attached to the non-dominant arm which was held relaxed on the couch. If the mean of three supine BP readings at the third visit met the criteria for hypertension given above, the subjects were entered into the study.

Exclusions

Subjects with any of the following were excluded; history of stroke, myocardial infarction, diabetes mellitus, renal impairment (creatinine >200 umols/l) or taking medications known to affect BP.

The study was approved by the Leicestershire ethical committee on medical research.

Methods

At both clinic visits after entry into the study three supine clinic BP measurements were made after five minutes of rest by the same investigator (MDF). The subjects then underwent 24 h ABPM using the Spacelabs 90207 BP monitor programmed to take readings every 20 minutes during the daytime (0700-2200 h) and every 30 minutes at night. Using the same-arm, sequential measurement technique, as described by Atkins et al (614), the clinic and ambulatory BP readings were found to be no more than 5 mmHg apart for all subjects. The BP monitor was attached at the end of the clinic session on the same arm used for the clinic BP determinations. The subjects then returned home with instructions to continue their usual activities and to relax the arm by the side of the body during a BP recording; the monitor was collected after 24h. All BP recordings were taken on week days. Following visit one, all subjects returned to the same clinic room without undergoing any medical intervention to repeat the clinic BP measurements, taken by the same investigator and to repeat the 24 h ABPM. The time interval for returning for visit 2 varied from 1 to 10 months.

Analysis

The mean of three supine clinic BP readings taken during the two study visits was used in the analysis. The 24 h ABP recordings were automatically edited using the BP criteria given in section 1.5 but were not subjected to further manual editing in order to reduce bias; this editing procedure was used for all studies described in this thesis. Only 24 hour recordings with > 85% of all possible readings were considered acceptable. The 24 hour period was arbitrarily divided into day and night-time periods using two definitions. The first defined daytime as 07:00-21:59 h and night-time as 22:00-06:59 h. The second definition was an attempt to classify daytime to better reflect the period of activity (10:00-19:59 hrs) and night-time to reflect time spent asleep (midnight to 05:59 hrs). The data were entered into a computer and the Minitab statistical package was used for analysis.

The reproducibility of BP measurements was assessed by: [1] the method of Bland and Altman (615), which involves plotting the individual BP differences between visit one

Table 3.1

Mean 24 h, daytime and night-time ambulatory BP (ABP) and clinic BP levels for visits 1 and 2 and the mean BP difference, SDD and CV between both visits, using two definitions of daytime and night-time

	SBP						DBP				
	Max No records	Visit 1	Visit 2	Mean Δ visits	SDD	CV(%)	Visit 1	Visit 2	Mean Δ visits	SDD	CV (%)
24-h ABP	63	151±14	152±16	-0.5	6.3	4.2	86±11	85±13	1.3	4.8	5.6
Daytime 1 ABP	30	157±13	159±18	-1.6	12.4	7.8	92±12	91±14	0.5	8.3	9.0
Daytime 2 ABP	45	154±13	157±17	-2.6	6.0	3.8	90±13	89±13	0.6	4.8	5.3
Night-time 1 ABP	12	141±18	136±19	4.5	12.0	8.7	78±14	73±14	5.2	7.9	15.9
Night-time 2 ABP	18	143±17	141±17	1.4	11.9	8.4	78±12	75±13	2.3	7.7	10.1
Clinic BP	3	178±18	179±17	-0.3	17.4	9.7	96±15	93±14	1.6	7.0	7.4

Values are expressed as means ± SD. SDD, standard deviation of the difference between visits; CV, coefficient of variation; daytime 1, 1000-1959h; daytime 2, 0700-2159h, night-time 1, 0000-0559h; night-time 2, 2200-0659h.

and two against the mean BP level and determining the levels of agreement (mean difference+ 2 SD), [2] calculating the SDD between visit 1 and 2, and [3] determining the CV for both clinic and 24 h ABP levels.

The clinic SDD was compared with the ambulatory SDD using the variance ratio (F) test (SDD clinic divided by SDD ambulatory)^2 with 21 degrees of freedom. Two-way analysis of variance was used to assess time and subject variability between visits. Pearson's correlation coefficient was calculated in order to assess the association between variables. Comparison of correlation coefficients was performed by the method of Fergusson (620).

Results

22 subjects satisfactorily completed the study with no adverse effects reported during 24 h ABPM, subjects who did not want to start anti-hypertensive drug treatment were studied for a prolonged period. The mean BP levels, SDD and CV for clinic and 24 h, daytime and night-time ambulatory BP measurements on visit 1 and 2 are shown in table 3.1. Clinic SBP ranged from 144 to 211 mmHg and DBP from 68-124 mmHg. Seven subjects had isolated systolic hypertension based on clinic readings (SBP > 160 mmHg and DBP < 90 mmHg). The median time interval between visits was 10 weeks (range 4-43 weeks).

Clinic and ambulatory BP differences

Despite clinic and ABP levels being within 5 mmHg of each other during the clinic validation testing, both mean 24 hour and daytime SBP levels were significantly lower than clinic BP levels.

	Systolic Blood Pressure (mmHg)	**Diastolic Blood Pressure (mmHg)**
Clinic - 24-h	27* (21,33)	9* (5,14)
Clinic - daytime [1]	20* (14,27)	3 (-2,9)
Clinic - daytime [2]	23* (17,29)	5 (0,10)

Table 3.2. Mean difference and 95% CI between clinic and 24-h or daytime ABPM averaged over two visits, using two definitions of daytime, [1] 10:00-19:59 and [2] 07:00-21:59. *$P < 0.05$.

The mean difference and 95% confidence intervals (CI) between clinic and 24 h or daytime ABP levels averaged over the two visits and calculated using the two definitions of daytime are shown in table 3.2. Mean 24 h and daytime ASBP were between 20-27 mmHg lower than clinic BP although only 24 hour DBP was significantly lower than clinic DBP levels.

There were significant, but weak, correlations for both mean 24 h and daytime SBP with clinic SBP but better correlations were found between mean 24 h and daytime DBP with clinic DBP as shown in table 3.3.

	r	*P*
SBP versus clinic SBP	0.49	0.001
DBP versus clinic DBP	0.65	<0.001
Daytime 1 SBP versus clinic SBP	0.40	0.008
Daytime 2 SBP versus clinic SBP	0.45	0.008
Daytime 1 DBP versus clinic DBP	0.61	<0.001
Daytime 2 DBP versus clinic DBP	0.65	<0.001

Table 3.3. Correlation between mean 24-h or daytime ABP measurements and mean clinic BP, using Pearson's correlation coefficient; daytime, [1] 10:00-19:59 h; [2] 07:00-21:59 h. Blood pressure readings from two visits (n=44) were used.

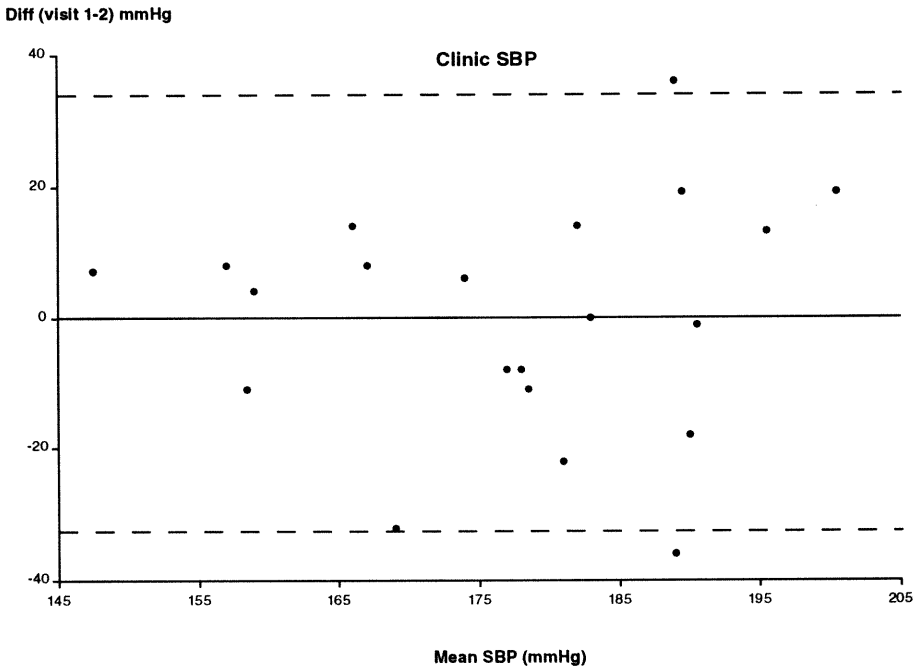
Group mean BP reproducibility

As shown in table 3.1 there was no significant change in the mean BP level for all 22 subjects between visits 1 and 2 whether measured by clinic or 24 BP monitoring.

Intra-individual BP reproducibility

The degree of BP reproducibility between visits for individual mean clinic and 24 h ABP measurements expressed as the SDD and CV are shown in table 3.1. Between visit SBP and DBP variability was significantly lower for mean 24 h ABP than for the mean clinic measurements (SBP $F = 7.68$, $p < 0.001$ and DBP $F = 2.12$, $p < 0.05$) with the SDD and CV for 24 h SBP measurements being less than half that of clinic SBP measurements although the difference for DBP was smaller.

The plots comparing the limits of agreement for the differences in individual mean clinic and 24 h ABP taken on both occasions for SBP and DBP are shown in figures 3.1 and 3.2.



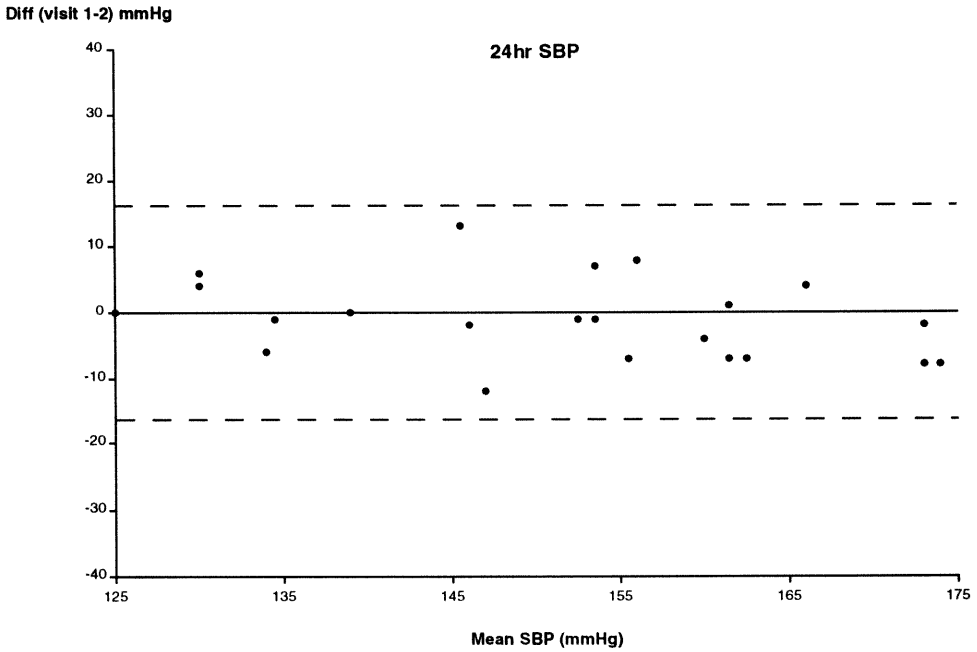
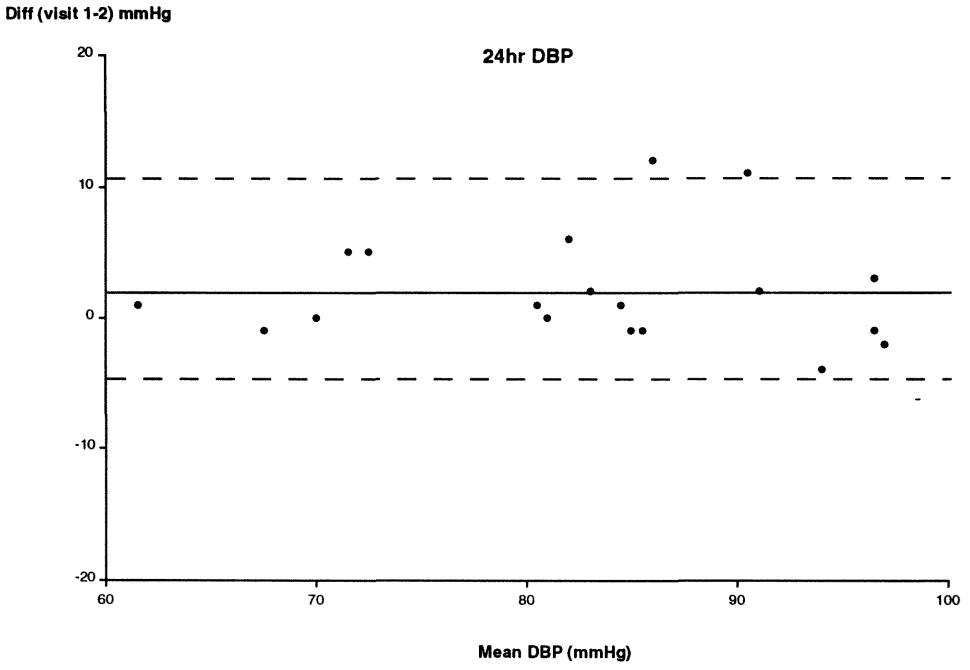


Fig 3.1. Individual (a) clinic and (b) 24-h ambulatory SBP differences (diff) between visits 1 and 2. (-) mean difference (---) ± 2SD.



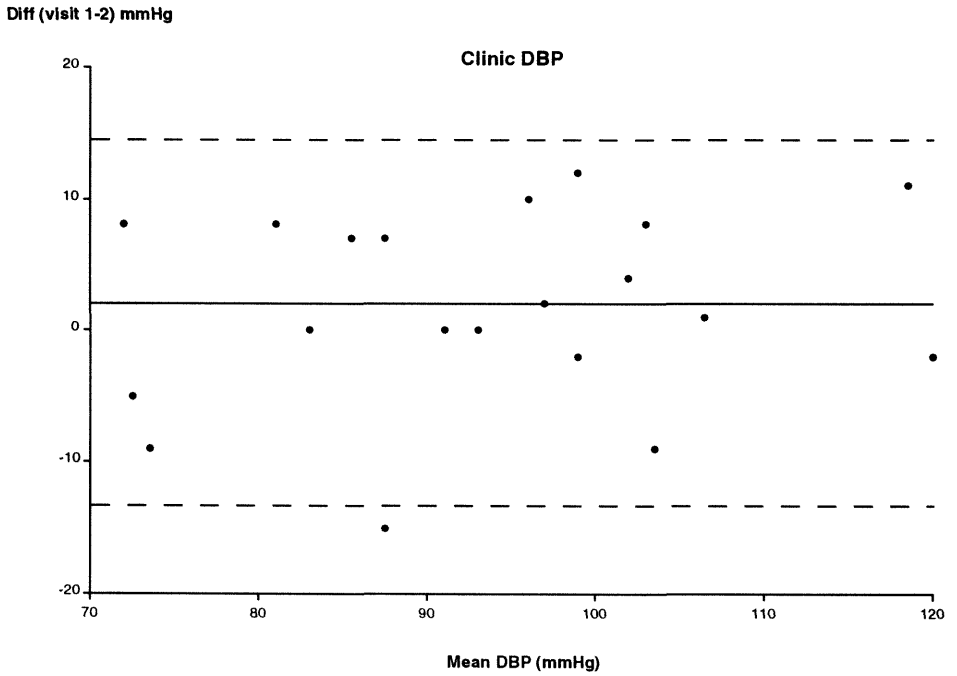


Fig 3.2. Individual (a) 24-h ambulatory DBP and (b) clinic DBP differences between visits 1 and 2. (-) mean difference. (---) $\pm$ 2SD

These data demonstrate visually that the differences between visit 1 and 2 for clinic BP, particularly for SBP, are substantially larger than for 24 h ABPM. This is confirmed by comparing the limits of agreement (mean +2 SD) for 24 h SBP: -13.6 to 12.1 mmHg v clinic SBP -35.1 to 34.5 mmHg and for 24 h DBP -8.3 to 10.9 mmHg v clinic DBP -12.4 to 15.6 mmHg.

The correlation coefficient for the mean 24 h SBP measurements between visit 1 and 2 was significantly greater than that for clinic SBP measurements ($r = 0.93$ v $r = 0.51$, $p < 0.01$; respectively). There was however no difference between correlations for repeated 24 h DBP and clinic DBP measurements ($r = 0.92$ v $r = 0.89$, respectively).

Effect of two definitions of day and night-time on BP variability

There was a significant increase in SBP and DBP inter-visit variability when daytime was defined as 10:00-19:59 h, giving 30 BP readings, compared with 07:00-21:59 h, giving 45 BP readings, (F test: SBP, $p < 0.001$; DBP, $p < 0.05$), as shown in table 3.1. The night-time BP variability was similar whether defined as 24:00 to 05:59 h or 22:00-06:59 h. There was a significant reduction in inter-visit daytime (07:00-21:59 h) BP variability compared with clinic BP variability for both SBP (F test, $p < 0.001$) and DBP (F test, $p < 0.05$), but not when compared with the shorter daytime period defined as 10:00-19:59 hrs.

The effect of time, mean BP level and age on inter-visit BP differences

The Bland-Altman plots (figure 3.1 and 3.2) show no effect of increasing BP levels on inter-visit BP differences. There was no significant correlation for the BP difference between visits 1 and 2 with length of time between visits, mean BP levels or age, for either clinic BP or 24 h ABP. in addition there was no correlation between the change in individual clinic BP levels from visit 1 to visit 2 and the change in 24 h SBP and DBP.

Discussion

In elderly untreated hypertensive subjects the use of mean 24 h or daytime (07:00-21:59 h) BP values significantly improves inter-visit BP reproducibility compared with taking the mean of three clinic BP measurements when repeated over periods of one to ten months. However using a shorter daytime monitoring period with fewer BP measurements reduces this degree of BP reproducibility.

In an attempt to reduce observer bias and digit preference the Hawksley random zero sphygmomanometer was used to take clinic BP measurements, this device has been

shown to underestimate both SBP and DBP compared with the usual mercury sphygmomanometer by 1-2 mmHg (616). However both the Hawksley random zero sphygmomanometer and ABPM readings were within 5 mmHg of each other when compared in clinic. If any small under estimate of BP with the random zero device exists it may slightly over estimate clinic - ABPM differences but should not affect estimates of inter-visit BP reproducibility.

Clinic - ABPM differences

Daytime ambulatory SBP and DBP measurements were 20-23 and 3-5 mmHg respectively lower than clinic measurements including those taken on the second visit, despite all subjects being familiar with clinic BP measuring procedures before entry into the study i.e. the 'white coat effect' persisted despite this prolonged period of BP assessment. The magnitude of this white coat effect is similar to that reported in some studies of younger hypertensive subjects (621, 622) but greater than that in others, particularly for SBP where differences of 10/5-13/3 mmHg have been reported (623-625) in middle-aged subjects.

Group mean BP reproducibility

There was no change in group mean BP levels between visits 1 and 2 for either clinic BP or 24 h ABPM levels. This might be expected with 24 h ABPM where previous studies have shown good reproducibility and also no or little placebo effect (585-586), but clinic BP values tend to fall with repeated measurements taken either on the same or on different occasions (582-584). Watson et al (587) reported clinic BP falls of 6/4 mmHg in young mild hypertensives over the first 3 visits each a week apart. In a report from the Syst-Eur Study in elderly subjects with isolated systolic hypertension, Staessen et al (605) found a fall in clinic BP after 1 year on placebo of 7/1 mmHg, and also a slight fall in 24 h SBP of 2 mmHg but not in 24 h DBP. The inter-visit time interval may be important as no fall in BP in a similar group of subjects was found after 1 month (604). Thus the placebo effect may be of relevance in longer term studies of elderly hypertensive subjects using 24 h ABPM. The subjects studied in the present study had undergone several previous BP measurements by the same investigator prior to entry into this study thereby reducing any effects of regression to the mean during the study period and making the subjects familiar with the measuring procedure. The BP differences observed between visits in the present study, therefore, are more likely to reflect intra-subject than time related variability.

Intra-individual BP reproducibility

The reproducibility of clinic and 24 h ABP measurements obtained in the present study is shown in comparison to other reports in table 3.4.

		Age	Visit interval	SDD Clinic		SDD 24 h	
Ref	**Author**	**years**	**(weeks)**	**SBP**	**DBP**	**SBP**	**DBP**
593	Marolf	-	1	11	8	8	9
598	Reeves	-	3	-	-	9	8
595	Drayer	-	6	-	-	8	6
606	Trazzi	43	4	16	9	7	5
591	Mancia	42	4	-	-	6	6
619	Mansoor	55	92	17	10	9.8	4.7
604	Thjis	60	4	19	7	9.5	5.5
605	Staessen	70	52	15.9	7.4	10.7	8.2
587	Watson	45	1	10	7	-	-
	Present Study	76	10	17.4	7.0	6.3	4.8

Table 3.4. Comparison of the present study with previous reports on reproducibility, given by the standard deviation of the differences (SDD), for BP taken on two occasions for clinic BP and 24 hr ABPM. t, number of weeks between visits; (-), information not available.

The SDD for repeated clinic SBP readings in the present study, 17 mmHg, was higher than the 10 to 14 mmHg reported for younger hypertensives subjects re-measured over a period of a few weeks although the DBP variability was similar (587,597,626,627). The increase in BP variability measured on a single occasion increases with age (628), perhaps due to the less compliant arterial system and decreased baroreceptor sensitivity (14,15) and may account for the increased SDD of clinic readings in the present elderly hypertensive group. Trazzi et al (606) have however reported the SDD of BP measurements made 4 weeks apart to be 16/7 mmHg for clinic BP and 7/5 mmHg for 24 h ABPM in hypertensives aged 19-68 y (mean 43y), results similar to those of the present study. Thijs et al (604) reported an SDD of 19/7 mmHg for clinic and 9.5/5.5 mmHg for 24 hour BP measurements over 4 weeks in elderly patients with isolated systolic hypertension. In three studies of younger hypertensive persons, repeating 24 h ABPM between 1 and 6 weeks, values for the SDD were 8/9, 5/5, 9/8 and 8/6 mmHg (593, 597, 598). Mansoor et al (619) repeated clinic BP

measurements and 24 h ABPM over 3-8 months in 25 hypertensives aged 29-77 y. The BP levels recorded for each method did not change between visits but the SDD for clinic BP was 17/10 mmHg and for 24 h ABP, 9.8/4.7 mmHg. The above results suggest that there is little or no change in the reproducibility of mean 24 h ABP measurements with age, although this may not be the case for clinic BP readings.

Although the reproducibility of 24 h ABPM measurements is greater than the mean of 3 clinic BP measurements taken by a doctor, if recordings are taken in a controlled environment by a nurse or by taking multiple readings with a static automatic sphygmomanometer, BP reproducibility may be similar to that of 24h ABPM measurements (598,628,629).

Correlation of BP's between visits is not the most appropriate measure of reproducibility as it measures the degree of relationship between two variables rather than the agreement (615). For comparison with other studies that have included correlation coefficients, those for 24 h SBP and DBP in the present study are similar to or greater than those reported in younger subjects (597, 599, 602, 603). Weber et al (596) found for 24 h ambulatory BP readings 2 weeks apart correlation coefficients of 0.72 for SBP and 0.76 for DBP in hypertensive subjects. The higher correlation coefficient in the present elderly group may be partly related to their greater range of BP's or to a greater similarity in daily activities compared to a younger group, where significant ABP differences between work days and non-work days have been found (630). The autocorrelations between visits for 24 h SBP were significantly greater than for clinic SAP, although ambulatory and clinic DBE correlations were similar.

The more appropriate method of assessing agreement between the two methods of BP measurement, the Bland -Altman plots (615) clearly reveals the narrower limits of agreement for 24 h BP compared to clinic measurements. The plots also reveal no change in variability with increasing clinic or 24 h BP levels, in addition there was no change seen with the time interval between visits , although this may have been due to the small number of subjects studied beyond 20 weeks.

Effect of different definitions of daytime and night-time on BP reproducibility

The 24 hour period was divided into day and night-time using two definitions, daytime defined as 07:00-22:00 h as suggested by the Scientific Committee on ABPM (631), and as 10:00-20:00 h as suggested by other workers (632, 633). This latter definition was an attempt to relate daytime more closely to periods of activity and night-

time to sleeping periods, excluding the periods of greater BP change that occur in the morning and evening. With the first definition of daytime, 50% more readings were obtained than with the shorter second definition, this had the effect of reducing the SDD for SBP by 50% and the SDD for DBP by 42%, to values almost identical with those obtained with 24 h monitoring. The higher SDD during the shorter daytime period may reflect not only fewer readings but also greater day to day variation in activity during these hours compared with the longer daytime period. Because physical activity is reduced, BP variability is expected to be lower at night, especially during sleep, compared with daytime values. Using subject completed diaries to define sleep and awake times, a more reliable method than using arbitrary times, Mansoor et al (619) did find a lower SDD for sleep (7.7/5.2 mmHg) than for awake BP (SDD: 10.7/5.8 mmHg). In the present study however SBP and DBP variability at night were similar to, or greater than, the daytime variability. This is probably a reflection of the poorer definition of sleep time, shorter sampling time and less frequent BP recordings undertaken at night. Other possible contributory factors to the increase in nocturnal BP variability are altered sleep patterns in the elderly (634, 635) and sleep disturbances due to the BP monitoring . However, although some degree of sleep disturbance does occur it has been shown that average BP's at night are similar whether arousal is provoked or not (636-638). Using a definition similar to that for our shorter daytime and night-time periods, Thijs et al (604) reported almost identical degrees of between visit variability in elderly subjects.

Effect of shorter monitoring periods on BP reproducibility

Four hours of ABPM during the daytime and two hours of monitoring at night within certain time spans have been shown to accurately represent daytime and night-time BP. In young hypertensives Sheps et al (639) considered a 6 h period of ABPM represented usual daytime ABP. In hospitalised elderly persons just 2-3 hours of monitoring represented 24 h and daytime mean BP's (640). However the intra-individual BP reproducibility of mean BP's derived from these short term monitoring periods is unclear.

Trazzi et al (606) examining young hypertensives found that non-invasive ambulatory BP reproducibility over a four week period was not improved by taking more than 24 measurements. However, these BP readings were randomly selected from the whole 24 hour period and the authors conclusions may not apply when shorter periods are considered, particularly in older hypertensive subjects. In the study of hospitalised elderly patients (640), although the mean of 2h of BP monitoring represented whole 24 h BPM levels well, on repeating ABPM 1 week later the SDD based on progressively increasing

monitoring periods only approached the SDD for the 24 h period when the mean BP derived from more than 12 h of ABPM (> 36 measurements) was used; results similar to those seen in the present study. Mancia et al (641) compared the reproducibility of hourly BP means with those from whole 24 h or daytime periods and found reproducibility was poor. However these hourly mean BP's represented the average of only 3-4 BP measurements, as noted above reproducibility may depend more on the number of readings taken than the period of time over which they are taken.

The results from the present study suggest that when carrying out 24 h ABPM in elderly hypertensive subjects, taking part in normal home activities, more than 30 BP measurements are required if a significant reduction in intra-individual BP variability, below that obtained with three clinic readings, is to be achieved. Whether the SDD is affected by taking the same number of readings over a shorter period is unclear, but the above evidence suggests it may not be.

Effects of BP reproducibility on sample size estimates for intervention studies

The reproducibility of BP measured as the SDD is of relevance in determining the number of subjects required in an intervention study to demonstrate with sufficient power the change in BP, if any, arising from the intervention. For a cross-over trial the number of subjects (n) required to show a given treatment difference (d) with a power of 85% at the 5% significance level is given by the equation $n = 10 \times SDD^2/d^2$ (642). Using data for SDD from the present study suggests that to detect an SBP treatment difference of 5 mmHg, 16 subjects would be required if a 5 mmHg difference in 24 h ABPM was to be detected but 120 subjects for the same difference in clinic SBP. To detect a DBP treatment difference of 4 mmHg, 14 subjects would be required on 24 h ABPM and 31 with clinic readings. Clearly small differences in the SDD will have a large effect on sample size requirements for cross-over trials. By taking multiple measurements or resting subjects for a prolonged period, the BP reproducibility can be improved. In elderly hypertensive subjects after 30-45 minutes of supine rest clinic SDD values of 7.3 mmHg for SBP and 7.8 mmHg for DBP were obtained after repeating measurements over 1 week (629). Using these values in the example of a cross-over study given above, between 21 and 38 subjects would need studying - still a greater number than if 24 h ABPM were used. It appears that for clinic measurements the SDD and hence the study sample size required for a cross-over trial is highly dependent on BP measurement conditions.

In a parallel group design trial it is not only intra-subject BP variability that is important and can be reduced by 24 h ABPM, but also inter-subject BP variability which is

little affected by 24 h ABPM. Hence for such trial designs there is little difference in sample size requirements whether 24 h ABPM or clinic measurements are used (643). Also in any study design, if the 24 h period is sub-divided e.g. into day and night periods or 1 hourly means, sufficient BP readings in each period will be required to maintain the SDD at levels for whole 24 h ABPM otherwise sample size will need to be increased if the power of the study is to be maintained.

Conclusions

24 hour ABPM gives greater intra-individual BP reproducibility than clinic measurements in elderly hypertensive subjects if more than 30 daytime measurements are taken, over a 15 hour period. Used in this way ambulatory BP monitoring will reduce the SDD of repeated BP measurements, increasing the power of intervention studies of a cross-over design to detect smaller BP differences for a given sample size compared to the use of clinic BP measurements.

CHAPTER 4

EFFECT OF MODERATE SODIUM RESTRICTION ON CLINIC AND 24 HOUR AMBULATORY BLOOD PRESSURE IN ELDERLY HYPERTENSIVE SUBJECTS

Summary

Introduction

Dietary sodium restriction can reduce BP in young and middle aged hypertensive subjects and epidemiological studies suggest that a greater hypotensive effect may be seen with increasing age, however no such long term trials of salt restriction have been conducted in elderly hypertensives.

Methods

17 untreated elderly hypertensive subjects, mean age 73 years, had clinic BP and 24 hour urinary electrolyte excretion recorded prior to reducing dietary sodium intake to 80-100 mmols/24 hours. Following a four week run-in period on the sodium restricted diet, subjects entered a 10 week double blind, randomised, placebo controlled cross-over trial of 80 mmols/24 hours sodium supplement or matching placebo whilst continuing with the restricted dietary sodium intake. Clinic and 24 hour ambulatory BP levels, plasma renin activity, aldosterone and urinary electrolyte excretion were recorded at the end of the low and high sodium phases.

Results

Reducing sodium intake by a mean of 79 mmols/24 hours (95% CI, 68-90 mmols/24 hours) resulted in a reduction in clinic supine SBP of 8 mmHg (CI 1-15 mmHg, $p < 0.05$). 16 patients underwent 24 hour ABPM, the difference in mean 24 hour SBP and DBP between the low and high sodium intake phases was not significant (5 mmHg, CI -3 to +12 mmHg, and 2 mmHg CI -2 to +6 mmHg, respectively). Plasma aldosterone and PRA levels increased although there was no change in weight from the high and low sodium phase.

Conclusions

The overall hypotensive response to moderate sodium restriction in elderly hypertensive subjects is not as great as predicted although large inter-individual differences were identified. Dietary sodium restriction may be of benefit as part of a non-pharmacological therapy in some elderly hypertensives.

Introduction

Sodium restriction has been shown in many, but not all trials, to lower clinic BP in hypertensive patients. There is evidence, reviewed previously, to suggest that the effect of salt restriction will be greater in older than younger persons. The InterSalt study (116) and other observational studies (121) show a closer relationship between sodium excretion and BP at older ages; 'salt sensitivity' has been reported to increase with age and to a greater extent in hypertensive than normotensive subjects (233) and finally analysis of salt restriction trials has suggested a greater hypotensive effect of a low sodium diet with increasing age and BP (169, 209). It has been suggested that an enhanced hypotensive effect of sodium restriction in older persons may be related to their lower renin levels and depressed renin-aldosterone response to a fall in sodium intake (644).

As discussed in section 1.1 the prevalence of hypertension and the absolute risk of cardiovascular events from hypertension are also greater in older than younger persons. Recently the benefits in terms of reduced cardiovascular morbidity and mortality from pharmacologically lowering high BP have been found to be particularly pronounced in the elderly. Despite these considerations no adequate study of moderate sodium restriction has been conducted in elderly hypertensive subjects.

Although the effects of reducing dietary sodium intake on clinic BP levels have been studied extensively in young subjects, there are few data on the changes in 24 hour ambulatory BP levels. The advantages of such BP monitoring in terms of greater individual BP reproducibility and reflection of 'usual' BP levels have previously been discussed (see section 1.5). Moore et al (196) studying the effects on BP of extremes of sodium restriction and loading over 7 days noted a fall in clinic but not 24 hour ambulatory BP levels in middle-aged hypertensive patients. However, Law et al (169) from a consideration of observational and trial data have emphasised the need for trials of sodium restriction to be of more than 4 weeks duration in order to demonstrate fully the predicted effects.

Hypothesis

The hypothesis to be tested is that moderate dietary sodium restriction lowers clinic and 24 hour ambulatory BP in elderly untreated hypertensive subjects.

Specific Objectives

1 To determine the clinic and 24 hour ambulatory BP changes following moderate sodium restriction in elderly hypertensive subjects.

2 To examine changes in the renin-aldosterone axis to changes in sodium intake and their relation to BP changes.

Subjects and Methods

Subjects

18 white subjects (14 female and 4 male) mean age 73 years, range 66-79 years, with essential hypertension were recruited from out-patient departments and general practitioners lists. Two subjects were newly diagnosed hypertensive, the remainder had been off all anti-hypertensive treatment for a minimum of six weeks.

Inclusion criteria

Fully ambulant and fit subjects aged between 65 and 79 y with essential hypertension defined as a clinic SBP ≥160 mmHg and/or DBP ≥95 mmHg (645) whilst off any anti-hypertensive treatment for at least 6 weeks were considered for inclusion in the study. On arrival at the clinic, subjects emptied their bladder and rested supine for 10 minutes before BP was measured using a Hawksley random zero sphygmomanometer and cuff of the appropriate size. Three measurements were taken in the supine position and then, after standing for 1 minute, a further three measurements were taken. The mean of each set of three readings was recorded. Blood pressure measurements were taken on three separate occasions one week apart at a similar time of day in the same quiet, warm room by the same investigator (MDF). If on the third visit mean supine BP met the inclusion criteria subjects were invited to participate in the study.

Exclusion criteria

Subjects with secondary forms of hypertension, diagnosed on clinic, biochemical and radiological investigations were excluded. Subjects were also excluded if they had a history of congestive cardiac failure, renal impairment (creatinine >200 umols/l), proteinuria (based on positive lab sticks result) or diabetes mellitus, severe hypertension (SBP > 220 mmHg or DBP > 115 mmHg) or if they were taking any therapy known to effect BP.

Ethical Approval

The study was approved by the Leicestershire Ethical Committee and all patients gave informed consent before entering the study.

Procedures

Two 24 hour urine collections and clinic BP measurements were made while subjects were on their usual diet. Prior to entering a four week run-in period patients were counselled by the study dietician to achieve a daily dietary sodium intake of 80-100 mmols but no specific advice was given regarding weight loss. A summary of the dietary advice given to the subjects is shown in appendix I. Subjects were instructed to maintain this level of sodium intake throughout the entire 14 week study period. Following the run-in period subjects entered a double blind randomised placebo controlled cross-over trial of five weeks low sodium diet, plus 80 mmols of sodium chloride (2 slow sodium tablets four times a day; Ciba-Geigy plc, Horsham, West Sussex) known as the "high sodium" phase or five weeks of low sodium diet plus matching placebo tablets (2 placebo tablets four times a day) known as the "low sodium" phase. Randomisation to sodium chloride or placebo tablets was performed in blocks of 6 with sealed cards being held in the pharmacy department.

Subjects attended the clinic before the run-in period, at week 2 and at the end of the run-in period and mid-way and at the end of each cross-over phase. At each clinic visit which took place between 09:00 and 10:00 hours the following measurements were taken: (I) the BP as described above, (II) the pulse rate over 60 seconds in supine and standing positions and (III) the body weight in light clothing without shoes, using the same regularly checked scales at each visit and for all subjects.

Laboratory Measurements

Blood

At the end of the run-in and each cross-over phase, blood samples were drawn after ten minutes supine rest for plasma renin activity (PRA), aldosterone and electrolyte estimation. Blood samples were collected from all subjects in pre-chilled EDTA tubes and placed immediately on ice and centrifuged at 15,000 rpm for 20 minutes in a pre-cooled (4° c) centrifuge within 10 minutes. Serum from each sample was decanted into two separate plastic tubes and stored at -70°c. Duplicate blood samples for PRA estimation were analysed by radioimmunoassay of angiotensin I (biodata renin MAIA kit, Serono Diagnostics Ltd, Woking, Surrey) and for aldosterone levels by radioimmunoassay

(aldosterone MAIA kit Serono Diagnostics). All samples from a given subject were measured in the same batch. The intra-assay coefficients of variation (CV) were 4.1% and 6.2% and the interassay CV was 8.7% and 9.8% for PRA and aldosterone respectively. All assays were carried out by the same investigator (MDF) who was blind to the order of the intervention phases.

Urine

During the last two weeks of each phase all subjects were asked to provide two consecutive 24-hour urine collections for estimation of volume, creatinine and electrolyte excretion. The volume of each 24-hour urine collection was noted and after mixing, two aliquots of 5 mls each were removed into glass tubes, and stored at -70°C. Samples for estimation of sodium and potassium were analysed by flame photometry and creatinine by an enzymatic dry chemical method (646).

Restricted sodium diet

At each visit commencing from the run-in phase, subjects and where appropriate, their spouses were seen by the study dietician who reinforced dietary advice, gave written information on the sodium content of foods and answered queries regarding the low sodium diet. Subjects were asked not to add salt at the table and to use a reduced sodium salt, (33% sodium chloride, 66% potassium chloride, Lo-salt, Klinge Foods Ltd, Scotland) if required for cooking which was provided free to all subjects. At the intermediate visit of each cross-over phase subjects were given instructions to complete a seven day food diary during the last week of the high and low sodium phases from which electrolyte intake was calculated. Compliance with sodium supplements and placebo was assessed on each visit by tablet count and those subjects taking less than 90% of trial medication were excluded from the study; compliance with the low sodium diet was assessed from the 24 h urinary sodium excretion.

24-hour BP monitoring

Home 24-hour non invasive ambulatory BP monitoring (ABPM) was undertaken at the end of the high and low sodium phases using a Spacelabs 90207 monitor (Spacelabs Inc, Redmond, Washington, USA). Monitors were fitted at the end of the clinic visit and using the same arm sequential measurement technique (614) BP monitor and clinic sphygmomanometer readings were all within 5 mmHg of each other. Ambulatory BP readings were taken at 20 minute intervals between 07:00 and 22:00 hours and at 30 minute

intervals between 22:00 and 07:00 hours, using a cuff of the appropriate size on the same arm used for clinic BP recordings. The daytime period for the 24 hour ABPM was arbitrarily defined as being from 10:00 to 19:59 hrs and night-time from 24:00 to 05:59 hrs. Subjects in whom less than 85% of the possible recordings were obtained had the recording repeated in the subsequent 24 hour period. Records were not manually edited to avoid introducing bias.

Analysis

Values are presented as means ± SD with 95% confidence intervals (CI) where appropriate. The study had the power to detect a clinic BP difference of 10/6 mmHg with a power of 80% of the 5% level assuming that the SD of the difference for clinic SBP was 14 mmHg and for DBP 7 mmHg (647). Using 24-hour ABPM and a sample size of 16 patients, a difference of 4.5 mmHg in SBP and DBP could be detected with a power of 80% assuming an SDD of 6 mmHg as reported in chapter 3. Differences between high and low sodium phases were analysed by the method of Hills and Armitage for a two period cross-over design trial looking for treatment effect and treatment-time interaction (648).

Results from 24-h ambulatory BP monitoring were analysed using the mean BP for each subject over 24-hours or day and night-time period where indicated. To reveal differences in BP between the two levels of sodium intake over a 24 hour period a subtraction plot of hourly BP means on the low sodium minus high sodium phase was plotted against time. Linear correlations were calculated using Pearson's correlation coefficient. A value of $p < 0.05$ was considered statistically significant.

Results

17 patients completed the study with no adverse effects reported, one subject being excluded due to poor compliance with the trial medication. Food diary results showed that dietary sodium and potassium intake remained similar during the high and low sodium phases (73 ± 14 and 66 ± 11 mmols/24-hours; and 70 ± 19 and 64 ± 13 mmols/24-hours respectively). Mean urinary sodium excretion during the run-in and placebo phases, shown in table 4.1, also suggested that compliance with the dietary restriction was satisfactory. Although subjects were not asked to alter their weight, between run-in and the high and low sodium phases weight fell by 1.3 ± 1.5 kilograms ($p = 0.003$), although there was no difference in weight between high and low sodium phases.

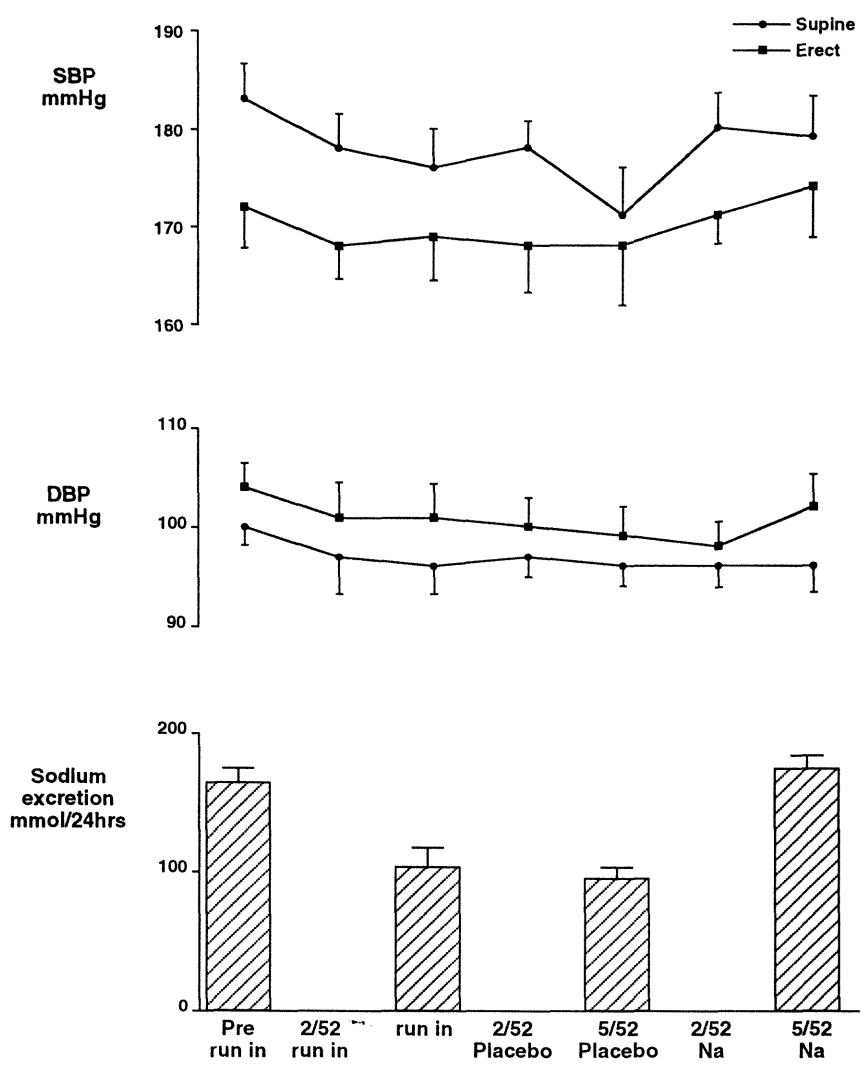


Fig 4.1. Mean supine (●) and standing (■) systolic (SBP) and diastolic blood pressure (DBP) and urinary sodium excretion on normal diet (Pre run in) and low-sodium diet run in with placebo (Placebo) and sodium supplementation (Na) phases. Values are expressed as means ± SEM.

Clinic BP and pulse rate

Clinic BPs for each visit are shown in figure 4.1 and those at completion of run-in, low and high sodium phases together with pulse rate changes are shown in table 4.1. Individual changes in clinic BP from placebo (low sodium) to sodium supplemented phase (high sodium) are shown in figure 4.2.

There was a non-significant fall in supine SBP from the period of the normal diet before the run-in to the end of the run-in phase on a low sodium diet of 7 mmHg (95% CI -16 to +2 mmHg). Similar but smaller changes were seen in supine DBP and standing BP levels as shown in figure 4.1.

Supine SBP was significantly lower at the fifth week of the low sodium phase compared with the fifth week of the high sodium phase by 8 mmHg (CI 1-15 mmHg; $p < 0.05$) with a smaller decrease in standing SBP of 5 mmHg (CI -1 to +12 mmHg; $p = 0.08$). There was no difference in DBP or pulse rate between the intervention phases (see table 4.1). There was no time-treatment interaction i.e. blood pressures were similar for subjects who had either four or nine weeks on the low sodium intake before starting the high sodium phase.

There was no difference in the orthostatic change in SBP and DBP between the low sodium (3 ±17/-3 ± 9 mmHg) and high sodium (6 ± 14/-3 ± 10 mmHg) phases.

24-hour ambulatory BP and pulse rate

One subject refused ABPM leaving 16 patients who had satisfactory 24-hour ABPM recordings at the end of the high and low sodium phases. The mean 24-hour, daytime and night-time ambulatory BP levels and mean 24 hour pulse rates at the end of low and high sodium phases are shown in table 4.1. There was no significant difference in mean 24 hour SBP or DBP between the high and low sodium phases (SBP difference: high - low sodium intake, 5 mmHg; CI -3 to +12 mmHg; DBP difference: 2 mmHg, CI -2 to +6 mmHg) and in mean 24 hour pulse rate. Changes in mean 24 h SBP and DBP from the low to high sodium phases for each subject are shown in figure 4.3.

For both high and low sodium phases, night-time BP was significantly lower than daytime BP (SBP: -12 ± 13 mmHg, $p<0.01$; DBP: -14 ± 10 mmHg, $p<0.0001$ and SBP: -14 ± 10 mmHg, $p<0.0001$; DBP -15 ± 8 mmHg, $p<0.0001$), respectively). The changes in mean daytime or night-time SBP and DBP between intervention phases were not significant. No period or time period interactions were found for clinic or ambulatory BP measurement changes.

Table 4.1

Changes in clinic blood pressure, pulse rate, weight, and urinary and plasma measurements among run-in and low- and high-sodium phases. Also shown are the changes in 24-h, day and night blood pressures by ambulatory blood pressure monitoring (ABPM) between the low- and high-sodium phases.

	Run-in	Low-sodium	High-sodium
Clinic			
Supine			
SBP (mmHg)	176±17	171±21	179±18*
DBP (mmHg)	96±11	96±8	96±11
Heart rate (beats/min)	77±10	74±10	75±10
Standing			
SBP (mmHg)	169±19	168±25	174±22
DBP (mmHg)	101±14	99±12	102±13
Heart rate (beats/min)	83±11	83±8	81±8
ABPM			
24-h mean			
SBP (mmHg)		145±15	150±16
DBP (mmHg)		85±13	87±12
Heart rate (beats/min)		78±10	76±9
Daytime			
SBP (mmHg)		150±15	153±14
DBP (mmHg)		90±12	91±12
Night-time			
SBP (mmHg)		136±15	141±20
DBP (mmHg)		76±13	77±14
Weight (kg)	69.1±8.2†	67.8±7.7	67.4±7.1
Urine			
Urinary sodium (mmol/24h)	104±59	95±36	174±40**
Sodium : creatinine ratio	12.7±7.1	12.0±4.3	22.9±7.6**
Urinary potassium (mmol/24h)	66±25	65±18	68±24
Potassium : creatinine ratio	8.0±2.9	8.3±2.3	8.8±3.4
Urine volume (ml/24h)	1773±498	1779±376	1768±415
Plasma			
PRA (ng/ml per h)	1.11±0.72	1.24±0.77	0.89± 0.56**
Plasma aldosterone (ng/l)	192±111	228±114	57±89*

Values are expressed as means ± SD. *$P < 0.05$, **$P < 0.01$, versus low-sodium; †$P < 0.005$, versus low- and high-sodium phases. SBP, systolic blood pressure; DBP, diastolic blood pressure; daytime, 1000-1959 h; night-time, 24000-0559 h; PRA, plasma renin activity.

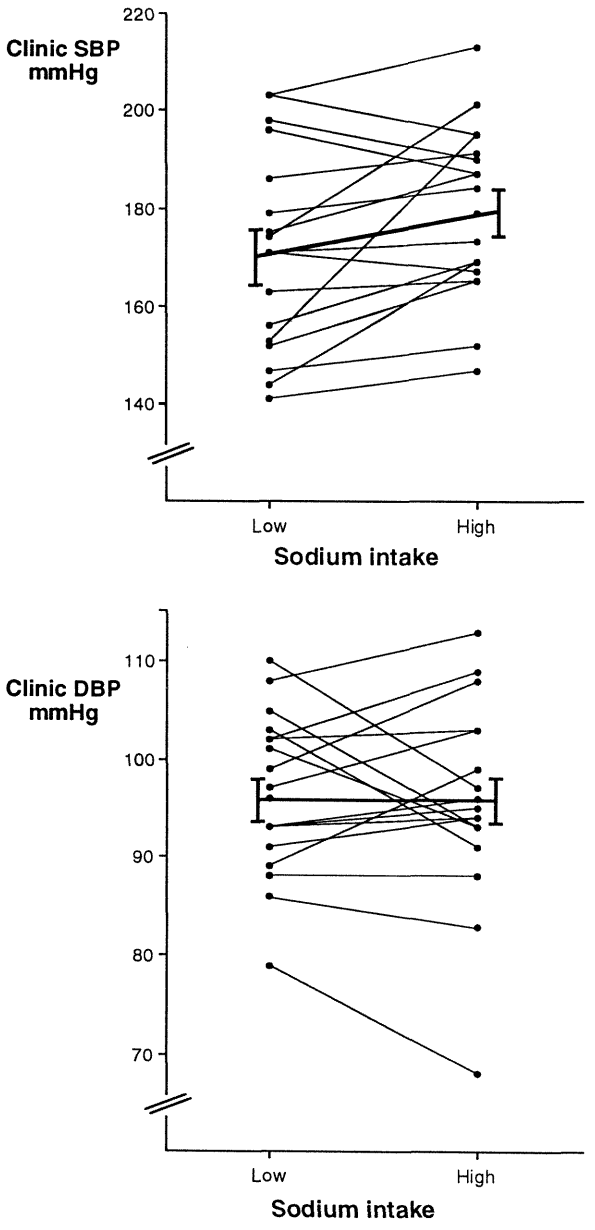


Fig 4.2. Individual changes in mean clinic blood pressure on the low and high sodium intakes (n=18).

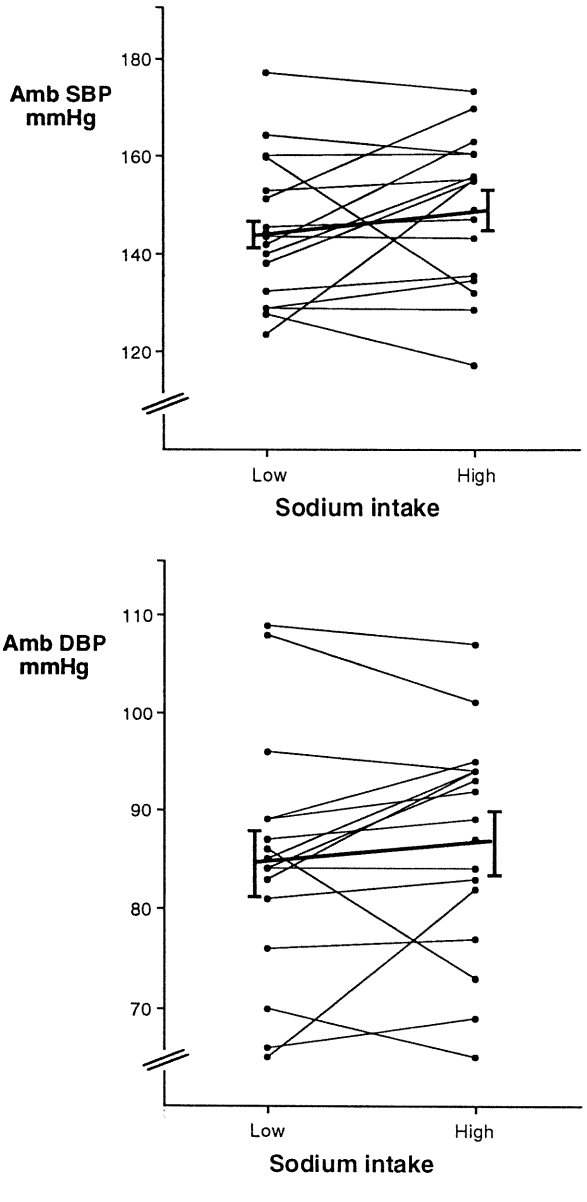


Fig 4.3. Individual changes in mean 24-h ambulatory blood pressure on the low and high sodium intakes (n=16).

Subtraction plots showing the mean hourly differences in SBP and DBP of low sodium BP levels minus high sodium BP levels are shown in Figure 4.4.

Relationship Between Clinic and Ambulatory BP Changes

No significant correlations were detected between either clinic or ambulatory BP changes and changes in sodium excretion between intervention phases. In addition there was no significant correlation between clinic or ambulatory BP change and baseline BP levels. Thirteen subjects had a fall in clinic supine SBP and ten in 24-hour SBP although there was no significant correlation between changes in clinic and ambulatory BP levels.

Effect of age on BP changes

There was a significant correlation between increasing age and the BP fall on the low sodium phase for clinic SBP ($r = 0.54$, $p = 0.03$); 24h ambulatory SBP ($r = 0.54$, $p = 0.03$) and 24h ambulatory DBP ($r = 0.59$, $p = 0.02$) but not for clinic DBP. On multiple regression analysis entering change in urinary sodium excretion and change in PRA level into the equation, a significant relationship remained between age and the BP fall for clinic SBP ($p = 0.01$); 24h SBP ($p = 0.03$) and 24h DBP ($p = 0.02$).

Biochemical changes

Urine electrolytes

The 24-hour urinary electrolyte and creatinine changes are shown in table 4.1. Sodium excretion during the phase on normal diet before run-in was 164 ± 40 mmols/24-hours and was unchanged between the run-in and low sodium phases but increased by 79 mmols/24 hours (CI 68-90 mmols/24 hour, range 52-142 mmols/24 hour; $p < 0.001$) between intervention periods. To allow for any incomplete 24 hour urine collections the urinary electrolyte excretion was also expressed as the ratio to creatinine. Using this correction a similar sodium:creatinine excretion occurred between run-in and low-sodium phases but a significant increase occurred at the completion of the high sodium phase (see table 4.1). There was no significant change in 24-hour urinary volume, potassium excretion or potassium:creatinine excretion between either intervention phase or run-in phase.

Blood

Serum electrolytes, urea and creatinine levels were unchanged throughout the study. Plasma renin activity and aldosterone levels (table 4.1) were higher in the low

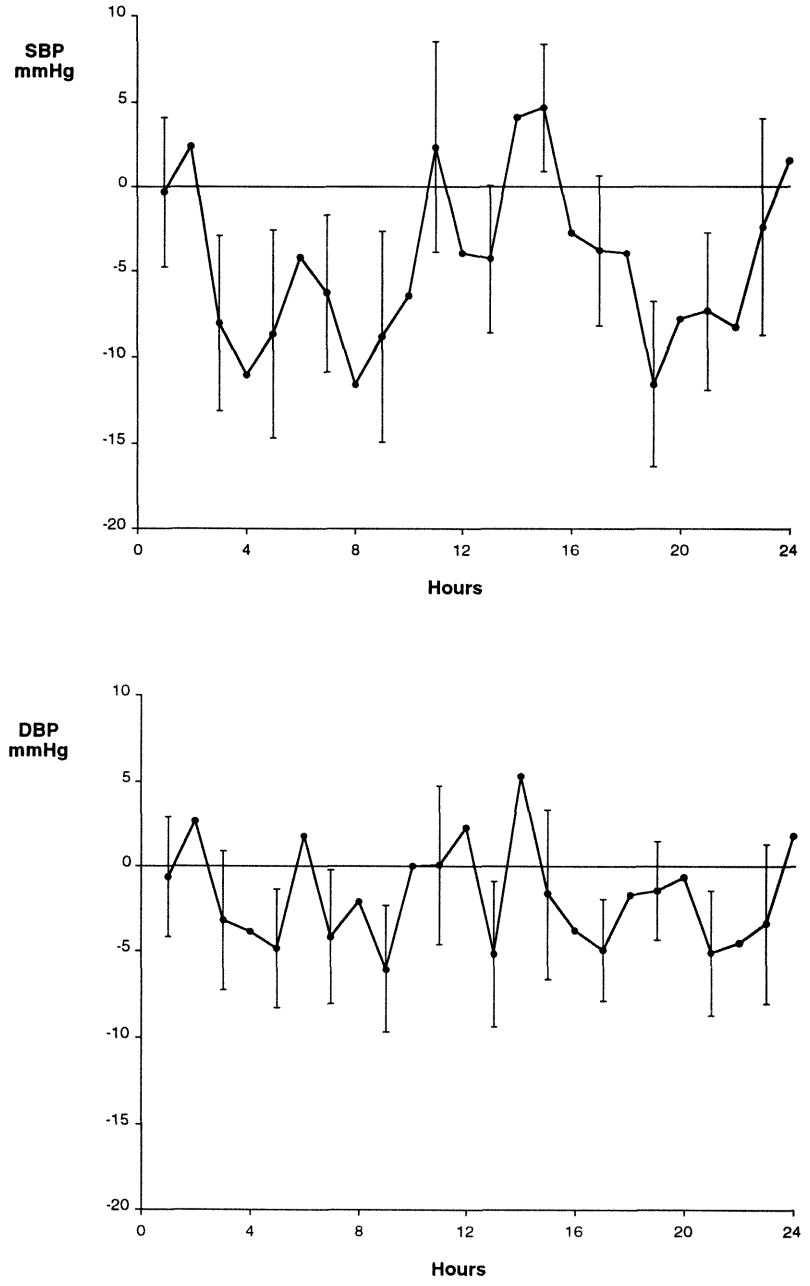


Fig 4.4 Subtraction plot of mean hourly SBP (upper panel) and DBP (lower panel) on placebo phase (low sodium) minus that on the sodium-supplemented phase (high sodium). Values are expressed as means $\pm$ SEM.

sodium phase (PRA difference 0.36 ng/ml/hour, CI 0.14 - 0.57 ng/ml/hour; $p < 0.01$; aldosterone difference 71 ng/ml, CI 11 - 131 ng/ml, $p < 0.05$).

Relationship of BP change to other variables

There was an inverse relationship between the changes in PRA and the changes in ambulatory SBP ($r = -0.61$, $p = 0.01$) and ambulatory DBP ($r = -0.53$, $p < 0.05$) between intervention phases, although no such relationship was found with clinic BP changes. There was no correlation between changes in PRA and age of subjects.
On examining the relationship between the BP fall on a low sodium intake and age, change in sodium excretion and change in PRA level on multiple regression analysis, with these 3 independent variables entered into the equation, the fall in 24h SBP and DBP was significantly related to increasing age and lower PRA level (24h SBP fall = 92-0.09[U_{sodium} diff]-1.5age-18[PRA_{diff}]; $p=0.01$, $R^2=48\%$; and 24h DBP fall = 59-0.03[U_{sodium}diff]-0.91age-8.1[PRA_{diff}]; $p=0.02$, $R^2=44\%$) although the fall in clinic SBP remained weakly related to increasing age (clinic SBP=121-0.26[U_{sodium}diff]-2.1age-4.8[PRA_{diff}]; $p=0.06$, $R^2=28\%$).

Discussion

This study has shown that in elderly hypertensive subjects a moderate reduction in sodium excretion of almost 80 mmol/24h for 5 weeks resulted in a significant fall in clinic supine SBP of 8 mmHg. The duration of sodium restriction used in this study has been considered sufficient to fully demonstrate the effects on BP predicted from observational studies. Although supine DBP, standing SBP and 24h SBP and DBP levels were lower following sodium restriction, the reductions were not significant. On going from the high to low sodium phase the expected increase in PRA and aldosterone levels were seen. The low sodium diet was well tolerated with only one subject being excluded because of poor compliance. In particular there were no complaints or findings of postural hypotension, a potential concern of a low sodium intake in elderly persons (249, 250).

Degree of sodium restriction

Sodium excretion during the high sodium phase (174 mmol/24h) was similar to the subjects normal excretion (164 mmol/24h), ie, prior to the run-in period. These levels of sodium excretion are similar to those reported in younger adults in the UK of 150 mmol/24h (116,130) and for elderly persons in Belgium where levels of 161 to 188 mmol/24h for men and 124-160 mmol/24h for women have been found (152). The degree

of sodium reduction obtained, as measured by the urinary sodium excretion rate and on dietary records, in the present study was achieved using regular dietary advice from a dedicated study dietician over several months and was similar to that achieved in many other studies of moderate sodium restriction (186,193,194,187,207). Greater reductions in dietary sodium intake would entail more intensive dietary counselling and more radical dietary changes risking poor dietary compliance and perhaps poor tolerability. A severe reduction in sodium intake in elderly persons may greatly increase their risk of developing postural hypotension (249). Adapting to a low sodium diet is probably mediated by altered experience of tasting salty food and changes in cognitive expectations rather than by physiological changes associated with alterations in the amount of sodium chloride available to the body (649a). This process of adaptation may take some weeks (649a), hence in those subjects reluctant or unable to rapidly reduce their use of sodium chloride at the table or in cooking, use sparingly of a low sodium salt substitute was encouraged with the ultimate aim of stopping this altogether. The degree of sodium restriction achieved in this study of almost 80 mmols/24 hours was well tolerated and complied with by nearly all subjects. Applegate et al (419) have previously highlighted the difficulties in maintaining even a moderate degree of sodium restriction for long periods as part of a non-pharmacological regimen for BP reduction in elderly hypertensives. The degree of sodium restriction aimed for in this study was at a level that could be achieved by the majority of subjects and maintained in the long term.

Clinic BP changes

The degree of sodium reduction achieved in this trial of almost 80 mmols/24 hours after five weeks lead to a significant decrease in supine clinic SBP only. The 8 mmHg (4.5%) fall in clinic supine SBP achieved was of the same order as, but not greater than, that reported in younger hypertensive subjects undergoing a similar degree of sodium restriction. MacGregor et al (186) reported a 7 mmHg (6%) fall in clinic supine SBP with a reduction of 76 mmols/24 hours in sodium intake for a similarly size group of younger hypertensive patients. The Australian National Health Study (193) found sitting SBP to be fell by 6 mmHg (3.9%) following a mean decrease in sodium intake of 52 mmols/24 hours. In an overview of trials in younger hypertensive subjects with a mean reduction in sodium excretion of 76 mmols/24 hour, Cutler et al (168) reported a fall in SBP of 4.9 mmHg. The more modest changes found in DBP are similar to those reported in other studies by Niarchos et al (649) and in the Australian Dietary Salt Study (193).

Using the equation provided by Law et al (169) in their analysis of data from trials of sodium reduction it could be predicted that in the present study, for the degree of sodium restriction achieved and the age and initial BP of the subjects studied, a reduction in SBP of 11 mmHg and in DBP of 4 mmHg would have been expected. However, despite the present study having the power to detect such a significant change in BP this was not found after five weeks of sodium restriction although the 95% confidence limits for changes in supine BP do embrace these estimates; a larger study may have shown the predicted changes. Due to age related physiological changes in general and renal pathophysiology in particular (see below) it may not be appropriate to extrapolate from studies in younger subjects to the elderly. Although in younger hypertensive persons a period of 4-5 weeks of sodium restriction is sufficient to achieve the predicted BP effects (169) this may not be so in the elderly where a longer period of sodium restriction may be required.

Ambulatory BP changes

In contrast to the significant fall in clinic SBP with sodium restriction, the decrease in 24 h ambulatory BP levels were smaller and not statistically significant. However, the confidence intervals for the BP fall on the low sodium intake were similar for both measurements of BP, were relatively wide and overlapped so it is uncertain if a true difference between clinic and ambulatory BP responses to sodium restriction exists. Examination of the subtraction plot of mean hourly SBP differences between low and high sodium phases show that for several hours of the day, significant reductions in SBP of 8mmHg or more occur.

Similar differences to those found in the present study between clinic and ambulatory BP monitoring have however been reported by Moore et al (196) who used greater extremes of sodium restriction and loading in middle aged hypertensive subjects but over a much shorter period.

Variability in BP response to sodium restriction

Although this study group consisted of those who theoretically might demonstrate the largest hypotensive response to sodium restriction there was, as reported in previous studies, a heterogeneous response (187-194). Four subjects had higher clinic SBP recorded during the low sodium phase, while six on 24-hour ambulatory monitoring had either no change or an increase in BP on the low sodium compared to the high sodium phase. However, only two subjects demonstrated an increase in both clinic and ambulatory BP on the low sodium phase with overall no significant correlation between clinic and ambulatory

BP changes. These contrasting changes depending on the method of measurement make the concept of salt sensitivity less attractive and lend support to the notion that the variation in BP response is partly, or largely, due to the variation in BP itself rather than to characteristics of the subjects. Of the variables studied, ie, initial BP level, changes in sodium excretion, changes in PRA and age, only the latter two were related to the 24 h ambulatory BP changes. It has been hypothesised that the BP reduction following sodium restriction may depend on the degree of blunting of the PRA response (650). This hypothesis was supported in the present study by the finding of an inverse correlation between changes in 24-h ambulatory SBP and DBP and changes in PRA levels from the high to the low sodium phase i.e. a greater BP fall was associated with a lower plasma renin response to sodium restriction; however, no such relationship was found between changes in clinic BP and PRA. The magnitude of the fall in 24 h ambulatory SBP and DBP on the low sodium intake was significantly and independently related to increasing age and the lower PRA response.

Effect of gender

The effect of gender on the BP response to sodium restriction could not be adequately assessed in this study because of the small number of males participating. Both Nestel et al (173) and Kumanyika et al (171) in normotensives have shown moderate sodium restriction to have a greater effect on SBP reduction in females compared to males.

Effect of age

Within the age range studied, 66-79 years, increasing age was weakly correlated with a greater fall in clinic SBP and 24h ambulatory SBP and DBP in response to sodium restriction which was not fully explained by changes in PRA or the level of urinary sodium excretion. The number of subjects studied and the narrow age range preclude any great weight being attached to these correlations. However a greater hypotensive effect of sodium restriction with increasing age has been reported in other studies (193,194,209); possible reasons for this are discussed below.

Biochemical changes

Although a significant reduction in PRA and plasma aldosterone levels was seen during the high sodium phase the percentage change in PRA was much smaller than that reported by MacGregor et al (186) for a similar degree of sodium restriction. They reported a 71% increase in PRA compared to the 41% increase in PRA levels seen in the

present study during the cross-over phase. Their subjects were however younger, the older age of subjects in the present study may have been responsible for some blunting of the PRA response (234, 235). Despite this attenuated PRA response to sodium restriction the hypotensive response was no greater than that reported in MacGregors study.

Possible mechanisms for the hypotensive effect of sodium restriction

Most hypotheses proposed to explain the tendency for an increased sodium intake to raise BP in certain persons are based on abnormal renal handling of sodium excretion. The pressure natriuresis hypothesis suggests that any stimulus leading to an elevation of BP, for example an increase in cardiac output or peripheral resistance, will cause an increase in urinary sodium and water excretion reducing blood volume until BP returns to normal (651). A renal abnormality in excreting a salt load would lead to BP being set at a higher level to allow for its excretion. de Wardener and MacGregor (652) hypothesised that in subjects whose renal excretion of sodium was impaired, there was a circulating sodium transport inhibitor secreted which, although leading to increased renal sodium excretion, also led to the development of hypertension. Blaustein (653) suggested that this sodium transport inhibitor could increase sodium concentration inside vascular smooth muscle cells by inhibiting sodium-potassium ATPase activity which in turn would raise intracellular calcium concentration through suppression of the sodium-calcium exchange and increase the tone of vascular smooth muscle leading to increased peripheral resistance and hypertension. In normotensive and hypertensive patients who respond with a rise in BP to sodium loading this has been shown to be associated with an increase in sodium retention, cardiac output, increased vascular resistance and to a smaller fall in PRA (180,184,654).

With increasing age, PRA and renal blood flow decrease; the fall in PRA is more marked in elderly hypertensives than normotensives and may be related to a decrease in renal mass, hyaline degeneration of the afferent renal arterioles and a decrease in juxtaglomerular beta-adrenergic receptor response (248). Hence older hypertensives, should have a reduced stimulation of PRA release on reducing sodium intake compared to younger persons and therefore less stimulation of angiotensin and aldosterone release, resulting in no change, a fall or an attenuated rise in BP depending on the degree of renin suppression. These age related changes in renal function may also result in a diminished capacity to excrete a given sodium load resulting in a greater sensitivity of BP to sodium intake (229).

Conclusions

This study has demonstrated that moderate sodium restriction in some elderly hypertensive subjects can significantly reduce clinic supine SBP. The reduction in mean 24-hour BP was not significant but confidence intervals were wide and similar to those found for changes in clinic BP on the low compared to high sodium intake. No predictors of the clinic BP response to sodium restriction were identified but a greater fall in 24 h ambulatory SBP and DBP was related to increasing age and a reduced stimulation of PRA to sodium restriction.

Although sodium restriction may be of only small overall benefit in reducing BP in elderly hypertensives, some individuals exhibit a marked hypotensive response. A moderate reduction of sodium intake can be recommended along with other non-pharmacological methods in an attempt to reduce BP in elderly hypertensive subjects.

CHAPTER 5

EFFECT OF POTASSIUM SUPPLEMENTATION ON BLOOD PRESSURE IN ELDERLY HYPERTENSIVE SUBJECTS

Summary

Introduction

An inverse correlation between potassium intake and BP levels has been noted in many epidemiological studies of middle-aged persons.

Aims

To determine the effects of a 60 mmol/day potassium chloride supplement on clinic and 24-hour ambulatory BP levels in elderly untreated hypertensive patients.

Methods

The study design was of a double-blind, randomised, placebo controlled, cross-over trial lasting eight weeks preceded by a four week run-in period. 18 untreated elderly hypertensive subjects, mean age of 75 years, range 66-79 years were studied. Prior to entry into the study each individuals daily dietary electrolyte intake was established and this was continued during the run-in and intervention periods. Following the four week run-in period subjects received potassium supplements or matching placebo, each for four weeks.

Following the cross-over trial an open, uncontrolled study of the effects of 48 mmol/day potassium chloride supplement taken for 4 months on 24-hour ambulatory BP was carried out in 8 subjects.

Results

Compared to the placebo phase after four weeks of potassium supplementation (60 mmol/24 h) there was a significant fall of supine clinic BP (SBP 10 mmHg, 95% CI, 3-17 mmHg, p = 0.01; DBP: 6 mmHg, CI 1-11 mmHg; p = 0.03), of standing SBP (8 mmHg, CI 1-15 mmHg; p = 0.02) and of 24-hour ambulatory SBP (6 mmHg, CI 1-11 mmHg; p = 0.02). There was no significant change in clinic standing DBP, 24-hour ambulatory DBP or pulse rate. Plasma renin activity levels increased by 52% and body weight fell 1.7 kg following potassium supplementation. Compared to placebo 24-hour urinary potassium excretion increased by 39 mmols/24-hours during the active phase of the study but urinary sodium excretion was unchanged.

In the 8 subjects undergoing the open study, after 4 months of 48 mmol/24 h potassium supplement, there was no significant difference in 24h ABP levels compared to 1 month of a 60 mmol/day potassium supplement (SBP: -13.1+11.9 mmHg v -10.6+7.6

mmHg, respectively; DBP: -7.9+11.5 mmHg v -6.9+6.8 mmHg, respectively) and urinary potassium excretion was 12 mmol/24h lower than during 1 month of 60 mmol/day

Conclusions

A 1 month 60 mmol daily supplement of potassium chloride reduced both clinic and 24-hour ambulatory SBP in elderly hypertensive patients. The fall in 24h ambulatory SBP was maintained in a sub-set of subjects after 4 months of a 48 mmol/day potassium supplement.

Introduction

Many epidemiological studies in young and middle-aged persons have, as discussed in section 1.3.2, reported an inverse correlation between potassium measured as dietary intake, urinary excretion or plasma levels and BP levels. In some of these studies, including the large InterSalt study (120) the correlation between potassium and BP was stronger than that between sodium and BP. The sodium:potassium ratio may be an even stronger correlate of BP than either cation alone (282). It has been suggested that a high sodium-low potassium environment is a cardinal factor in the development and maintenance of essential hypertension (655). A contrast has also been made to the low sodium-high potassium environment man spent the majority of his evolutionary time in as a hunter-gatherer and the present time when a relatively high sodium-low potassium diet is consumed by most Westernised populations (655).

Variations in potassium intake have not only been associated with BP levels , Tobian et al (656) have reported protective effects of a high potassium intake for renal lesions and strokes, independent of BP changes, in salt fed rats. In addition Khaw et al (657), found in man that a higher potassium intake was associated with a lower death rate from stroke independent of BP levels.

In 1928 Addison reported that the giving of potassium salts to hypertensive patients lowered their BP (273), since then many (315, 321, 325-327) but not all studies (317, 322, 324) have shown potassium supplementation can reduce BP in hypertensive persons. A recent overview (332) of such trials estimated that SBP could be reduced by 8 mmHg and DBP by 4.5 mmHg with an increase in potassium excretion of 86 mmol/24h. Despite the evidence for a hypotensive effect of an increased potassium intake there have been no studies reported on the effect of potassium supplementation in elderly hypertensive persons. Not only is hypertension highly prevalent in this age group but changes in nutrition may predispose them to a particularly low potassium intake (334).

Hypothesis

Potassium supplementation reduces both clinic and ambulatory BP in elderly untreated hypertensive subjects.

Study objectives

1 To examine clinic and 24-hour ambulatory BP changes following potassium supplementation.

2 To examine changes in plasma renin activity following potassium supplementation and their relation to changes in BP.

3 To examine the long term effect of potassium supplementation on 24-hour BP

Methods

Subjects

Subjects were considered for entry into this trial using the same inclusion and exclusion criteria given in chapter 4 for the sodium restriction study. Eighteen subjects, mean age 75 y, range 66-79 y with essential hypertension SBP $\geq$ 160 mmHg and/or DBP $\geq$ 95 mmHg) diagnosed as previously described in chapter 4, were recruited from general practitioners lists (n = 9) and hospital medical outpatient clinics (n = 9). Five subjects were male and 10 had previously been taking anti-hypertensive medication which was stopped 6 weeks prior to the BP screening visits.

Procedures

Study design

During a four week run-in period subjects underwent two further sets of clinic BP measurements to establish baseline BP levels. Subjects then entered a double-blind randomised placebo controlled cross-over trial of four weeks flavoured potassium chloride elixir taken as 10 mls three times daily giving a total of 60 mmols/24 hours or took an equivalent measure of matching flavoured placebo. The potassium chloride solution was prepared by the pharmacy department of Leicester Royal Infirmary. To make the potassium chloride solution more palatable and to render the taste of potassium and placebo solutions similar, a strong cherry flavour was added to each.

Randomisation to potassium chloride or placebo was performed in blocks of 6 with sealed cards being held in the hospital pharmacy department. Subjects were asked to take the elixir regularly between 07:00-08:00 hrs, 13:00-14:00 hrs and 19:00-20:00 hrs including on the day of the clinic visit. The elixir was supplied every fortnight in 2 bottles with sufficient for 3 weeks in case of delayed return to clinic. Acceptable compliance with

taking the elixir was defined as returned containers showing less than 20% of the expected amount.

All subjects with their spouses, where appropriate, underwent a dietary assessment by the study dietician during the run-in phase to assess their usual sodium and potassium intake. Participants were given information on foods and recipes with the aim of maintaining a near constant intake of their usual level of electrolytes during the study period. Subjects were seen at each clinic visit by the dietician to assess their dietary intake and to answer any queries relating to their diet.

Measurements

The following measurements were taken in clinic at two weekly intervals from the start of the run-in phase, (1) supine and standing BP, (2) pulse rate and (3) body weight; all measurements being made using the methods as previously described in chapter 4. All clinic visits and measurements were performed between 09:30 and 11:30 hrs.

At entry and at the end of each four week phase supine blood samples were taken for PRA and electrolyte estimation after 15 minutes supine rest. During the last week of each intervention phase subjects were asked to supply two 24-hour urine collections for estimation of urinary volume, electrolyte and creatinine excretion. Within 48 hours of the end of each four week phase 24-hour non-invasive ambulatory BP monitoring was performed.

BP readings

All clinic BPs were taken by the same investigator (MDF) using a random zero sphygmomanometer. The mean of three readings after five minutes resting supine and after one minute standing were taken as previously described.

24-hour non-invasive ABPM was performed in 16 subjects using the Spacelabs 90207 monitor. The monitor was attached to the same arm that was used for clinic BP measurements, and was programmed to take readings at 30 minute intervals during the 24-hour period. Methods and criteria for checking the BP monitor against the standard sphygmomanometer, for accepting satisfactory ABPM recordings and any editing of records were as previously described in chapter 4. Daytime period for the 24-hour ABPM was arbitrarily defined as being from 10:00 hrs - 19:59 hrs and the night-time period from midnight to 05:59 hrs.

Assay for plasma renin activity

Supine blood samples taken for PRA were collected in glass tubes containing EDTA and placed directly into ice and then centrifuged for 15 minutes at 3000 rpm in a pre-cooled centrifuge set at 4°C. Supernatant was decanted and stored at -70°C. Samples were analysed for PRA in two batches, all samples for one subject being analysed in the same batch and by the same investigator (MDF). PRA analysis was carried out by radioimmunoassay of angiotensin I (biodata renin MAIA kit, Serono Diagnostics Ltd, Surrey). The intra-assay coefficient of variation was 4.1% and the inter-assay coefficient of variation 8.7%. Aliquots from 24 h urine samples were analysed for sodium, potassium and creatinine as described in Chapter 4.

Open study of long-term potassium supplementation

On completion of the 8 week double-blind placebo controlled cross-over study the last 10 participants recruited were invited to enter an open study of the effects of long term potassium supplementation on 24h ABP levels. Eight subjects (mean age 77y, 7 female) accepted and were asked to supplement their usual diet with 48 mmol of potassium daily (SandoK, 2 tablets twice daily [Sandoz, Camberley, Surrey]). After 4 months 24h ABP was carried out and two 24h urine collections made for estimation of urinary electrolyte excretion.

Statistical analysis

The cross-over study had a power to detect a clinic BP fall of 10/6 mmHg with a power of 85% at the 5% level taking the SD of the difference for clinic SBP as 14 mmHg and for clinic DBP as 7 mmHg (647). With a sample size of 16 patients using 24-h ABPM a difference of 5 mmHg in SBP and DBP could be detected with a power of 85% assuming an SDD of 6 mmHg for this method, as described in chapter 3. Differences between placebo and potassium phases were analysed by the method of Hills and Armitage for a two period cross-over design trial looking for time and treatment carry-over effects (648). Linear correlations of normally distributed data were calculated using Pearson's correlation coefficient. Correlations between change of a variable and its initial value were adjusted by taking the mean of the initial and final values [Oldhams transformation] (658). Values are presented as mean ± SD with 95% CI where indicated. Statistical significance was taken at the 5% level.

Results

Cross-over study

All 18 subjects completed the study with no adverse effects reported. Compliance for the trial medication was good, as judged by the volume of elixir returned at each clinic visit being within 10% of that expected.

Clinic BP changes

Clinic BP and pulse rate values for the run-in and placebo phases were similar as shown in table 5.1 and 5.2. Compared to the placebo phase following four weeks of potassium supplementation (see table 5.1 and figure 5.1) there was a significant fall in clinic supine SBP of 10 mmHg (95% CI, 3-17 mmHg, $p = 0.01$) and in supine DBP of 6 mmHg (95% CI, 1-11 mmHg, $p = 0.03$) and in standing SBP of 8 mmHg (95% CI, 1-15 mmHg, $p = 0.03$). Standing DBP and pulse rate were similar in all three phases. No significant period ($p > 0.3$) or interaction effects ($p > 0.3$) were found in the analysis of the clinic or ambulatory BP changes.

	SBP (mmHg)	DBP (mmHg)	Pulse rate (beats/min)
Clinic supine BP (n = 18)	187 ± 20	96 ± 8	74 ± 8
Clinic standing BP (n = 18)	179 ± 19	101 ± 10	83 ± 10
24 h ABP (n = 16)	160 ± 16	91 ± 9	76 ± 8

Table 5.1: Baseline clinic supine and standing systolic blood pressure (SBP) and diastolic blood pressure (DBP) for all 18 patients with the 24-h ambulatory blood pressure and pulse rate values of the 16 patients in whom this was performed. Values are expressed as means ± SD

Orthostatic BP changes

There was no significant difference in the orthostatic (supine - standing BP) response between run-in: 9 (CI 3 to 15) / -6 (-10 to -1) mmHg, placebo: 9 (2 to 15) / -3 (-7 to 1) mmHg and potassium 7 (2 to 12) / -6 (-9 to -2) mmHg phases.

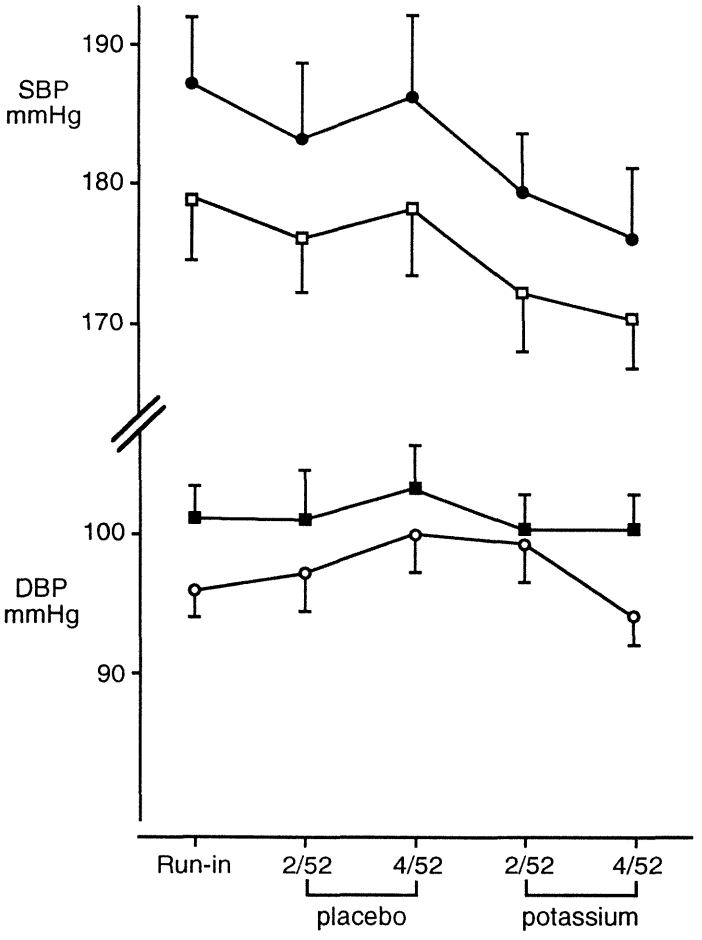


Fig 5.1. Supine systolic blood pressure (SBP ●), supine diastolic blood pressure (DBP ○), standing SBP (□) and standing DBP (■) values during the run-in, 4-week placebo and 4-week potassium phases for the 18 untreated elderly hypertensive patients. Values are expressed as means ± SEM.

Table 5.2

Changes in clinic (18 patients) and 24-h ambulatory blood pressure and pulse rate (16 patients) between the placebo and potassium phases. *P* values are given for differences between the placebo and potassium phases.

	Placebo	Potassium	Difference	*p* value
Clinic Supine BP (n = 18)				
SBP (mmHg)	186 ± 24	176 ± 20	10 ±14 (3-16)	0.01
DBP (mmHg)	100 ± 14	94 ± 20	6 ± 10 (1-11)	0.03
Pulse rate (beats/min)	74 ± 9	73 ± 11	2 ± 8 (-3-6)	NS
Clinic Standing BP (n = 18)				
SBP (mmHg)	178 ± 19	170 ± 15	8 ± 14 (1-15)	0.03
DBP (mmHg)	103 ± 13	100 ± 11	4 ± 7 (0-7)	NS
Pulse rate (beats/min)	80 ± 8	78 ± 12	3 ± 12 (-4-9)	NS
24 Hr ABP (n = 16)				
SBP (mmHg)	160 ± 18	154 ± 15	6 ± 9 (2-11)	0.02
DBP (mmHg)	89 ± 12	87 ± 13	3 ± 6 (-1-6)	NS
Pulse rate (beats/min)	75 ± 9	74 ± 9	2 ± 6 (-3-6)	NS
Daytime ABP 1000-1959 hrs (n = 16)				
SBP (mmHg)	167 ± 16	159 ± 13	8 ± 8 (4-12)	0.02
DBP (mmHg)	95 ± 13	93 ± 12	3 ± 6 (0-7)	NS
Night-time ABP 2400-0559 (n = 16)				
SBP (mmHg)	147 ± 25	139 ± 22	7 ± 12 (0-14)	0.05
DBP (mmHg)	78 ± 16	75 ± 15	3 ± 11 (-3-9)	NS

Values are expressed as means ± SD with 95% confidence intervals. SBP, Systolic blood pressure; DBP , diastolic blood pressure; NS, not significant.

24 Hour ABPM

Of the 18 subjects one refused 24-hour ABPM and in another insufficient readings (< 85%) were obtained. There was no difference in mean 24-hour BP between the run-in and placebo phases (160 ± 16/ 91 ± 9 vs 160 ± 18/ 89 ± 12 mmHg, respectively). A subtraction plot of the hourly mean BP differences between the potassium and placebo phases (mean hourly BP during potassium - mean hourly BP during placebo) for the 16 patients are shown in figure 5.2.

24-hour ambulatory SBP was lower (6 mmHg, 95% CI, 1-11 mmHg, $p = 0.02$) following the potassium compared to the placebo phase and though 24-hour DBP showed a similar trend after potassium with a fall of 3 mmHg (95% CI, -1 to + 7 mmHg) this difference was not statistically significant. In addition 24-hour pulse rates were unchanged throughout the study.

Daytime (10:00-19:59 hrs) SBP, but not DBP was lower by 8 mmHg (95% CI, 2-14 mmHg, $p < 0.02$) during the potassium than the placebo phase of the trial. A similar pattern was seen for nocturnal BP changes where the difference in SBP (potassium - placebo) was 7 mmHg (CI 0-14 mmHg, $p = 0.05$), although nocturnal DBP was unchanged between phases. However, the mean fall in SBP and DBP between day and night (ie, the degree of nocturnal dipping) was similar during potassium supplementation or placebo (19 ± 14/18 ± 10 mmHg and 20 ± 19/16 ± 14 mmHg, respectively).

Clinic supine SBP values were significantly higher than daytime ABPM values in both phases of the trial (mean SBP difference 19 mmHg, CI 11-26 mmHg, $p < 0.01$ during the potassium phase and 22 mmHg, CI 12-32 mmHg, $p < 0.01$ during the placebo phase). For DBP the clinic - daytime difference of 5 mmHg during the potassium phase was not significant although for the placebo phase a 7 mmHg difference (CI 2-12 mmHg, $p < 0.05$) was significant.

Correlations between clinic and ambulatory BP changes

A significant but weak correlation was found between the changes in SBP and 24-hour ambulatory SBP ($r = 0.52$, $p < 0.05$) from placebo to potassium phase. No significant correlations were found between the changes in clinic BP or ABPM values and the baseline BP values adjusted by Oldham's transformation.

Individual BP changes

The individual changes in mean clinic and mean 24-hour ambulatory SBP and DBP levels between placebo and potassium phases are shown in figure 5.3. Compared to

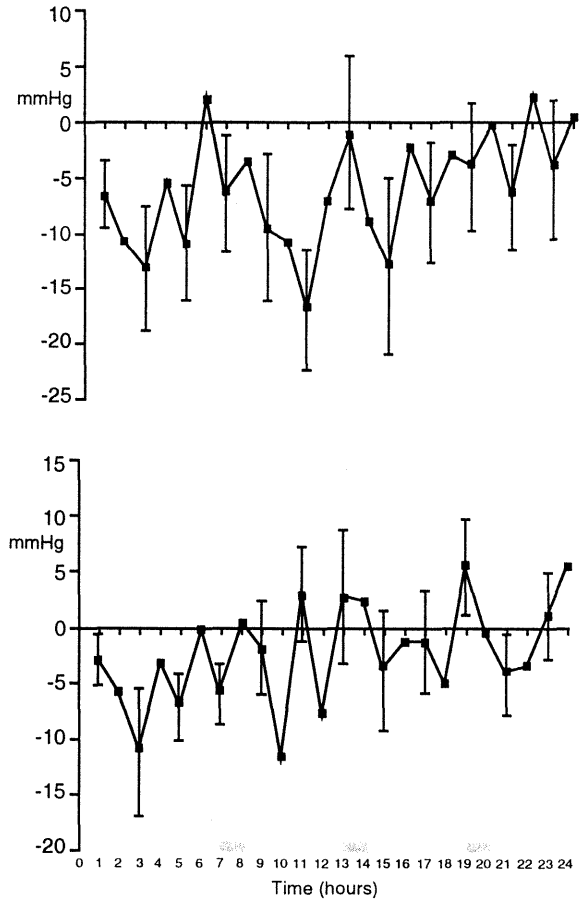


Fig 5.2. Placebo subtracted 24-h systolic (upper panel) and diastolic (lower panel) BP profiles during potassium supplementation (n=16). Negative values indicate BP lower on potassium. (☎) indicates time at which potassium was taken. Alternating standard error bars are shown; values are mean ± SEM.

placebo, there was either no change or an increase in clinic SBP in six subjects (range 0-9 mmHg) and in clinic DBP in five subjects (range 1-12 mmHg) during potassium supplementation. On mean 24-hour ABPM values potassium supplementation did not reduce SBP in four subjects or DBP in six subjects. In only two subjects was there an increase in both clinic and mean ambulatory BP levels during potassium supplementation.

Biochemical changes

Biochemical changes are shown in table 5.3. Serum potassium showed a small but significant rise following potassium supplementation but no patients became hyperkalaemic (potassium >5.6 mmol/l). Serum sodium, urea and creatinine levels were unchanged throughout the trial. PRA was higher following the potassium compared to the placebo phase (the difference being 0.69 ng/ml/hr, 95% CI, 0.21-1.17 ng/ml/hr; $p < 0.01$). PRA levels during run-in and placebo phases were similar.

Urinary electrolyte changes

Urinary electrolyte changes between all three phases are shown in table 5.3. The mean values for the two 24-hour urine collections were analysed. There was no significant difference in 24-hour urinary electrolyte excretion between the run-in and placebo phases. The rise in urinary potassium excretion during potassium supplementation was 39 mmols/24 hrs (29-48 mmols/24 hrs, $p < 0.001$) and though values increased in all patients the response was variable (range 6-81 mmols/24 hrs). As expected a significant rise was also seen in the urinary potassium : creatinine ratio during the potassium supplement phase. Urinary sodium excretion showed a small but non-significant increase during the potassium phase (13 mmols/24 hr, CI -15 to 41 mmols/24 hr, $p = 0.4$).

Changes in body weight

Body weight fell following potassium supplementation compared to placebo by 0.7 kg (0.1-1.3 kg; $p = 0.02$) from 72.0 ± 7.9 kg to 71.3 ± 8.0 kg.

Correlations between changes in BP and changes in urinary electrolyte excretion and plasma renin activity

No significant correlations were found between the changes in clinic or the changes in 24-hour ABPM values and the changes in urinary potassium excretion, the sodium : potassium ratio or serum PRA values.

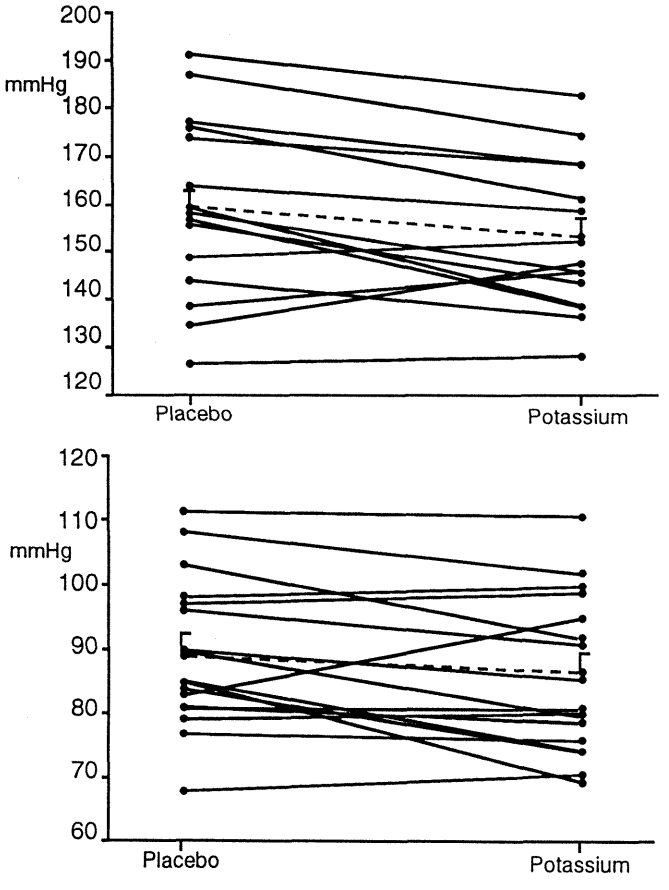


Fig 5.3. Individual 24-h systolic (upper panel) and diastolic (lower panel) BP responses following potassium supplementation (n=16). (·----·) mean changes for the whole group.

	Run-In	Placebo	Potassium	*p* value
Urine				
Potassium (mmol/24 hr)	63 ± 27	60 ± 23	99 ± 27	< 0.01
Potassium : Creatinine ratio	6.8 ± 1.9	7.0 ± 2.8	11.6 ± 3.4	< 0.01
Sodium (mmol/24 hr)	115 ± 40	123 ± 45	136 ± 52	NS
Sodium : Creatinine ratio	12.6 ± 3.6	14.0 ± 3.7	16.0 ± 8.5	NS
Volume (ml/24 hr)	1444 ± 527	1567 ± 599	1587 ± 739	NS
Sodium : Potassium ratio	2.02 ± 0.86	2.23 ± 1.00	1.45 ± 0.71	<0.01
Weight (kg)	71.1 ± 7.5	72.0 ± 7.9	71.3 ± 8.0	0.02
Serum				
Potassium (mmol/l)	4.2 ± 0.4	4.3 ± 0.3	4.4 ± 0.3	0.3
Sodium (mmol/l)	141 ± 2	140 ± 2	141 ± 2	NS
Creatinine (umol/l)	88 ± 12	87 ± 13	90 ± 15	NS
PRA (ng/ml/hr)	1.45 ± 0.86	1.32 ± 1.01	2.01 ± 1.56	<0.01

Table 5.3: Serum electrolyte, creatinine, plasma renin activity, urinary electrolyte and body weight changes during the run-in, placebo and potassium phases (18 patients). *P* values are given for the differences between the placebo and potassium phases.

Open study of long-term potassium supplementation

The 24h ABP levels and 24h urinary sodium and potassium excretion at the end of the run-in phase, cross-over placebo and potassium supplementation phases and after 4 months of 48 mmol/24 h potassium supplementation for the 8 subjects who completed the open study are shown in table 5.4 and figure 5.4.

For these subjects there was a significant reduction in mean 24h SBP between the placebo phase and after 1 month of potassium elixir (-11±8 mmHg; $p = 0.01$) and in daytime SBP and DBP (-12±7 mmHg, $p < 0.01$ and -7±7 mmHg; $p = 0.04$, respectively) but not in night-time BP. After 4 months of SandoK (48mmol/day) there was no significant difference in 24 h ABP levels compared to 1 month of 60 mmol/day potassium elixir. Compared to the placebo phase after 4 months of SandoK mean 24h systolic BP remained significantly lower (-13±12 mmHg; $p=0.04$) as did daytime SBP (-15±13 mmHg; $p = 0.02$) although the changes in 24h DBP (-7.9+11.5 mmHg; $p = 0.1$) and night-time BP were not significant.

Urine electrolytes

Urinary electrolyte changes are shown in table 5.4. In the cross-over study the 24h urinary potassium excretion of the 8 subjects during the potassium supplementation phase was 102 mmol/24h (46±17 mmol/24h greater during the placebo phase). After 4 months of 48mmol SandoK, 24h urinary potassium was 90 mmol/24h, (34±25 mmol/24h greater than during the placebo phase, $p=0.02$). There was no significant difference in 24h urinary sodium excretion after 4 months of potassium supplements and during the placebo phase (74+17 v 92+28 mmol/24h, $p=0.1$)

Weight

Body weight for each phase is shown in table 5.4 . There was a significant fall in weight of 1.9+1.7 kg ($p = 0.02$) from the end of the cross-over period to the completion of the 4 month potassium phase.

	Run-in	Placebo	4 week Potassium 60 ml/24 h	4 months Potassium 48 ml/24 h
Blood Pressure & Heart Rate				
24 h SBP (mmHg)	162 ± 12	160 ± 6	147 ± 13	145 ± 14*
24 h DBP (mmHg)	90 ± 11	89 ± 11	83 ± 12	81 ± 9*
24 h heart rate (beats/min)	76 ± 8	75 ± 9	75 ± 14	76 ± 8
Urinary Electrolytes				
24 h Sodium (mmol/24 h)	103 ± 37	98 ± 28	98 ± 35	83 ± 17
24 h Potassium (mmol/24 h)	54 ± 14	56 ± 23	102 ± 28	90 ± 35*
Weight (kg)	72.1 ± 7.7	72.0 ± 7.9	72. 3 ± 9.1	71.3 ± 8.0*

* $p < 0.05$ v placebo

Table 5.4. Changes in 24 h BP, heart rate (HR), urinary electrolyte excretion and in weight for the 8 subjects who continued with potassium supplements for 4 months following the cross-over study (mean ± SD).

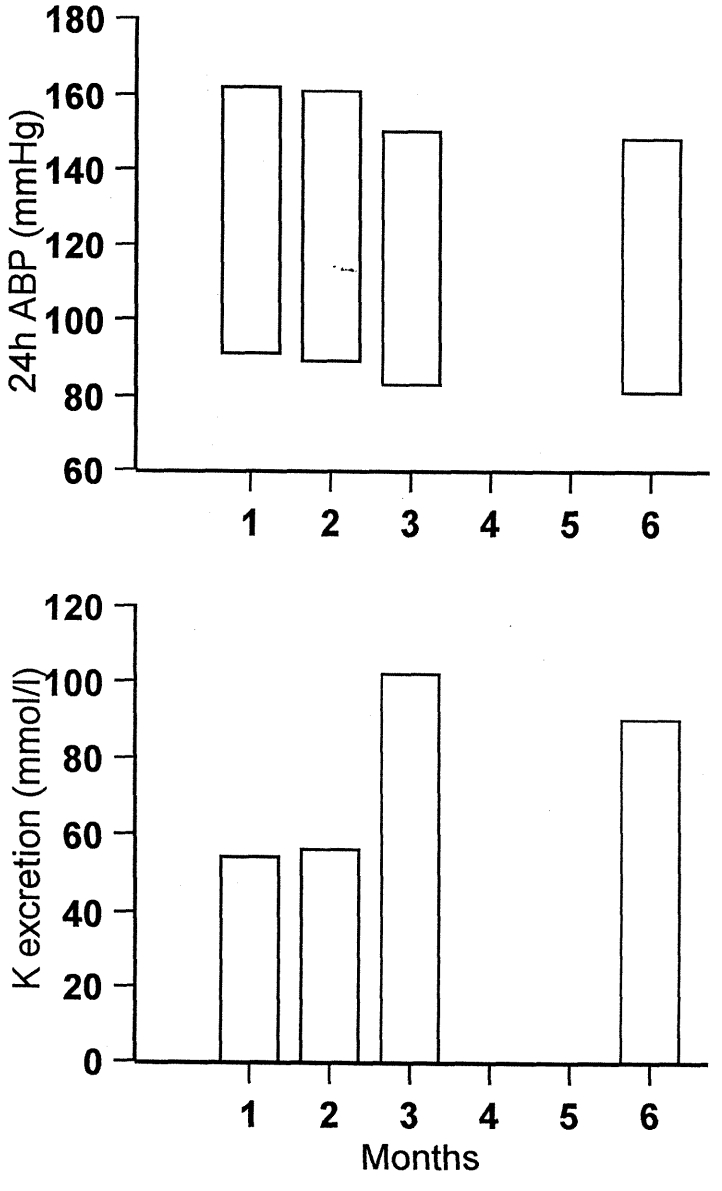


Figure 5.4: Change in 24 h BP levels with changes in 24 h urinary potassium excretion in the 8 subjects who continued with potassium supplement following the cross-over study

Discussion

This study has shown that an increase in potassium intake of 60 mmols/day for one month, resulted in a significant reduction of clinic and 24 h BP in elderly untreated hypertensive subjects. In a sub-group of subjects taking a lower potassium supplement of 48 mmol/day for a longer period of 4 months the hypotensive effect was maintained. The increased potassium intake was well tolerated with no adverse effects reported on direct questioning and no withdrawals from the study. In particular there were no complaints of dyspepsia or evidence of hyperkalaemia.

Cross-over study

Clinic BP changes

The decrease in clinic supine BP of 10/6 mmHg is similar to that reported in six studies of younger hypertensives that used an analogous study design and a similar degree of potassium supplementation (315, 316, 318, 320, 325, 326). The average fall in BP reported in these studies ranged from 39/17 mmHg to 2/0 mmHg with an average fall overall of 12/7 mmHg. This is similar to the clinic BP fall reported in the present study and suggests potassium supplementation has a similar effect in older as in younger hypertensive subjects. In comparison with pharmacological treatment this degree of BP reduction is similar to that achieved by a mainly diuretic based regimen in the EWPHE Study at three months (659). The greater fall in SBP than DBP with potassium loading has been previously noted (315) as has the time dependency of the response (322).

24-hour ABPM Changes

Potassium supplementation resulted in a significant decrease in 24-h ambulatory SBP but not DBP with a similar reduction in both daytime and night-time SBP. The hypotensive effect of potassium appears greater on clinic than ABPM levels whether daytime or 24-h values are compared. However, the mean fall in ambulatory SBP and DBP for the period during which clinic BPs are measured, i.e., 09:30-11:30 hrs, in the 16 patients in whom it was recorded was 12/4 mmHg, values similar to those recorded for these patients in clinic (11/6 mmHg).

The plot of placebo subtracted 24-hour ABPM values shows falls, more marked for SBP than DBP, following the three time periods when it was expected the potassium elixir would have been ingested. This raises the possibility that the hypotensive effect of a single

potassium load is of a few hours duration only. The chronic BP lowering action of potassium loading could thus be the result of repeated acute hypotensive episodes though this is highly speculative and requires further investigation.

In the only other report to date of potassium and ambulatory BP, Richards et al (195) studied the effects of potassium loading on 24 h intra-arterial BP levels in younger hypertensive subjects (aged 19-52 y). Despite the study lasting 4 weeks and achieving a urinary potassium excretion of nearly 200 mmol/24h no overall hypotensive effect was seen. There was however no significant change in PRA levels on the high potassium intake and the 24h BP measurements were performed in hospital with patients resting supine for 13 hours.

Relationship of BP changes to urinary electrolyte changes and PRA

In common with findings by Smith et al (317) and Siani et al (321), neither the changes in clinic or ABP levels were related to changes in urinary potassium, sodium excretion or PRA levels. Valdes et al (327) did however report that subjects responding with a BP fall to a potassium supplement of 64 mmol/day had a greater increase in PRA levels than non-responders. Blaufox et al (660) in the TAIM Study also found that the hypotensive effect of dietary electrolyte changes in younger mild hypertensive patients was directly related to the baseline PRA value.

Long-term potassium supplementation

As this was a small, open uncontrolled study, only changes in mean 24h ABP measurements were analysed as these are free of observer bias, placebo effect and as reported in chapter 3 exhibit reduced variability compared to clinic BP measurements. Despite a lower potassium supplement of 48mmol/24h which produced a urinary excretion of 90 mmol/24h, mean 24h ABP levels after 4 months were maintained at similar levels to those following just 4 weeks of a 60 mmol/24h potassium supplement. Sodium excretion remains similar throughout all phases of the study but with mean values similar to those seen during moderate sodium restriction (see Table 4.1) despite no specific advice to alter sodium intake. It is probable that the lower sodium intake after 4 months was related to the general advice to increase the consumption of food containing higher concentrations of potassium. eg, fruit and vegetables, which tend to have a lower sodium content. The low mean sodium intake during the run-in period may reflect the effect of discussing in general terms the possible role of dietary factors on blood pressure during the process of obtaining

informed consent required prior to participation in the study. There was also a small but significant reduction in weight over the 4 month open study which may have contributed to the reduction in BP. It has been estimated that weight loss of 1 kg is associated with a clinic BP fall of 1.6/1.3 mmHg (471), (probably less for change in 24 h ABPM) suggesting that the weight loss in this study would account for an ambulatory BP fall of no greater than 3/2 mmHg. This still leaves a substantial BP fall of 10/6 mmHg attributable to the potassium supplement. In a meta-analysis of potassium studies, Capuccio and MacGregor (332) also noted that a longer duration of treatment was associated with a greater hypotensive effect. In particular Siani et al (321) in younger hypertensive subjects have reported that the hypotensive effect of potassium supplements (48 mmol/24h) progressively increased with time up to 15 weeks when a fall in supine BP of 14/11 mmHg was recorded. A subgroup of these patients went on to take half the initial dose of potassium (24 mmol/24h) for a further nine weeks. Although BP levels increased on this dose they remained lower than during the baseline period. This study and the work presented here suggest that the hypotensive effect of potassium increases with time and that only modest increases in dietary potassium intake could have significant hypotensive effects if maintained over long periods. It is possible that a threshold level of potassium intake exists above which further increases have little hypotensive effect.

Mechanisms of the hypotensive effect of potassium

The hypotensive action of potassium may be related to its effects on the renin-angiotensin system and be reflected by changes in PRA as suggested by Svetkey et al (661). Increasing potassium intake can initially produce a natriuresis (316) which may account for the decrease in body weight and rise in PRA levels as seen in the present study. However many other studies have shown suppression of PRA levels with increased potassium intake (662-664), although Valdes et al (327), as in the present study also found a significant increase in PRA and fall in BP with potassium supplements. It has been reported that potassium supplementation becomes less effective at lowering BP as sodium intake decreases (317). It is postulated that with a usual sodium intake, potassium will cause a natriuresis but will also inhibit the expected release of renin, while on a low sodium intake where the stimulation to renin release will be greater, the natriuretic and renin suppressing effects of potassium will be attenuated (317). Ullian et al (665) have reported a fall in plasma volume and cardiac output during potassium supplementation. Subjects in the present study maintained orthostatic control of BP suggesting they were able to compensate

for any reduction in plasma volume or cardiac output induced by potassium supplementation that may have occurred. A natriuresis may have occurred initially during the active phase of this study which was not evident at the time of urine collections. However, a natriuretic effect is unlikely to fully explain the decrease in BP with potassium loading as both this study and others (315) have demonstrated that the hypotensive action increased with the duration of potassium supplementation. Other possible mechanisms for the hypotensive effect of potassium in addition to effects on sodium balance and the renin-angiotensin system are briefly discussed below.

Direct vasodilator effect

In contrast to the inhibition of the sodium potassium ATPase enzyme by a high sodium intake, there is evidence that an increased potassium intake enhances its activity and consequently leads to vasodilatation (666-668). Infusion of potassium into the brachial artery of humans causes forearm vascular resistance to decrease in a dose dependent manner (669,670). Because this vasodilatory effect of potassium is not affected by adrenergic antagonists (669), but is inhibited by ouabain, an inhibitor of the sodium potassium ATPase enzyme, the vasodilator action of potassium is probably mediated through the sodium potassium ATPase pump (665).

Stimulation of the kallikrein-kinin system

There is evidence that potassium stimulates the production of renal kallikrein an enzyme which catalyses the formation of the vasodilator hormone kallidin (327). In addition kallidin has natriuretic properties which could explain some of the natriuresis following potassium loading (671).

Other possible effects

Effects of potassium on endothelial function (672,673), the sympathetic nervous system and baroreflex sensitivity (674) have been reported which would contribute to the BP lowering effects of an increased potassium intake.

Generalised application of increased dietary potassium intake in hypertensives

An equivalent increase in potassium intake to that achieved in this study (approximately 40 mmol/24h) could be achieved with minor alterations to the dietary habits of most elderly people. Taking two glasses of fruit juice, two pieces of fruit and additional vegetables or salads daily will increase potassium intake by 40-60 mmol/24h.

Siani et al (331) have shown that increasing dietary potassium intake from foods is feasible and effectively lowers BP over a period of one year. All patients in the present study were fit and tolerated the increased potassium intake without problems. However, this may not be the same for all elderly subjects, particularly those with significant renal impairment who may be at risk of hyperkalaemia.

Conclusions

A moderate increase in potassium intake can significantly lower BP in elderly hypertensive persons. Further large scale studies are needed to assess the efficacy and safety of increasing dietary potassium intake in the non-pharmacological approach to reducing BP in a wider range of elderly hypertensive patients.

Summary

Introduction

Epidemiological studies have suggested that caffeine consumption is associated with hypertension and ischaemic heart disease in elderly individuals. Caffeine ingestion following a period of abstention does have an acute pressor effect, although after several days of regular caffeine consumption this response is blunted or absent in the few studies conducted in young and middle aged normotensive and hypertensive subjects.

Objectives

The aims of the present study were to examine the haemodynamic and neurohumoral responses to prolonged caffeine ingestion in elderly subjects over a wide BP range.

Methods

18 fit ambulant elderly subjects, of mean age 78 years (range: 68-86 years, 11 male) were placed on a caffeine-free diet for 2 weeks prior to entering a double-blind, randomised, placebo controlled, cross-over study of 4 weeks caffeine (as capsules 250 mg twice daily) or matching placebo while continuing caffeine restriction. Clinic and 24 hour ambulatory BP were assessed at the end of each 4 week phase along with plasma caffeine, noradrenaline, adrenaline and renin activity levels.

Results

All 18 subjects, with a clinic SBP and DBP in the range 105-225 mmHg and 54-108 mmHg respectively, completed the study with successful 24h BP recordings being obtained on both occasions in twelve subjects. There was no significant change in clinic or 24h ambulatory SBP, DBP or pulse rate or in any of the pressor mechanisms studied between the placebo and caffeine phases of the study. Furthermore there was no correlation between base-line BP levels and the change in BP between placebo and caffeine phases.

Conclusion

4 weeks of regular caffeine ingestion in the amounts normally consumed daily has no significant effect on clinic or 24 hr BP levels in elderly subjects, irrespective of BP levels. It is unlikely that chronic caffeine consumption exerts a significant pressor effect in this age group.

Introduction

Regular caffeine consumption as tea, coffee and cola drinks is common, estimates in the USA suggest 80% of adults are frequent coffee drinkers (675). Epidemiological studies have implicated caffeine as a risk factor for coronary heart disease (338-341) and hypertension. The relationship of caffeine consumption with BP is unclear, some studies reporting a positive association (355,356), others an absent or inverse association (359-364). Recently Burke et al (357) have highlighted the positive association between caffeine intake and BP in the elderly. There is evidence that acute caffeine ingestion following a period of abstention has a pressor effect in young (366, 378), middle-aged (376) and elderly normotensive subjects (373,375). In middle aged (382) and elderly untreated hypertensive subjects (385) BP increases of 12/7 mmHg have been reported shortly after ingesting approximately 250 mg of caffeine. There have been few controlled studies undertaken of the haemodynamic and neurohumoral responses following prolonged caffeine ingestion in young or old subjects. In young normotensive persons some, (378, 389-391) but not all (377,386,388), studies have shown incomplete tolerance to this acute effect of caffeine when it is taken regularly. Available evidence suggests that in young and middle aged hypertensive subjects the pressor effect to caffeine after several days consumption is small or absent (392-394), though many of these studies have had methodological problems or have been too small to detect a clinically significant pressor response. There have however been no formal controlled studies of the effects of sustained caffeine ingestion in elderly subjects on clinic and 24-h ABPM measurements. Changes in the activity of the sympathetic nervous system and plasma renin activity have been demonstrated following caffeine ingestion and are thought to be related to its pressor effect (366) although other studies have shown no such changes following either acute (385) or chronic caffeine administration (392).

Hypothesis: Regular daily caffeine ingestion has no pressor effect in elderly subjects.

Specific study aims

(1) to evaluate the effect of long term regular caffeine ingestion on clinic and 24 hour blood pressure levels and

(2) to examine changes in postulated pressor mechanisms after long term caffeine administration.

METHODS

Subjects

Eighteen fit, ambulant, subjects living at home, 11 male, mean age 75±5 years, range 68-86 years, were recruited from attenders at a hospital out-patient department at Leicester General Hospital and from volunteers. No subject took any regular medication, though all subjects were regular caffeine users, defined as having an intake of 3 or more tea or coffee drinks daily as assessed by the study dietician (mean daily caffeine intake 380 mg, range 200-780 mg). Fourteen subjects were normotensive and 4 newly diagnosed hypertensive (SBP ≥ 160 mmHg and/or DBP ≥ 95 mmHg) with BP recorded using the methods described in chapter 4. The SBP and DBP range was 105-225 mmHg and 54-108 mmHg respectively. All subjects were non-smokers and had a body mass index (BMI) of 24.4±3 kg/m^2.

Exclusions

Subjects were excluded if they had evidence of ischaemic heart disease, cerebrovascular disease, postural hypotension (fall in SBP >20 mmHg), or renal impairment (plasma creatinine > 150 μmol/l) or took any medication known to affect BP.

Ethical committee approval

All subjects gave their written consent for the study which was approved by the Leicestershire Ethics Committee.

Procedures

All subjects entered a 2 week run-in period during which they were advised by the study dietician to abstain from all caffeinated products and to use only the decaffeinated tea and coffee supplied by the investigators free of charge. At the end of the two week run-in period subjects were weighed and height was recorded without shoes and in light clothing; their diet history was checked for possible lapses of caffeine abstention and further supplies of decaffeinated tea and coffee were given. The mean of 3 blood pressure (BP) and pulse rate determinations were then made using a semi-automatic recorder (Dinamap 8100, Criticon, Tampa, Florida, USA standardised against a mercury sphygmomanometer) in both the supine position after 20-30 minutes rest and after 2 minutes standing, all measurements being made in a warm (20-24°C), quiet room between 10:00 hours and 12:45 hours. Whilst on the decaffeinated diet all subjects then entered an 8 week double-blind,

randomised placebo controlled cross-over study of 4 weeks caffeine capsules 250 mg twice daily or matching placebo. At the end of each 4 week phase subjects returned to the same clinical trials room between 10:00 - 12.00 hours having taken the last capsule the previous evening, where they were weighed after emptying their bladders. A cannula was inserted retrogradely in a dorsal hand vein, patency being maintained with heparinised saline flushes (Pumphep, Leo Laboratories Ltd, Risborough, UK). The hand and forearm were retained within an electrically heated, thermostatically controlled warm glove set at 55°C to obtain arterialised venous blood samples. After 30-45 minutes the following measurements and samples were taken: (a) arterialised blood samples were withdrawn from the IV cannula for estimation of plasma noradrenaline, adrenaline, caffeine and plasma renin activity, (b) the mean of 3 clinic supine and standing BP and pulse rate determinations taken as previously described in chapter 4 and (b) prior to returning home the SpaceLabs 90207 BPM, programmed to take readings every 20 minutes during daytime and 30 minutes at night, was attached to the same are used for all other BP determinations. BP and pulse rate data from the ABPM were then downloaded on to a personal computer, only recordings with more than 85% of the maximum number of programmed readings was accepted for analysis, no manual editing of results was undertaken. Daytime BP was taken as from 07:00 to 22:00 hours. Compliance with study medication was checked at the end of each phase by capsule count.

Assay methods

Arterialised blood samples for plasma noradrenaline and adrenaline levels were taken into chilled EDTA/glutathione tubes which were immediately centrifuged at 3,000 rpm at 4°C for 10 minutes (Mistral 6000, MSE, Loughborough, UK), the plasma being stored at -70°C. Duplicate samples were assayed blind by a technician using high performance liquid chromatography (HPLC) with electrochemical detection by the method of Macdonald and Lake (676). Sensitivity was 0.05 nmol/l for noradrenaline and 0.08 nmol/l for adrenaline. Interassay coefficients of variation were 8.1% for noradrenaline and 13.2% for adrenaline determinations. Samples taken for measurement of PRA were added to chilled disodium EDTA tubes and immediately centrifuged and stored as above. Duplicate samples were assayed by one investigator (MDF) using a radioimmunoassay kit

(Biodata Renin MAIA, Serona Diagnostics Limited, Woking, UK). Sensitivity was 0.1 ng/ml and interassay CV was 4%. Plasma caffeine samples were analysed by a technician using HPLC and hydroxyethyl theophylline as an internal standard (Perkin Elmer, Beaconsfield, UK). Sensitivity was 1 mg/l and the interassay CV was 6.6%. Plasma samples for the assays from each subject were all analysed in the same batch.

Statistical analysis

Results are presented as mean ± standard deviation; 95% confidence intervals are given where indicated. The study had a power of 85% to detect a clinic BP difference between the two phases of 10/6 mmHg at the 5% significance level, assuming the SD of the difference for SBP as 14 mmHg and DBP 7 mmHg (647). Using a 24-hour ABPM a difference of 5.5 mmHg in SBP and DBP could be detected with a power of 80% assuming an SD of the difference of 6 mmHg (as shown in chapter 3) with a sample size of 12 subjects. Differences between caffeine and placebo phases were analysed by the method of Hills and Armitage for a two period cross-over study (648).

Results

All 18 patients completed the study although only 12 had satisfactory 24-hour ABP recordings, 2 subjects refusing and 4 having less than 85% of maximum readings in one of the recordings. All subjects took >90% of the trial medication during the study as judged from the capsule count. At the end of the run-in period clinic supine SBP and DBP ranged from 105-225 mmHg and 54-108 mmHg respectively, 11 (61%) of the subjects had SBP >140 mmHg.

Clinic BP and pulse rate changes

Supine and standing clinic BP and pulse rate were similar at the end of run-in, placebo and caffeine phases as shown in table 6.1. In particular there was no significant difference between placebo and caffeine phases in supine SBP (3 mmHg, 95% CI - 6,12 mmHg) or DBP (- 1 mmHg, CI 6,-7 mmHg) respectively.

24 hour ABPM and pulse rate

24-hour, day and night-time BP and pulse rate were also similar in the placebo and caffeine phases (see table 6.1). There was a significant difference between clinic SBP and daytime SBP for the caffeine phase but not for the placebo phase (17 mmHg, CI 1-32 mmHg, $p = 0.035$; and 13 mmHg, -5-31 mmHg, $p = 0.14$ respectively).

There was no significant difference in DBP between mean clinic and daytime ABP measurements.

Orthostatic BP fall

No significant difference was observed in the degree of orthostatic fall in SBP between the placebo and caffeine phases (placebo: supine-standing, 4±21/-2±8 [NS]; caffeine: supine-standing, 7±16/-3±8 [NS]). Pulse rate increased from supine to standing positions in all three phases of the study ($p < 0.001$) but there was no significant difference between placebo and caffeine phases.

Correlations with BP changes

There was no significant correlation between baseline BP or age and change in BP from placebo to caffeine phases.

Plasma catecholamine and renin activity

There was no change in plasma adrenaline, noradrenaline or renin activity values between the phases (see table 6.1). Plasma caffeine levels were undetectable in all plasma samples except for 4 subjects who had caffeine levels at the lower limit of detection (≤ 1.1 mg/l) at the end of the caffeine phase. There was no significant correlation between the change in plasma catecholamines or renin activity and the change in BP from placebo to caffeine phases.

Clinic BP	**Run-In**	**Placebo**	**Caffeine**	**Difference**
Supine				
SBP mmHg	149±28	147±25	150±24	3 (-6,12)
DBP mmHg	76±15	76±13	75±10	-1 (-7,5)
PR beats/min	74±12	73±13	75±13	2 (-2,6)
Standing				
SBP mmHg	148±13	143±29	143±25	0 (-11,10)
DBP mmHg	78±15	78±15	78±10	0 (-6,6)
PR beats/min	82±13	82±15	83±14	1 (-4,5)
Ambulatory Monitoring				
24-h SBP mmHg		134±11	137±15	3 (-5,12)
24h DBP mmHg		75±7	77±7	2 (-3,7)
24h PR beats/min		75±10	79±12	3 (-2,8)
Daytime SBP mmHg		135±9	139±13	4 (-4,12)
Daytime DBP mmHg		78±6	79±8	2 (-4,8)
Plasma				
Noradrenaline (nmol/l)		4.3±2.2	4.1±1.7	-0.2 (-0.9,0.4)
Adrenaline (nmol/l)		0.21±0.8	0.28±0.16	0.06 (-0.02,0.14)
PRA (ng/mg/hr)		1.5±0.7	2.1±1.8	0.6 (-0.3,1.5)

Table 6.1. Changes in clinic supine and standing BP, pulse rate (PR), ambulatory BP and plasma noradrenaline, adrenaline and plasma renin activity (PRA) for the run-in, placebo and caffeine phases; (Mean ± SD) and difference between caffeine - placebo phase mean (95% CI). None of the changes reached statistical significance.

Discussion

This study has demonstrated that in a group of elderly regular caffeine users with a wide BP range, sustained caffeine ingestion for a period of four weeks had no significant effect on clinic or mean 24-hour BP levels, despite the study having the power to detect a clinically significant BP change (>5 mmHg). In addition the amount of daily caffeine used in the present study (250 mg bd) has previously been shown to produce a significant pressor response shortly after ingestion of a single dose in elderly normotensive (375) and hypertensive subjects (385) following a prolonged period of caffeine abstention. Although the 3 mmHg difference in clinic and 24-hour ambulatory SBP between placebo and caffeine phases was not statistically significant at the 5% level, the study only had a power of 0.54 at this level of significance to detect such a difference. On an individual basis this 3 mmHg mean difference is small and probably of little clinical significance, although on a population basis such a BP increase may well be of significance and could possibly account for an increase in cardiovascular morbidity and mortality. In addition there was no change in orthostatic BP responses, heart rate or plasma adrenaline, noradrenaline and renin activity levels between either phase.

Although the group studied consisted of subjects with a wide range of BP levels, for the purpose of analysis, subjects were not arbitrarily divided into hypertensive or normotensive groups, rather an attempt was made to correlate BP levels with changes in variables between each phase. However no significant correlations were found between baseline BP levels and changes in BP or any other variable between placebo and caffeine phases of the study.

This study was of short duration and involved subjects who were regular caffeine users, therefore the results should not be extrapolated uncritically to long-term consumers or to irregular users of caffeine. Four (22%) of the subjects were defined as having hypertension although another 7 (39%) had 'high normal' SBP levels (>140 mmHg). The results are therefore relevant to the large number of elderly persons with mildly elevated BP levels who have a high absolute risk of cardiovascular disease.

Caffeine levels and BP

Caffeine levels taken approximately 12-hours after ingestion of the capsule at the end of the placebo and active phase were, as expected, either undetectable or at the lower limit of detection - presumably the effect in some subjects of caffeine metabolism being saturated following repeated regular caffeine ingestion (678). Despite these low or absent levels of caffeine, further ingestion of caffeine after 12 hours did not lead to a rise in BP. There is therefore no evidence of a supposed sustained pressor effect of caffeine being the result of repeated acute BP increases following caffeine consumption.

It has previously shown in elderly hypertensive (385) and normotensive subjects (374) that a small but significant pressor effect of caffeine occurs following 48 hours but not after 12 hours of caffeine abstention. Overall these reports and the present study suggest that any initial pressor effect following caffeine ingestion after a period of abstinence is abolished with continued consumption presumably through tolerance to its effects. This is also supported by the work of Smits et al (369) who found the acute response to caffeine depended on the individuals half-life for caffeine metabolism. Those with the lowest basal caffeine concentration showed the greatest pressor effect.

Comparison with other studies

The results of the present study in the elderly are in agreement with several previous studies that have shown little or no effect of repeated caffeine consumption on BP and heart rate in younger subjects. Eggertsen et al (423) examining young and elderly treated hypertensives found no change in 24-hour, day or night ABP or in heart rate after 2 weeks of caffeine or placebo although anti-hypertensive treatment itself may have reduced any possible pressor effect seen. Myers and Reeves (377) in young normotensive subjects reported a small increase in daytime ABP on the first day of caffeine consumption with values returning to baseline by the third day. This finding is consistent with data obtained using conventional BP measurements showing after repeated caffeine consumption that an initial rise in BP on the first day returns to baseline levels within a few days (386). Other studies also using ambulatory BP monitoring (378, 390, 391) have shown incomplete tolerance to the pressor effect of caffeine when taken over several days; increases in SBP of

2-5 mmHg and in DBP of 1-3 mmHg have been reported that are compatible with results from the present study.

Further studies, also in younger subjects, may not have had the power to conclusively demonstrate changes in BP (392) or have suffered from methodological problems of not being double-blinded (389) or using caffeinated or decaffeinated drinks when the ingestion of liquid alone can result in a significant pressor effect (679).

Effect of caffeine on pressor mechanisms

During the acute response to caffeine not only BP but also plasma adrenaline has been found to increase (372, 373,383) although fewer studies have reported any change in plasma noradrenaline and plasma renin activity (366). In keeping with an absent or slight pressor response seen in the present study and results from other chronic caffeine studies (392) no changes in plasma catecholamines or plasma renin activity after 4 weeks of regular caffeine ingestion were found. However, changes in plasma catecholamines and renin activity may not be central to the mechanism of any pressor effect of caffeine (397); there is evidence suggesting attenuation of adenosine induced vasodilatation following acute caffeine infusion (680) and of chronic caffeine consumption potentiating the hypotensive action of adenosine (681). Effects of caffeine on other pressor mechanisms were briefly discussed in section 1.33.

Conclusion

In conclusion, regular consumption of caffeine (the equivalent of 4-5 cups of coffee) over a period of 4 weeks has no or little effect on clinic or 24 h blood pressure, heart rate, plasma catecholamine or renin activity levels in elderly subjects. It is unlikely that sustained caffeine consumption on an individual basis exerts a clinically significant pressor effect in this age group, though the effects of lifetime use of caffeine on blood pressure cannot be assessed from this study. The findings in epidemiological studies of a relationship between coffee consumption and BP in the elderly may be through some confounding variable.

CHAPTER 7

THE EFFECT OF ANTI-HYPERTENSIVE DRUG WITHDRAWAL AND SUBSTITUTION WITH NON-PHARMACOLOGICAL THERAPY ON BLOOD PRESSURE IN ELDERLY SUBJECTS

Summary

Objectives

To determine (a) the proportion of elderly hypertensive subjects currently attending a hospital hypertension clinic who are suitable for a trial of anti-hypertensive drug withdrawal; (b) the proportion of suitable patients who can be successfully withdrawn from drug therapy whilst receiving non-pharmacological advice for a period of up to 2 years, and; (c) the factors associated with successful treatment withdrawal.

Methods

105 consecutive hypertensive subjects, 53% female, mean age 76 years (range 65-84 years) on pharmacological anti-hypertensive therapy for more than one year were studied. Of these 105 patients 78 (74%) had a clinic SBP <175 mmHg and DBP $<$ 100 mmHg, a level that was taken as being suitable for drug therapy withdrawal. Anti-hypertensive drug therapy was withdrawn in this group and non-pharmacological advice to lower BP instituted. Clinic BP and weight were subsequently recorded monthly for 12 months in all subjects and at every three months in those who had a possible follow-up period of 24 months. 24 h ambulatory BP was measured at baseline and repeated one month off therapy. 24 h urine electrolytes were also assessed at baseline and at 12 months or before restarting drug therapy.

Results

Of the 105 subjects, 74 (70%) had a follow-up of 12 months, 4 were withdrawn from the study and 64 were available for two years of follow-up. After 12 months 20 (25%) of those withdrawn remained normotensive whilst continuing with non-pharmacological therapy. Logistic regression analysis revealed a lower (a) on treatment clinic and 24-hour SBP, (b) ECG [SV_1 + RV_6] voltage and (c) BMI at baseline were predictors of those who would remain off therapy at one year. After 12 months of non-pharmacological advice weight fell in subjects with BMI $\geq$ 26 kg/m^2 by 2.6 $\pm$ 4.8 kg ($p <$ 0.05). 24-hour urinary sodium and potassium excretion did not change significantly but there was an increase in the potassium : creatinine ratio from 7.0 $\pm$ 2.2 to 8.5 $\pm$ 3.2, $p <$ 0.01, after 12 months.

Conclusions

Following anti-hypertensive drug withdrawal and institution of non-pharmacological therapy 25% of elderly hypertensives were able to remain off drug treatment for 12 months or more with good BP control.

Introduction

Recent guidelines on the management of hypertension suggest that patients who have had a prolonged period of controlled hypertension can attempt a reduction or even complete cessation of their anti-hypertensive treatment while maintaining non-pharmacological therapy and undergoing regular long-term BP monitoring (530, 531). Whether patients can remain normotensive after withdrawal of pharmacological anti-hypertensive therapy has been addressed in several studies, mostly involving middle-aged hypertensive persons although one recently reported study was concerned with elderly persons (551).

Use of non-pharmacological methods of BP reduction following drug withdrawal in middle-aged hypertensives has been shown to almost double the chance of success although these studies involved intensive counselling regimens which are unlikely to be available in everyday practice (547, 548). The benefits of a moderate reduction in dietary sodium intake and an increase in potassium intake in lowering BP in elderly hypertensive subjects have been demonstrated in Chapters 4 and 5 of this thesis. In addition, low intensity exercise training in older subjects has also been reported to lower elevated SBP by up to 20 mmHg and hypotensive effects of weight loss in overweight hypertensives and of alcohol reduction have been reported although not specifically in elderly hypertensive subjects.

Despite the potential for non-pharmacological therapies to lower BP in older hypertensive subjects no studies have previously reported the use of such therapies in maintaining normotension after withdrawal of anti-hypertensive drugs in elderly patients.

Hypothesis

The hypothesis is that substitution of non-pharmacological therapy for anti-hypertensive drug treatment can maintain BP control in a significant proportion of elderly hypertensive subjects with BP controlled on drug therapy.

Objectives

Specific objectives of this study were to determine:

(a) the number of elderly hypertensive patients suitable for consideration of a trial of anti-hypertensive drug withdrawal in an unselected clinic population,

(b) the proportion of suitable patients who could be successfully withdrawn from drug therapy whilst receiving non-pharmacological advice, and

(c) the factors associated with successful drug withdrawal.

Methods

Subjects

Ambulant subjects with a diagnosis of hypertension and on pharmacological treatment for more than one year and > 65 years of age were recruited directly from general practice lists (36%), hospital out-patients (53%) and in-patients (11%). Subjects were considered to be hypertensive if they were currently taking anti-hypertensive medication, the diagnosis of hypertension being made by their general practitioners in all cases. Because of the duration of hypertension, in many subjects records of BP levels kept by their GPs at the time of diagnosis were often not available.

Exclusion criteria

Subjects were excluded if they had symptoms or signs of angina, congestive cardiac failure, a history of myocardial infarction or stroke within the proceeding six months, renal impairment (creatinine >200 μmol/l), were taking anti-hypertensive medication for a reason other than hypertension or were on other medications known to significantly affect BP or had other diseases that would significantly effect survival, eg, terminal illness.

Consecutive patients meeting these criteria were enrolled into the study. The study was approved by the Leicestershire Ethical Committee and subjects gave their written informed consent.

Procedures

Investigations whilst on anti-hypertensive therapy

1) Clinic BP Measurements: Prior to treatment withdrawal clinic BP measurements were made on at least three separate occasions over a two to three month period in a quiet warm room after subjects had emptied their bladders and at least two hours after their last meal. Clinic BPs were recorded as detailed previously in the supine and standing positions after one and three minutes with a standard mercury sphygmomanometer using a cuff of the appropriate size, taking the mean of three readings at each visit after five minutes rest. All measurements were taken by the same investigator (MDF).

2) 24-h Ambulatory BP: 24-h BP was recorded on the last visit prior to treatment withdrawal using the SpaceLabs 90207 BPM programmed to take readings every 20 minutes during daytime (07:00 - 22:00 hrs) and every 30 minutes at night (22:00-07:00

hrs). Using the same arm sequential measurement technique, monitor and sphygmomanometer BP readings were within 5 mmHg of agreement. Criteria for acceptability of ABPM records were as given previously in chapter 4.

3) Echocardiography: Echocardiography was carried out by a technician unaware of the study aims using and Hewlett Packard 77023 unit equipped with a 3.5 MHz transducer. Measurements were taken from a 2D guided M-mode tracing and LV mass calculated according to standard methods (682,683) and then expressed as LV mass index (LV mass/body surface area).

4) ECG: A standard 12 lead ECG was recorded and the size of the S-wave deflection in lead V1 and the R-wave deflection in lead V6 were recorded.

5) Urinary Electrolyte Excretion
Whilst on anti-hypertensive therapy patients were asked to collect two 24-hour urine collections for estimation of urinary sodium, potassium and creatinine excretion.

6) Anthropometric Data: The body weight and height without shoes and in light clothing were recorded.

7) Medical History: Details of smoking, alcohol intake, duration and type of anti-hypertensive therapy and past medical history including angina, myocardial infarction and stroke were recorded.

Criteria for anti-hypertensive drug withdrawal

If the average of clinic BPs from the last two visits met the criteria: clinic supine or standing SBP $<$ 175 mmHg and DBP $<$ 100 mmHg, anti-hypertensive treatment was withdrawn. Patients taking more than one anti-hypertensive agent, had each reduced in a stepwise fashion if withdrawal BP criteria were met.

Non-Pharmacological advice

On withdrawal of drug therapy patients were given the following routine non-pharmacological advice at each clinic attendance by the investigator (MDF).

1) to achieve weight loss of at least 4kg or 10% of initial weight at a rate of 0.5 kg/week,in those with a BMI $>$ 26 kg/m^2,

2) to reduce sodium intake to below 100 mmols/day,
3) to increase potassium intake to above 80 mmols/day,
4) to aim for a minimum aerobic exercise level of 30 minutes walking daily,
5) to reduce alcohol use in those taking over 14 units per week in men and over 10 units per week in women,
6) advice to stop smoking where relevant.

Only those overweight (BMI >26 kg/m^2) were offered an appointment with the dietician. Other than spending 10 minutes discussing the beneficial effects of weight loss, dietary change and exercise on BP and health in general at each visit, no intensive programme of dietary and lifestyle adjustment or special arrangements were used to encourage such changes.

Follow-up investigations

Following withdrawal of pharmacological treatment, clinic BP and weight were recorded, as described above, monthly for 12 months in all subjects. Those subjects with a potential follow-up period of a further 12 months (i.e., two years in total) had BP measured every three months. 24 h ABPM was repeated one month off therapy and two 24-hour urine collections were made at the end of the 12 month period or before re-starting anti-hypertensive drug treatment.

Criteria for re-starting pharmacological therapy

Pharmacological anti-hypertensive therapy was restarted if mean clinic supine SBP was $\geq$ 160 mmHg and/or DBP $\geq$ 90 mmHg on two consecutive visits, i.e., BP levels at which treatment is recommended in elderly patients in the 1993 BHS guidelines (531).

Analysis

Differences in continuously distributed variables between groups remaining normotensive or hypertensive at 12 months were assessed by students paired t-test for normally distributed data and values are given as mean $\pm$ SD. Non-parametric data were analysed by the Mann Whitney test and values are given as median and range. Differences between discrete variables were tested using the Chi-squared test. Significance was taken at the 5% level.

Associations of variables with either normotensive or hypertensive groups at 12 months were examined using logistic regression on the SAS 6.02 programme. Step-wise

multiple logistic regression analysis is a technique for determining which variables independently contribute to influencing a dependent variable. The step-wise regression analysis programme on SAS was used to determine which of the single variables identified on the logistic regression analysis as being at, or close to significance, when entered into the regression equation were independent predictors of return to hypertension or maintenance of normotension at 12 months. Variables entered into the step-wise regression analysis were on-treatment SBP and DBP, mean 24 h ambulatory SBP and DBP, ECG (SV1+RV6) voltage, BMI, age and left ventricular mass index.

Results

Withdrawal from pharmacological treatment

Of 105 consecutive patients on anti-hypertensive treatment 27 (26%) had mean clinic BP on the third visit greater than the withdrawal criteria (SBP $<$ 175 mmHg and DBP $<$ 100 mmHg). Of the remaining 78 patients in whom pharmacological therapy was stopped, three were withdrawn from the study because diuretics were re-started. Reasons for re-introduction of diuretics were the development of dependent ankle oedema in two subjects and development of mild left ventricular failure in one subject. One patient died of newly diagnosed carcinoma of the lung during the two years of follow-up. In the remaining 74 patients (70% of the original group), all had a potential follow-up period of at least 12 months and 64 were available for up to two years.

Baseline characteristics

The baseline characteristics of the 74 subjects are shown in table 7.1. It can be seen that the majority of subjects were taking thiazide diuretics and more than a half were taking two or more anti-hypertensive drugs. Reliable echo-LV mass determinations were obtained in 40 patients. Complete 24 h ABP recordings ($\geq$ 85% of programme readings) were obtained in 56 patients prior to drug withdrawal and in 49 one month following withdrawal. Mean 24 h ABP levels were significantly lower than mean clinic BP levels. For those subjects undergoing ABPM mean clinic SBP was 149 $\pm$ 19 mmHg and mean 24-hour ABPM 134 $\pm$ 14 mmHg ($p < 0.001$); mean clinic DBP was 81 $\pm$ 11 mmHg and mean 24-hour DBP 77 $\pm$ 10 mmHg ($p < 0.001$).

Number of subjects		74	
Age (yrs)		76±5	(range 65-84)
% female		53	
Clinic Supine	SBP (mmHg)	150±19	range (112-175)
	DBP (mmHg)	82±11	range (56-100)
Clinic Standing	SBP (mmHg)	143±18	range (110-174)
	DBP (mmHg)	82±11	range (64-100)
24hr Ambulatory	SBP (mmHg)	134±14	range (106-160)
(n = 56)	DBP (mmHg)	77±10	range (56-100)
LVMI n = 16	Males (g/m^2)	182±41	range (110-260)
n = 23	Females (g/m^2)	155±33	range (106-223)
Treatment duration (yrs)		10	range (1-15)
BMI ≥ 26 kg/m^2		33	(44%)
≥ 30 kg/m^2		13	(17%)
Number of subjects taking:			(%)
thiazide		42	57
beta-blocker		32	43
calcium antagonist		22	30
monotherapy		33	45
double therapy		35	47
triple therapy		6	8
			(%)
current smokers		8	11%
current alcohol	< 20 u/week M < 15 u/week F	38	51%
current alcohol	> 20 u/week M > 15 u/week F	5	6%
ex/never drink		31	43%
Sodium excretion	>150 mmol/day	18	24%
Potassium excretion	<50 mmol/day	19	26%

Table 7.1 Baseline characteristics of the 74 elderly hypertensive subjects before withdrawal of antihypertensive drug therapy and institution of nonpharmacological methods of BP reduction.

Patients remaining off treatment

The number of patients remaining off treatment throughout the 12 months study period is shown in figure 7.1. At the end of 12 months 20 (25%) were on no anti-hypertensive therapy with well controlled BP levels (SBP < 160 mmHg and DBP < 90 mmHg). Of the 64 patients available for a potential follow-up period of two years 13 (20%) who were normotensive at 18 months remained so at two years.

Restarting anti-hypertensive treatment

The majority (75%) of patients re-starting therapy did so in the first three months. The change in clinic SBP levels one month off treatment compared to baseline levels is shown in Figure 7.2. 23% of patients had either an increase or decrease in clinic SBP of 5 mmHg or less and 11% of patients exhibited a fall in BP of between 5-15 mmHg following treatment withdrawal.

	HT	**NT**
n	54	20
Age (yrs)	75 ± 5	76 ± 6
% Male	45	55
CSBP (mmHg)	156 ± 19	142 ± 16*
CDBP (mmHg)	83 ± 12	80 ± 9
24h SBP (mmHg)	139 ± 13	130 ± 12*
24h DBP (mmHg)	76 ± 14	76 ± 8
BMI (kg/m^2)	26.7 ± 3.4	24.8 ± 4.3
Treatment duration (yrs)	10 ± 6	10 ± 7
ECG [SV_1 + RV_6] (mm)	26.9 ± 9	20 ± 6*
Monotherapy (%)	47	41

* $p < 0.05$ n = number of subjects; CSBP, Clinic SBP; CDBP, Clinic DBP; BMI, body mass index

Table 7.2: Pre-withdrawal characteristics of those subjects returning to hypertension (HT) (SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg) within 1 year of treatment withdrawal compared to those remaining normotensive (NT).

There was no significant difference in baseline characteristics between those patients restarting therapy and those remaining off therapy at one year with respect of age, sex, the number of anti-hypertensive agents taken, alcohol intake, cigarette use, history of vascular

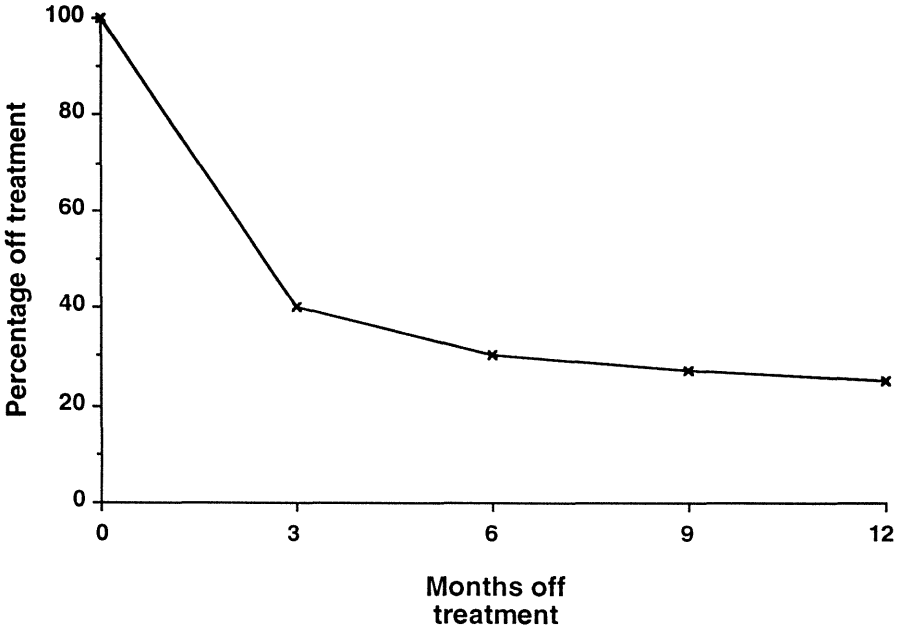


Fig 7.1. Percentage of total number of subjects (n=74) remaining off antihypertensive drug therapy during 12 months of follow-up.

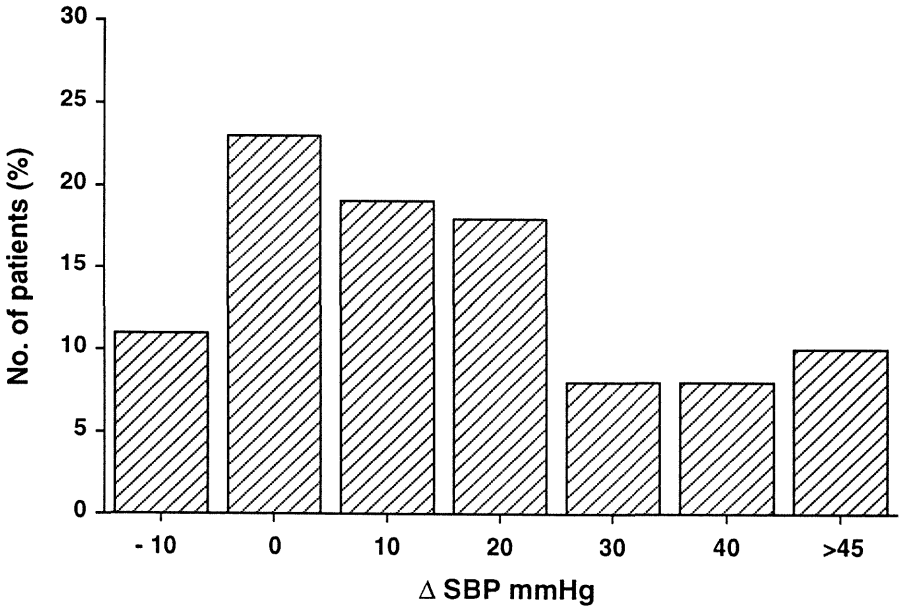


Fig 7.2. Change in clinic SBP (mmHg) one month after stopping therapy from baseline (ie, on treatment) levels. A minus sign indicates a fall in SBP.

disease, treatment duration, LV mass index, clinic or mean 24-hour DBP. However, clinic and 24 hour SBP and ECG [SV1 + RV6] voltage were greater in those who returned to hypertension as shown in table 7.2.

Predictors of early return to anti-hypertensive drug treatment

The pre-withdrawal characteristics of patients returning to treatment within the first 3 months, compared to those remaining normotensive after this time, i.e., early reverters is shown in table 7.3. Again a higher clinic SBP, 24 h SBP and ECG [SV_1 + RV_6] voltage and in addition a younger age are associated with an early return to treatment.

	HT	**NT**
n	38	36
Age (yrs)	74.5 ± 5	77 ± 4
% Male	42	54
CSBP (mmHg)	159 ± 17	138 ± 15*
CDBP (mmHg)	84 ± 11	80 ± 9
ASBP (mmHg)	140 ± 14	128 ± 10*
ADBP (mmHg)	79 ± 10	75 ± 9
BMI (kg/m^2)	26.8 ± 3.5	26.6 ± 3.9
Treatment duration (yrs)	10 ± 7	10 ± 6
ECG [SV_1 + RV_6] (mm)	26 ± 9	20 ± 6*
Monotherapy (%)	51	43
LVMI (g/m^2)	161 ± 39	176 ± 34

* $p < 0.05$

Table 7.3: Pre-withdrawal characteristics of those subjects returning to hypertension (HT) within 3 months of treatment withdrawal compared to those staying normotensive (NT)

Logistic regression analysis

Factors predictive of return to treatment or maintenance of normotension were investigated by logistic regression analysis. Supine SBP and DBP, ambulatory SBP and DBP, ECG [SV_1 + RV_6] voltage and BMI were significantly associated with return to treatment during the study period. Treatment duration, LV mass and past history of

vascular disease were variables not significantly related to maintenance of normotension or return to hypertension. Significance levels for these factors are shown in table 7.4.

Stepwise logistic regression analysis showed a lower supine clinic SBP, 24-h ASBP, ECG [SV_1 + RV_6)] voltage and BMI at baseline were significant predictors of those who remained off therapy to one year.

Variable	***P***
Supine SBP	0.004
Mean 24 hr Ambulatory SBP	0.01
Mean 24 hr Ambulatory DBP	0.03
ECG [SV_1 + RV_6]	0.03
Supine DBP	0.07
BMI	0.1
Prev. Stroke	0.3
Prev. MI	0.3
Diabetes	0.2
Treatment Duration	0.9
Number of Drugs	0.9

BMI, body mass index,

Table 7.4: Logistic regression analysis of variables at baseline associated with those patients returning to hypertension within 1 year or remaining normotensive at 1 year following drug withdrawal.

Effect of non-pharmacological advice

For all subjects weight fell significantly by 1.8 ± 4.2 kg ($p < 0.05$) over the 12 month period although the 44% of subjects with a BMI ≥ 26 kg/m², a level above which mortality has been reported to increase in elderly subjects, had a greater weight loss (2.6 ± 4.8 kg, $p < 0.05$) over this period.

Changes in 24 h urinary electrolyte excretion from baseline and following non-pharmacological advice are shown in table 7.5. 24 h urinary sodium excretion was low and did not change significantly after 12 months. However an increase in the potassium : creatinine ratio was seen (7.0 ± 2.2 to 8.5 ± 3.2, $p < 0.01$) although the increase in 24 h urinary potassium excretion of 10 mmol/24 h or 16% of baseline level did not quite reach the 5% significance level ($p=0.08$). In those subjects with initial sodium excretion in the upper quartile range, i.e., > 150 mmols/day, there was a mean fall from 172 ± 25 to 145 ± 34 mmols/day, $p = 0.15$) and in subjects with initial potassium excretion in their lower quartile, i.e., < 50 mmols/day there was an increase from 46 ± 5 mmols to 59 ± 17 mmols/day, $p = 0.06$.

	Baseline	**Month 12***	**p**
Weight (kg)			
All subjects	71.2±8.4	69.4±7.0	<0.05
Subjects BMI ≥26 kg/m²	73.2±7.9	70.6±6.6	<0.05
24 hr urinary electrolyte excretion			
Na (mmol/24 hrs)	126±43	117±41	0.3
Na : Cr	14.3±4.5	14.1±6.1	0.5
K (mmol/24hr)	62±18	72±22	0.06
K : Cr	7.0±2.2	8.5±3.2	<0.01
Na : K	2.17±0.81	1.88±1.04	0.09

mean ± SD are shown
BMI, body mass index
Na, sodium Cr, creatinine K, potassium
* or until restarting of therapy

Table 7.5: Body weight and 24h urinary electrolyte excretion at baseline (prior to anti-hypertensive drug withdrawal) and after 12 months of non-pharmacological therapy, or to reintroduction of drug therapy.

Levels of plasma electrolytes, urea, creatinine and uric acid prior to and following treatment withdrawal are shown in table 7.6. No significant change in any of these variables was seen.

	On-Treatment	3 Months Off-Treatment
Sodium (mmol/l)	138 ± 4.3	139 ± 3.0
Potassium (mmol/l)	4.0 ± 0.5	4.2 ± 0.4
Urea (mmol/l)	6.3 ± 2.2	5.9 ± 1.7
Creatinine (μmol/l)	97 ± 21	93.7 ± 17
Urate (μmol/l)	370 ± 80	359 ± 98

Table 7.6: Changes in serum biochemistry whilst on antihypertensive treatment and 3 months following treatment withdrawal.

Discussion

This study has shown that nearly 20% of an unselected group of treated elderly hypertensive patients, excluding those with recent stroke and myocardial infarction, can remain normotensive, off pharmacological therapy for one year when routine non-pharmacological advice was given. This was however, an uncontrolled study and the effects, if any, of the non-pharmacological treatment on maintaining normotension cannot be directly assessed. Furthermore the criteria for re-starting anti-hypertensive drug therapy were based on clinic BP levels that were substantially lower than the withdrawal BP criteria, but which are now regarded as the level at which treatment should be started in the elderly. If BP criteria for drug therapy withdrawal was set at or below the level for re-starting therapy there would clearly be a greater chance that a higher proportion of the withdrawal group would remain without drug treatment. However, the proportion of the total treated hypertensive elderly population meeting these lower BP criteria for a trial of drug treatment withdrawal would be substantially lower than that given here.

Patients with clinic BP levels in the hypertensive range, but substantially reduced home BP levels have been labelled 'white coat hypertensives' and probably have a lower cardiovascular risk than predicted by clinic measurement (684). 18% of patients in the

present study had clinic SBP > 160 mmHg and mean 24-hour SBP < 140 mmHg one month off treatment. If these patients are considered white coat hypertensives who do not require anti-hypertensive drug treatment, up to a fifth more patients could remain off drug therapy.

Time course for return to drug therapy

A faster rate of return to treatment in the initial follow-up period has also been seen in other studies (540, 547, 548). In the present study these 'rapid reverters' were similar to the 'slower reverters' except for evidence of higher BP levels and a greater ECG [SV_1+RV_6] voltage. Fagerberg et al (540) found 'rapid reverters' in their study to have higher LV mass than 'slow reverters' but similar baseline BP levels. These findings suggest that persons with BP levels at the upper end of the normotensive range with evidence of LVH may rapidly revert to hypertension. However, Ekbom et al (551) found that the majority of those who returned to treatment within 1 year did so for reasons other than hypertension. In the first month only 3 (10%) of the 30 that restarted therapy did so because of increased BP levels.

The percentage of patients remaining off drug therapy with time is shown in figure 7.1. For the majority of patients who had to be restarted on treatment, this occurred in the first three months after withdrawal. A sub-group of the original cohort followed up for two years showed no further reversion to hypertension between 18 months and 2 years.

Comparison with other studies

Previous studies in younger patients have shown between 0-75% of patients can remain normotensive following anti-hypertensive drug withdrawal without the use of non-pharmacological methods. The large variation in success rate reported is likely a reflection of the wide variation in patient selection and BP criteria for withdrawal and restarting treatment.

In a recently reported five year study of treatment withdrawal in 333 elderly hypertensives, 20% were able to remain off therapy after five years (551). As in the present study the majority of patients returning to treatment did so early on, approximately 75% in the first year.

With the substitution of non-pharmacological therapy in middle aged hypertensives withdrawn from drug treatment, Stamler et al, (548) found that after 4 years, weight, salt and alcohol reduction allowed 39% of participants to remain off drug therapy compared to only 5% not receiving such advice. In the former group weight fell after 4

years by 1.8 kg in overweight subjects and 24 h sodium excretion fell by 60 mmol from 166 to 106 mmol/24 h. Langford et al (547) reported that 50% of subjects withdrawn from treatment for just over 1 year remained normotensive if given dietary therapy. Weight loss or sodium restriction could more than double the success in withdrawal of drug therapy in these middle aged hypertensives. In that study falls in weight of 4 kg in overweight persons and in sodium excretion of 59 mmol/24 h from a baseline of 158 mmol/24 h were achieved. However in all these studies special dietary measures and counselling sessions were held which are unlikely to be available in routine practice for the majority of patients. For example in the study of Langford et al (547) nutritional intervention consisted of 8 initial consecutive weekly group sessions, then monthly sessions with individual consultation if needed. The present study used routine rather than special resources for encouraging non-pharmacological advice so as to reflect what could practically be achieved with elderly patients in usual clinical practice. With the use of such a regimen we found that over half of all patients lost some weight, while those with a BMI > 26 kg/m^2 {(a level above which mortality starts to rise in the elderly (411)} lost a mean of 2.6 kg over one year. The fall in mean 24-h urinary sodium excretion of 9 mmol/24 h was modest and not statistically significant, but baseline levels of 126 mmol/24 h were low compared to the UK average of 150 mmol/24 h (116), perhaps because of the prior awareness of the possible benefits of reduced sodium consumption in hypertension. The mean baseline urinary potassium excretion was also low and increased significantly although again quite modestly after one year of dietary advice. If more intensive dietary advice had been given it is likely that greater reductions in weight loss, sodium excretion and other favourable life-style changes would have been achieved leading to a higher success rate with anti-hypertensive drug treatment withdrawal. Weinberger et al (552) for example observed that over a six month period treated hypertensive patients who reduced their sodium intake to ≤ 80 mmols/day were able to markedly reduce their medication compared to less compliant hypertensive subjects.

Predictors of return to drug therapy

Several variables at the time of anti-hypertensive drug withdrawal have been reported to influence or predict the success of therapy withdrawal (685) and have been discussed in Section 1.4. Lower pre-treated and treated BP levels have generally been associated with maintenance of normotension following withdrawal of treatment although age, sex and duration of treatment or of hypertension have had little influence. In the present study, lower on-treatment clinic and mean 24-h SBP was associated with successful

treatment withdrawal for one year or more, but little effect of age, sex, treatment duration or the number of anti-hypertensive agents taken was seen. In contrast Ekbom et al (551) in their five year follow-up study of elderly hypertensives withdrawn from treatment found monotherapy in low dose was associated with a greater chance of remaining untreated for a longer period, but as in the present study a low BP prior to withdrawal of treatment also had such an association. Being overweight at the time of drug withdrawal was found to be an independent predictor or return to hypertension, an association previously reported by Stamler et al (548), although not by Langford et al (547) in younger subjects. As actual body weight and weight changes are closely related to hypertension and BP levels, being obese appears to remain a risk factor for hypertension once therapy is withdrawn in this elderly group.

A lower ECG [SV_1 + RV_6] voltage whilst on treatment was also associated with maintenance of normotension. A similar finding was reported by Imataka et al (686) who found both a lower ECG [SV_1 + RV_5] voltage and a lower SBP prior to treatment were favourable signs for successful drug withdrawal. However, unlike Fagerberg et al (540), we did not find echocardiogram determined LV mass or LV mass index was predictive of return to treatment or maintenance of normotension, although the number of subjects studied was too small to adequately assess this.

Potential for withdrawal of anti-hypertensive drug treatment

The present study was started prior to the results of three recent anti-hypertensive treatment trials (75-77) and BHS Guidelines (531) recommending treating patients with SBP $\geq$ 160 mmHg and/or DBP $\geq$ 90 mmHg. The BP criteria for withdrawal in the present study were higher, yet despite this and the finding that patients had been on treatment for a median period of ten years, over one quarter of patients had repeated BP measurements above these criteria and were not eligible for a trial of treatment withdrawal. Inadequately controlled hypertension may be one of the main factors limiting the potential for a trial of treatment withdrawal.

Potential for non-pharmacological intervention

The potential for non-pharmacological intervention in this elderly group of hypertensives was greatest with regard to weight loss where 44% of subjects had an initial BMI $\geq$ 26 kg/m^2 and 17% had a BMI $\geq$ 30 kg/m^2. Urinary sodium excretion for the group as a whole (126 mmol/24 h) was low by Western standards, the UK median being 150 mmol/24 h (116) and similarly current smoking and excessive alcohol use appeared

uncommon in this elderly group. However only 8% of participants had a urinary potassium excretion in excess of 80 mmols/day suggesting a greater potential for increasing dietary potassium intake in this group

Mechanisms for maintenance of normotension

This study was not designed to assess the mechanisms for maintenance of normotension following drug withdrawal and these have been discussed previously in section 1.4. It is likely that some patients may never have been truly hypertensive, especially if BP was measured on only one or two occasions before therapy was started. General Practitioner's records regarding the diagnosis of hypertension were not available for inspection.

'Spontaneous remission' of mild hypertension, either due to the natural history of the condition, or more likely an effect of regression to the mean is seen over long periods of follow up. In the Australian National Blood Pressure Trial (66), DBP fell to < 95 mmHg without anti-hypertensive drugs over a three year period in half of the patients with mild hypertension.

That over 10% of patients had a fall in SBP of more than 5 mmHg one month after stopping therapy also suggests some subjects were not fully compliant with their treatment and maintained well controlled BP levels despite this.

Conclusion

This study has shown that of those eligible for treatment withdrawal approximately 20-25% were able to remain normotensive for two years off pharmacological therapy with the substitution of non-pharmacological therapy. A higher on treatment BP, increasing left ventricular mass on ECG criteria and increased body weight predicted a greater chance of the need to reintroduce anti-hypertensive drug therapy. Elderly hypertensive patients with well controlled hypertension, but without evidence of cardiac failure or angina, particularly those over the age of 80 years where the benefits of treatment are less clear, could be considered for a trial of anti-hypertensive drug withdrawal substituted by non-pharmacological therapy.

CHAPTER 8

THE USE OF NON-PHARMACOLOGICAL THERAPY IN THE TREATMENT OF ELDERLY HYPERTENSIVE PATIENTS IN GENERAL PRACTICE

Summary

Objective

To assess the reported use of pharmacological and non-pharmacological (NP) therapy by General Practitioners in the management of hypertension in elderly patients.

Methods

All 451 General Practitioners in Leicestershire were asked using a postal questionnaire about their age and BP criteria for initiating anti-hypertensive treatment, their usual first line anti-hypertensive therapy and their use of specific NP therapies in those aged ≥ 65 years.

Results

366 (81%) of questionnaires were returned. 96% of General Practitioners would treat 'high BP' in patients aged up to 80 years; 36% of respondents had no age limit for starting anti-hypertensive treatment whilst in those who did, it varied from 70 to 99 years. The median BP for starting treatment in a patient aged 65-70 years was 170/100 mmHg with a range of 140-220/90-120 mmHg, the BP criteria for treatment increased with age. Isolated systolic hypertension would not be treated by 34% of respondents.

The majority of doctors would use pharmacological therapy, particularly thiazide diuretics as first line treatment, only 17% of GP's claimed to use NP methods as first line therapy. The routinely recommended methods were weight reduction (90%), a decrease in alcohol intake (59%), increasing exercise (37%), dietary salt restriction (36%), relaxation (25%) and increasing potassium intake (2%).

Conclusions

Although almost all General Practitioners would treat 'high BP' in older adults, at least up to the age of 80 years, the majority would use pharmacological rather than NP therapy for first line treatment. In addition the level of BP at which treatment was initiated varied markedly between doctors and the median SBP and DBP levels were higher than those recommended by national and international hypertension guidelines. There is potential for a more widespread use of NP therapy in elderly patients currently diagnosed hypertensive and in subjects with milder degrees of hypertension who are not currently treated.

Introduction

There is evidence in general that various non-pharmacological (NP) strategies can reduce high BP (see chapter 1) and mounting evidence that elderly hypertensives can also benefit. How often such NP therapy is discussed and relevant advice given by general practitioners - who manage the vast majority of elderly hypertensive patients - is unknown. Previous studies on health education and promotion suggests that the full potential of the GP consultation is not realised (687,689). This may be explained by the shortage of time in the consultation, personality and interest of the doctor and scepticism of the benefit to be gained (688).

The use of various NP therapies as initial treatment in mild hypertension and its continued use combined with anti-hypertensive drug therapy is recommended in National and International Hypertension Guidelines (530), including those of the British Hypertension Society (531). The use of specific NP therapies and the extent of promotion of NP methods in general practice with regard to hypertension in older adults may be more limited than in younger subjects as the benefits of pharmacological anti-hypertensive treatment have only recently been demonstrated in the elderly. However, the prevalence of hypertension increases with age and the absolute benefit of anti-hypertensive treatment in terms of cardiovascular disease prevention are greater in older than younger patients. The elderly may therefore have as much or more to gain from NP strategies to lower BP than younger subjects. However the extent to which NP therapy is recommended in the management of hypertension in elderly patients has so far not been explored.

Hypotheses

(a) NP therapies are infrequently recommended in elderly hypertensive patients.

(b) there is potential for a more widespread use of NP therapy in the management of elderly hypertensive persons than currently exists.

Specific Objectives

To determine:

1) the age and BP criteria for initiating anti-hypertensive treatment in elderly patients,
2) the proportion of general practitioners in Leicestershire who would use pharmacological or NP methods as first line treatment of elderly hypertensive patients,
3) the type and frequency of use of such NP methods in elderly patients.

Methods

A survey on aspects of general practitioners management of hypertension in elderly persons was undertaken by use of a questionnaire. The questionnaire was posted with an accompanying letter to all 451 Leicestershire general practitioners on the Family Practitioner Committee list in 1991. The accompanying letter explained the objectives of the study and that data would be analysed anonymously. General practitioners were urged to answer questions in terms of their actual practice rather than what they considered best practice. Returned forms were identified by a number specific for each doctor. Those not responding after six weeks received a second mailing; there was no further intervention if a reply was not received after a further six weeks.

The areas of interest covered by the questionnaire are given below and a copy of the survey questions are shown in appendix 2;

(a) whether an age limit was imposed on treating a person with definite sustained hypertension;

(b) the BP level at which treatment would be initiated in a newly diagnosed hypertensive person of various ages;

(c) the level to which the SBP would have to be raised in a person > 75 y with isolated systolic hypertension (SBP ≥ 160 and DBP ≤ 90 mmHg) before considering treatment;

(d) the anti-hypertensive treatment of first choice and

(e) the non-pharmacological methods routinely used.

Analysis

Results were entered into a database on a personal computer and analysis was carried out on the Minitab statistical package. Data were entered on an anonymous basis, the GPs specific number was not entered into the PC. Medians and percentages were calculated as appropriate.

Results

A total of 366 (81%) of questionnaires were returned, six were blank, leaving 360 (80%) suitable for analysis.

For a patient with a confirmed BP of 199/115 mmHg, 36% of respondents had no age limit for initiating treatment; of the 58% who did the median age limit was 80 (range 70-99) years. There was considerable variation in the systolic and diastolic BP values at

which doctors would start treatment in each age group, with levels tending to increase with age as shown in table 8.1.

		Median (range) BP (mmHg) for starting treatment	
Patients Age (years)	**Treating n (%)**	**Systolic**	**Diastolic**
65-69	353 (98)	175 (140-220)	100 (90-120)
70-79	346 (96)	180 (150-240)	106 (90-120)
80-89	223(62)	190 (150-240)	110 (90-135)
≥90	112 (31)	195 (150-240)	110 (90-135)

Table 8.1 The number of general practitioners treating elevated BP and the median BP and range at which antihypertensive therapy would be started, if at all, in relation to a patients age.

As shown in table 8.2 isolated systolic hypertension would not be treated at all by 34% of doctors, while only 16% would treat if SBP was under 200 mmHg .

SBP (mmHg)	No (%) who would treat
160-179	4 (1)
180-199	53 (15)
200-220	104 (29)
>220	68 (19)
Would not treat	121 (34)
Don't know	10 (3)

Table 8.2 Number (percentage) of general practitioners who would treat isolated systolic hypertension at the SBP level shown and those who would not treat.

Sixty-two (17%) of respondents claimed to use NP methods as first line therapy, the remainder using drug therapy, mostly thiazide diuretics. Only 25 (7%) of doctors indicated that they would rarely or never use NP therapy.

Ninety-four percent of general practitioners completed the question regarding routine use of specific NP therapies and the results are shown in table 8.3. The most commonly advised therapy was weight reduction, used by 90%, followed by reduction of alcohol intake (59%), an increase in exercise (37%), dietary salt restriction (36%), relaxation therapy (5%) and an increase in potassium intake (<2%).

Non-pharmacological therapy	n	(%)
Salt restriction	125	36
Increased Potassium	5	2
Weight reduction	313	90
Alcohol reduction	205	59
Relaxation therapy	90	25
Exercise programme	129	37
Don't know	7	2

Table 8.3 The number (%) of general practitioners routinely using the listed non-pharmacological therapies.

Discussion

Use of anti-hypertensive therapy in elderly patients

Most general practitioners would treat patients with elevated BP up to the age of 80 years where the benefits of anti-hypertensive treatment have been shown with intervention studies. However the benefit of anti-hypertensive treatment in the very elderly is unclear (690); not all epidemiological studies have shown a survival disadvantage from high BP in this age group. In the SHEP study (75) anti-hypertensive treatment reduced strokes equally in those < 80y and > 80 years although the EWPHE (73) and STOP (76) studies reported no benefit from treatment in subjects aged > 80-84y. Despite this

uncertainty it was the reported practice of the majority of doctors surveyed to treat patients up to the age of 90 years and often beyond this age.

The reported median BP level at which anti-hypertensive treatment would be instituted increased with age and for patients 65-79 years was greater than the criteria (SBP ≥160 mmHg and /or DBP ≥ 90 mmHg) for starting anti-hypertensive therapy given by the British Hypertension Society guidelines and other relevant organisations (530, 531). The range of BP levels over which such therapy would be introduced was also wide suggesting a readiness to treat the smaller number of patients with very high BP levels and a reluctance to intervene in the much larger number of older subjects with more mild BP elevations, a group who remain at considerable risk from cardiovascular disease. In addition one third of GP's would not treat isolated elevations of SBP, for the majority that did very high elevations of SBP would have to be recorded. Overall these results suggest the need for more widespread and appropriate use of anti-hypertensive therapy in elderly patients with mild hypertension.

Use of non-pharmacological therapy

The majority of doctors reported using pharmacological therapy, in particular thiazide diuretics as first line treatment of a newly diagnosed elderly hypertensive. A minority claimed to use NP methods first line although only 7% claimed never to use such methods at all suggesting that many GPs may use NP therapy in conjunction with anti-hypertensive drug treatment. However, national guidelines from the British Hypertension Society (531) recommend using NP methods as initial therapy in mild to moderate hypertension during the 3-6 month assessment period whilst deciding the need for drug treatment.

The most commonly used NP methods, weight and alcohol reduction are probably the most effective used alone and in combination with anti-hypertensive drugs making these rational choices as the most popular methods (691). Although increased aerobic type exercise has been shown in younger hypertensive patients to have hypotensive effects, specific counselling on this was infrequently given to the elderly. Advice on alteration of dietary electrolyte intake was not commonly given by GPs, which is surprising in the case of sodium restriction which is popularly believed to be a method for reducing high BP. As described in chapter 4 there is evidence that some elderly hypertensives can lower their BP by reducing their sodium intake by 80 mmol/24 h. The usual level of sodium intake (measured as 24 h urinary excretion) in elderly hypertensive persons is not well characterised. Although estimates from the study described in chapter 4 suggest a

level of 164 mmol/24 h, study of a larger sample of treated elderly hypertensive patients has shown an average 24 h urinary sodium excretion of 126 mmol, only one quarter had a sodium excretion ≥ 150 mmol/24 h. These data suggest that the opportunities for a significant reduction in BP from restricting sodium intake to moderate levels of 80-100 mmol/24h are perhaps limited.

Advice on increasing potassium intake was reported to be given by very few respondents yet as described in chapter 5 this may be a more effective method of lowering high BP than reducing sodium intake. In addition potassium intake has been reported to be lower in elderly compared to younger persons (334), although the mean potassium excretion in older hypertensives estimated from the run-in phases of studies described in chapters 4 and 5 (60-66 mmol/24h) was similar to that reported in other studies of middle aged groups. In the control groups of 15 studies of potassium supplementation shown in table 1.9, the mean 24 h urinary potassium excretion was 60 mmol (95% CI 54-65 mmol/24h). There is the potential for the majority of older hypertensives to increase their dietary potassium intake moderately to levels of 80-90 mmols/24h.

There is little evidence for relaxation therapy leading to sustained reduction in BP and in view of the time required to be invested in such therapy it is surprising that up to one-quarter of GP's report advising this method.

National and international recommendations for lifestyle changes

Reports from several organisations involved with the management of hypertension recommend the use of various lifestyle modifications to lower high BP. The fifth Joint National Committee on the Detection Evaluation and Treatment of High BP (JNC V) report (530) recommends lifestyle methods be used as definitive or adjunctive therapy for hypertension and suggests that physicians should vigorously encourage their patients to adopt them. The lifestyle modifications recommended by the JNC V (530), the World Health Organisation / International Society of Hypertension (WHO/ISH) (645) and the BHS (531) are shown in table 8.4. The following are not recommended by these organisations, either because of insufficient evaluation or little evidence of benefit: increasing calcium and magnesium intake, altering dietary fat intake and relaxation and biofeedback therapies. The WHO/ISH (645) also advises that efforts to lower BP by lifestyle modifications should normally precede decisions about drug treatment for mild hypertension. Such methods are also recommended for patients with more severe hypertension in whom drug requirements could be reduced.

	JNCV	BHS	WHO/ISH
Weight reduction in overweight subjects (>10% of ideal weight)	✓	✓	✓
Restriction of alcohol intake (≤ 2u/day)	✓	✓	✓
Regular aerobic exercise, eg, walking, cycling, swimming	✓	✓	✓
Reduce sodium chloride intake (<100 mmol/day)	✓	✓	✓
High dietary potassium intake (from food source)	✓	x	x
Avoid high saturated fat intake	x	✓	x
Increase calcium intake	x	x	x
Increase magnesium intake	x	x	x
Use of relaxation	x	x	x
Use of biofeedback	x	x	x

✓ recommended
x not recommended
* all recommended cessation of smoking

Table 8.4 Lifestyle methods that can be used as definitive or adjunctive therapy for hypertension recommended by the Joint National Committee on the Detection, Evaluation and Treatment of Hypertension (JNCV), the British Hypertension Society (BHS) and the World Health Organisation/International Society of Hypertension (WHO/ISH)

Beard et al (692) in a report dealing specifically with the management of hypertension in the elderly also recommend weight reduction, exercise, and moderation of alcohol and salt intake, either alone or in combination with anti-hypertensive drugs. They considered moderation of salt intake to be particularly beneficial in elderly patients, in those with cardiac failure and on diuretics. Dietary potassium supplementation was recommended, not so much for its hypotensive effects but for possible benefits in protecting against stroke. It appears from the present survey that many of these recommendations are not currently being put into practice.

Conclusions

Results from this survey of reported practice in the management of elderly hypertensive patients suggest that there is a reluctance by many doctors to treat mild hypertension in older persons and to use NP methods as first line therapy. Although some methods considered effective (weight and alcohol reduction) were advised by many doctors, other life-style changes (an increase in exercise and potassium intake) were not. This may be related to the paucity of data on the effects of NP therapy on BP levels and cardiovascular disease in the elderly and how best to implement such therapy.

CHAPTER 9

CONCLUSIONS

The work reported in this thesis sought to test the following hypotheses in elderly subjects (a) that non-pharmacological intervention in the form of moderate dietary sodium restriction, potassium supplementation and a reduction in caffeine ingestion could reduce BP levels assessed by conventional and 24 h ABPM, (b) that non-pharmacological therapy could satisfactorily be substituted for anti-hypertensive drug treatment in elderly hypertensive subjects, (c) that non-pharmacological methods are infrequently used by general practitioners as initial therapy for hypertension and (d) that the automatic BP monitor used in the studies was of acceptable accuracy and that average BP levels obtained by 24 h ambulatory BP monitoring were more reproducible than conventionally obtained BP measurements.

At the initiation of the studies undertaken for this thesis, 24-h ABPM had rarely been conducted in elderly subjects and there were no data on the accuracy or reproducibility of such BP measurements in this age group. The initial study in normotensive and hypertensive elderly subjects showed that the SpaceLabs 90207 ambulatory BP monitor was of acceptable accuracy according to the AAMI and the BHS criteria for the measurement of DBP. For the measurement of SBP the automatic monitor obtained a grade 'C' using the BHS criteria but was outside the acceptable limits given by the AAMI. However, the SBP discrepancies between the SpaceLabs 90207 and a mercury sphygmomanometer increased with increasing SBP level and mean arm circumference. When subjects with the highest SBP ($\geq$ 200 mmHg) were excluded from analysis the monitor was of acceptable accuracy according to the AAMI criteria. Therefore over the range of normotension and mild to moderate hypertension the SpaceLabs 90207 BP monitor was found to be of an acceptable degree of accuracy in elderly subjects. All comparisons between the BP monitor and the mercury sphygmomanometer have however been conducted in static conditions, there is a need to test ambulatory BP devices for accuracy during truly ambulatory conditions.

The reproducibility of mean 24-h ambulatory BP derived values in elderly hypertensive subjects over periods of 4-40 weeks was found to be significantly improved compared to the mean of three clinic BP recordings. A minimum of 30 BP readings spread throughout the daytime was found necessary to significantly reduce intra-individual BP variability, measured as the standard deviation of the differences, when compared to 3 clinic BP readings. Age, BP level or time between measurements did not significantly influence BP reproducibility. The greater degree of reproducibility of mean 24 h

ambulatory BP values over mean clinic measurements increased the power of the planned intervention studies to detect a given BP difference.

It has been predicted from analysis of observational and intervention studies conducted in young and middle aged subjects that elderly persons would show a greater hypotensive response to a given degree of sodium restriction. In chapter 4 it was reported that moderate sodium restriction of 80 mmol/day in elderly hypertensive subjects resulted in a significant reduction of clinic supine SBP only, the mean fall in average 24-h BP levels were not significant. However the 95% confidence intervals for the changes in clinic SBP (-1 to 12 mmHg) and DBP (-3 to 5 mmHg) and 24 h SBP (-3 to 12 mmHg) and DBP (-2 to 6 mmHg) are compatible with the predicted reduction in BP of 11/4 mmHg for the degree of sodium restriction achieved and age of the subjects. Study of a larger sample size may have given greater precision to these estimates of BP change. On considering individual BP responses to sodium restriction, as reported in younger subjects, a large degree of variability was seen. Subject characteristics predicting a hypotensive response to 24 h SBP and DBP were a lower PRA rise following sodium restriction and greater subject age; no predictors of response to changes in clinic BP were identified. Further studies are required to identify which elderly subjects will have a blunted renin response and a reduction in BP with sodium restriction. The moderate degree of sodium restriction achieved in this trial was well tolerated by all subjects, in particular there was no evidence of orthostatic hypotension. However sodium restriction was maintained for only 5 weeks and the hypertensive subjects were a selected group of healthy independent elderly persons. Whether moderate sodium restriction would be so well tolerated over a longer duration and in a group of frailer elderly persons can only be answered by further studies. In general moderate sodium restriction in the short term is of modest hypotensive efficacy in some elderly hypertensive subjects although it may produce clinically significant BP reductions in certain older hypertensive subjects; methods to easily identify those who respond in this way are required. The moderate degree of sodium restriction aimed for (80-100 mmol/day) can be achieved without major dietary changes for most people; a reduction in the use of certain convenience and tinned foods and by less or no use of salt in cooking or at the table. As shown in chapter 7 the number of elderly hypertensive persons with high sodium intakes ($\geq$ 150 mmol/24 h) is relatively small so the overall effectiveness of this measure must be called into question.

In contrast to the modest BP falls with sodium restriction, four weeks of moderate potassium supplementation in elderly hypertensive subjects resulted in a clinically and statistically significant fall in clinic SBP and DBP and mean 24-h SBP. In addition a reduced potassium supplement taken for an additional four months maintained the original BP reductions. Increasing dietary potassium intake by an equivalent amount (approximately 40 mmols/day) could be achieved through simple dietary changes e.g. taking two pieces of fruit, an extra portion of vegetables and a glass of fruit juice daily. However this level of potassium intake represents an increase of between a half and two-thirds of the usual intake for the elderly group studied. It is unclear if this level of intake could be maintained in the long-term although work in younger subjects has suggested dietary potassium intake may be increased by 20 mmol daily for a period of 1 year. In comparison with studies of potassium supplementation in younger subjects there is no evidence of a greater clinic hypotensive effect in elderly hypertensives, although there were no equivalent studies in younger subjects using 24 hour ABPM with which to make comparisons. The potassium supplementation was well tolerated with specifically no episodes of hyperkalaemia seen after 4 weeks of 60 mmol daily or an additional 4 months of a 48 mmol daily potassium supplement. Again the subjects studied were a selected group of healthy elderly hypertensives with no evidence of significant renal impairment. It is unclear how well tolerated a long term dietary potassium increase would be in less healthy persons, those taking pharmacological agents that may reduce potassium excretion and those subjects with renal impairment who may be at risk of hyperkalaemia. The mechanisms underlying the hypotensive effect of potassium were not investigated and remain uncertain despite many recent studies, further investigation of the mechanisms involved should prove of value in understanding the pathogenesis of hypertension and perhaps also in its management.

The effect of regular caffeine consumption on clinic and 24 h ABP values was described in chapter 6. Four weeks of twice daily caffeine intake (250 mg twice daily), the equivalent of 4-5 cups of coffee was found to have no significant pressor effect in elderly persons with a wide BP range. A small pressor effect ($\leq$ 3 mmHg in SBP) could not be ruled out as the study did not have sufficient power to detect a change of this magnitude. Consistent with the absent, or at most small, pressor effect of chronic caffeine ingestion, no changes in catecholamines or PRA levels were detected, however caffeine could be affecting other physiological systems. Although a potential 3 mmHg rise in SBP may not be clinically significant on an individual basis, it may have an important population effect.

In addition caffeine intake cannot be purely equated to drinking caffeine containing beverages, such as coffee and tea which contain many other biologically active compounds. The epidemiological data relating caffeine containing foods, mainly coffee, to coronary heart disease and BP remains controversial. Further studies on the long-term effects of caffeine containing beverages on the cardiovascular system in man and on biochemical systems are required to fully elucidate any possible cause and effect.

In Chapter 7 the effects of anti-hypertensive drug withdrawal in previously diagnosed hypertensive elderly subjects and substitution with non-pharmacological therapy on the course of BP for up to two years was examined. A quarter of elderly hypertensive patients with initially controlled BP levels were able to maintain normotension off drug treatment for over one year and one-fifth for two years. The majority of subjects returning to anti-hypertensive drug treatment did so within the first 3 months. Predictors of return to hypertension - a higher on treatment casual and 24 h ambulatory SBP level, higher body mass index and greater ECG [SV_1+RV_6] voltage - were identified. The overall potential in a mainly clinic based group of elderly treated hypertensives for a successful trial of anti-hypertensive drug withdrawal was limited by the high prevalence of poorly controlled hypertension. The potential for non-pharmacological intervention with regard to weight loss was substantial, with almost half of an elderly hypertensive group having a BMI > $26kg/m^2$, a level above which total cardiovascular mortality has been shown to increase in elderly persons. The high prevalence of excess weight in older hypertensives has particular relevance as being overweight was a predictor of return to hypertension on withdrawal of drug therapy. In general there was a greater potential for advocating a moderate increase in dietary potassium intake, where levels of urinary excretion were generally found to be low, than for advising a moderate reduction in dietary sodium intake where almost 50% of subjects had levels of urinary excretion < 120 mmol/24 h, thereby limiting any effect on BP of a reduction in sodium to 80-100 mmol/24 h. Only a small minority of the group reported that they were current smokers or had a high alcohol intake suggesting a reduction in use of either would have little significant effect on the BP levels or cardiovascular risk of the whole group, although on an individual basis smokers and heavy drinkers would benefit from abstaining.

Although the present study showed that with non-pharmacological therapy 20% of elderly hypertensives could remain well controlled for up to 2 years without anti-hypertensive drug treatment, it is not possible to say, because of the study design, what course the BP would have taken if non-pharmacological therapy was not used or if drug

treatment had been continued. There is now a need for a placebo controlled randomised study of anti-hypertensive drug treatment withdrawal followed by non-pharmacological intervention versus continued drug therapy.

The Leicestershire GP Survey of Hypertension Management in the Elderly revealed that only a minority of general practitioners reported use of non-pharmacological methods as first-line therapy in elderly hypertensive patients. Of those that would recommend such therapy weight and alcohol reduction were the most commonly advocated, but less than a half would recommend exercise, sodium restriction, and only 2% increased potassium intake. In addition the level of BP at which hypertension would be treated by any method was substantially higher than levels currently recommended by the BHS. In particular isolated systolic hypertension a not uncommon finding in elderly hypertensives would not be treated at all by one third of respondents and only by a half if SBP exceeded 200 mmHg. Overall there is potential for a more widespread use of non-pharmacological therapy in elderly patients currently diagnosed hypertensive and in subjects with milder degrees of hypertension who are not currently treated.
As the majority of elderly hypertensive persons are treated in general practice the efficacy and feasibility of non-pharmacological therapy needs to be conducted in this setting.

Increasing dietary potassium intake and reducing sodium intake together with other non-pharmacological methods can reduce BP in elderly hypertensive patients and it allows some to be successfully withdrawn from anti-hypertensive drug treatment. There is a greater potential for the use of non-pharmacological methods than is currently practised and a need for better control of hypertension in elderly hypertensive persons in this age group. There are approximately 1 million persons aged over 65 years with hypertension in the UK, the use of non-pharmacological methods has the potential to help reduce high BP levels without a concomitant increase in anti-hypertensive drug use.
Such anti-hypertensive agents are associated with adverse side effects, some predictable and others which have a more subtle effect on the quality of life; whether the use of non-pharmacological methods would result in a lower prevalence of adverse effects whilst showing similar efficacy at lowering BP and cardiovascular morbidity and mortality for a similar cost is unknown.

Further work

Despite the demonstration of significant hypotensive effects that can result from using certain non-pharmacological therapies to lower BP in younger and increasingly now in older hypertensives there remains much scepticism regarding the benefits of such therapy in comparison to pharmacological anti-hypertensive treatment. This is not surprising given that drug therapy can easily be prescribed, its costs are known and such therapy can reduce not only BP levels but also cardiovascular events. In contrast non-pharmacological therapy can be difficult to effectively implement, it requires more resources, particularly time from a health professional and a greater degree of patient involvement and compliance compared to taking tablets. Even if such therapy is initially successful maintaining life-style changes e.g. weight loss and increased exercise in the long term is perceived to be difficult. In addition non-pharmacological methods have not been tested in randomised controlled trials involving elderly subjects, particularly those $\geq$ 70 years with regard to their effects on cardiovascular morbidity and mortality and the long term effects on other cardiovascular risk factors e.g. left ventricular hypertrophy and serum lipids have rarely been studied. In the Treatment of Mild Hypertension Study involving subjects aged up to 69 years anti-hypertensive drug treatment and life-style therapy produced similar changes in reduction of left ventricular mass. There is also a perception that life style methods will result in fewer adverse effects and improve quality of life compared to anti-hypertensive drug treatment although in practice this may not always be so. In one of the few trials where this has been studied, the Treatment of Mild Hypertension Study found treatment with a beta-blocker or a thiazide diuretic produced a modest increase in overall quality of life measures compared to life-style therapy only. In the Trials of Anti-hypertensive Intervention and Management use of a moderate sodium restricted diet resulted in increased fatigue although this was not a problem reported in the Trials of Hypertension Prevention study where psychological well being scores increased on the restricted sodium diet compared to a control group. There have also been no studies in the elderly to assess the efficacy of non-pharmacological therapy in persons with 'high normal' BP levels who remain at an increased risk of cardiovascular disease compared to those with a lower BP level and who make up the vast majority of those at risk. In addition how best to change peoples behaviour and attitudes so as to encourage and effectively implement life-style changes has received very little attention. Extra resources such as dieticians, nurses or counsellors will be required, with the potential of making the cost-benefit ratio for treating hypertension unfavourable compared to drug treatment.

Specifically there is a need for further studies to:

* examine the effect of other non-pharmacological therapies that have so far not been adequately tested in elderly hypertensive persons e.g. weight loss and exercise regimes.

* investigate the long term effect of combined life style therapies in comparison to drug treatment on BP, cardiovascular risk factors and cardiovascular morbidity and mortality in prospective randomised controlled studies.
* assess the cost-benefit, feasibility and effect on quality of life of non-pharmacological therapy versus drug treatment in a wide range of elderly hypertensive persons.

* evaluate the efficacy and overall benefit of non-pharmacological therapy in elderly subjects with 'high normal' BP levels.

* examine methods of effectively implementing and maintaining life-style changes.

Many questions remain to be answered regarding the role of non-pharmacological therapies in the management of high BP in the elderly, this thesis merely acts as a starting point.

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Appendix I

Low Sodium Diet. Information given to subjects to achieve a sodium intake of 80-100 mmol/24h

Restriction of discretionary salt:

(i) Try not to add salt during cooking, if you have to use the salt substitute (Lo-Salt) provided.

(ii) At the table try tasting food prior to adding salt. If it is unpalatable use a little of Lo-Salt, try reducing the amount you use every few days.

Add flavour to your food by using herbs and spices.

Avoidance of foods with a high salt content.

Most manufactured foods contain a large amount of added salt, try to avoid these, eg.

(i) Tinned foods - including vegetables, beans, soups. If possible prepare your own vegetables, etc.

(ii) Sauces/stocks/gravy, eg, tins/jars/packets of pasta sauce, chicken stock, gravy etc. Try preparing your own sauce.

(iii) Bread. If you eat several slices a day, eg, in sandwiches, toast, etc, try to limit yourself to no more than 3-4 thin slices/day.

(iv) Meats, eg, sausages, bacon, gammon and ham all contain a large amount of salt. Try eating less of this type of meat, instead try poultry or fish.

Foods with a low salt content

Most fresh foods have a low salt content. Try eating more freshly prepared vegetables, eg, potatoes, carrots, peas, broccoli, parsnips.

Take in more fruit, eg, apples, oranges, bananas, also use fruit in baking, eg, tarts, pies.

A list of foods to choose and avoid are given in the next sheet.

Appendix I (cont)

Foods to Choose	Foods to Avoid
Meat	
Plain roast meats Chicken/Turkey	Bacon, ham, tinned meat, eg, corned beef, salami, bought pies, meat paste
Homemade (without salt) - burgers - sausages - pates	Burgers, sausages, pate.
Fish	
All fresh fish, eg, white fish, salmon, tuna, mackerel	Tinned fish, eg, pilchards, sardines, tune (brine/oil). Shellfish, eg, prawns, crab, cockles. Smoked fish, eg, kippers, bloaters, smoked haddock Fish pastes Fish in sauce
Dairy	
All milks Low salt butter/margarine Cottage cheese Unsalted cream cheese Yoghurt Egg	Salted butter/margarine All other cheese
Vegetables/Fruit	
All fresh/frozen vegetables Tinned vegetables in water Low salt baked beans Pulse vegetables, eg, butter beans, chick peas, cooked without salt or tinned in water. All fresh/tinned dried fruit.	Ordinary tinned vegetables Ordinary baked beans Tinned pulse vegetables

Appendix I (cont)

Foods to Choose	Foods to Avoid
Savoury Snacks	
Unsalted nuts Salt free crisps (ie, varieties with salt packet removed)	Salted nuts Plain and flavoured crisps and other savoury snacks. Twiglets Savoury biscuits, eg, Ritz, cheeselets.
Gravies	
Gravy browning	Stock cubes, gravy, salts, gravy powders, gravy granules, cartons of gravy.
Miscellaneous	
Homemade soup (without salt) Herbs and spices (fresh or dried) Worcester sauce Mint sauce Vinegar, pepper, garlic, lemon juice, mustard.	Tinned and packet soup Pickles, chutney, sandwich spread, olives. Packet and boiled sauces. Oxo, Bovril, Marmite and other yeast extracts. Tinned ravioli and spaghetti

Appendix II

Relevant sections from the questionnaire sent to all Leicestershire General Practitioners.

How does the level of blood pressure influence your decision to treat?

1 If you decided to initiate treatment in a 70 year old which of the following treatments would you use?

	First Choice (tick one)	Rarely or never use (tick as appropriate)
Calcium antagonist		
Thiazide diuretic		
ß-Blocker		
α - Blocker		
Methyl Dopa		
ACE Inhibitor		
Non Pharmacological Methods		
Don't know		

2 If you do use non-pharmacological methods which do you use routinely (tick as appropriate).

Salt restriction	
Potassium supplements	
Weight reduction	
Alcohol reduction	
Relaxation therapy	
Exercise programme	
Don't know	

3 Is there any age above which you would not institute therapy for a blood pressure of 199/115 mmHg?

Yes : above age _____

No age limit ☐

Don't know ☐

Appendix II (cont)

4 At what blood pressure level would you usually start treatment in the following age groups?

Age group	Systolic	Diastolic	Would not treat any level	Don't know
65-69				
70-79				
80-89				
90 and over				

5 Would you treat a patient aged over 75 with diastolic blood pressure below 90 mmHg but systolic pressure:

Systolic BP	Tick one
160 - 179 mmHg	
180 - 199 mmHg	
200 - 219 mmHg	
Would not treat	
Don't know	

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