ELECTROLYTES IN EARLY PRIMARY HYPERTENSION

AN EPIDEMIOLOGICAL APPROACH

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ELECTROLYTEN IN VROEGE PRIMAIRE HYPERTENSIE

EEN EPIDEMIOLOGISCHE BENADERING

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE
GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR M.W. VAN HOF
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 18 JUNI 1986 DES NAMIDDAGS
TE 2.00 UUR

DOOR

DIEDERICK EGBERTUS GROBBEE

GEBOREN TE ZWOLLE

Promotiecommissie

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The principal difficulty in your case, remarked Holmes, ... lay in the fact of there being too much evidence ... Of all the facts which were presented to us we had to pick just those which we deemed to be essential and then piece them together in their order, so as to reconstruct this very remarkable chain of events.

Sir Arthus Conan Doyle
The Naval Treaty

Acknowledgment

The studies in this thesis were possible by a generous grant from the Netherlands Heart Foundation. The EPOZ study, the framework in which most of the studies were conducted, was supported by grants from the Netherlands Prevention Fund. Additional funding was kindly provided by SANDOZ BV, and the NIZO laboratory Ede.
Contributions to various parts of the studies were made by CIBA BV Arnhem, NISTRIA BV Moergestel, UNITED DAIRYMEN Woerden and the Pharmaceutical Department, Erasmus University Rotterdam.
Biochemical determinations in some of the studies were possible by the invaluable contribution of the laboratory of the Department of Internal Medicine I, Erasmus University Rotterdam, the endocrinological laboratory of the Bergweg Ziekenhuis Rotterdam, the laboratory of the Department of Internal Medicine of the Zuider Ziekenhuis Rotterdam, and the NIZO laboratory, Ede.

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Some of the paragraphs in this thesis will be published as an article. The following co-authors have contributed to these studies and the preparation of the manuscripts:

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Chapter 6.	Paragraph 6.1:	A. Hofman, J.T.R.C. Roelandt, F. Boomsma, M.A.D.H. Schalekamp, H.A. Valkenburg.
	Paragraph 6.2:	A. Hofman.
Chapter 7:		A. Hofman.

INTRODUCTION

1.1 Rationale

In a letter I received from Dr Morris J. Brown he wrote 'As regards the pathogenesis of hypertension ... I am becoming firmly of the view that the study of established hypertension is akin to studying the stable after the horse has bolted. Somehow we have to derive methods for studying patients while the hypertension is still developing'. In these two sentences Dr. Brown has formulated the basis of this thesis.

At least three characteristics of "primary hypertension" make the study of this condition in epidemiology highly attractive and profitable. Firstly, hypertension is no disease in the classical sense, but a risk indicator for cardiovascular morbidity and mortality.(1) Secondly, and in close combination with the first characteristic, hypertension is defined by an arbitrary deviation from a norm, a quantitative rather than a qualitative phenomenon.(2) These two notions provide the opportunity to investigate determinants of elevated blood pressure in relation to blood pressure distributions as observed in the population. Moreover, dynamic characteristics and responses of blood pressure to intervention may be studied in subjects not yet eligible for pharmacologic treatment of high blood pressure by conventional adult clinical standards, or even in normotensive individuals. Thirdly, the concept of an elevated blood pressure is not limited to a certain age group. Indeed, evidence is accumulating that the development of primary hypertension is the consequence of a process that starts early in life.(3) Therefore, the use of epidemiological methods, i.e., aiming at the study of health and illness in populations,(4) in young subjects with an increased risk of developing frank hypertension in the future, may clarify mechanisms involved in the pathogenesis of hypertension and may direct ways of intervention on elevated blood pressure at an early stage.

The studies presented in this thesis were conducted on the basis of this reasoning. The subjects that participated in the investigations were characterized by a blood pressure level persistently in the upper part of the blood pressure distribution for their age group. In addition, for a number of variables they were compared with normotensive youngsters derived from the same population, and thus sharing the same environment and background. This was made possible by the unique availability of data on blood pressure and related characteristics from a cohort of 1,597 children and young adults living in Zoetermeer, who took part in a follow-up study comprising yearly examinations since 1975 (the EPOZ study).

1.2 Structure of the report

The main investigations of this thesis are presented in chapter 6. They are formed by two randomized trials on the effect of sodium restriction, potassium supplementation and calcium supplementation on the blood pressure of young subjects with mildly elevated blood pressure. Apart from the evaluation of the efficacy of the intervention, the objectives of these studies were to provide further insight in mechanisms involved in the association between dietary electrolytes and blood pressure. In chapter 2, some methodological concepts of intervention studies, in particular of randomized trials, are discussed. Chapter 3 and 4 comprise brief reviews on aspects of the pathogenesis of early primary hypertension, and the parts played by sodium, potassium and calcium. Some observations on differences in variables potentially associated with elevation of blood pressure between hypertensive and normotensive subjects, are presented in chapter 5. Finally, chapter 6 will deal with theoretical and practical aspects of non-pharmacologic intervention on high blood pressure in childhood.

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Chapter 2

THE RANDOMIZED TRIAL IN EPIDEMIOLOGICAL RESEARCH
methodological aspects

2.1 INTRODUCTION

This chapter will deal with methodological aspects of randomized trials. Randomized trials are referred to here, as experiments involving human subjects. In a way the randomized trial is a cohort study, from which it differs with regard to the planned nature of the intervention. A second characteristic of the randomized trial is that the effect(s) of the intervention are evaluted by comparing the intervention group to another group of subjects to whom no-intervention or alternative intervention is given: the control- or reference-group. Randomized trials are sometimes called randomized controlled trials, but in our view the addition of the word "controlled" does not add to a better understanding of what kind of study is indicated. It is hard to see how a randomized trial could be conducted "uncontrolled".

Although randomized trials can be applied to patients as well as to any other group of human subjects this particular type of study is in general known as the "clinical trial". This term is, however, a misnomer, as trials, like the ones discussed in chapter 6, may well be conducted in a non-hospitalized population, and may concern subjects without any known disease and thus are not "clinical" in a strict sense.

Trials come in many forms but, in the present context, they have one single necessary attribute in common: the element of randomization.(1) We will briefly discuss the role of randomization in trials, different classifications of trials, the advantages of blinding procedures, aspects and implications of patient selection and compliance, and finally some problems inherent to the use of experimental methods in humans. The statistical methods and techniques available to evaluate the hypothesis under study will not be discussed here, as a number of excellent reviews provides the necessary details.(2-6)

2.2 THOU SHALT RANDOMIZE

Uncontrolled trials have the potential to give a very distorted view of the efficacy of a therapy or any other intervention. The use of a control, or reference, group permits an internally valid evaluation of a treatment by limiting the possibility that confounding factors may account for the observed effect. In addition, to attribute an (enhanced) effect observed in a trial to the intervention applied, it is essential to take any possible measure to ensure that the two or more groups of subjects undergoing different intervention regimens, i.e., intervention and control groups, are not different in any relevant characteristic other than the treatment(s) received.

This basic principle of the conduct of trials aims at guaranteeing the internal validity of a study.

Attempts to evaluate therapeutic procedures can be traced back to prehistoric times.(7) Most early medical experiments are, however, more appropriately named quasi-experiments.(8) In quasi-experiments interventions are tested but the experimental or comparison group is not predesignated. Although the quasi-experiment may provide valuable information and still has a place in medical research, a major problem is formed by its high liability to be affected by bias as will be discussed below. It is mainly in the second part of this century that the concepts and scientific foundations of trials, have experienced increased attention and have shown an impressive growth. Pre 20th century medicine was largely based on uncontrolled observations, though some early attempts to change this attitude have been made.(7,9-11) Lind, in 1753, conducted a comparative trial of the most promising treatment of scurvy.(12)Twelve patients received six different treatments and after only six days a remarkable effect of oranges and lemons was observed. Although the statistical power of this study is without doubt rather limited, it was the first known example of the use of concurrent control subjects receiving alternative treatments, and the efficacy of the use of oranges and lemons in treating scurvy has been firmly established since.

One of the first approaches developed to reduce the possibilities of major differences in treated patients and control subjects was the procedure of assigning two treatments to alternate patients. This was applied by Fibiger in a trial of therapeutic serum against diphteria.(13) Helmont suggested to allocate each group to one treatment by casting lots.(14) Here a random act was introduced to form one or more groups. Amberson and coworkers divided twenty-four patients into two groups "individually matched" by the flip of a coin.(15) There are, however, disadvantages to this method as indicated by Armitage.(16) First, the two groups, however carefully matched, may differ substantially in some important characteristics which were ignored in the matching. Secondly, there is no way of measuring the relevant random error, since we cannot tell by how much the responses in the two groups might have differed if the treatments had been identical: there is inadequate replication.

The first genuine randomization procedure was applied by Fisher and MacKenzie in 1923 in agricultural experiments evaluating the effect of manure on the crops of different potato varieties.(17,18) The first randomized trial to evalute a medical intervention in human subjects was conducted by the Medical Research Council to test the efficacy of streptomycin in the treatment of pulmonary

tuberculosis.(19,20) The design of this study forms a landmark in the evolution of the randomized trial. In particular the contribution of Sir Austin Bradford Hill, member of the scientific committee that was responsible for the conduct of this trial, needs to be mentioned.(1) Several methods have since then been developed to carry out random assignment. Which procedure is chosen largely depends on the design of the trial.(16,21)

The principal advantage of the use of randomly selected control subjects over a non-randomized control group in a trial is the guarantee of internal validity of a study by the act of randomization.(22) Randomization can avoid systematic error, i.e., bias. The intervention(s) studied will be compared with no or another intervention under broadly similar circumstances.

The potential of randomization as a means of controlling confounders is accentuated in the study of intended effects, as are most intervention studies including the ones presented in chapter 6. According to Miettinen,(23) perceived risk or poor prognosis provides an indication for intervention. Therefore the mere act of selecting subjects for a particular study constitutes a confounder. Indication is by definition a correlate of the determinant under study, and thus a determinant of the null outcome.

It is often suggested that due to randomization, groups become "equal" or "similar". This is in general not true. Unless very large numbers are included, certain dissimilarities in the distributions of baseline characteristics will inevitably occur, due to random variation. It is, however, unlikely that these will affect in particular those characteristics potentially associated with a response to treatment. Moreover, these differences are not resulting from biased allocation, but stem from a stochastic procedure. Accordingly valid comparability is assured. The argument for randomization is not that no truths can emerge without it, but that without it moderate biases can easily arise.

Although not an advantage of randomization per se, in a randomized controlled design masking of the identity of treatment or the use of placebos is made more feasible, both on ethical and practical grounds, than when a predesignated reference group is used. As will be discussed later, blinding of both participants and investigators studies with blood pressure as the outcome variable is a prerequisite to reliably assess intervention efficacy.

Since the early work by Hill and others in the trials of Medical Research Council, the concept of randomization has been firmly established as part of the scientific basis of clinical trials. There remains, however, debate about the necessity of randomization. Various alternatives, in particular the use of historical controls, have been suggested.(24,25) Part of this controversy is based on the

question whether randomization is ethically justified when there is already some evidence suggesting that subjects may benefit from the intervention studied. Strictly spoken the ethical basis of the randomized trial depends upon the absence of convincing data about the relative merits of a planned intervention, but in general there are at least indications from previous animal or non-experimental observations that subjects on intervention will do better than controls.(26) Therefore, to quote Hill 'a trial should be begun at the earliest possible opportunity, before there is inconclusive though suggestive evidence of the value of treatment. Not infrequently, however, clinical workers publish favourable results on three or four cases and conclude their article by suggesting that this is the method of choice, and that what is required now is a trial on an adequate scale. They do not seem to realize that by their very publication they have vastly increased the difficulties of that trial or, indeed, made it impossible'.(20)

Another situation in which the use of randomized concurrent controls may be difficult is when a trial is used for a very rare or severe disease and the numbers of eligible patients available are small.(27) A clinical trial using historical controls will require a smaller sample size to test the null hypothesis with equivalent statistical power.(28)

On ethical grounds, and to overcome some of the difficulties mentioned above, it is most important to inform the subjects eligible for a study as extensively as possible before they enter into the trial. The legal basis for this so-called "informed consent" varies in different countries, and differences in practical implementation may be possible, but it has to be guarded as a leading principle in experimental medicine.(29)

2.3 DIVERSITY IN UNIFORMITY

Characteristics as diverse as purpose, duration, inference, design and a number of others have been used to classify randomized trials. Although often arbitrarily, some of these classifications are useful in interpreting findings of trials with different designs and composition of study groups. In the following paragraphs an attempt will be made to inventory the main distinctions that can be made between different types of trials.

2.3.1 Diversity due to the purpose of the trial.

Three major groups can be distinguished according to the purpose of the trial:

1. The efficacy of a certain therapeutic intervention like a drug,

a surgical procedure, or a change in diet is compared with either no intervention at all, or with another type of therapeutic intervention. The participants are, in general, patients having a certain well-defined disease, and the end-points used to evaluate the intervention effect are such as prolongued life expectancy or a change in natural history of the disease studied.

2. The assessment of intervention aiming at primary or secondary prevention through risk factor modification. The participants in this type of trial may belong to a defined population or are characterized by certain individual behaviors, biological factors, or aspects of the environment. Endpoints to evaluate the value of the intervention may be indicators of reduced risk, i.e., reduced incidence of the disease, or a reduction in mortality. Also, a change in the level of a risk factor may be used to evaluate the intervention. These studies are sometimes referred to as prophylactic trials or field trials.
3. The randomized trial can be used to identify causal or pathogenetic mechanisms involved in the aetiology of a disease or an increased risk. The experiment enables a maximum of control by the investigators over the study situation permitting to isolate the effect of one single factor on a defined condition. It is a very powerful tool in the study of causality. This type of study can be conducted in patients as well as in normal healthy subjects, depending on the questions under study.

Obviously, type 1 and type 2 studies can provide type 3 information. A trial can, however, be planned exclusively to assess and quantify the relation between a certain factor, like the intake of sodiumchloride, and another variable, like blood pressure. The intervention studies presented in chapter 6 show a combination of type 2 and type 3 purposes. By measuring not only the change in blood pressure, but also a number of outcome characteristics as indicators of mechanisms involved in blood pressure regulation, an attempt has been made to clarify the way whereby certain electrolytes may affect blood pressure.

2.3.2 Diversity due to the inference of the trial.

Another distinction, originally made by Schwartz and Lelouch,(30) primarily concerns type 1 and 2 trials. They propagated the concept of "explanatory" and "pragmatic" approaches. The explanatory trial seeks to determine whether one treatment is more effective than another or no treatment, while the objective of a pragmatic trial is to demonstrate which of two treatments, when administered in the

population at large, will give better results. In other terms, the first approach aims at understanding, while the second aims at decision-making. Consequently, treatment may be defined in two ways. Either ordinary current practice may be adhered to ("normal" conditions), or else more exacting conditions may be introduced which could only be met in the course of a trial ("laboratory" conditions). The implications of this distinction will be observed not only in the form in which a certain intervention is applied. Also, it may affect the selection of participants invited to enter the trial. In a pragmatic trial the study groups may need to reflect the whole spectrum of patients expected to be eligible for treatment. In an explanatory study, as in a type 3 study, one may select subjects expected to respond and/or comply well to a certain intervention.(31) This concept has been extended by Feinstein.(32) In his view the two approaches may have differences in impact, not only on policies aiming directly at answering the questions raised by practicing clinicians or workers in basic medical research, but also on the way in which the trial is designed and how the data are analyzed, in a manner that will yield unbiased results. Therefore Feinstein, somewhat sceptically, proposed to use the term "fastidious" instead of explanatory. Within this same framework Miettinen has suggested to describe the objective of a trial as "premise" or "practice" evaluation.(33)

2.3.3 Diversity due to the stage of an investigation.

A third classification is in particular used in the proces of the development and testing of a new drug:(21)

- Phase I trials. The first experiments with a new drug in humans. The main purpose of this type of study is to evaluate the clinical pharmacology and toxicity of a drug. Participants are volunteers and in general randomization procedures are not used.
- Phase II trials. These studies are conducted as an initial clinical investigation to assess the treatment effect. Small numbers of patients are closely monitored. Here also in general no randomization is carried out.
- Phase III trials. These trials are randomized clinical trials, in a strict sense, with purposes as summarized for type 1 trials. Participants in these studies are randomly allocated to one of two or more treatment groups.
- Phase IV trials. This term is used for postmarketing surveillance, monitoring of side effects, as well as for marketing and promotion activities itself.

This classification involves four types of so-called trials but only

one of these (phase III) can be regarded as a genuine randomized trial. Moreover, explanatory aspects most clearly form the basis for phase I and II trials, while phase IV is in general entirely pragmatic. The terms are, however, frequently used and they are not necessarily restricted to trials involving new pharmaceutical products.

2.3.4 Diversity due to duration of the trial.

Yet another classification of subtypes of experiments was made by Kleinbaum et al.(34) They defined three groups of trials based on the approximate duration of the study and the selection of subjects:

1. The laboratory experiment. This type of experiment has the shortest duration, hours to days, and is used to estimate acute biological or behavioural responses to a certain intervention, believed to be indicative of risk for a disease. The study population is seldomly representative of the target population and may indeed be very highly restricted.
2. The "clinical" trial. This type has a longer duration, from days to years, and is usually restricted to a selected population, such as a group of screened subjects, diagnosed patients or other volunteers.
3. The community intervention trial. This type of intervention study has a long duration, at least six months, and is conducted within a particular sociopolitical context of a naturally formed population (community). These studies are predominantly dealing with aspects of primary prevention by intervention on single or multiple risk factors.

2.3.5 Diversity due to the design of a trial.

The parallel-group design.

In the discussion on randomization in the previous paragraphs the element of comparison was based on comparisons between subjects. The subjects that are compared are randomly allocated to one, or more, treatment and reference groups. This method of conducting trials is called a "parallel-group" design, and it has implicitely been used as "the" example of a randomized trial in the two introductory paragraphs of this chapter.

The crossover trial.

As subjects tend to express a wide variation in response to treatment and the efficacy of most interventions is only moderate,

substantial numbers of participants are needed to reliably assess treatment effects in conventional parallel group studies.(35) This phenomenon has resulted in recent years in a number of very large multicentre randomized trials.(36) However, under certain conditions it is possible to apply two or more types of intervention, e.g. two types of drugs, to one subject over several equal periods of time.

The advantages of within-subject comparisons were already appreciated in the second half of the nineteenth century, when Claude Bernard conducted his first experiments in physiology by comparing the effects of successive treatments applied to one preparation.(37) The crossover study was introduced in medicine in 1950, when Quin and coworkers performed a trial on the effects of various agents on rheumatoid arthritis.

Within subject comparisons have several advantages over between subject comparisons. The influence of patient characteristics that determine the general level of response can be "subtracted out" of the treatment comparison. Biologic variation within an individual can, of course, not be removed, but if within subject variability is small relative to between subject variability, a crossover design based on a small sample of subjects can provide the same statistical power as a much larger parallel study.(38,39) Therefore, research questions may potentially be answered with the use of relative small groups, and/or the same study group may be used to answer multiple questions. This is illustrated by the crossover intervention study on sodium, potassium and blood pressure reported in chapter 6.

Crossover trials have besides advantages also some serious disadvantages, which make their use in many studies less attractive.(39,40) The main problem is, that one may compare the same subjects but one wants to compare "similar" baseline states.(32) If a patient receives one treatment for two weeks and a second treatment in the next two weeks, one must be assured that he has the same baseline state at the inception of both treatments. This condition may be affected in two ways. Firstly, serial changes resulting from either changes within an individual (like a reduction of symptoms), or from environmental changes (like seasonal influences), may make the first baseline status different from the second "baseline" status. Secondly, a particular treatment may have carry-over effects which influence the second period. As a remedy for the latter phenomenon a wash-out period, with no effective treatment, is sometimes used. Both the magnitude of serial and of carry-over effects can be tested by statistical methods. Moreover, various statistical techniques allow adjustments for trends and carry-over effects.(41) However, when the results of a trial suggest a definite interaction between treatments and periods, a treatment comparison should be based on the first period alone. A potential

hazard is, that tests lack sensitivity to adequately establish definite interaction, mainly because the statistical power of the study is based on the purpose of assessing treatment, not interaction, effects.

A special type of carry-over effect may occur when the treatment applied affects a deficiency resulting from long-term relative shortage of a certain factor, e.g. vitamin B-12 in pernicious anemia. In these instances, removal of the underlying cause of disease by eliminating the deficiency may seriously disbalance treatment periods.

As a general rule, as long as the existence and magnitude of carry-over effects of a certain intervention are not yet firmly established a crossover design should not be the first choice. This reasoning made us to conduct the sodium-potassium trial in a crossover design, whereas for the calcium trial a parallel group design was used (paragraph 6.2).

The effects of serial changes on the study outcome may be eliminated by an equal distribution of possible sequences of intervention between groups of equal number. This is realized by the randomization procedure commonly applied in crossover studies. Participants who enter into the trial are randomly allocated to one of the possible sequences (two sequences in a two-period crossover study and six in a three-period crossover study etc.).

Crossover trials are very powerful in the evaluation of small effects in groups of limited size. However, although the crossover design has the potential advantage of economy and of providing a direct comparison of intervention within the same subject, the parallel group design allows a more straightforward data-analysis, and its efficacy is less dependent on assumptions about the process of the disease or condition under study.

2.4 BLINDING PROCEDURES

Confounding bias has already been mentioned as a serious threat of the internal validity of a study. A problem that may, however, effectively be reduced by randomization procedures. Another source of bias encountered in the conduct of a trial is "information bias" or "assessment bias". Blinding of participants, investigators, or both, for the treatment applied in a trial may minimize the distortion that may occur when either of these groups is aware whether a certain participant is in the treatment or the reference group. The use of placebos, an inert and innocuous substance or situation closely resembling the treatment employed in a study, may provide a possibility to make blinding practicable. The word and concept of a "placebo" were first used in a medical trial by Diehl

and coworkers, using a saline solution as a control treatment versus prophylactic vaccinations against colds.(42) Since then, the value of blinding procedures in trials has been widely recognized, although still many research workers as well as practising clinicians question the need of blinding as a conditio sine qua non in evaluating treatment effects. As indicated in the previous paragraphs, randomization is a safeguard against sources of bias potentially affecting treatment evaluation. One might wonder whether this is not enough of a guarantee to obtain unbiased results. There remain, however, ways in which bias may occur, when everyone involved in the trial is aware of which treatment each patient is receiving. The problems that may give rise can be summarized by the categories of participants in the trial:(21)

The subjects undergoing treatment. When a subject is aware whether he receives the intervention or the control treatment, this notion may affect the outcome of the intervention by psychological mechanisms. For example, subjects changing their dietary habits in a randomized trial studying dietary effects on elevated blood pressure, may also try to more lose weight or increase physical activity, in contrast to a reference group receiving no intervention at all. Obviously, the extent to which these factors are of relevance in a particular study is depending on the nature of the intervention and the type of endpoints used to evaluate treatment efficacy. Also, knowledge of the intervention may affect a subject's attitude towards compliance, attendance for evaluation etc., resulting in increased numbers dropping out in one of the groups or an unequal distribution of compliance across intervention groups.

The treatment team. Those involved in the practical conduct of the study, for example physicians, research assistants or dieticians, form the treatment team. Knowledge of intervention status of the subjects in the study groups by members of the treatment team may affect the outcome of the study in particular when decisions must be made on dose modification, frequency of evaluation, need for additional treatment, or adjustment of the diet during the trial. Also, subjects known to receive a new and promising treatment might be monitored more closely than those on a control treatment. Indeed, for several reasons, physicians in these situations may inadvertently treat control subjects as a second class group.(43)

Those performing the evaluation. One key is that those responsible for assessing patient outcomes are as objective as possible. There is potential danger that evaluators will err towards more favourable responses on the new treatment. Assessment bias may occur in particular when the evaluation of the response is based on subjective criteria involved in clinical judgement. This concept was emphasized in the Medical Research Council's first randomized trial on streptomycin in pulmonary tuberculosis: the extent of improvement of X-ray shadows was determined independently by individuals, ignorant of the treatment schedule.(19) To reduce assessment bias in the measurement of study endpoints, it is also possible to increase the objectivity of the data derived from certain devices used to measure these. For example, the London School of Hygiene and Random Zero sphygmomanometers were developed to reduce observer bias in blood pressure studies.(44,45) The latter of these devices was used throughout the studies presented in this book.

To achieve blinding of either of these groups for intervention status, several methods have been developed. According to which of these groups is blinded a trial is classified single or double blind. Stricktly spoken, as three groups are involved, a trial could be triple blind. In general, those carrying out the trial in practical terms are often also performing the evaluation of the results and the latter term is never used.

There are some additional advantages of blinding in a randomized trial. Blinding may avoid interference with the randomization process if a subject is liable to refuse cooperation after discovering that the undesired treatment was allocated. Furthermore, blindness may prevent individual ethical qualms when a potential effective agent is being compared with a control treatment. The ways in which the process of double blinding may be checked have been reviewed by investigators of the Aspirin Myocardial Infarction Study.(46) A special method of achieving blindness that is often applied is the use of a placebo. A placebo can be any type of treatment, exactly the same as the true intervention, but lacking any known effect. This may be a placebo drug, or a placebo psychotherapy, but also a placebo "reduced sodium intake" as shown in the sodium-potassium trial presented in paragraph 6.1. It is, however, not necessarily true that a placebo has no effect on the condition under study when no rationale exists for therapeutic efficacy of the placebo given. The mere act of providing for example

placebo pills may well affect subjective, or even objective, aspects of disease or feelings of well being, the so-called "placebo effect".(47,48) Therefore it may be an advantage as well as a problem to exclude any placebo effects by using placebos as a control treatment, since a placebo can without doubt have beneficial properties. This may be dependent on the ultimate goal of a trial in analogy with the differences in approach between explanatory and pragmatic trials. Placebo effects must either be equalized between the two groups (explanatory approach), or included within the "true" effect (pragmatic approach).(30)

Apart from the value of blinding procedures in intervention studies, these may also evoke specific problems. A main problem may arise when efforts to preserve double blindness affect the original design or protocol of the study. The investigators may be forced to modify the intervention originally planned when it appears that blinding is not feasible. In a rather trivial situation, adequate placebos may be unavailable. This happened, for example, in the calcium study presented in chapter 6. At first it was decided to use calcium tablets permitting a single dose daily. The company producing these tablets had, however, major problems in creating placebo tablets with the same organoleptic characteristics as the vera tablets. Therefore it was decided to use calcium citrate powders in a dosage of nine a day. This did, according to our impression, affect compliance and resulted in the cessation of use of powders during the trial by some, and a reduction in overall effective dosage for the total group towards the end of the study. Furthermore, a particular placebo intervention may distract qualified subjects to participate in the trial. In the sodium-potassium trial (paragraph 6.1) the notion that, during part of the study, the effort put in reducing sodium intake would be counteracted by the concurrent use of sodium tablets, made several subjects decide not to participate. Other problems associated with blinding may result from ethical considerations. As stated in a Lancet editorial, patients in randomized trials might be "deceived".(49) Furthermore, it may be ethically unjustified to assign a subject to placebo intervention when an alternative standard therapy with established efficacy is available.(43,50,51) Finally, for some interventions appropriate blinding by placebo maneuvers is virtually impossible to achieve. An example of this is provided by the difficulties in assessing the effects of alcohol on blood pressure in a double blind fashion.(52) In conclusion, where randomization is a basic characteristic of the trial, the extent to which and the procedures whereby blinding must be achieved is depending on the nature of the intervention, the condition to which intervention is applied, the methods to assess efficacy, and the

type of endpoint studied. With regard to intervention aiming at a response in blood pressure, in our opinion, blinding is crucial. This may be illustrated by a comparison of studies on sodium restriction and blood pressure as presented in chapter 4 (4.1). Blinded studies showed an overall 40% lesser response in systolic blood pressure to intervention than open studies suggesting that knowledge of intervention status may substantially affect the results.

2.5 SELECTION OF PARTICIPANTS AND GENERAL APPLICABILITY OF FINDINGS

A precise definition of which patients are to be included in the trial is essential whatever type of trial is planned. When a type 1 or 2 study is conducted from a pragmatic point of view, the subjects included need to be representative of the future population to whom the intervention, if effective, is going to be applied. Therefore, one must try to include as large as possible a proportion of subjects satisfying the entry criteria for the study. If not, general recommendations based on the results of the study may be spurious or, in other words, the external validity of the trial is reduced. For an explanatory trial, or an intervention study designed to give information on aetiological aspects, it may be important to select subjects in whom the maximum benefit, as indicated by the objectives of the study, can be expected. The explanatory approach is aimed at scientific understanding. In these instances, representativeness for a larger group of subjects or general applicability of the intervention procedure is of lesser importance.

Due to the strict protocol and the planned character of the intervention applied in the trial, in combination with randomization and possibly the use of a placebo or other measures to blind those in the trial for the intervention, a substantial number of potential participants may drop out even before the study has started. The number of subjects entered into the trial is liable to be dependent on a "filtration proces". As in any cohort study the filtration proces eventually resulting in the study groups can be cited according to eight different populations:(32)

1. The target population. Essentially, these are the people to whom the results of trial will presumably apply when generalized. This population consists of all subjects sharing a particular condition to which the intervention maneuver is assumed to be directed.
2. The available group. This group consists of those individuals belonging to the target population that are part of the population or group in which a particular group of researchers is working and planning to conduct the trial.

3. The candidate group. These are those members of the available group that come to the attention of the investigators. For example, when a study is going to be performed within a cohort study that has already started, some members of this cohort may temporarily or definitely have ceased to participate or attend certain examinations.
4. The eligible group. Those members of the candidate group that fulfill the criteria to be entered into the trial are eligible for the study. These criteria may be of very different nature, like a set of diagnostic criteria, age or living distance from the research centre.
5. The qualified group. This group consists of those eligible that are not to be excluded because of certain exclusion criteria like the use of a certain drug or pregnancy.
6. The receptive group, is formed by those that are qualified and thereby willing to participate according to the protocol. The act of randomization, or the use of a placebo as well as the necessity to undergo a certain intervention, like a reduction in sodium intake, may well prevent people to join the study group.
7. The admitted group. The receptive group forms in general the group that can enter the study and is then called the admitted group. When the receptive group is too large to be studied in a certain protocol, the number may be reduced by randomly selecting an admitted group from the receptive group. This group is then randomized into one or more intervention and control groups, or intervention sequences in case of a crossover study.
8. The counted group. Some subjects may drop out just before intervention starts, but after randomization. This can result from a variety of causes ranging from the participant changing his mind, to an adverse drug reaction.

In any of the phases of the filtration process the number of subjects forming the next group will reduce. For most studies it will be difficult or impossible to accurately establish to what extent all these different steps have contributed to the overall reduction. It may follow, therefore, that any discussion on general applicability of the results of the trial is arbitrary to begin with. The aim of the study, explanatory or pragmatic, therapeutic or aetiologic, will determine how much effort is to be put in getting, and keeping, all eligible subjects into the trial. This may even affect the design of the trial or prompt the investigators to alter the protocol of the study. However, in face of external validity of a study, it is important to report the number of eligible subjects and, when possible, indicate reasons why this number is different

from the number of participants, when the results of a trial are presented.

2.6 BENEFITS AND COSTS

The randomized trial is one of the most powerful tools in epidemiological research. It provides the only way to establish unequivocally the efficacy of intervention, or effect of any other deliberately altered factor on a given condition. The randomized trial may be used to evaluate pharmacologic and non-pharmacologic treatment, to establish the value of prophylactic measures and to test a hypothesis of causality.

The conclusions drawn from randomized trials stemm from comparisons between or within subjects. The basic methodological concept underlying these comparisons is randomization. The randomization procedure forms a safeguard against unspecified disturbances affecting the internal validity of a study, in particular selection bias and confounding, by assuring that any dissimilarities between study groups is solely due to random variation, i.e., to chance.

Randomization creates, however, also problems in handling differences in baseline characteristics between groups. These problems are aggravated when differences are observed in characteristics potentially associated with the outcome of the intervention applied, which constitutes confounding by definition. Probabilistic statistical methods cannot be used to test any baseline differences because, due to randomization, the null-hypothesis that any unequal distribution of characteristics between groups is only due to chance is invariably true. One can even calculate the distributions of differences between baseline variables when randomization should be performed an infinite number of times. What then should be done when, for example, in a particular study baseline blood pressure levels are substantially higher in the group receiving a placebo than in the treatment group? It is conceivable that this would erroneously lead to an overestimation of treatment effects as there was a difference between groups to begin with. When, however, adjustments are made for baseline differences in blood pressure, for example by comparing change in blood pressure rather than difference in blood pressure on intervention, bias may be introduced because of the selective adjustment of a variable potentially associated with the intervention and the outcome. Moreover, this will deliberately affect the baseline state and thus could be seen as an elegant way to spoil the randomization. Therefore, in a strict sense, the choice is between either no adjustments at all, or adjustment for

differences in all variables of which, nonetheless, only a limited number are included in the study. The latter might be achieved by calculating the coefficients of multiple regression between all baseline variables and the achieved blood pressure under intervention in the control group, and use these to adjust changes in blood pressure in the treatment group. Thus, the choice would be between a multivariate analysis or just comparing means of the outcome variable. As an alternative approach the use of a confounder score, made up of several potential confounding variables, for which multivariate adjustments are made, has been suggested.(33) This, however, seems a compromise that is not easily justified, as it may even increase the arbitrary nature of the adjustment. In practice, the quantitative difference in outcome when adjustments for only one, or for all baseline variables are made, will presumably in general be limited. Nevertheless, this is largely dependent on the kind of intervention and outcome, on the condition or disease studied, and on the number of subjects included.

In conclusion, it may seem that, due to the solid methodological foundation of the randomized trial, everything is under control. This apparent control, however, may also induce serious analytical problems. The highly structured nature of the randomized trial forms both the power and the weakness of this type of research. Apart from the great advantages summarized in the previous parts, the apparent rigidity of the design implies that, for example, more complex associations and multiple interventions are rather difficult, if not impossible, to study. Moreover, randomization and blinding procedures pose ethical problems to the study of certain interventions and may impair compliance. The way in which balancing costs and benefits will affect the nature and design of a study is determined by the scientific question posed, but also by practical considerations of resources, both in terms of funding and participation.

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Chapter 3.

SOME ASPECTS OF THE EARLY PATHOGENESIS OF PRIMARY HYPERTENSION

3.1 Introduction

This chapter provides a short treatise of the pathogenetic mechananisms that have been described in primary hypertension, and in particular of those mechanisms that may play a part in its early phase. There is a substantial literature on this subject to which reference will be made when appropriate. The scope of this chapter is, however, to place the data provided in the following chapters in a pathophysiological perspective and no effort is made to give an extensive review of the work accomplished in this area. Although hypertension is commonly classified into primary ("essential") hypertension and secondary hypertension with a known pathological cause,(1) elevation of blood pressure whatever its cause inevitably results from alterations in one or more of the systems that regulate arterial pressure.(2) Changes in pressure regulating systems and the resulting rise in blood pressure are not necessarily disturbances,(3) as they may serve a defined purpose. In these instances high blood pressure may be seen as a side-effect, be it harmful, of a homeostatic response. For example keeping the renal blood flow intact behind a stenosis. In primary hypertension, however, the physiologic value of the increased systemic pressure is unclear and what remains are the defenite effects of high blood pressure on cardiovascular morbidity and mortality. Because of this notion, use of the term "essential" hypertension should be omitted, as this term suggests that the elevated pressure is of importance or even indispensable in an individual. In the next three paragraphs, some remarks will be made on the haemodynamics of early hypertension. In addition, the promises and difficulties of the measurement of catecholamines in the study of elevated blood pressure will be discussed. These notions serve as an introduction to chapter 5, paragraph 5.1.

3.2 Haemodynamics in hypertension

Under normal circumstances, at rest as well as during various stressful conditions, the blood pressure in the systemic circulation is kept within certain limits. The circulation may be regarded a system of "fluid" running through "tubes".(4) The relation between the total blood flow (cardiac output) and the total peripheral resistance is constantly regulated and a rise in blood pressure will essentially be determined by a rise in either of these factors or in both. This notion can, according to Poiseuilles law, be mathematically described by the function MAP=f(CO,TPR) (MAP: mean arterial pressure, CO: cardiac output, TPR: total peripheral resistance).(5) Notwithstanding that, strictly spoken, this function

is only valid for a laminar flow it satisfactorily describes the physiological basis for a deviation of systemic blood pressure from its normal range.

The haemodynamic mechanisms behind increased pressure vary. Firstly, they depend on on the cause of hypertension. For primary hypertension it is generally been accepted that the main haemodynamic characteristic in adults is an increase in total peripheral resistance, with cardiac output being usually lower than in normotensive subjects of the same age.(6,7) Central haemodynamics in primary hypertension may, however, be different at different ages.(6-12) As has been mentioned, a change in blood pressure results either from a change in cardiac output and/or from an change in total peripheral resistance. Both these two determinants may represent functional modifications in the contractile state of heart or vessels, or relate to structural alterations in these organs. In this chapter we will discuss the evidence relating cardiac output and total peripheral resistance to elevated blood pressure in the young.

3.3 Haemodynamics in the onset of primary hypertension

There is a ongoing debate on the haemodynamics in the course of elevated blood pressure in childhood. Two hypothesis compete.(8) The first hypothesis states that primary hypertension in its early state is characterized by high cardiac output which, as a secondary phenomenon, initiates a rise in peripheral resistance. The importance of the elevated cardiac output then gradually decreases and finally hypertension is maintained solely by raised peripheral resistance. According to the second hypothesis, elevated blood pressure at all ages is related to an increase in peripheral resistance.

The concept of elevated cardiac output leading to elevation of arterial blood pressure was put forward by Patterson and Starling in 1914, and further elaborated by Borst and Borst-de Geus in 1963.(13,14) In this concept, increased cardiac output leads to hyperperfusion of the tissues, and as an autoregulatory response vasoconstriction will result. There is considerable confusion about the use of the term "hyperkinetic circulation" in this respect.(15) It appears, however, appropriate to apply this term to the proposed elevated cardiac output in the initial state of elevated blood pressure. The characteristics of the subjects in which the haemodynamics of early hypertension have been studied vary markedly, as do the methods used to assess cardiac output.(5) In some studies a debatable definition of the stage of hypertension, "labile" or "borderline", was used as an indicater of early hypertension, while

in other studies the age of the subjects, i.e., young subjects with elevated blood pressure, determined the existence of early hypertension. Essentially, two different approaches have been used in determining cardiac output, the first being invasive, the second non-invasive by means of echocardiographic methods.

The haemodynamic abnormality in prolongued primary hypertension rests in an elevation of peripheral resistance. According to a number of studies, in hypertension in its early phase cardiac output is elevated in combination with a normal total peripheral resistance.(5,6,15-20) In these studies invasive methods were used to evaluate cardiac output in young subjects and hypertensive subjects classified as labile or borderline. Observations in young hypertensive subjects using echocardiographic methods to measure cardiac output have, however, not confirmed these findings.(21-24) The study presented in chapter 5 of this thesis also is at variance with earlier findings which have suggested elevated cardiac output in early hypertension. In our study, although a substantial difference in blood pressure between the two groups was present, cardiac output and cardiac index was similar in hypertensive and normotensive subjects.

Findings in studies using invasive methods to determine cardiac output may record a different haemodynamic response to the stress evoked by the method applied, in hypertensive as compared to normotensive youngsters, and may thereby present an epiphenomenon of the procedure.

At present, evidence for a hyperkinetic or high-cardiac output state in early hypertension is unconvincing,(8) and appears to favor the concept that primary hypertension from its early phase is characterized by elevated total peripheral resistance.

3.4 Catecholamines in hypertension

Most of the haemodynamic characteristics of both early and established hypertension may be explained by participation of the sympathetic nervous system.(25) When some fifteen years ago sensitive techniques for measuring plasma catecholamines became available, and evidence increased that those levels reflect sympathetic neural activity, the study of this relationship in hypertension became feasible.(26) At one time it was thought that all hypertensive subjects were characterized by sympathetic overactivity.(27,28) This could not be confirmed by most studies conducted thereafter.(29) Still, there may be a subgroup of hypertensive individuals with elevated catecholamine levels. In particular, studies in children and young adults showed a consistent pattern of higher noradrenaline levels in hypertensive subjects than

in normotensive subjects.(30) Findings concerning plasma adrenaline levels are less conclusive, and a limited number of studies on plasma dopamine were all showing nonsignificant differences between normotensive and hypertensive groups.(30)

Several methodological difficulties may explain the inconclusive findings. The use of plasma levels of catecholamines, and in particular of noradrenaline, has been criticized by some authors in that its use may provide only a crude index of sympathetic nervous system activity, and lack sensitivity.(31) In addition, it has been suggested that, when overall sympathetic activity in hypertensive subjects turns to be similar to normotensives, regional differences in organ-specific sympathetic nervous tone could eventually reflect the role of the autonomic nervous system in the elevation of blood pressure.(32)

Nevertheless, even though these considerations may account for some of the negative findings in studies reporting catecholamine levels in hypertension, they do apply less to studies in which substantial differences in one or more plasma catecholamine levels were observed. Furthermore, although techniques are developed to more specifically measure regional sympathetic nervous activity, they still are of limited practical use in the study of larger groups of subjects. Also, these methods are usually based on the infusion and measurement of isotope labelled catecholamines, which may disturb any physiological associations that exist between various catecholamines.

Goldstein, in his review of studies on sympathetic nervous activity in hypertensive and normotensive subjects, has pointed at another source of difficulties that may account for the inconclusive findings in a number of studies.(30) In particular differences between hypertensive and normotensive groups with regard to source population (for example, hypertensive patients compared with laboratory personnel serving as a reference group), age (hypertensive patients were often older, and plasma noradrenaline levels may rise with age), and a number of other factors, may lead to spurious results. However, Goldstein in the same review concludes that when patient age and other factors were considered simultaneously, virtually all studies of young, established hypertensives were positive with respect to plasma noradrenaline.

A third remark that may be made on the interpretation of differences in catecholamine levels between hypertensive and normotensive groups is that these reflect differences in arousal between these subjects.(31) The discomfort of venipuncture may increase catecholamine levels more in hypertensive subjects. Although an interesting observation by itself, this would indicate that basal sympathetic activity need not be altered in hypertension.

This suggestion calls for the need of an indwelling catheter when obtaining plasma samples in this type of study as a partial remedy.

In the comparative study presented in chapter 5.3, an attempt has been made to take the aforementioned issues into account. Hypertensive and normotensive subjects were selected from the same population and were all within a narrow, young, age group. Moreover, an indwelling venous catheter was used to obtain blood samples and hypertensive and normotensive subjects were all studied according to the same strictly standardized protocol. This led us to conclude that not only average plasma noradrenaline levels may be elevated in young hypertensive individuals, but also substantial differences may be observed in plasma adrenaline and dopamine levels. The latter finding is of particular interest, since attention has recently been raised for a putative role of dopamine in a number of renal and cardiovascular mechanisms that may be associated with blood pressure regulation.(33,34) Dopamine may have hypotensive properties, for example by counteracting some of the blood pressure raising effects of noradrenaline. Finally, interrelationships between catecholamines were studied, and the observations were suggestive of altered associations between the various catecholamines in hypertensive subjects compared to the normotensive reference group. A differential arousal between these groups seems unlikely, as no significant differences in pulse rate were observed.

Definite conclusions about the part played by the sympathetic nervous system in elevated blood pressure can not be made at present. However, the observational evidence favours the assumption that the autonomous nervous system may be altered in hypertension. In addition, theoretical considerations have pointed at the plausibility of initiation and aggravation of high blood pressure by sympathetic (over-) activity.(2,12,35,36)

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Chapter 4

ELECTROLYTES AND BLOOD PRESSURE

4.1 INTRODUCTION

The blood pressure level of an individual is the result of an interaction of both genetic and environmental factors, of an interplay between "nature" and "nurture".(1,2) Nurture includes a variety of factors of which some dietary constituents have been most extensively studied.(3,4) Although the magnitude of the effect of dietary factors, relative to other environmental influences, is not yet clearly established,(5) the role played by the diet, in particular by dietary electrolytes, in the pathogenesis of high blood pressure has become increasingly clear. In this chapter we will briefly discuss observational and experimental evidence that links three major dietary electrolytes, sodium, potassium and calcium, to blood pressure. In addition, an attempt has been made to indicate possible pathogenetic mechanisms that may explain the putative role played by these dietary constituents in blood pressure regulation. The considerations expressed in these reviews played a part in the design of the intervention studies presented in chapter 6, and some of the questions put forward by the current theories have been addressed in these experiments. One of the reasons that the diet has gained great attention in hypertensiology is that it may provide an attractive means of influencing blood pressure levels, either at the individual level or on a population scale. The potential of dietary intervention in the young will be discussed in chapter 7.

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4.2 SODIUM AND BLOOD PRESSURE

4.2.1 Introduction.

A classical work on medicine by the chinese "yellow" emperor comprises the first written indication of an association between sodium and blood pressure in stating that high salt intake makes "the pulse hard".(1) This may be seen as the start of an ongoing, and by times heated, discussion about the role of sodium intake in the aetiology of primary hypertension, leading to the general opinion that sodium has indeed "something" to do with hypertension, but to less unanimity as to what extent and in what range of intake this relation is apparent, and much controversy about the efficacy of sodium reduction in hypertensive subjects.(2-11)

We will briefly review the evidence regarding the various components of the putative association between sodium and blood pressure, referring to some of the numerous reviews on this subjects when appropriate. The vast amount of data from animal studies, in which hypertension is produced by salt-loading and related procedures, will not be discussed here. In the subsequent paragraph the available data from trials studying the effects of a reduction in sodium intake on blood pressure will be analysed.

4.2.2 Sodium intake and blood pressure.

Inter population studies

The collective results of a great number of, mostly anthropological, studies describing sodium intake and blood pressure levels in different populations show, when combined, a highly significant association between systolic and diastolic blood pressure and sodium intake (or excretion) in both men and women, as reviewed by Meneely and Dahl,(13) and more recent extensively by Gleiberman and Simpson (Figure 4.2.1a, 4.2.1b).(14,15)

These findings are influenced by the inclusion of several populations having a diet virtually lacking sodium and almost no cases of hypertension, like the Yanomano Indians of Brazil and tribes living in the Solomon Islands, and populations using extremely large amounts of sodium like in some regions of Japan.(16,17) Obviously, these people are different in many more ways from people living in Europe or the USA, than with respect to sodium intake alone. This indicates an important source of bias when comparing different populations according to a certain characteristic, like sodium intake, which is sometimes referred to

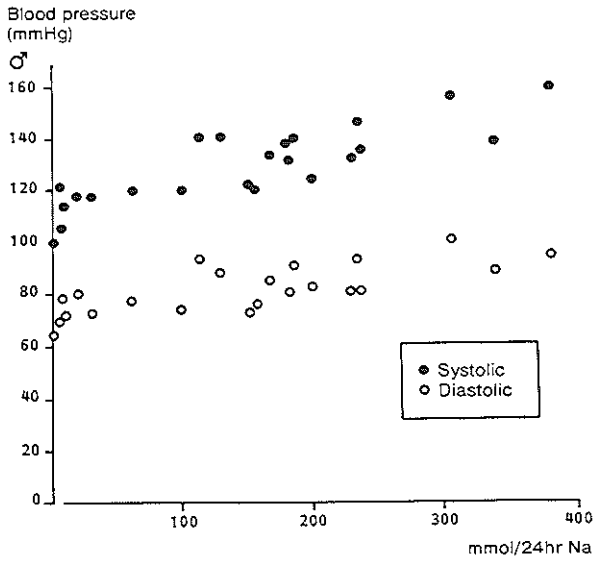

Figure 4.2.1a. Relationship between systolic and diastolic blood pressure and daily sodium intake or excretion in male populations, aged 50 to 59 years. Reproduced from 15.

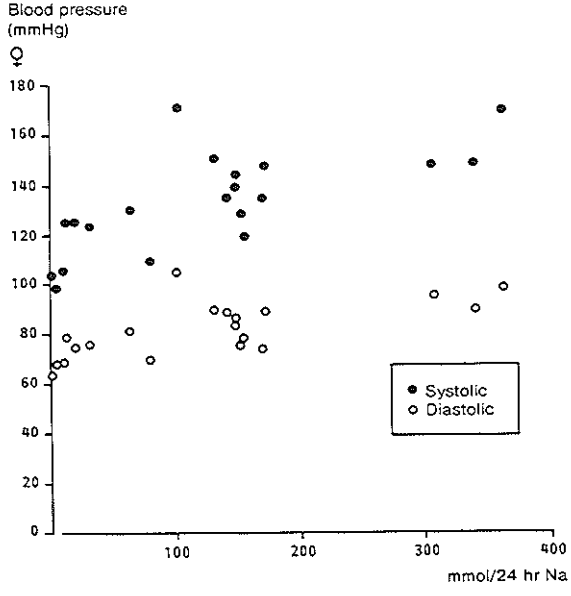

Figure 4.2.1b. Relationship between systolic and diastolic blood pressure and daily sodium intake or excretion in female populations, aged 50 to 59 years. Reproduced from 15.

as the "ecological fallacy". Several differences exist between most low-sodium/low-blood pressure societies, and westernized societies where average sodium intake and blood pressure are higher. In more primitive societies people lose weight with age, in the western world they gain weight with age. Furthermore, people in primitive societies tend to be more physically fit, a factor that has been associated with blood pressure level.(18) Also, between populations dietary habits, not only differ in sodium intake, but also in other factors that may affect blood pressure level, like potassium. Finally, low-salt communities tend to be small, and live in relative isolation under stable conditions unexposed to the turbulence and physical and emotional stress inherent to westernized societies.

In addition, many of the interpopulation studies suffer from methodological shortcomings in data collection and handling, and this makes a comparison even more difficult. Data on body weight and dietary factors other than sodium are often lacking, and measurements of sodium intake and excretion and of blood pressure are far but standardized.

In conclusion, however, the evidence from interpopulation studies is suggestive that at least a very low and a very high sodium intake are associated with a relative low and high prevalence of high blood pressure. A large and thoroughly standardized interpopulation study is currently being conducted under auspices of the council on epidemiology of the International Society and Federation of Cardiology, the INTERSALT project. Although one might be sceptical with regard to yet another study because some problems can never be totally solved, this study can perhaps provide us with some clear data on the extent to which sodium intake is related to blood pressure between populations.

Intra population studies

Contrary to the findings in inter-population studies, in most withinpopulation studies no relationship between an individuals sodium intake and blood pressure has been observed.(19,20) Several factors may explain difficulties in finding an association within a population.

Firstly, most intra-population studies use a single 24 hour urine specimen to estimate sodium excretion. In western societies sodium intake is highly variable, and it is notoriously difficult to characterize an individual on this basis. Liu and coworkers suggested that a series of seven 24 hour urine samples may be needed to adequately estimate an individual's sodium intake,(21) and Simpson calculated that twelve samples would be required to

characterize the sodium output of an individual subject with 95% accuracy.(22) A single estimation of urinary sodium output in a population appears to give a reliable value for mean sodium output, but it characterizes the individual poorly. Watt and Foy estimated, that in order to have a 90% chance of detecting a regression slope of 0.1 mmHg/mmol Na (the strength of association observed between populations and used to approximate the effect of a reduction in sodium intake on blood pressure), 5,720 subjects are required if each provides only one 24 hour urine sample.(23)

Secondly, even when a person's sodium intake could be assessed reliably, this can only indicate current sodium use which does not necessarily relate to the sodium intake over the remaining part of his life.

Thirdly, the association between sodium intake and blood pressure may be nonlinear, implying that a certain threshold level exists beyond which the association is no longer apparent. This so-called saturation phenomenon has first been suggested by Meneely and Batterbee.(24) According to some authors, at an intake of about 70 mmol sodium per day a threshold level would exist, above which no clear effect of sodium on blood pressure would be detectable.(25) Indeed, when communities are studied where the range of sodium intake is wider and intra-individual variation in sodium intake is less, direct relationships between blood pressure levels and sodium excretion have been shown.(26,27)

The obvious alternative explanation for the lack of a sodium-blood pressure relationship within western communities is, however, that no relationship exists between sodium and high blood pressure.

A different concept might be that the sodium-blood pressure association only applies to certain susceptible subgroups within a population. As genetic factors appear to be involved in the aetiology of hypertension,(28) inherited differences in sodium sensitivity may affect blood pressure in certain individuals. A positive family history for hypertension could be a factor distinguishing salt-sensitive from non salt-sensitive subjects.(29) However, this could not be established in a recent double-blind study by Watt and coworkers.(30) Also, age may modify the response of blood pressure to sodium intake.(31) This would implicate that susceptibility to dietary sodium is an acquired rather than an inherited characteristic. This is in agreement with an analysis of the data from thirteen randomized trials of sodium restriction on blood pressure, which showed reduction of sodium intake to be more effective in older subjects (Chapter 4.3).

Analyses from data obtained in the Health and Nutrition

Examination Survey (HANES) by MacCarron and coworkers have added much to the present controversy.(32) They reported an inverse association between dietary sodium intake and absolute blood pressure level as well as prevalence of hypertension (Figure 4.2.2).

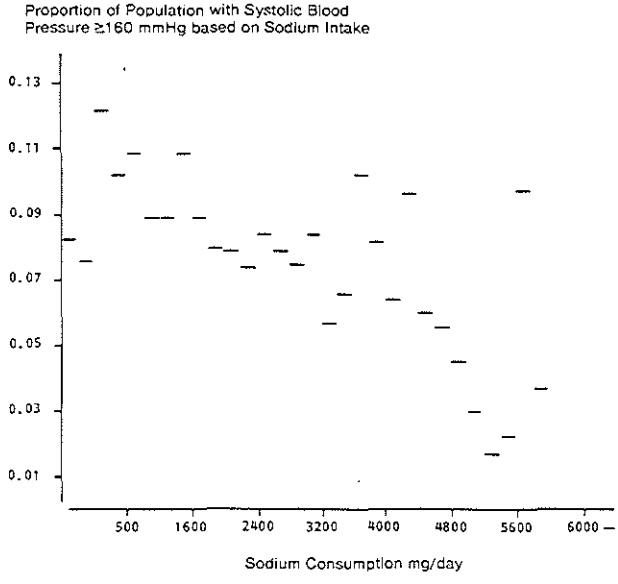

Figure 4.2.2. Prevalence of hypertension in the National Health and Nutrition Examination Survey, 1971–1974, for different strata of sodium intake. Reproduced from 32.

This study has been subject to much debate and a second analysis of the same data by Harlan et al. did not confirm the first report in all aspects.(33) The findings of MacCarron and his group are, however, in agreement with data from the Ten State Survey, where groups of subjects consuming more sodium, showed lower prevalences of hypertension.(34)

No definite conclusions can be drawn on the basis of the combined intrapopulation studies conducted thus far. Moreover, intrapopulation studies are in part conflicting with, and on the average not confirmative of, findings of studies comparing different populations. These latter studies, however, are hampered by a number of methodological and statistical difficulties, which may invalidate the judgement based on their findings.

4.2.3 Studies on the effect of sodium restriction on blood pressure.

The evidence of a blood pressure lowering effect of moderate sodium randomized trials on a reduction of sodium intake in subjects of varying age and different levels of blood pressure (paragraph 4.3).

One study needs to be mentioned separately. Hofman and in coworkers, a double blind randomized trial, have reported a reduction of rate of increase in blood pressure in newborns fed with a low sodium baby-food formula.(74) This provides the only evidence at hand that sodium intake may be associated with the aetiology of elevated blood pressure. As has been mentioned, this finding does not necessarily imply that a reduction of sodium intake may be used to reduce a blood pressure level that is high already.

4.2.4 Pathophysiological aspects of the sodium-blood pressure relationship.

Several theoretical concepts have been developed to connect dietary sodium intake and blood pressure. Three hypotheses have obtained particular attention.

The autoregulation theory

Borst and Borst-de Geus postulated that an increase in cardiac output, leading to hyperperfusion of the tissues,(35) and resulting in autoregulatory vasoconstriction and increased peripheral resistance, might be responsible for sodium induced elevation of blood pressure. In this concept, the primary abnormality of hypertension would be a renal defect leading to sodium and water retention, increased venous return and elevated cardiac output. This was extensively studied by Guyton and coworkers.(36,37) Doubt remains however, whether an increase in cardiac output is a common characteristic of early primary hypertension, and whether autoregulatory responses can be chronically maintained.(38)

Although the initial enthousiasm for this theory has somewhat declined, it is likely that abnormal renal sodium handling is involved in primary hypertension.(39) Moreover, kidney cross-transplantation experiments in inherited hypertension in rats have been strongly suggestive that the kidney is implicate in the aetiology of high blood pressure.(40)

The natriuretic hormone/Na+-Ca2+ exchange/hypertension hypothesis

The second hypothesis is based on the initial suggestion by Dahl and coworkers that a circulating factor, or hormone, is present in

hypertensive animals, which is capable of inducing natriuresis in other animals.(41) Haddy and Overbeck(42) and Blaustein(43) subsequently applied this theory to volume expanded hypertension. Blaustein suggested a mechanism whereby a raised level of a sodium transport inhibitor could increase vascular reactivity by slowing down sodium-calcium exchange across arteriolar smooth muscle cell membranes.(44)

According to DeWardener and MacGregor,(45) those who will develop primary hypertension may have an inherited reduced ability of the kidneys to excrete the dietary sodium load normally encountered in westernized societies. This would result in an initial slight increase in blood volume, stimulating the release of natriuretic hormone to restore sodium balance back to normal. The combined results of the natriuretic factor on the kidney and on smooth muscle cells would result from inhibiting Na-K-ATPase, leading to natriuresis in the kidney, and to increased contractile tone in the arteriolar wall, by reduced transcellular membrane sodium-potassium pump activity (Figure 4.2.3). This theory has gained much support, although only limited experimental evidence is available thus far to provide the necessary empirical foundation (See Swales(46)).

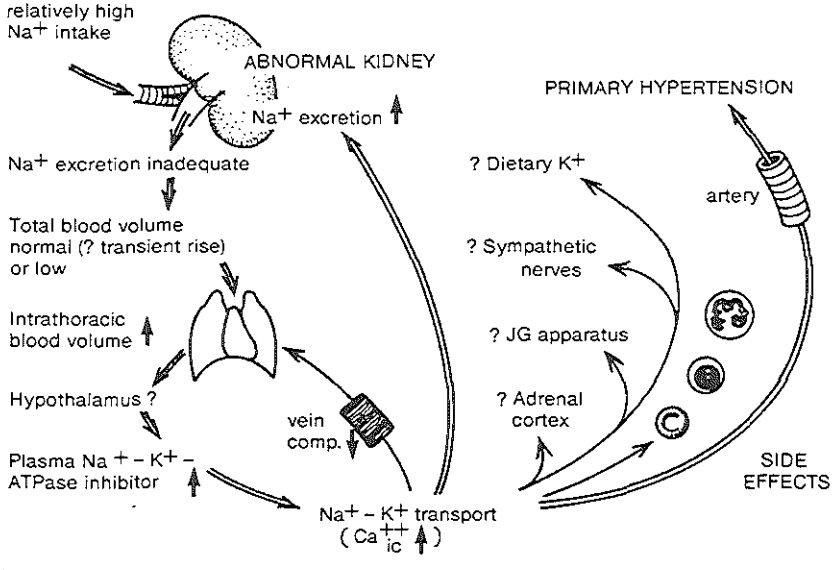

Figure 4.2.3. Sequence of events to explain a postulated defect in the kidney's ability to excrete sodium, leading to a rise in the concentration of a circulating sodium transport inhibitor, and a rise in peripheral resistance in primary hypertension. Adapted from MacGregor GA, Hypertension 1983;5 (supp III):80.

There is circumstantial evidence for the existence of a natriuretic hormone, as reviewed by De Wardener and Clarkson,(47) but the molecular structure of the hormone is still obscure, and attempts to purify a peptide with natriuretic and Na-K-ATPase inhibiting properties have not yet yielded clear results. After 25 years, only one possible relevant substance, the Atrial Natriuretic Factor (ANF), has been identified.(48,49) This peptide, however, decreases vascular reactivity and lacks an effect on Na-K-ATPase. Recent evidence suggests that circulating atrial natriuretic peptides are raised in adult hypertensive subjects and this finding has been interpreted as supportive of the view that the ability of the kidney to excrete sodium is reduced in primary hypertension.(50) From a theoretical point of view, the possibility that inhibition of Na-K-ATPase activity increases vascular reactivity has encountered little objection. The postulated resulting natriuresis is, however, still subject to debate. Therefore, the natriuretic hormone and the factor inhibiting Na-K-ATPase may well turn out to be two or more distinct substances. Moreover, inhibition of the red cell sodium-potassium pump has been observed in a number of conditions not associated with hypertension, as in hypothyroidism, uraemia, and obesity.(46)

Finally, although abnormalities of the ouabain sensitive, i.e., Na-K-ATPase dependent, sodium-potassium pump have been the subject of many investigations both in humans and rats, the results are equivocal. Findings of reduced sodium pump activity mainly concern leucocytes.(51,52) This was also observed in normotensive relatives of hypertensive patients which may indicate that reduced Na-K-ATPase activity is at least not the sole determinant of elevated pressure.(53) Alternatively, impaired sodium-potassium transport may be an early indicator of primary hypertension before the elevation of blood pressure level has become apparent.

Altered cellular membrane function as the source of hypertension

An impressive amount of data has accumulated during recent years to support the hypothesis that one or multiple alterations of cellular membrane function may play a part in the development of primary hypertension (For a more extensive discussion see Swales(46), Postnov(54), Tosteson(55), Parker(56,57), Garay(58), de Wardener(59)). The view that disturbances in cellular electrolyte handling are in some way associated with elevated blood pressure is founded on the concept that any rise in peripheral resistance due to enhanced vascular smooth muscle tone must result from raised intracellular calcium levels (For theoretical considerations see paragraph 4.4.5).

The basis for studying intracellular sodium and other electrolyte concentrations in hypertension, was laid by the initial observations of Tobian and Binion of elevated sodium and water content in the arterial wall of hypertensive subjects.(60) Losse and coworkers were the first to report increased intracellular sodium levels in red blood cells of patients with primary hypertenson.(61) They extended their observations by demonstrating increased net sodium flux across the red cell membrane.(62) In a group of 90 young untreated subjects with persistently mildly elevated blood pressure levels, we observed a significant positive association between intra erythrocyte sodium concentration and systolic blood pressure ($b = 2.4$, $SE = 1.2$, $p = 0.05$), and a negative association between intra erythrocyte potassium concentration and systolic blood pressure ($b = -0.7$, $SE = 0.3$, $p = 0.03$). This suggests that either red cell permeability to sodium was raised in these hypertensive youngsters, or sodium extrusion mechanisms were reduced.

The main transport mechanisms involved in cellular sodium handlin are shown in Figure 4.2.4. Extracellular sodium concentration is higher, and potassium concentration lower, than intracellular sodium and potassium concentration. Electrochemical gradients drive Na+ and K+ across the cell membrane in opposite directions. Intracellular Na concentration tends to rise by passive permeability and by the anion-carrier [1][2]. The stationary intracellular sodium concentration is maintained by the ATPase dependent Na-K pump, exchanging internal Na+ for external K+ [3], and to a lesser degree by the chloride-dependent Na+-K+ co-transport system [4]. The physiological role of the Na+-Na+ countertransport system [5], exchanging intra- and extracellular Na+ on a one-to-one ratio is still unclear. The co-transport can be inhibited by furosemide. The counter transport is measured by preloading erythrocytes with lithium and comparing its extrusion into solutions that contain physiological concentrations of sodium, or no sodium at all. This method has led to the more common name of "sodium-lithium" countertransport for this transport system. An alternative way for sodium to be extruded from the cytosol is by the energy dependent Ca+-Na+ pump (the "calcium pump", see figure 4.5.3). This transport system exchanges three Na ions for one Ca ion. Garay and coworkers, in 1979, reported a reduction in net Na+-K+ fluxes in erythrocytes of hypertensive patients.(63) In a subsequent study they attributed this observation to reduced activity of the Na+-K+ co-transport.(64) Furthermore, while Na+-K+ co-transport appeared to be reduced in hypertensive patients and part of their offspring, there was no overlap for values between subjects with essential and secondary hypertension.(65) In the same year, Canessa and collaborators observed high Na+-Li+

countertransport fluxes in essential hypertensive patients.(66) Since then, a series of studies, including a combined study by the groups of Garay and Canessa,(67) has been conducted. The studies involve different groups of patients and the use of several biochemical methods. Moreover, they focused on erythocytes as well as on a number of other cell types.

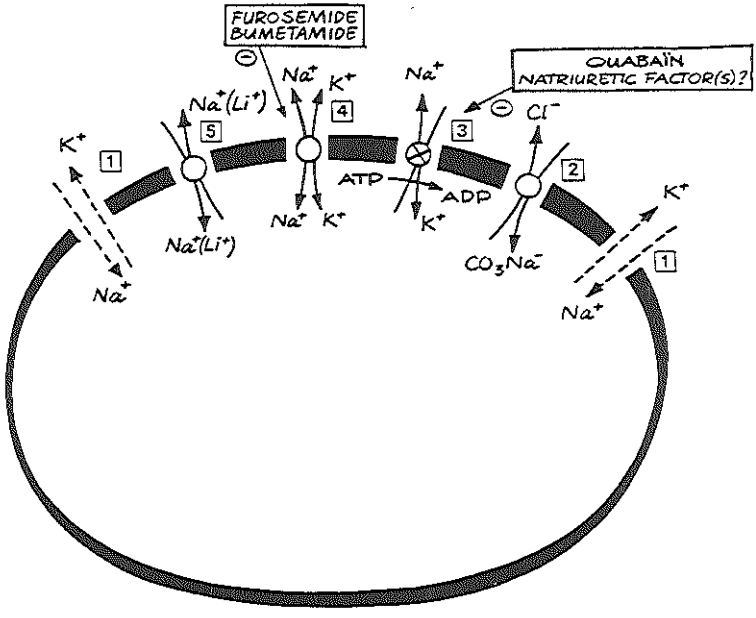

Figure 4.2.4 Compilation of postulated membrane transport mechanisms involved in cellular sodium and potassium homeostasis.

The results from these investigations have shown major discrepancies, making any definite conclusions on the pattern of disturbances in sodium transport mechanisms in hypertensives difficult.(68) Several factors may explain these inconclusive findings. Differences in patient selection may account for some of the dissimilarities. Most studies provide limited data on the way control groups were obtained. Furthermore, as hypertensive subjects tend to be more obese, and obesity has been associated with alterations in cellular sodium handling,(69) this may induce differences between groups. Also, race, age, and anti-hypertensive treatment may affect study outcomes. Anti-hypertensive drugs may

influence sodium efflux rate,(70) but almost all studies have been conducted in previously treated patients, in which medication had been stopped for a varying period before the study. Alternatively, differences in biochemical methods and in sampling and storage of cells, could in part be responsible for the different findings. At the very least, there appears to be a substantial heterogeneity in disturbances in cellular electrolyte handling in primary hypertension. On the basis of the findings thus far, one could suggest a number of subgroups of hypertensive patients, in some of which intracellular sodium is elevated due to a membrane leak for sodium; in some an apparent leak is compensated by enhancement of one, or more, transport mechanisms; in still others reduced extrusion forms the main determinant of increased intracellular sodium content; and finally in some no clear alteration of intracellular sodium handling is present.

It remains insufficiently clarified how these disturbances in sodium handling can lead to elevation of pressure. Indeed, it is still not clear whether these alterations are at all implicated in the pathogenesis of high blood pressure. As indicated at the beginning of this paragraph, eventually the mechanism(s) involved should lead to elevation of intracellular calcium. A plausible explanation has been provided by Blaustein in relation to the concept of a natriuretic hormone (see previous paragraph and reference 44). In this hypothesis the effects of Na+-K+-ATPase inhibition might be replaced by oth er factors resulting in raised intracellular sodium levels and, thereby, in activation of the calcium pump. However, the alterations in sodium transport mechanisms observed in some hypertensive patients and in normotensive relatives of hypertensive subjects, may also reflect an epiphenomenon related to another primary defect rather than being causally related to the elevation of blood pressure.

Following this reasoning, some workers have postulated a genetic membrane defect in primary hypertension. These alterations of the cell membrane function might affect a variety of membrane characteristics, including cation transport, passive electrolyte movements, and intra- and extra-cellular Ca+ binding. Some of these phenomena are discussed in more detail in paragraph 4.5. There is substantial evidence for decreased calcium binding by cell membranes of hypertensive humans and rats.(71) It is conceivable that the primary abnormality of the cell membrane would reside in the phospholipid component as well as the glycoprotein structure.(54) In theory this could, by destabilization of the cell membrane, affect handling of sodium and potassium, in particular permeability and the Na+ - K+ pump, as a secondary phenomenon.(46) The final consequence would then be an increased concentration of free calcium

in the cytosol of contractile cells, and also in other tissue involved in blood pressure regulation, like the sympathetic nervous system.

The existence of a widespread alteration in membrane function is compatible with the notion that the rise in peripheral resistance as observed in primary hypertension is not clearly limited to specific vascular beds but may involve the whole vascular system, including the veins.(72) In this view, the kidney resets to avoid salt and water loss due to increased pressure, i.e., operates with the renal function curve shifted with respect to systemic blood pressure.(54)

4.2.4 Conclusion.

There are numerous data indicative of a role for sodium in the aetiology of primary hypertension. The magnitude of the association between sodium and blood pressure, as well as the mechanism(s) involved, are still unknown.

At a time that the contribution of a number of other dietary and non-dietary factors in determining blood pressure level has become increasingly clear, it may be questioned whether the attention paid to a solitary role of sodium salts in blood pressure elevation is justified. It is conceivable that the relatively simple way of determining sodium intake (by urinary sodium excretion) has stimulated this great interest.(73) Moreover, sodium is one of the few dietary constituents that enters our daily food almost entirely artificially, either in the household (30%) or in manufacturing (30%), and sodium intake is therefore easily manipulated. This may also influence the choice for a reduction of sodium intake in assessing the hypotensive properties of dietary changes.

Two ways whereby sodium intake may affect blood pressure have been suggested. Firstly, a high sodium intake may induce elevation of blood pressure. Secondly, a reduction of sodium intake may lower an already elevated blood pressure. Furthermore, either of these actions may apply to certain subgroups of normotensive or hypertensive subjects susceptible to sodium. It is important to note that these two phenomena are not necessarily linked. It is conceivable that sodium intake determines blood pressure levels, but that changing sodium intake does not affect the level of blood pressure already achieved, or vice versa, i.e, different mechanisms may be implicated in the aetiology and the treatment of hypertension. In other words, sodium intake may be related to high blood pressure as a "clue" or as a "cure".

Data on the first effect stem predominantly from interpopulation studies, but these findings have not been convincingly confirmed by

studies within populations. The latter type of study is less liable to confounding by other factors. However, as has been pointed out, methodological difficulties may also account for the inconclusive results. The only experimental study conducted thus far on the effect of sodium on rise of blood pressure,(74) conducted in Dutch newborns, has indicated that a higher sodium intake may indeed increase the slope of blood pressure in the first years of life. This finding calls for confirmation by further intervention studies.

The hypotensive property of large reductions of sodium intake to levels below 20 mmol/day is generally accepted. This type of dietary intervention has, however, serious drawbacks. Most obviously because severe sodium restriction is unpalatable and is likely to result in significant loss of compliance when implemented for a longer period or outside the clinic. In addition, a sodium restriction that is this drastic may pose medical risks. The efficacy of less great changes in dietary sodium intake, to levels of about 80 mmol/day is less well documented.

It appears that moderate sodium restriction is predominantly effective in older patients with moderate to severe hypertension. These patients, however, are likely to be eligible for treatment with drugs. This notion may raise questions to the usefulness of widespread reductions of sodium intake as part of public-health measures or intervention programs to shift the blood pressure distribution of a whole population to lower levels. Although it may seem acceptable to disencourage the overenthousiastic use of sodium during the preparation of food, a more aggressive "low-salt for all" campaign appears at present not to be sufficiently justified.

Finally and unfortunately, no definite criteria are available at the moment to detect those at increased risk to respond to a high sodium intake with blood pressure elevation, or those most liable to show a fall in blood pressure on sodium restriction. Although the available evidence is suggestive of marked heterogeneity in the response to sodium in both normotensive and hypertensive subjects, further studies are clearly indicated.

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4.3 DOES SODIUM RESTRICTION LOWER BLOOD PRESSURE? Data from thirteen randomized trials

Introduction

The merits of sodium restriction in primary hypertension are subject to an ongoing and sometimes heated debate. Although important pieces of evidence have been derived from observational studies, most would agree that the ultimate test for the effect of a reduction in dietary sodium on blood pressure is the experiment. We reviewed thirteen randomized trials of sodium restriction on blood pressure, with special reference to the question which variables predict the effect of sodium restriction on blood pressure.

Methods

Data from trials

The data of twelve studies, comprising thirteen randomized trials, were used.(1-12) From these studies the following characteristics were recorded (Table 4.3):

1- The design of the study. Whether a study was performed in a blinded or open fashion, and whether a parallel-group or crossover design was employed.
2- The number of participants of whom complete data sets were obtained, the mean age of the study groups, and the duration of the intervention period.
3- The initial systolic and diastolic blood pressure levels. Readings in supine position were used when provided. When the study comprised a lead-in period, the blood pressure measured at the start of the intervention period was used.
4- Daily sodium and potassium intake, based on the 24 hour urinary electrolyte excretion. When no data on urinary sodium were included, the intake was based on an estimate of the sodium content of the diet.(10) Some reports did not provide data on potassium intake or excretion.(1,2,9)
5- The maximum achieved reduction in sodium intake and the change in potassium intake during intervention.
6- The change in systolic and diastolic blood pressure during intervention. Depending on the design of the study the difference between intervention and control period (crossover studies),(1,3,4,6,8,10-12) or the difference in change of blood pressure from baseline between the intervention and the control group (parallel-group design),(2,5,7,9) was used.

7- The statistical significance of the results. In most studies a t-test for unpaired or paired observations was performed. Results were considered significant when a two-sided p-value was less than 0.05.

8- The year the study was published. Although studies on sodium restriction in individuals have been conducted since the beginning of this century, studies before 1970 often were very small, and frequently did not match current criteria for design and data analysis.(13) Therefore only studies published from 1970 to 1985 were included. From one study unpublished data were used.(12)

Table 4.3. Compilation of data from the studies included in the analysis

Ref	T	D	P	N	A	Sys	Dia	Na	K	dNa	dK	dSys	dDia	p	Y
1	0	2	28	22	41	175	112	191		-98		-6.7	+3.2	1	73
2	0	1	730	62	60	163	97	191		-38		-2.0	-7.0	1	78
3	0	2	14	20	23	125	73	210	71	-170	-6	-2.7	-3.0	0	81
4	1	2	28	19	49	154	97	162	65	-76	-6	-10.0	-5.0	1	82
5	0	1	84	90	49	141	87	150	77	-113	+3	-5.2	-3.4	0	82
6	1	2	28	18	52	137	83	143	54	-56	+3	-0.5	-0.3	0	83
7	0	1	365	28	55	163	99	149	60	-21	+5	-8.7	-6.3	0	83
8	0	2	35	12	40	150	92	210	55	-100	+8	-5.2	-1.8	0	84
9	0	1	28	94	46	157	101	130		-58		-3.0	-2.5	0	84
10	0	2	24	113	16	103	61	113	49	-70	+16	-0.6	-1.4	0	84
11	1	2	28	31	23	111	64	128	64	-60	-1	-0.5	+1.4	0	85
11	1	2	28	35	22	114	63	131	61	-74	-6	-1.4	+1.2	0	85
12	1	2	42	40	24	137	73	129	77	-72	-3	-0.8	-0.8	0	

Index to the table:

Ref : reference number.
T : type of study: 0 = open study, 1 = double-blind study.
D : design: 1 = parallel-group, 2 = crossover.
P : duration of period of sodium restriction (days).
N : number of participants.
A : mean age (years).
Sys : initial mean systolic blood pressure (mmHg).
Dia : initial mean diastolic blood pressure (mmHg).
Na : mean sodium intake during the control period or at baseline (mmol/24h).
K : mean potassium intake during the control period or at baseline (mmol/24h).
dNa : change in sodium intake during intervention (mmol/24h).
dK : change in potassium intake during intervention (mmol/24h).
dSys: change in systolic blood pressure during intervention (mmHg).
dDia: change in diastolic blood pressure during intervention (mmHg).
p : statistical significance of the results: 0 = ns, 1 = sign. (< 0.05).
Y : year of publication.

Data analysis

Although substantial differences between the studies exist, they were accorded equal weight. The data analytic approach was two-fold. First, predictors of the fall in blood pressure during sodium

restriction were studied in simple linear and multiple linear regression analysis, in which the fall in blood pressure was the outcome variable and its potential predictors were entered as determinants in the model. Second, studies were grouped on the basis of their design and on the statistical significance of the results, and differences between the groups were tested using a t-test for unpaired observations. The results of statistical tests are expressed as two-sided p-values.

Results

General aspects

The studies included in this analysis are summarized in the table. In all of them a fall in systolic blood pressure during sodium restriction was observed, with an average of 3.6 mmHg, ranging from 0.5 mmHg to 10.0 mmHg. Diastolic blood pressure showed on the average a fall of 2.0 mmHg. However, although ten studies showed a fall in diastolic blood pressure, ranging from 3.0 mmHg to 7.0 mmHg, in three studies diastolic blood pressure rose, ranging from 1.2 mmHg to 3.2 mmHg. Only three studies showed a statistically significant fall in systolic blood pressure during reduction of sodium intake. Five studies were performed double-blind, and all of these date from the last three years. Six studies had an intervention period of four weeks or shorter, three were five to twelve weeks, and two took one year or more. A total of 584 subjects participated in the trials, with a mean age of 38.5 years, the average age by study ranging from 16 to 60 years of age. Five studies were conducted in adolescents or young adults. The average sodium intake in the trials combined was 157 mmol/24 hour, and average potassium intake was 64 mmol/24 hour. No significant associations between initial blood pressure level and sodium or potassium intake were found. There is a tendency for initial sodium intake to fall with year of publication of the study. This association, which remained after adjustment for age ($b = -5.1$ mmol/yr, $SE = 2.4$, $p = 0.05$), may indicate an overall downward trend in sodium consumption in the Western world. The achieved reduction in sodium intake ranged from 26 to 170 mmol/24 hour (mean 78 mmol/24 hour).

Which variables predict a fall in blood pressure?

The fall in systolic blood pressure on sodium restriction increased with initial blood pressure level (Figure 4.3.1). For diastolic blood pressure the association did not reach statistical significance. Also, the fall in systolic as well as diastolic blood pressure increased with age. This finding was more prominent for diastolic pressure (Figure 4.3.2). After adjustment of initial blood pressure level for age and vice versa neither of the associations

did reach statistical significance. No apparent relationship was observed between the fall in blood pressure and initial sodium or potassium intake, nor was the fall in blood pressure related to achieved reduction in sodium intake. No associations were found between duration of the trial and the number of subjects included.

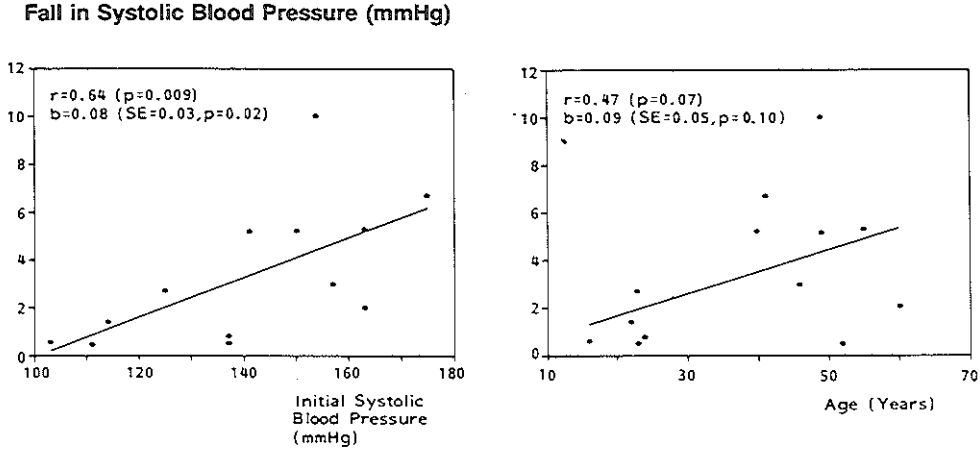

Figure 4.3.1. Fall in systolic and diastolic blood pressure during sodium restriction by initial blood pressure level.

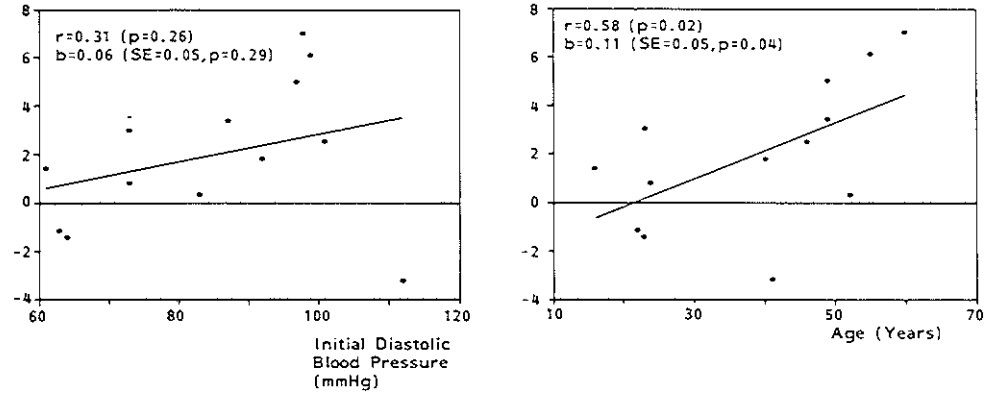

Figure 4.3.2. Fall in systolic and diastolic blood pressure sodium restriction by age.

Open and blinded studies

Blood pressure is very liable to be affected by a variety of other factors apart from a reduction in sodium intake. Therefore, uncontrolled and open studies may show a fall in blood pressure over and beyond the effect of sodium restriction. Blinded studies (n = 5) were in general of shorter duration than open studies (n = 8). In open studies baseline sodium intake was higher: 168 mmol/24h (SE = 13) in open, and 139 mmol/24h (SE = 6) in blinded studies (p = 0.07). The fall in systolic and diastolic blood pressure observed in open studies tended to be greater. The average fall in systolic blood pressure was 4.3 mmHg (SE = 0.9) in open and 2.6 mmHg (SE = 1.8) in blinded studies, and for diastolic blood pressure these figures were 2.8 mmHg (SE = 1.1) and 0.7 mmHg (SE = 1.2), respectively. These differences failed to reach statistical significance.

"Positive" and "negative" results

Only three studies reported a statistically significant "positive" result. Positive studies were more often not-blinded, tended to include less women, and the subjects in these trials were older. Baseline sodium intake was higher in positive studies (181 mmol/24h, SE = 10) than in negative studies (150 mmol/24h, SE = 11) (p = 0.06), but the average achieved reduction of sodium intake was similar: 71 mmol/24h (SE = 18) in positive and 80 mmol/24h (SE = 13) in negative studies.

Discussion

This analysis of thirteen studies on the effect of sodium restriction on blood pressure supports the general hypothesis that a reduction in sodium intake may lower blood pressure. The hypotensive action of sodium restriction appears to be largely restricted to systolic blood pressure and is small, ranging from 0.5 to 10.0 mmHg, with an average fall of 3.6 mmHg. The fall in blood pressure appears to increase with the level of initial blood pressure and with age. This suggests that sodium restriction is of limited value in young subjects, and in patients with mild hypertension. On the basis of our analysis it is impossible to say whether age or degree of hypertension is a better predictor of the effect of sodium restriction.

To appreciate these observations, some issues need to be addressed. Only three studies showed a statistically significant fall in blood pressure during sodium restriction. Moreover, as the present analysis is necessarily based on a small sample size, some predictors of lesser magnitude may not have been detectable due to

the limited statistical power. This suggests that any generalizations from the literature might be hazardous. However, a separate analysis, including three trials which did not have a control group,(14-16) supported the present findings in almost every respect. In all studies that comprised a lead-in period, blood pressure tended to fall in this period without any planned intervention. Accordingly, blood pressure levels at the first screening are higher than at the start of the intervention. In this analysis the latter of these blood pressure readings was used. In comparison with the first reading, our interpretation of "initial" blood pressure may overestimate the association between initial blood pressure level and fall in blood pressure on sodium restriction.

The specific objectives of the studies included in the analysis vary. This is reflected in the procedures used to select participants. In some studies, subjects were selected from a general population,(12) whereas in other studies only patients attending an hypertension clinic,(4) or sharing genetic predisposition for high blood pressure(11) were eligible. Moreover, in most studies, due to the nature of the intervention, several potential participants refused to be included. This implies that general applicability of the results may be limited.(17,18)

Obviously, no conclusions can be drawn from this analysis regarding an additive effect of sodium restriction to antihypertensive medication. Moreover, the type of studies dicussed here give primarily information on the hypotensive potential of sodium restriction, not on a role for dietary sodium in the aetiology of high blood pressure. It remains doubtful whether more trials will give more "positive" information. We observed a a negative association between year of study since 1980 and net fall in systolic and diastolic blood pressure on sodium restriction: $b = -1.2$ mmHg/year ($SE = 0.8$, $p = 0.08$) for systolic, and $b = -1.2$ mmHg/year ($SE = 0.4$, $p = 0.02$) for diastolic blood pressure. This finding may, of course, result from differences in case selection in more recent trials, but it may also be associated with the observed downward trend in sodium intake in the last decade.

A question as yet insufficiently answered is whether a subgroup exists in which sodium restriction may be most effective. The findings in the present analysis suggest that sodium restriction may lower blood pressure predominantly in older patients with relatively high blood pressure levels. Genetic factors have also been implicated in the response of blood pressure to sodium restriction. From a recent report by Watt and coworkers a positive family history for hypertension appears not to be related to sodium susceptibility,(11) but the findings in an open study by Skrabal et

al. suggest the opposite.(3) Initial plasma catecholamines, in particular dopamine may be associated with the fall in systolic blood pressure on sodium restriction.(12) The value of plasma renin, prostaglandins, cellular electrolytes, and circulating natriuretic factors in discriminating sodium sensitive and non-sensitive hypertensive patients needs further consideration. The smaller net changes in blood pressure observed in blinded as compared to open studies once again suggest that blindness is a prerequisite for trials in blood pressure research.

In conclusion, this meta-analysis suggests that sodium restrictio may reduce blood pressure, but that the effect is small and largely restricted to systolic blood pressure. The fall in blood pressure seems to increase with initial blood pressure level and age. This implies that sodium restriction may, unfortunately, be of limited use in those who are appear to be most eligible for non-pharmacological treatment, namely young patients with mild hypertension.(19,20)

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4.4 POTASSIUM AND BLOOD PRESSURE

4.4.1 Introduction.

The evidence that the dietary intake of potassium is associated with blood pressure, as well as the evidence that potassium supplementation may lower elevated blood pressure, is much more limited and fragmentary than for sodium. We will briefly review the data obtained in observational surveys and intervention studies in humans on the relation between potassium intake and blood pressure. Part of this review is based on discussions of the subject by Dustan,(1) Langford,(2) Meneely and Battarbee,(3) Simpson,(4) Tannen,(5) and Treasure and Ploth.(6)

4.4.2 Potassium intake and blood pressure.

Inter-population studies

The interest in potassium intake as a factor involved in the aetiology of elevated blood pressure has grown in the shadow, and somewhat as a consequence of the attention payed to dietary sodium. As discussed in the previous parts of chapter 4, the strongest evidence for a role of sodium in the aetiology of high blood pressure comes from inter population studies.(7) However, a low sodium intake is by far not the only difference between populations with a high and a low prevalence of hypertension.(8) In general, low sodium intake is accompanied by a high potassium intake. A low potassium intake may therefore be considered as a silent conspirator in hypertension. Moreover, as first suggested by Priddle and further elaborated by Meneely and Ball,(9,10) it might not be the level of sodium intake per se that determines the level of blood pressure, but rather the ratio of sodium to potassium could be of importance mediating the effect of sodium on blood pressure.(11) This hypothesis was based on observations of a protective effect of potassium supplementation in animals fed toxic amounts of sodium chloride.(12) Froment and coworkers showed a high-order correlation between populations, of the urinary sodium/potassium ratio with blood pressure.(13)

Intra-population studies

The majority of studies on potassium intake and blood pressure has been conducted within populations. The first report on a relation

between blood pressure level and potassium intake stems from Sasaki and collaborators in 1959.(14) They observed a difference in average blood pressure levels of the inhabitants of two villages in northern Japan, while sodium intake appeared to be similar. Yet, those living in the village with the lower blood pressure had a much higher potassium intake. A study in 104 young black females participating in a school survey showed no correlation between sodium excretion and blood pressure. There was, however, a significant positive association between blood pressure level and urinary sodium/potassium ratio ($r = 0.34$, $p = 0.02$).(15) This finding was confirmed in a subsequent report on another group of females of the same age.(16) Sever and coworkers reported higher blood pressure levels in members of an urban living African tribe, than in members of the same tribe living in a rural environment.(17) Although potassium excretion was the same in both groups, sodium intake was higher in those living in the urban setting, resulting in an urinary sodium/potassium ratio that was almost doubled in the urban group. In a large study of a Japanese population, blood pressure rose with decreasing urinary potassium excretion and with increasing urinary sodium/potassium ratio.(18) A study performed in the Belgian army failed to demonstrate a significant association between 24 hour potassium (and sodium) excretion and blood pressure.(19) However, the same investigators observed a decrease in blood pressure with increasing 24 hour potassium excretion in a Korean population.(20) It was calculated that a 100 mmol/24 hour increase in potassium excretion was associated with a systolic blood pressure that was on the average 6.4 mmHg lower.(21) In another Belgian study in 528 adults this figure was even higher: 12 mmHg/100mmol/24 hour for systolic and 6 mmHg/100mmol/24 hour for diastolic blood pressure after adjustments for body weight and age. In the same paper no significant associations between electrolytes and blood pressure were reported in 160 youths, aged 10-19 years.

In conclusion, there appears to be growing evidence that potassium intake is inversely associated with blood pressure levels, and/or that the sodium/potassium intake ratio is positively associated with blood pressure levels, within populations.

4.4.3 Studies on the effect of potassium supplementation on blood pressure

The experimental data on the hypotensive properties of potassium in humans are limited, although studies on the effect of potassium supplementation on blood pressure have a long history. In 1928 Addison placed five hypertensive subjects on a low sodium diet and supplemented this diet with either sodium or potassium salts.(22)

Supplementation with sodium resulted in a rise in blood pressure, whereas blood pressure decreased on potassium salts. In other early studies by Thompson and McQuarrie and associates, blood pressure in hypertensive children rose on a high sodium intake and this rise was attenuated when potassium chloride was added to the diet.(23,24) In this respect, it must be emphasized that the Kempner diet, often used to demonstrate the efficacy of sodium restriction in hypertension, not only lowers the intake of sodium enormously but also leads to a considerable increase in potassium intake.(25,26) This diet may reduce the sodium/potassium ratio by 99%.(6)

The evolution of idears and experiments on diet and blood pressure in general and of sodium and potassium in particular has been reviewed by Chapman and Gibbons untill the nineteen-fifties.(27) In recent times a series of studies has renewed the interest in the effects of potassium supplementation on blood pressure, either on a normal-, a high-, or a low-sodium diet. Luft and coworkers studied six normotensive subjects on a very high (1500 mmol/24 hour) sodium diet with and without potassium replacement.(28) Sodium loading in these subjects resulted in a small rise in blood pressure and a marked urinary potassium loss. On a high sodium diet with extra potassium, blood pressure was elevated to a lesser degree and a greater natriuresis appeared, than when no extra potassium was added to the diet. In another study in 20 normotensive subjects, a low sodium/high potassium diet for two weeks resulted in a statistically non-significant drop in systolic pressure of 2.3 mmHg and of 3.2 mmHg diastolic blood pressure.(29) Moreover, on this diet an average reduction of blood pressure rises induced by mental stress or noradrenaline infusion of 10 mmHg was observed ($p < 0.001$). In a study by Iimura and associates, supplementation with 10 mmol potassium per 24 hour for two weeks in 20 hypertensive patients lowered the mean arterial pressure by 11 mmHg.(30) This reduction in blood pressure was accompanied by decreases in body weight and body fluid volume.

The first double blind trials studying the effect of potassium supplementation on blood pressure were conducted by Khaw and Thom,(31) and MacGregor and coworkers,(32) in normotensive and hypertensive subjects, respectively. Potassium was supplemented by 64 mmol/ 24 hour during two weeks in normotensives and four weeks in hypertensives. In both studies diastolic blood pressure fell significantly, 2.4 mmHg and 4.0 mmHg respectively. Systolic blood pressure showed a significant 7.0 mmHg fall in hypertensive subjects, and a non significant 1.1 mmHg fall in normotensives. In two subsequent open studies, small groups of hypertensive patients were put on diets containing 64 mmol potassium per 24 hour for eight days and 200 mmol potassium per 24 hour for four weeks respectively.

Only slight and statistically nonsignificant alterations in blood pressure were observed.(33,34) Furthermore, another study by MacGregor and associates failed to show an effect on blood pressure when potassium was added to a sodium restricted diet.(35) Contrary to this, in fourty young mildly hypertensive subjects participating in a randomized crossover trial,(36) a significant fall in systolic blood presure was observed after six weeks of a combination of sodium restriction and supplementation with 72 mmol potassium per 24 hour. Moreover, the fall in blood pressure was accompanied by a significant fall in cardiac output.

These findings put forward the question whether the hypokalemia that frequently accompanies the use of diuretics in the treatment of hypertension, may also have a bearing on the achieved reduction of blood pressure in these patients.(37,38) In a double-blind crossover study, Kaplan and coworkers administered potassium (60 mmol/ 24 hour) for six weeks to 16 hypertensive patients who had diuretics-induced hypokalemia and who continued to take a constant amount of diuretics.(39) In association with an average rise in serum potassium concentration of 0.56 mmol/l, the mean blood pressure fell by an average of 5.5 mmHg ($p = 0.004$).

To summarize, the findings on potassium and blood pressure thus far are inconclusive, but the weight of the evidence is suggestive of an antihypertensive action of potassium. This effect may be more pronounced in hypertensive subjects, which may indicate that potassium supplementation interferes with the pathophysiologic phenomena resulting in increased blood pressure.(5) The way whereby potassium may affect blood pressure is still unclear, and potential mechanisms will be discussed below. In our study, however, potassium supplementation appeared to reduce cardiac output, a finding which is compatible with a direct effect of the cation on the cardiac muscle cell.

4.4.4 Pathophysiological aspects of the potassium-blood pressure relationship.

The role of potassium in blood pressure regulation fits, in part, in the mechanisms involved in sodium-related blood pressure elevation as discussed in chapter 4 paragraph 2. The theoretical basis for a link between blood pressure and potassium is, nonetheless, much less well developed than for sodium. Although the evidence is far from conclusive, the following ways whereby potassium may influence blood pressure have been proposed.(6)

1. Modification of neural regulation of blood pressure by affecting turnover and storage of central or peripheral catecholamines. Evidence has accumulated that increased sympathetic nervous

system activity is associated with the early phase of primary hypertension.(40-43) Enhanced autonomous nervous system activity may set the stage for chronic elevations of blood pressure maintained by the kidney.(44) Elevations in serum potassium may reduce vascular sensitivity to circulating catecholamines.(45) There is also evidence that re-uptake of noradrenaline by sympathetic nerve terminals is influenced by the relative external concentration of sodium and potassium.(46) Dahl and coworkers reported reduced pressor and heart rate responses to intravenous noradrenaline in subjects on a high potassium diet.(47) Moreover, normotensive humans on a high potassium diet show less rise in blood pressure in response to mental stress.(29) Varying effects of potassium supplementation on plasma noradrenaline have been reported. In some studies a rise was observed,(30) whereas in others plasma noradrenaline fell.(48,49) We observed no significant changes in plasma noradrenaline, adrenaline, and dopamine in fourty subjects after six weeks of daily supplementation with 72 mmol potassium-chloride.(36)

It appears that the extent to which potassium may modify neural mechanisms involved in the pathogenesis of hypertension is, as yet, not sufficiently clarified to justify definite conclusions.

2. An effect of potassium on a number of other pressor mechanisms has been suggested. Most prominent are observations that potassium may suppress renin secretion rates either when given acutely,(50,51) or chronically.(52) The site of inhibition of renin secretion by potassium appears to be at the macula densa.(53) In general, it seems that inhibition of plasma renin activity is most likely to occur when a high potassium intake is combined with sodium restriction.(5) However, during six weeks of potassium supplementation combined with a reduction in sodium intake we did not observe any change in plasma renin activity in young mildly hypertensive subjects.(36) As will be discussed below, potassium supplementation may result in a marked natriuresis which may give rise to a paradoxical increase in plasma renin.(54) This could imply that the net result, of a combined direct inhibition of renin secretion by potassium in combination with a renin secretory stimulus by volume contraction, would be no change at all. Apart from its effects on renin secretion, potassium may alter the responsiveness of the resistance vasculature to angiotensin II.(30) Evidence is conflicting, since no-change, as well as increased and decreased sensitivity to the pressor effect of angiotensin II on a high potassium intake have been reported.(5) Finally, in a study by

Zinner and collaborators, urinary kallikrein excretion rose with increasing urinary potassium excretion.(55) As early as 1934, Elliott and Nuzum reported reduced urinary kallikrein in hypertensive individuals.(56) The significance, however, of the kallikrein-kinin system in the aetiology of high blood pressure is still uncertain.(57)

Data on the effects of potassium supplementation on renin, angiotensin, and other pressure regulating systems are still equivocal. Therefore, at this moment, no clear conclusions can be drawn.

3. The natriuretic properties of potassium are known since Thomas Willis advocated its use for the treatment of dropsy in 1679.(58) Since the first half of the twentieth century a more systematic study of the natriuresis produced by potassium supplementation has started.(59) A high potassium intake may increase renal blood flow,(60) but the natriuretic effect of potassium does not appear to be related to alterations in renal haemodynamics.(50) There is considerable debate concerning the precise nephron site where a high potassium level inhibits sodium reabsorbtion.(61,62) Natriuresis induced by potassium has been observed in hypertensive patients.(30) In a study on potassium supplementation, in combination with sodium restriction in young mildly hypertensive subjects, no clear natriuresis was observed as judged by the body weight.(34) This is in agreement with findings in other studies.(32,48,49) Part of this may be explained by an associated increase in aldosterone levels.(63)

   In conclusion, the significance of natriuresis in relation to the antihypertensive properties of potassium supplementation remains to be elucidated.

4. An alternative way whereby potassium may affect peripheral resistance and thereby blood pressure, is by direct effects on the arteriolar smooth muscle cell. A vasodilatory effect of potassium on resistance vessels has been observed at plasma levels well in the range found in subjects on a high potassium intake.(64,65) Potassium induced vasodilation may be blocked by ouabain, indicating that the effect is mediated by the ATPase dependent sodium-potassium pump (for details on cellular sodium and potassium transport systems see figure 4.2.4).(66) Moreover, an acute reduction of serum potassium level has been shown to reduce Na-K-ATPase activity and to increase the contractile activity of cardiac and arterial smooth muscle.(67) It has been suggested by Blaustein,(68) and De Wardener an MacGregor,(69) that a circulating natriuretic substance leading to an increased intracellular sodium concentration and subsequently to increased intracellular calcium levels, elevated smooth muscle tone, a rise

in peripheral resistance and thus to high blood pressure, might be reponsible for primary hypertension related to a high sodium intake (see figure 4.2.3). The proposed natriuretic factor would act by inhibiting Na-K-ATPase activity.(70) An increased potassium intake may counteract this mechanism by stimulating the sodium-potassium pump. A hypotensive action of potassium could thus be explained by altered vascular smooth muscle tone, but the same mechanism might also affect the sympathetic nervous cell.(71) In rats it has been shown that partial replacement of sodium by potassium in the diet leads to a reduced stimulation of the sympathoneural and sympathoadrenal system by cold.(72) As is discussed in chapter 4, paragraph 2, it is possible that inhibition of the sodium pump in hypertension is secondary to a primary disturbance of membrane structure leading to increased intracellular sodium and, eventually, calcium levels.(73,74) However, irrespective of the primary mechanism leading to altered intracellular electrolyte handling, by stimulating Na-K-ATPase potassium may act against these disturbances. Although no changes in various pressor systems were observed in a study of combined sodium restriction and potasssium supplementation for a period of six weeks, systolic blood pressure fell significantly, and this was accompanied by a fall in cardiac output of 0.4 l/min/m^2 BSA.(34) In agreement with this Omvik and Lund-Johanssen, after moderate sodium restriction in 19 mildly hypertensive patients for six month, observed a fall in cardiac output that significantly correlated with the achieved fall in sodium/potassium ratio.(75)

In conclusion, the available evidence is suggestive of a direct effect of potassium on the arterial and cardiac cell. This effect may account for the hypotensive potential of potassium supplementation.

4.4.5 Conclusion.

Evidence is accumulating, from both inter, and intra population studies that a high potassium intake and/or a low sodium/potassium ratio are associated with lower blood pressure levels. Potassium supplementation may lower blood pressure in normotensive and, more clearly, in hypertensive subjects. Moreover, potassium supplementation in patients treated with diuretics may not only prevent hypokalemia, but also add to the antihypertensive treatment.

Most studies on the effect of a high potassium diet on blood pressure aimed at an increase in potassium intake of approximately 60 mmol/24 hour. Depending on initial potassium intake, this

supplementation resulted in an average daily potassium intake of about 130 mmol/24 hour.

A potassium intake of this magnitude is not hazardous in subjects with normal kidneys, but might pose a risk in patients with compromised renal function.(5) Therefore, some authors have expressed their concern about these risks, and also about the doubtful cost/benefit ratio of potassium therapy.(76-78) However, the potential hypotensive effect of potassium would not imply that 'whole nations are to be put on potassium pills'. On the contrary, as needs to be further clarified, it may well be that not potassium per se but a low dietary sodium/potassium ratio is the primary determinant of blood pressure level. In this regard, it is interesting that while the dietary sodium/potassium ratio is about 2 to 4 in Westernized societies,(2) it has been estimated that the diet of our paleolithic ancestors had a sodium/potassium ratio between 0.01 and 1.0.(79) Moreover, the effect on blood pressure may be associated with the relative contributions of other dietary components, like calcium and magnesium, or even non-dietary environmental variables. Also, an increase in dietary potassium can be achieved in alternative ways, for example by replacing common table salt by potassium containing "low salt" mixtures.(80)

In conclusion, there are great attractions in the concept of a low sodium/high potassium diet as an additive or even alternative to antihypertensive treatment,(81) and more studies of longer duration including larger numbers of participants are needed to evaluate the benefits and confirm the safety of these dietary changes.

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4.5 CALCIUM AND BLOOD PRESSURE

4.5.1 Introduction.

The main characteristic of primary hypertension is an increase in peripheral resistance resulting from increased vascular smooth muscle tone.(1,2) Although structural changes in the vascular wall may add to the rise in vascular resistance observed during the development of high blood pressure, these changes are not likely to initiate the rise in blood pressure, nor to account fully for its haemodynamic profile.(3,4) It is well established that rapid changes in intracellular ionized calcium (Ca++) levels play a central role in the regulation of contractile activity of muscle cells.(5) Any condition associated with an increase in the strength of contraction of vascular smooth muscle must either alter the intracellular Ca++ level itself, change the response of the contractile apparatus to Ca++, or exert both effects.(6)

Apart from its role in the contraction of vascular and cardiac smooth muscle, Ca++ is a major intracellular messenger in the response to noradrenaline, adrenaline, and angiotensin, the release of noradrenaline, the rate of secretion of aldosteron by adrenal glomerulosa cells, and probably the release of renin from juxtaglomerular cells.(7) Furthermore, many vasodilatory and other antihypertensive agents exert their effects by interference with calcium dependent mechanisms, or by reduction of intracellular calcium concentration.(8-10) The way whereby calcium participates in these phenomena, however, goes beyond the scope of this review and will not be discussed here.

Whatever mechanisms are involved in the pathogenesis of primary hypertension the final consequence must be, in all likelyhood, a disorder of cellular calcium mechanism or, more specifically, in the functioning of the cell membrane.(11) In recent years a variety of disorders of cellular calcium metabolism involving cellular calcium concentration, membrane binding, and transport kinetics, have been described in subjects with hypertension and in animal models. Also, several reports suggest that general calcium handling may be altered in primary hypertension.(12-14) These findings indicate a putative role for the calcium ion in the pathogenesis of primary hypertension.(14a)

We will briefly review the evidence that disorders of calcium handling are implicated in primary hypertension. The structure of the review will be somewhat different from the previous parts of chapter 4. Contrary to the discussion on electrolyte intake and blood pressure in the reviews on sodium and potassium, in

considering data on calcium and blood pressure we will extent this part by also addressing points raised regarding calcium excretion, and plasma calcium levels in relation to blood pressure. The role of cellular calcium handling in hypertension will be discussed separately, though in combination with speculations on the pathogenetic mechanisms that may explain the relation between altered calcium metabolism and blood pressure elevation. In a subsequent paragraph attention is payed to the part played by the parathyroid gland in hypertension.

4.5.2 General calcium handling.

Calcium intake: inter- and intra-populationstudies.

The therapeutic properties of natural mineral waters have already been recognised by the ancient Egyptians, the Greeks and the Romans. In the sixteenth century Paracelsus was among those who stimulated the public interest in the healing properties of mineral springs and watering places.(15) At the end of that century some early biochemical analysis were carried out using water from the Epsom spring and attention was focused at the salt content of the water as a potential source of the purgative virtue described to the well. In recent times Kobayashi was the first to suggest an association between drinking water and cerebrovascular mortality.(16) Stitt reported higher mean blood pressure levels in inhabitants of soft-drinking water towns as compared with those living in a hard-drinking water area.(17) The same was observed in the MRC Twelve Towns study, the most marked difference being in casual diastolic blood pressure.(18) However, these findings were not comfirmed by some other studies and remained subject to much debate.(19) In the late sixties Langford and Watson suggested that the combination of a low calcium intake and high sodium consumption might represent a hypertensiogenic situation.(20) More convincing evidence has come from a series of observational studies relating dietary calcium intake to blood pressure level and the prevalence of hypertension.(21-29) Although the assessment of dietary calcium intake is difficult a rather consistent pattern emerges, suggesting that calcium intake is inversely associated with both prevalence of hypertension and level of blood pressure. This observation is one of the very few examples of an association between a nutritional marker and blood pressure within populations.

In conclusion, the evidence that a (relatively) low calcium intake increases the risk of developing high blood pressure is quite strong. The mechanism whereby low calcium intake induces blood

pressure elevation is, however, less clear. As will be discussed later, a low calcium intake may influence serum calcium levels and stimulates the release of parathyroid hormone I. This may, either direct or indirect, affect cellular calcium homeostasis and peripheral resistance.

Calcium excretion

Increased urinary calcium excretion has been demonstrated in hypertensive patients, and in several large population studies a significant positive correlation was observed between urinary calcium and blood pressure.(30-33) In some, but not all, studies serum calcium levels and calcium intake were studied concurrently and the elevated calcium excretion appears to be unrelated to alterations in these factors.

Differences in the intake of dietary sodium are known to affect calcium transport on a tubular level.(34) In particular, dependence of renal calcium clearance on sodium clearance might imply that increase in calcium excretion is merely the result of changes in renal sodium handling.(35) However, in two studies urinary calcium and sodium excretion were studied simultaneously and the urinary calcium to sodium ratio was also found to be increased in hypertensive patients.(30,32) These findings are suggestive of the existence of a renal calcium "leak" in hypertensive subjects. The observations in humans are partly confirmed by animal studies.(36-38) In spontaneously hypertensive rats (SHR), however, hypercalciuria was found to be dependent on food or calcium intake, and no detectable net renal calcium loss was present.(39) Definite answers to these questions can only be derived from balance studies carried out in a metabolic ward. At present no unequivocal conclusions can be made.

Plasma calcium levels

There are several reports on plasma calcium concentration in relation to blood pressure levels, the results, however, being inconclusive. This may, in part, be due to differences in calcium determination. Plasma calcium is present as protein-bound calcium, complex bound calcium, and free calcium ions (Figure 4.5.1).(40) Total calcium can be measured accurately by atomic absorbtion spectometry and other methods, but may not give a reliable indication of the biologic active calcium fraction as the proportion ionized is affected by variations in the concentration of serum protein, particularly albumin, and blood pH.(41) No algorithm derived to adjust total calcium values for the effects of protein

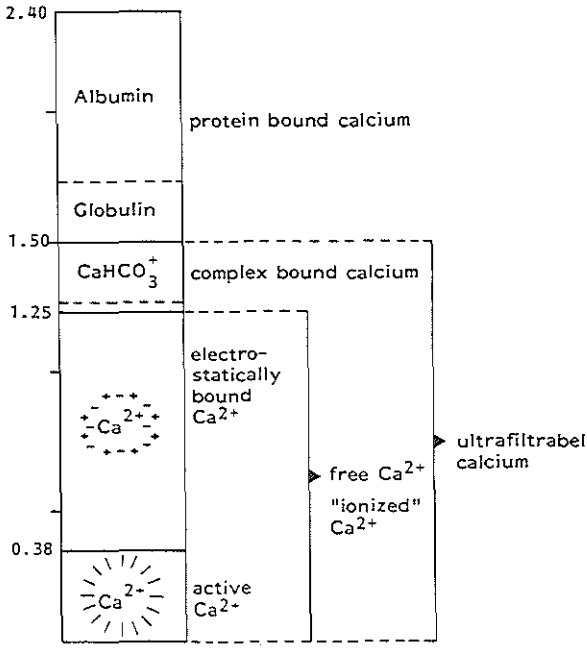

Figure 4.5.1. The calcium fractions of blood plasma. Reproduced from 41.

binding seems to predict adequately the physiologically important free calcium.(42) The most widely used direct way to measure ionized calcium is by the use of an ion-selective electrode.(43) Although the interpretation of the values observed by this method is still subject of controversy, the importance of measurement of ionized calcium apart from total calcium in order to estimate the individual's calcium status appears to be well established.(44) Recently, attention has been focused on the more easily measurable dializable calcium as an alternative.(45) Bulpitt et al. were the first to observe a positive relation between serum total calcium and systolic blood pressure.(46) These findings were confirmed in a large study in Belgian men, and by several other investigators.(30,47,48) Others observed a negative association between both serum total calcium and phosphorus, and systolic blood pressure in hypertensive subjects.(31) Decreased serum total calcium levels were observed in a group of mildly hypertensive youngsters, compared to age matched controls from the same population (Paragraph 5.3). In a study by Erne and coworkers serum total calcium levels were lowest in established hypertensive patients, highest in normotensives, and intermediate in borderline hypertensive

subjects.(49) Serum ionized calcium levels were reported to be reduced,(50) increased,(51) or equal(52) in hypertensive subjects compared with normotensive subjects. Interestingly, most case-control comparisons show reduced serum total or ionized calcium levels where data from cross sectional studies are equivocal. Alternatively, ionized calcium may be selectively reduced in patients with low-renin hypertension.(53) In genetically hypertensive rats both reduced serum total and ionized calcium levels have been reported.(54-56) Salivary ionized calcium levels were found to be decreased in hypertensive subjects.(57) Moreover, reduced serum phosphate levels have been related to high blood pressure.(58,59)

There are several explanations for the conflicting findings in different studies. Serum total calcium levels may be affected by haemoconcentration as observed in hypertension.(60) Also, the positive relation between serum total calcium and blood pressure was observed in large normal populations, and these studies do not exclude the possibility that a subgroup exists combining high blood pressure with low calcium levels.(13) Moreover, since age is inversely related to serum total calcium levels the association between calcium and blood pressure may be different in different age groups.(61) Differences in selection of patients may account for certain discrepancies. For example, antihypertensive drugs, and especially diuretics, tend to increase serum ionized calcium concentration.(62)

At this time no firm conclusions can be drawn linking serum total and ionized calciumlevels to blood pressure, although there appears to be at least a subgroup of hypertensive patients in which serum total and/or ionized calcium levels are reduced.

4.5.3 Cellular calcium handling.

Intracellular calcium levels

Techniques for intracellular calcium determination have only recently been developed and various biochemical approaches are used. Calciumlevels in the extracellular fluid are much higher than intracellular levels (Figure 4.5.2). The resting (or basal) concentration of free intracellular calcium varies between 10 -8 and 10 -7 mol/l. Changes in intracellular free calcium can be derived from either extracellular or intracellular sources.

Calcium may enter the cell from the extracellular fluid by at least three different influx pathways: voltage dependent (or potential-operated) channels, receptor operated channels, and the

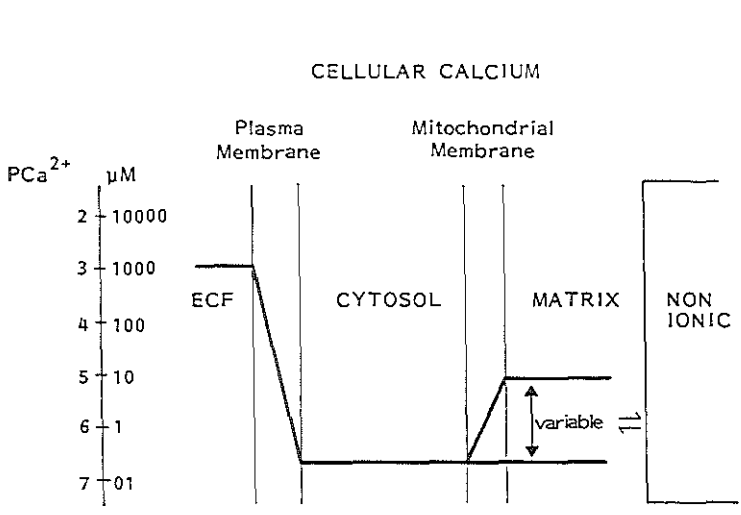

Figure 4.5.2. Schematic representation of cellular calcium metabolism, emphasizing the roles of the plasma and mitochodrial membranes in the maintenance of a low calcium concentration in the cell cytosol. Reproduced from 11.

so-called Na+ channel(11) (Figure 4.5.3). It has been suggested that calcium is transported from the cytosol to the extracellular space predominantly by two mechanisms. Firstly, by the energy requiring calcium pump, or Ca2+-Mg2+-ATPase. Secondly, by the Na-Ca exchange pathway which is driven by a Na gradient maintained by the Na-K pump (Figure 4.5.3) The exchange of calcium between cytosol and calcium pools of cellular organelles constitutes an alternative way whereby cellular free calcium level is determined.(11)

In hypertensive subjects increased intracellular free calcium levels have been reported in erythrocytes, platelets and adipocytes.(49,63-65) Moreover, a close correlation between platelet calcium and arterial pressure has been observed.(49,66)

Calcium binding and membrane transport

By far the greatest proportion of intra- and extracellular calcium is bound to anionic sites on plasma protein and membrane-associated phospholipids. Membrane-bound calcium represents approximately 95% of nonskeletal calcium, and includes besides the cell membranes also the membranes of intracellular organelles like the mitochondria and the endoplasmatic reticulum.(67,68) Several groups have studied inner and outer cell membrane binding in hypertensive humans and animals. Bound calcium influences membrane function in several ways. There are binding sites for calcium on the inner and the outer sides of the cell membrane. A number of disturbances of membrane calcium

binding have been put forward in hypertension, all eventually resulting in elevated intracellular calcium levels and thereby contributing to elevation of blood pressure (Figure 4.5.4).

The outer side of the cell membrane contains both high and low affinity binding sites. On the outer aspect of the cell membrane it can be shown that calcium is able of inhibiting its own influx and a decrease in the (fast) component of the smooth muscular contractile response.(69,70) Total removal of calcium from extra-cellular fluid results in a marked increase in permeability to the ion. This is impressively demonstrated in a phenomenon called "calcium paradox": massive inward movement of calcium ions in cardiac muscle cells occurs when extra-cellular calcium concentration is restored after a short period of perfusion with a calcium-free solution.(15) The mechanism whereby outer membrane-bound calcium exerts its effect on the calcium influx remains to be elucidated. A specific inactivation of potential operated calcium channels has been postulated.(14) Complete or near complete removal of calcium from extra-cellular fluid of smooth muscle cells and erythrocytes also increases permeability for potassium and other monovalent cations.(72,73) Calcium binding to the outer side of the cell membrane is reported to be reduced in spontaneously hypertensive rats when compared with normotensive controls.(74,75) There is some evidence that reduced outer surface calcium binding also exists in hypertensive patients.(72,75,76)

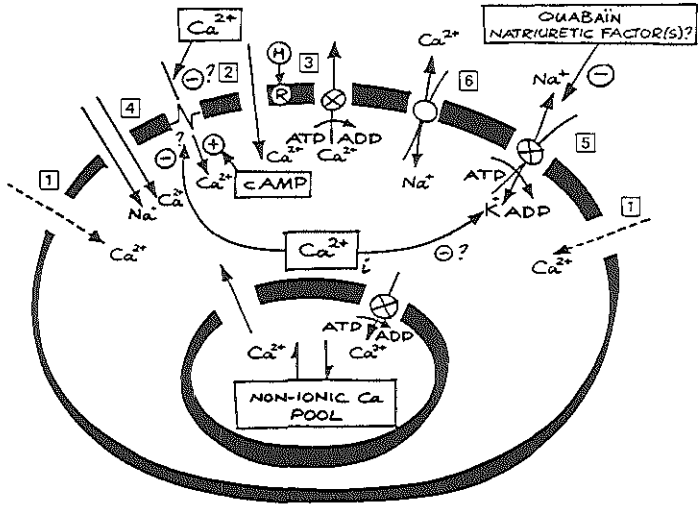

Figure 4.5.3. Compilation of postulated membrane transport mechanisms involved in cellular calcium homeostasis.

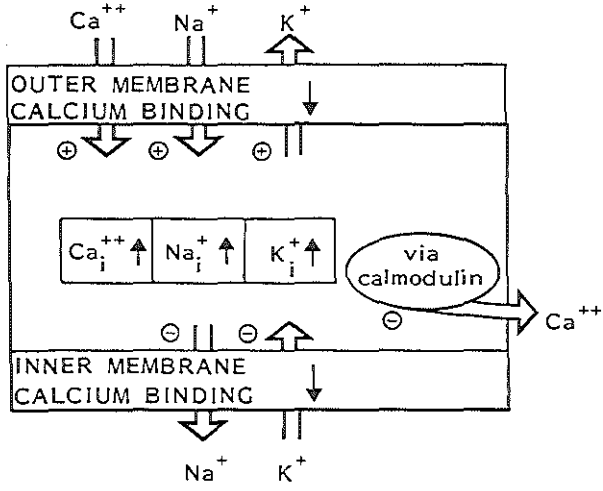

Figure 4.5.4. Effects of changes in inner and outer plasma membrane calcium binding on intracellular sodium, potassium and calcium concentration.

The calcium binding to the inner side of the cell has been assessed by studies in human and rat cells. Due to the relatively low ionic calcium concentration within the cell, inner calcium binding sites involve high affinity binding. Erythrocytes of hypertensive patients show a substantial decrease in the amount of calcium bound to the inner side of the cell membrane.(77) Reduced calcium binding to inner side binding sites has been observed in erythrocytes of spontaneously hypertensive rats as compared with normotensive controls.(78) A similar reduction has been reported in fat, heart, liver and neural cells from hypertensive rats.(79,80) Decreased inner membrane-bound calcium has been linked to inhibition of Na-K-ATPase activity, leading to increased intracellular sodium concentration. Elevated intracellular sodium levels may result in reduced calcium transport out of the cell, and thus to raised intracelular free calcium levels (for details see paragraph 4.2.4).(81,82) The observation in red blood cells and Purkinje fibers that increased inner membrane calcium binding leads to hyperpolarisation may suggest that impaired inner membrane binding favours depolarization and activation of potential operated channels.(83,84)

Evidence is accumulating that many calcium dependent effects are mediated by binding to, and activation of, the intracellular calcium binding protein calmodulin.(85) Calmodulin (18,000 molecular weight), has four calcium binding sites and no intrinsic enzymatic activity, but is capable of interacting with other proteins to modify their function in a variety of ways. No clear changes in

cellular calmodulin content in hypertension have been reported. Yet, in hypertensive subjects both affinity for calcium by the calcium plump, and the maximum activity of the calcium pump appear to be reduced and these characteristics of the pump are mainly controlled by calmodulin.(86-88) An alteration of the inner membrane calcium-calmodulin binding kinetics leading to impaired calcium pump function may be responsible for these findings.

In conclusion, the existence of changes in both inner- and outer-membrane calcium binding in hypertension has been observed in a series of studies. Deficient calcium binding to cell membranes in the smooth muscle cells could account for a greater membrane lability and sensitivity for vasoactive agents.(89) Also, alterations in membrane function may lead to an increase in intracellular free calcium and thereby influence the state of tonic contraction of contractile tissue. Together with reports of increased intracellular free calcium levels these findings support the view that altered cellular calcium metabolism is implicated in the pathogenesis and/or aetiology of primary hypertension.

4.5.4 Parathyroid hormone in hypertension.

The first suggestion of an association between hypertension and parathyroid gland activity stemms from Helstrom and coworkers reporting that hypertension is frequently observed in patients with hyperparathyroidism.(90) This observation has been confirmed by several authors, and according to Lafferty hypertension is twice as common in hyperparathyroid patients as in the general population.(94) Furthermore the occurence of hyperparathyroidism closely follows the pattern of the occurrence of primary hypertension in Western society i.e., a greater prevalence of hypertension in hyperparathyroid patients that are older and in blacks.(59,91-94) Moreover, the incidence of primary hyperparathyroidism in patients with hypertension is about eight times higher than average.(92)

In 1980 the first, preliminary, data were presented indicating that parathyroid gland activity is enhanced in primary hypertension.(31) These findings were confirmed by Strazzullo and coworkers.(32) No differences in serum calcium were observed, but renal calcium excretion was elevated in hypertensive patients. Both studies are based on the determination of total immunoreactive parathyroid hormone in plasma. This not only represents the intact hormone, amino acid sequence 1-84, but includes all fragments derived either from peripheral metabolism of the active molecule or degradation of precursors of the hormone within the parathyroid

reported in patients with hyperparathyroidism but not in subjects with elevations in serum calcium secondary to other causes.(113) By contrast, hypertensive subjects with primary hyperaldosteronism show frank elevations of parathyroid hormone levels, in the absence of clear alterations in serum ionized or total calcium and combined with suppressed plasma renin activity.(114) It is conceivable that in these patients parathyroid levels were raised secondary to a tendency of calcium loss resulting from mineralocorticoid excess.(115)

Alternatively, sodium volume expansion may trigger parathyroid gland activity. It has been demonstrated that both exogenous and endogenous parathyroid hormone decrease renal proximal sodium reabsorbtion leading to increased sodium excretion.(116,117) The observation of natriuretic properties attributed to parathyroid hormone, might provide a rationale for a role of this hormone in the sodium, calcium and blood pressure interrelationships as suggested by DeWardener and Blaustein.(118,119)

It is, as yet, unclear whether the association between the parathyroid gland activity and blood pressure is more pronounced in the early pathogenesis of primary hypertension. In our studies it appeared that plasma parathyroid hormone levels are more clearly elevated in young hypertensives than in older subjects.(98) In experiments in spontaneously hypertensive rats, Schleiffer and coworkers observed a permissive role for the parathyroid gland in blood pressure rise.(120) Parathyroidectomy in young animals, while keeping serum calcium normal, resulted in a delay of the rise in blood pressure for 42 weeks. No effect was observed when this procedure was performed in adult rats. The association between parathyroid gland activity and/or parathyroid hormone and blood pressure might be different in different age groups. Levels of parathyroid hormone have been shown to change markedly during life.(121) Also, during pregnancy, a state associated with increased risk of developing high blood pressure, parathyroid hormone levels progressively increase in combination with elevations in serum ionized calcium indicating that a different "setpoint" appears to be operative.(122)

In conclusion, parathyroid gland activity appears to be associated with elevations of blood pressure. There are indications that parathyroid hormone itself may affect blood pressure. This could result from modulation by parathyroid hormone of the rate of transmembrane calcium fluxes in vascular smooth muscle cells, thereby increasing intracellular free calcium levels and ultimately leading to increased peripheral resistance. More evidence is clearly needed, and in particular methods for measurement of intracellular calcium levels may provide valuable additive information.

4.5.5 Studies on the effect of calcium supplementation on blood pressure.

There is limited published evidence for an antihypertensive effect of oral calcium loading either in normotensive or hypertensive subjects. This is in apparent contrast with the increasing evidence that reduced dietary calcium intake is associated with elevation of blood pressure. The first observation of a blood pressure lowering action was reported by Belizan and coworkers from a controlled trial of oral calcium against placebo in 57 young normotensive subjects for 22 weeks.(123) The calcium supplemented group showed a significant decrease in diastolic blood pressure amounting a reduction of 5.6% and 9% from the initial values, for women and men respectively. Preliminary data from a randomized trial on calcium supplementation in hypertensive patients suggest that calcium may lower blood pressure in some but not all patients, dependent on plasma renin levels.(124,125) In a randomized crossover study by McCarron and coworkers, supplementation with one gram of calcium for eight weeks resulted in a fall in blood pressure in hypertensive, but not in normotensive subjects.(126) In a 4-year clinical trial to assess age-associated bone loss in women, aged 35 to 65 years, calcium suppletion decreased systolic blood pressure in hypertensive women on medication, but not in normotensive women.(127)
Calcium supplementation of 2 gram daily was reported to lower blood pressure in normal pregnant young women.(128) Preliminary data from a study by Strazzullo and coworkers of a placebo controlled crossover trial in eightteen patients with borderline hypertension, nine of whom continuing their previous antihypertensive medication, suggest that calcium may lower blood pressure in a minority of hypertensive subjects.(129) Calcium supplementation in this study appears to have no additive effect to antihypertensive drug treatment. Also, young subjects showed greater blood pressure responses to an increase in calcium intake. We performed a double-blind randomized controlled trial of calcium supplementation with one gram daily in ninety young subjects with persistently elevated blood pressure levels.(130) Increased calcium intake for a period of twelve weeks resulted in a significant decrease in diastolic blood presure, in particular in youngsters with low serum total calcium and/or high plasma parathyroid hormone levels. These findings suggest that a subgroup of hypertensive individuals exists, susceptible to calcium supplementation, and characterized by alterations in calcium metabolism indicative of a relative calcium need. Future studies in subjects selected on the basis of these characteristics may provide further insight in the mechanisms involved and establish the efficacy and feasibility of calcium

supplementation as a means of intervention on high blood pressure.

4.5.6 Conclusion.

Ultimately, intracellular calcium determines the state of tonic contraction of the vascular smooth muscle cell.(131) Thus, irrespective of pathophysiological mechanisms involved, calcium forms the final common denominator of increased peripheral resistance and hypertension.

Several disturbances in cellular and general calcium metabolism have been observed in hypertensive subjects and spontaneously hypertensive rats. The main findings regard elevations in intracellular calcium concentration, reduced ATP-dependent transmembrane calcium transport, reduced intracellular calcium binding capacity, reduced extracellular binding capacity, reductions in serum total- and/or ionized-calcium levels, increased renal calcium loss, reduced dietary calcium intake, and increased plasma parathyroid hormone concentrations. Either of these factors might play a part in one or more pathways leading to elevations in intracellular calcium as summarized in Figure 4.5.7. These findings, be it in combination or apart may account for elevation of blood pressure in some, or all, hypertensive patients.

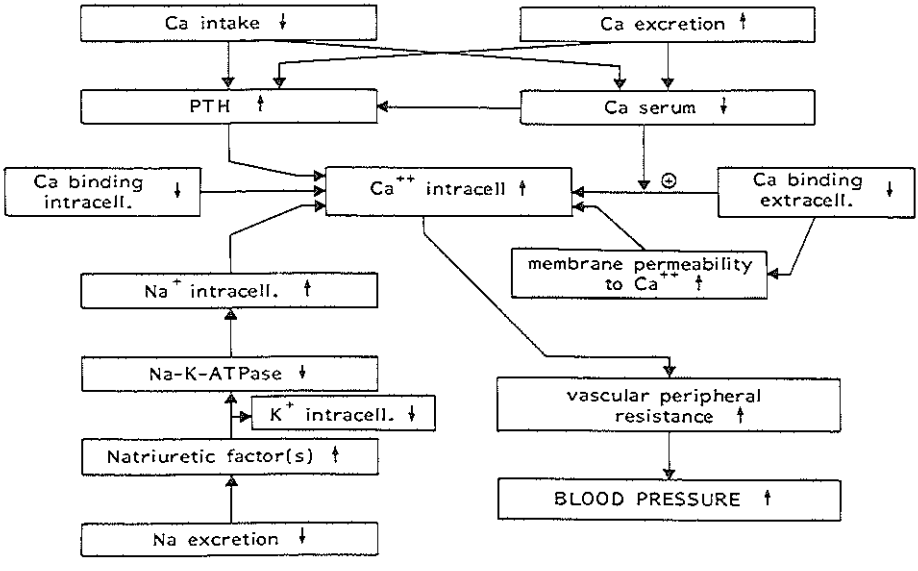

Figure 4.5.7. Hypothetical flow-chart representing potential mechanisms involved in elevation of peripheral resistance and blood pressure by alterations in calcium and sodium metabolism.

It is as yet not sufficiently clear to what extent changes in calcium homeostasis are of aetiological significance, whether they result from the hypertensive proces itself, or perhaps enforce other mechanisms involved in hypertension. It appears that calcium supplementation could be beneficial in hypertensive subjects, in particular when a relative calcium deficiency, as judged by serum calcium and parathyroid hormone levels, is present. Further intervention studies in subgroups of hypertensive patients with monitoring of determinants of calcium metabolism are needed to establish the value of increases in calcium intake as a means of lowering blood pressure in hypertension. Moreover, this approach may elucidate the role played by calcium in the aetiology of high blood pressure.

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Chapter 5

DETERMINANTS OF ELEVATED BLOOD PRESSURE

5.1 INCREASED PLASMA DOPAMINE, NORADRENALINE AND ADRENALINE CONCENTRATIONS IN YOUNG PEOPLE WITH PRIMARY HYPERTENSION

5.1.1 Introduction.

The discovery and experimental use of the potent hypotensive action of specific dopamine receptor agonists has renewed the interest in the role of endogenous dopamine in the development of primary hypertension in man.(1) There are several lines of evidence suggesting that central dopaminergic mechanisms play an important part in the development of hypertension in animal models as well as in humans.(2,3) Studies on the peripheral action of endogenous dopamine are scarce but there is considerable evidence that dopamine may act as a neurotransmittor in peripheral tissue in addition to being a precursor of noradrenaline.(4) A pivotal role for dopamine in renal sodium handling appears to be well established.(5) Although methodological problems complicate the measurement of peripheral sympathetic nervous activity, the development of sensitive radioenzymatic assays enables catecholaminergic characterisation of hypertensive and normotensive subjects. Previous reports of increased levels of plasma noradrenaline in relatively young hypertensive subjects support the hypothesis that essential hypertension in its early phase is associated with an altered state of the autonomous nervous system.(6) However, the evidence for an increased release of adrenaline in essential hypertension is less conclusive.(7) The same holds true for dopamine, as no study has reported significant differences in plasma dopamine concentrations between normotensive and primary hypertensive subjects.

To investigate the levels of peripheral catecholamines in early primary hypertension and to study their interrelationships we measured plasma dopamine, adrenaline and noradrenaline levels in 40 untreated young people with stable mild hypertension and in 40 age- and gender-matched normotensive controls from the same open population. Also, plasma renin and cardiac output were measured in these groups.

5.1.2 Subjects and methods.

Population

Between 1975 and 1980 blood pressure was measured in 4,649 subjects out of 5,670 eligible (82%) in a study of blood pressure and other risk indicators for cardiovascular disease. They were 5 to 19 years of age and residents of two districts of a Dutch town. Of the initially examined subjects 1,597 were selected for yearly follow

up, as described previously.(9) Youngsters were designated as stable mild hypertensive if they had at least three blood pressure readings of 140 and/or 90 mmHg or over, during seven to nine years of follow up. A control group, matched for age and gender was randomly selected from the remainder of the same population. Fourty hypertensive and 40 normotensive subjects were selected for this study.

Methods

All hypertensive and normotensive subjects were examined between 14.00 and 20.00 hours according to a rigorously standardised protocol.

Blood pressure was measured on the left arm using a random zero sphygmomanometer after 10 minutes of rest and before venipuncture by two trained paramedical observers. For the present analysis the mean of three readings in sitting position was used. The beginning of the fifth Korotkoff phase was taken as diastolic pressure.

A blood sample was obtained using an indwelling venous catheter after 20 minutes recumbency. The blood sample was placed in ice-cold tubes, centrifuged, and stored at -70° C until assayed. Plasma catecholamines were measured using the COMT radioenzymatic method.(10) Plasma renin was determined by radioimmunoassay as the concentration of active enzyme.(11) Average urinary electrolyte excretion was estimated from one 24-hour urine specimen. From one subject in the normotensive group no plasma and urine sample was obtained.

Two-dimensional echocardiography was performed in supine left lateral decubitus position. Subsequent quantitative analysis was based on the parasternal short axis, apical long axis and four chamber views. The modified Simpson-rule formula was used for the calculation of end-systolic and end-diastolic left ventricular volumes from three consecutive cardiac cycles.(12) End-diastolic minus end-systolic volume yielded stroke volume and cardiac output was obtained by multiplying stroke volume by heart rate. Cardiac index was calculated by dividing cardiac output by body surface area.(13)

Data-analysis

The data analytic approach aimed both at the analysis of differences between variables in hypertensive and normotensive subjects, and at differences in associations between variables within the hypertensive and the normotensive group. For each variable a t-test for unpaired observations was used. Only complete matched pairs were

taken in the analysis. P values corresponding to a two tailed test of significance are given. Relations between catecholamines and blood pressure were analysed in two ways. First, subjects were categorized according to the median of either of the catecholamines within the hypertensive and normotensive group and differences in blood pressure between these subgroups were studied. Second, a quantitative analysis of associations within hypertensive and normotensive groups was performed by multiple linear regression analysis with adjustments for confounding variables, when appropriate.

Results

Anthropometric characteristics and blood pressures of the hypertensive and normotensive youngsters are shown in table 5.1.1. Plasma noradrenaline, adrenaline and dopamine levels were all substantially and significantly higher in hypertensive than in normotensive subjects (Table 5.1.2). Plasma renin was higher, though not significantly, in the hypertensive group. There were no differences in mean serum sodium and potassium values, nor in 24 hour sodium and potassium excretion. The mean values of cardiac output and cardiac index did not differ between the groups (Table 5.1.2).

Multiple regression analysis revealed several relationships between variables measured and these are summarized in table 5.1.3.

TABLE 5.1.1. Blood pressure and anthropometric characteristics in young subjects with and without mild hypertension.

	Hypertensives (n = 40)	Normotensives (n = 40)	p value
Age (y)	24±3	24±3	*
Body weight (kg)	77±11	74±9	0.18
Systolic blood pressure (mmHg)	142±11	125±11	<0.001
Diastolic blood pressure (mmHg)	82±11	74±8	<0.001
Sitting pulse rate (beats/min)	72±10	72±10	

Results are given as mean ± SD.

* matching variable.

TABLE 5.1.2. Plasma catecholamines, renin, urinary electrolyte excretion and haemodynamics in young subjects with and without mild hypertension.

	Hypertensives (n = 40)	Normotensives (n = 39)	p value
Plasma noradrenaline (pg/ml)	302±23	157±9	<0.001
Plasma adrenaline (pg/ml)	91±13	37±4	<0.001
Plasma dopamine (pg/ml)	72±7	46±4	<0.01
Noradrenaline/dopamine ratio	5.2±0.6	4.2±0.6	0.18
Plasma renin (u-units/ml)	12.6±1.1	10.1±1.2	0.13
24 h urinary sodium (mmol)	136±8	141±14	0.76
24 h urinary potassium (mmol)	68±4	71±7	0.70
24 h urinary creatinine (mmol)	17.0±0.7	18.0±0.6	0.48
Cardiac output (l/min)	4.8±0.3	4.9±0.3	0.81
Cardiac index (l/min/m2)	2.7±0.2	2.6±0.1	0.48

Results are given as mean ±SEM.

TABLE 5.1.3. Coefficients of multiple linear regression of associations observed in hypertensive and normotensive groups separately. Each coefficient is adjusted for differences in other variables.

Normotensive subjects

Dependent variable	Independent	b	SEM		p
Systolic BP	Body weight	0.52	(0.17)	mmHg/pg.ml-1	0.01
Systolic BP	Noradrenaline	0.08	(0.03)	mmHg/pg.ml-1	0.01
Systolic BP	Adrenaline	-0.07	(0.07)	mmHg/pg.ml-1	0.37
Systolic BP	Dopamine	-0.11	(0.06)	mmHg/pg.ml-1	0.09
Noradrenaline	Dopamine	0.24	(0.37)	pg.ml-1/pg.ml-1	0.53
Adrenaline	Body weight	0.33	(0.43)	pg.ml-1/kg	0.39
Renin	Body weight	0.13	(0.15)	units/kg	0.41

Hypertensive subjects

Dependent variable	Independent	b	SEM		p
Systolic BP	Body weight	0.12	(0.19)	mmHg/pg.ml-1	0.55
Systolic BP	Noradrenaline	-0.01	(0.01)	mmHg/pg.ml-1	0.91
Systolic BP	Adrenaline	-0.05	(0.02)	mmHg/pg.ml-1	0.06
Systolic BP	Dopamine	-0.02	(0.05)	mmHg/pg.ml-1	0.74
Noradrenaline	Dopamine	1.11	(0.61)	pg.ml-1/pg.ml-1	0.08
Adrenaline	Body weight	2.67	(1.38)	pg.ml-1/kg	0.05
Renin	Body weight	0.24	(0.11)	units/kg	0.04

Body weight was positively related to plasma renin and adrenaline. This association was observed in the hypertensive group and also when the group was analysed as a whole, but not in the normotensive subjects. Dopamine was positively related to noradrenaline in the total group and, to a lesser extent, in hypertensive and normotensive subjects separately. Systolic blood pressure was positively associated with body weight in the normotensive group but not in the hypertensive group. Also, a strong relation between noradrenaline and systolic blood pressure was observed in the normotensive group and in the groups combined, but not in the hypertensive group. This is illustrated in figure 5.1.1, showing differences in systolic blood pressure in hypertensive and normotensive subgroups based on a higher or lower than median plasma noradrenaline. Dopamine showed a weak negative association with systolic blood pressure in the normotensive group. In hypertensives systolic blood pressure was inversely related to adrenaline, on the average resulting in a lower systolic blood pressure in those with a higher plasma adrenaline (Figure 5.1.2).

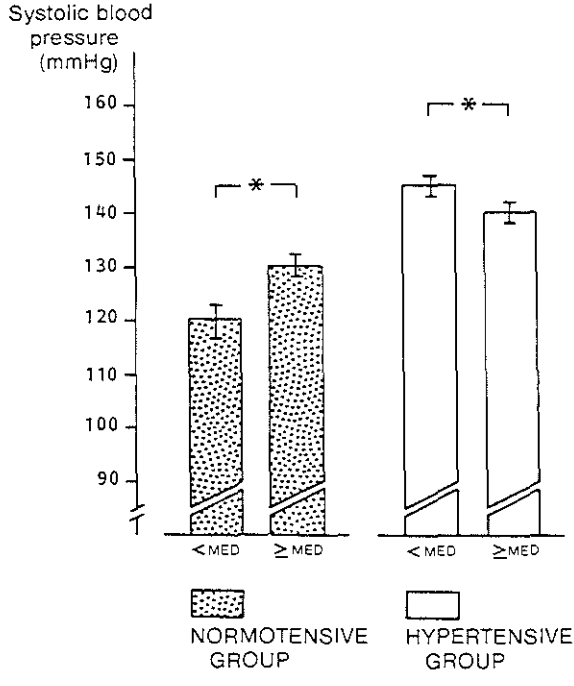

Figure 5.1.1. Systolic blood pressure in subgroups of normotensive and hypertensive subjects according to the median of the distribution of plasma noradrenaline (* $p < 0.05$).

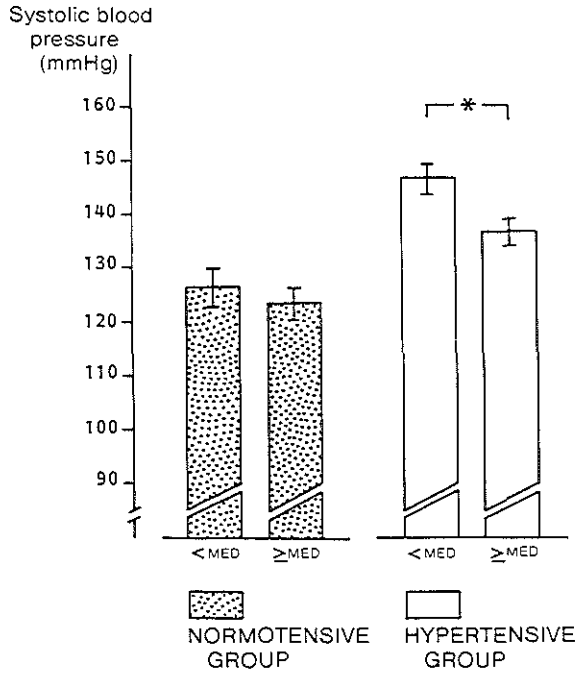

Figure 5.1.2. Systolic blood pressure in subgroups of normotensive and hypertensive subjects according to the median of the distribution of plasma adrenaline (* $p < 0.05$).

Discussion

Our findings of raised plasma catecholamine levels in young hypertensive subjects confirm previous reports of elevated plasma noradrenaline and adrenaline levels in primary hypertension and extend these findings to dopamine, thereby providing evidence that an altered state of the autonomous nervous system may be implicated in the early phase of primary hypertension.(14) In the hypertensive subjects the distribution of plasma catecholamines is skewed, indicating an increased proportion of individuals with high catecholamine levels in this group without a clear bimodality (Figure 5.1.3).

The importance of degree and stability of hypertension, age, source population, sampling technique, and assay used in studying differences in catecholamines between hypertensive and normotensive subjects, and the impact of differences in methods on the outcome of studies, have been repeatedly stressed.(8) Therefore, in the present study the normotensive youngsters included in the reference group were individually matched for age and gender with the hypertensive subjects, and drawn from the same population.

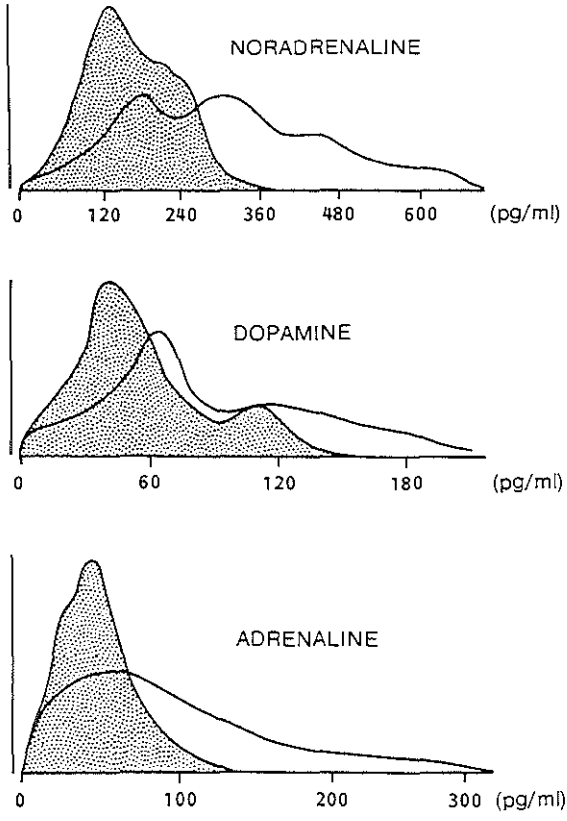

Figure 5.1.3. Distributions of plasma noradrenaline, adrenaline and dopamine concentration in normotensive and hypertensive subjects.

Under physiological circumstances noradrenaline must be considered predominantly as a neurotransmittor.(15,16) Although several methodological comments have been made concerning the interpretation of plasma noradrenaline levels, it appears justified to conclude that plasma catecholamine levels provide a good index of overall sympathetic nervous system activity.(17) Moreover, studying physiological interrelations of catecholamines does not permit infusion techniques and thus excludes several other approaches.

Contrary to noradrenaline, adrenaline is a hormone in the traditional sense. Infusion of adrenaline to plasma levels within the range we observed in the hypertensive group may have direct metabolic effects and plasma concentrations as low as 80 pg/ml impair glucose tolerance in normal subjects.(18,19)

The finding that both plasma adrenaline and renin were related to body weight, partially confirms previous reports based on urinary

excretion of metabolites of catecholamines.(20,21) Due to these findings body weight must be regarded as a confounding variable when comparing differences in plasma renin and adrenalin and blood pressure within groups of hypertensive subjects. It appears that the relation between body weight and these hormones is less clear in normotensive subjects. The physiological mechanism underlying these findings needs further consideration.

We observed a significant positive relation between plasma noradrenaline and systolic blood pressure in the normotensive group. Other studies have shown that plasma noradrenaline levels tend to increase with age.(22) A different association between blood pressure and noradrenaline may exist in different age groups. This might provide an explanation for the inconclusive findings regarding plasma noradrenaline and blood pressure by other investigators.(23) The lack of an association in hypertensive subjects may indicate an altered response of blood pressure to noradrenaline in this group. It may also be the result of a negative feedback, suppressing the physiological association.

A positive association was found between noradrenaline and dopamine in the groups combined, in hypertensive subjects and, although less clear, in normotensive subjects. Until recently dopamine was regarded primarily as a precursor for noradrenaline, but evidence is accumulating for an independent role of dopamine in peripheral neurotransmission.(5) The observed positive association is compatible with either of these possibilities. The biological effects of dopamine on kidney and peripheral vasculature are counteracting the effects of noradrenaline, as it causes natriuresis, and vasodilation in renal, mesenteric, and coronary beds.(1,4,5,24-27) The observed negative association between dopamine and systolic blood pressure in normotensive subjects suggests that dopamine and noradrenaline may have antagonistic roles in blood pressure regulation. A failing counterregulation of dopamine in response to elevated noradrenaline levels might result in an elevated blood pressure, but although in our groups the noradrenaline/dopamine ratio was higher in the hypertensive group this difference failed to reach statistical significance.

An puzzling finding is the slight inverse relation between systolic blood pressure and plasma adrenaline in hypertensives. This observation is in conflict with an hypothesis regarding the role of adrenaline in hypertension by Brown and Macquin, but confirms a recent report by the same group.(28,29) It may be that in patients in which the blood pressure in not maintained by sympathetic activity, adrenaline is actually a weak vasodilator as a result of peripheral b^2 stimulation (M.J. Brown, personal communication).

In conclusion our findings of increased levels of plasma

noradrenaline, adrenaline and dopamine provide evidence for enhanced autonomous nervous system activity in the early phase of primary hypertension. We did not observe an increase in cardiac output in the hypertensive group, indicating that no apparent "hyperkinetic" circulatory state is present in these subjects. In normotensive youngsters systolic blood pressure is positively associated with plasma noradrenaline and negatively with plasma dopamine, in hypertensive subjects these relationships are altered.

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Chapter 5

DETERMINANTS OF ELEVATED BLOOD PRESSURE

5.2 INTACT PARATHYROID HORMONE [1–84] IN PRIMARY HYPERTENSION

Introduction

Altered calcium metabolism has been implicated in the aetiology of primary hypertension.(1,2) Increased levels of circulating parathyroid hormone have been interpreted as supporting this view. Hypertension is a common finding in primary hyperparathyroidism,(3,4) and the prevalence of hyperparathyroidism is considerably higher in subjects with primary hypertension than in normotensive subjects.(5) Two studies comparing hypertensive and normotensive subjects have shown higher levels of serum parathyroid hormone (PTH) concentrations.(6,7) The concentrations of PTH given in these reports concern total concentrations of the intact-PTH molecule as well as part of its metabolites. Recently a new two-step immunochemical method for estimating serum intact-PTH has been developed.(8,9) We measured serum intact-PTH levels in 83 hypertensive patients aged 20 to 69 years, and in 83 normotensive subjects selected from the same open population and matched for age and gender.

Subjects, materials and methods

Between 1975 and 1978, 10,532 out of 13,462 (78%) inhabitants aged 5 years and over of two districts of the town Zoetermeer, near the Hague in the Netherlands, participated in a survey of cardiovascular risk indicators as described previously.(10,11) In all subjects blood pressure was measured with a random zero sphygmomanometer.(12) The readings were made in sitting subjects on the left arm, by eight trained paramedical observers. Two readings were obtained in time separated by a count of the pulse rate and their mean was used in the analysis. Diastolic pressure was based on the fifth Korotkoff sound. A history of high blood pressure was taken and information was obtained about the use of anti-hypertensive and other drugs. Serum samples were drawn and stored frozen (-20°C).

For the present study 83 subjects (48 men) aged 20-69 years with a mean arterial blood pressure (MAP = diastolic blood pressure + pulse pressure / 3) of 120 mmHg or more were selected, and designated as hypertensive. From the subjects below the 25th percentile of the overall blood pressure distribution of MAP (i.e. MAP <90 mmHg) 83 normotensive subjects matched for age and gender (according to 5-year strata), were randomly selected using computer-generated random numbers within sex specific five-year age strata.(13) Subjects on antihypertensive or other drugs that might affect blood pressure were excluded from this study.

Serum intact-PTH concentration was measured by a two-step immunochemical method.(8,9) The first step involves extraction and

concentration of plasma PTH moieties with solid phase linked amino-terminal PTH antibodies. In the second step, the initial PTH immunoextract is analysed with a sensitive midregion radioimmunoassay.

Due to technical reasons no serum calcium values were determined.

Data analyses

The data analytic approach was two-fold. Firstly, for group mean comparisons the t-test for unpaired observations with pooled variances was used. The p values correspond to a two-tailed test of significance. Secondly, weight adjusted values of intact-PTH were calculated by entering weight as an independent variable in a model for multiple linear regression with intact-PTH as the oucome variable. All analyses were performed for the total group, and for three age groups separately: < 40 years, 40-54 years and > 54 years respectively.

Results

The anthropometric characteristics of the total group are shown in table 5.2.1. and for the subgroups for different age strata in table 5.2.2..

Serum creatinine levels were 1.00 mg/dl (SE = 0.02) in hypertensive and 0.96 mg/dl (0.02) in normotensive subjects (p = 0.19). Within the three age strata a significant higher mean serum creatinine level was observed in those aged 40 to 55 years, 1.04 mg/dl (0.04) in hypertensive and 0.95 mg/dl (0.02) in normotensive subjects (p = 0.05).

Table 5.2.1. Anthropometric Characteristics and Mean Blood Pressure Values of the Two Study Groups.

	Hypertensive subjects	Normotensive subjects
Age (years)	49 (1)	49 (1)
Body weight (kg)	79 (2)	67 (1) **
Height (cm)	171 (1)	171 (1)
Systolic blood pressure (mmHg)	175 (2)	117 (1) **
Diastolic blood pressure (mmHg)	110 (1)	68 (1) **
Mean arterial pressure (mmHg)	131 (1)	84 (1) **

Results are given with SEM between parentheses.

** p < 0.001

Table 5.2.2. Anthropometric Characteristics and Mean Arterial Blood Pressure of the Two Study Groups Stratified by Age.

	Hypertensive subjects	Normotensive subjects	
Age group: < 40 year	(n=22)	(n=22)	
Age (years)	30 (1)	30 (1)	
Body weight (kg)	83 (3)	67 (2)	**
Height (cm)	174 (2)	173 (2)	
Mean arterial pressure (mmHg)	122 (2)	80 (1)	**
Age group: 40-54 year	(n=35)	(n=35)	
Age (years)	49 (1)	49 (1)	
Body weight (kg)	80 (2)	69 (2)	**
Height (cm)	171 (2)	171 (2)	
Mean arterial pressure (mmHg)	135 (1)	85 (1)	**
Age group: >54 year	(n=26)	(n=26)	
Age (years)	62 (1)	61 (1)	
Body weight (kg)	75 (2)	66 (1)	*
Height (cm)	168 (2)	168 (1)	
Mean arterial pressure (mmHg)	134 (2)	85 (1)	**

Results are given with SEM between parentheses.

* $p < 0.01$
** $p < 0.001$

No statistically significant differences in serum intact-PTH levels between the two groups were found. The regression coefficients of MAP on PTH in the hypertensive and normotensive groups separately and combined, were not significantly different from zero. However, multiple linear regression of PTH on age, body height and weight yielded a negative association between PTH and body weight (b=-1.26 pmol.l-1.kg, SE = 0.7). This finding and the observed differences in body weight between the hypertensive and normotensive groups prompted us to adjust the intact-PTH levels for these differences in body weight, using a model for multiple linear regression. After adjustment for differences in body weight a

significant difference in PTH was found between hypertensive and normotensive subjects in those aged 20-39 years, but not in older subjects (Table 5.2.3.).

Table 5.2.3. Mean Values of Serum Intact-PTH (pmol/l): Observed Values and Values Adjusted for Differences in Body Weight.

	Unadjusted		Adjusted	
Age (years)	HT	NT	HT	NT
20-39	1.72(0.21)	1.49(0.20)	1.94(0.20)	1.28(0.18)*
40-54	1.42(0.18)	1.59(0.19)	1.46(0.16)	1.64(0.20)
55-69	1.45(0.26)	1.33(0.16)	1.46(0.24)	1.28(0.14)
Total	1.51(0.14)	1.48(0.12)	1.58(0.10)	1.42(0.10)

Results are given with SEM between parentheses. HT = Hypertensive subjects, NT = Normotensive subjects.

* $p < 0.05$

Discussion

No differences in intact-PTH concentrations between hypertensive and normotensive subjects were observed when the data were analysed without other differences between the two groups taken into account. However, body weight appears to be related to both blood pressure and intact-PTH level and must therefore be considered a confounding variable in studying the association between PTH and blood pressure. When adjustments were made for differences in body weight, significantly elevated levels of intact-PTH were found in a subgroup of young primary hypertensive subjects. Although these findings must be interpreted with caution, this may give further evidence that increased parathyroid gland activity might play a part in the early pathogenesis of primary hypertension. Further studies are required to assess whether the potential role of PTH in hypertension has aetiological significance.

Some methodological comments must be made. There are two previous reports on enhanced parathyroid function in primary hypertension and both studies were based on patients attending hypertension clinics.(6,7) Control groups were blood donors and healthy volunteers. Selecting patients and controls from different populations may induce differences in PTH levels, or any other variable for that matter, that are unrelated to the difference in blood pressure. We removed known hypertensives from the study groups and selected normotensive controls from the same source population.

Besides, we were able to create a relatively large contrast in blood pressure between the two study groups.

Contrary to the approach in previous studies, we used a combined biochemical and radioimmunochemical method that selectively isolates and estimates levels of the circulating intact-PTH [1-84]. Intact-PTH comprises less than 10% of total midregion or C-terminal PTH immunoreactivity. Most of the circulating PTH metabolites contain the M- and C-terminal regions of the intact hormone. Bioactivity, however, resides in the N-terminal sequence.(14) Reduced renal clearance of nonbioactive PTH fragments may result in increased serum total-PTH levels without alteration of intact-PTH.(8) Reduction of glomerular filtration rate is present in most patients with severe hypertension. There is less evidence of renal impairment in milder forms of hypertension. However, reduction of renal clearance of PTH metabolites may be of relevance in chronic hypertensive subjects. This can in part be responsible for reported increased levels of total immunoreactive PTH in hypertension and stresses the advantages of the use of more selective methods to determine the intact fraction of serum total-PTH. The observed relation between body weight and PTH needs further elucidation regarding the mechanisms involved. There are no previous reports describing this phenomenon although the same has been observed for plasma catecholamines.(15) Moreover, the observed relation between body weight and intact-PTH is not necessarily also existing between total-PTH levels and body weight. As an hypothetical explanation it might be suggested that heavier subjects eat more, and have therefore a higher calcium intake and subsequent lower plasma PTH levels.

The serum-samples used in our analysis are comparatively old, and this may have influenced the results. There are no studies on the reproducibility of the assay we used in serum-samples that were stored frozen for some time. However, if there is any effect of time on the serum intact-PTH levels, it is likely that this would tend to reduce immunoreactivity to the same extent in serum derived from hypertensive as from normotensive subjects. Besides, the values observed in the samples used are in agreement with the range of serum intact-PTH levels found in fresh samples.(9)

There are several possible explanations for raised levels of serum PTH in hypertensive subjects. McCarron et al.(6) have raised the possibility that a urinary calcium leak is responsible for an enhanced activity of the parathyroid gland. An increase in serum PTH secundary to renal calcium loss would not necessarily be restricted to the early phase of primary hypertension. Schleiffer et al. performed parathyroidectomy in young spontaneously hypertensive rats, keeping a normal serum calcium.(16) This resulted in a delay

of the rise in systolic blood pressure for 42 weeks. These findings support the hypothesis that alterations in PTH homeostasis may be of special relevance in the early stages of primary hypertension. Serum PTH levels in hypertensive subjects may be influenced by calcium intake, increased sympathetic nervous system activity and several other mechanisms. Recent evidence has related higher intakes of calcium with lower systolic bloodpressure.(17) When plasma noradrenaline levels in young hypertensive and normotensive subjects are compared, the former show significantly higher plasma noradrenaline levels.(18)

As there are several lines of evidence relating PTH to hypertension, the question arises wether PTH itself contributes to the elevation of blood pressure. The intracellular calcium concentration is known to be the most important determinant of the state of tonic contraction of the vascular smooth musle cell.(19) A known effect of PTH is an increase of the cytosolic free calcium concentration.(20) Circulating natriuretic substances have been implicated in the aetiology of primary hypertension.(21) PTH has natriuretic properties. The exact nature of the relation between PTH and arterial pressure, however, cannot be determined from our data and remains to be elucidated.

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5.3 RAISED PLASMA INTACT PARATHYROID HORMONE LEVELS IN EARLY PRIMARY HYPERTENSION

5.3.1 Introduction.

An association between parathyroid gland activity and blood pressure was first suggested by Helstrom and coworkers, who reported an increased prevalence of hypertension in primary hyperparathyroidism.(1) Furthermore, the prevalence of hyperparathyroidism in primary hypertensive subjects is considerably higher than in the general population.(2) The hypertension appears not to be secondary to renal damage resulting from hypercalcemia in hyperparathyroidism.(3,4) Whether or not blood pressure falls after parathyroidectomy in patients with primary hyperparathyroidism is still subject to debate.(4,5) Two studies have shown increased circulating total immunoreactive parathyroid hormone (PTH) levels in hypertensive patients.(6,7) Preliminary data suggest that serum intact parathyroid hormone (PTH [1-84]) may be elevated in young hypertensive subjects.(8) The level of PTH [1-84] gives a more accurate index of parathyroid gland activity than total PTH, because PTH [1-84] is unaffected by alterations in renal clearance of PTH metabolites as may result from chronic hypertension.(9,10) We studied plasma PTH [1-84] levels in a group of young subjects with blood pressure levels persistently in the upper range of the blood pressure distribution, and a group of normotensive reference subjects selected from the same population.

Materials and methods

Population

From 1975 to 1979 all 5 to 19 years residents of two districts of the Dutch town of Zoetermeer, were invited to take part in a survey of risk-indicators for cardiovascular disease and 4,649 of them participated (82%). Of the initially examined children, 1,597 were selected for annual follow-up as described previously.(11) None of the subjects received any specific intervention during the follow-up. From this cohort the participants for the present study were selected. Stable mild hypertension was defined as at least three blood pressure readings of 140 mmHg systolic and/or 90 mmHg diastolic or over at yearly examinations during seven to nine years of follow-up, without identified secondary hypertension. Of 130 eligible, 90 subjects (77 males) agreed to participate in the study, which formed part of an intervention study following shortly thereafter. Fourty normotensive reference subjects of the same ages, who had participated in a previous study,(12) were selected from the remainder of the follow-up cohort.

Measurements

Blood pressure was measured with a random-zero sphygmomanometer, between 4 and 8 pm, after 10 minutes of rest and before venipuncture, by two trained paramedical observers. Three readings were obtained on the left arm with the subject sitting, and the mean was used in the analysis.

A plasma sample was obtained in chilled EDTA-tubes and stored frozen until assayed. All subjects collected one 24-hour urine sample. Serum and urinary total calcium and creatinine were measured by standard methods. The plasma PTH [1-84] concentration was determined by a recently developed two-step immunochemical method.(10)

Data analysis

For group mean comparisons t-tests for unpaired observations with pooled variances were used. To assess relations between variables, simple linear regression analysis was performed, separately for hypertensive and normotensive subjects. The p values correspond to a two-tailed test of significance.

Results

The results are summarized in table 5.3. Plasma PTH [1-84] levels were 2.34 pmol/l (0.11) in hypertensive subjects and 1.47 pmol/l (0.13) in controls ($p < 0.0001$, Figure 5.3). The distribution of PTH [1-84] was shifted as a whole to higher levels in the hypertensive subjects. Serum total calcium concentration was lower in hypertensive youngsters than in normotensive reference subjects. There were no differences in 24-hour urinary calcium excretion or in serum creatinine between the groups.

Table 5.3. Characteristics of the study subjects.

Variable	Hypertensive group (n = 90)	Normotensive group (n = 40)	p value
Age (years)	24.3 (0.3)	24.4 (0.5)	0.44
Blood pressure (mmHg)			
Systolic	143.2 (1.1)	125.0 (1.8)	< 0.0001
Diastolic	83.0 (1.1)	74.3 (1.2)	< 0.0001
Body weight (kg)	77.9 (1.3)	73.5 (1.5)	0.03
PTH [1-84] (pmol/l)	2.34 (0.11)	1.47 (0.13)	< 0.0001
Serum calcium (mmol/l)	2.36 (0.01)	2.42 (0.01)	0.002
Serum creatinine (umol/l)	73.8 (1.5)	74.0 (1.7)	0.91
Urinary calcium (mmol/24 h)	4.17 (0.28)	3.89 (0.39)	0.27

Values are means. SEM between brackets.

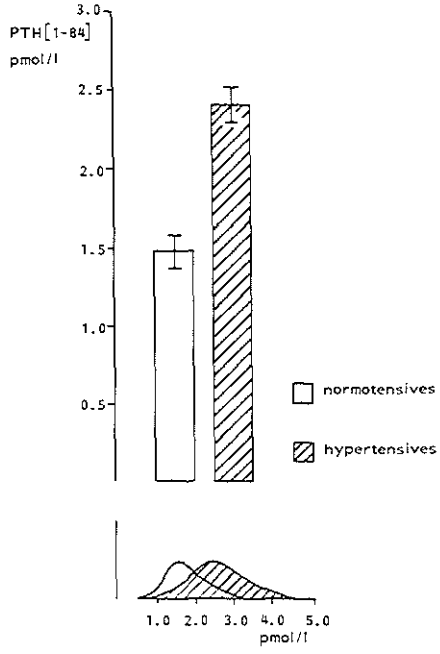

Figure 5.3. Means (± SE) and distributions of plasma PTH [1-84] in young hypertensive subjects and normotensive controls.

Within the hypertensive group, both systolic and diastolic blood pressure increased with plasma PTH [1-84]: b = 2.3 mmHg/pmol/l (SE = 1.1, p = 0.05) and b = 2.2 mmHg/pmol/l (SE = 1.1, p = 0.05) respectively. In the normotensive group associations of essentially the same magnitude were found (b = 4.6 mmHg/pmol/l (SE = 2.9) for systolic and b = 2.5 mmHg/pmol/l (SE = 1.9) for diastolic blood pressure), but the regression coefficients failed to reach statistical significance. No direct relationship between serum calcium and blood pressure was observed. Moreover, PTH [1-84] was not significantly associated with serum total calcium, either in the separate or combined groups.

Discussion

Our findings of raised levels of plasma PTH [1-84] provide evidence that circulating intact parathyroid hormone may be increased in mildly hypertensive youngsters. Furthermore, in hypertensive subjects both systolic and diastolic blood pressure appear to be positively related to plasma PTH [1-84]. These observations support the hypothesis that enhanced parathyroid gland activity is implicated in the early phase of primary hypertension. This may

consist of autonomous hyperfunctioning of parathyroid tissue or result from other causes (secondary hyperparathyroidism).(13) These possible causal processes include increased renal calcium loss or reduced dietary calcium intake. Both have been reported in hypertensive subjects.(6,7,14) The effects on parathyroid gland activity may be mediated by a slight reduction in serum calcium levels as observed in this and previous studies.(15) We did not observe differences in urinary calcium excretion. However, it is difficult, if not impossible, to characterize the calcium excretion of an individual with a single urine specimen.

Basal parathyroid gland activity may also be influenced by sympathetic nervous system activity.(16) This view is consistent with findings in a previous study based on a similar group of hypertensive youngsters selected from the same population, in which increased levels of plasma noradrenaline, adrenaline and dopamine were observed.(12)

The question remains whether PTH itself contributes to the elevation of blood pressure or whether increased parathyroid gland activity is merely a result of alterations in calcium metabolism associated with hypertension.(17) Long-term administration of PTH increases blood pressure in humans and rats.(18,19) PTH may raise the calcium concentration in the smooth muscle cell, thereby increasing contractility and consequently peripheral resistance.(20) Studies in spontaneously hypertensive rats suggest that parathyroid gland activity may affect blood pressure predominantly in the early phase of the development of hypertension.(21) In humans, studies on calcium metabolism in the onset of primary hypertension are clearly indicated, and in particular the possible role of the parathyroid gland in early hypertension merits further evaluation.

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Chapter 6

DIETARY INTERVENTION ON ELEVATED BLOOD PRESSURE

6.1 SODIUM RESTRICTION AND POTASSIUM SUPPLEMENTATION IN YOUNG PEOPLE WITH MILDLY ELEVATED BLOOD PRESSURE

Introduction

Electrolytes have been implicated in the aetiology and treatment of hypertension. The possibility of reducing high blood pressure by rigorous sodium restriction, to levels below 30 mmol/day, has been demonstrated by several workers.(1,2) Studies restricting daily sodium intake to a lesser extent have yielded conflicting results.(3-8) In 1928 Addison was the first to suggest that potassium salts may reduce blood pressure.(9) The role of potassium supplementation in blood pressure control is now explored with renewed interest, since both epidemiologic and animal model studies have suggested potassium as a depressor.(10,11)

Dietary intervention in the management of high blood pressure is of special importance in young people. There is a tendency of lowering the threshold values for treating hypertension over the last few decades and this means that a growing number of younger subjects is regarded as requiring treatment. Nonpharmacologic intervention by changing dietary habits might be a valuable alternative to life-long medication, of which the benefit-risk ratio is not clear.(12)

To study the effect of moderate sodium restriction and the combination of sodium restriction and potassium supplementation in young people with high blood pressure, we conducted a double-blind randomised three-period crossover trial in 40 untreated young adults with mildly elevated blood pressure.

Materials and methods

Population

Between 1975 and 1980 all persons who were 5-19 years of age and residents of two districts of Zoetermeer, a suburban residential area near the Hague in the Netherlands, were invited to participate in a study of blood pressure and other risk-indicators for cardiovascular disease (EPOZ-study).(13) Blood pressure was measured in 4,649 subjects out of 5,670 eligible (82%). Of the initially examined subjects, 1,597 were selected for annual follow-up. This group comprised all children in the upper decile of the distribution of one or more of the cardiovascular risk-indicators, plus a control group randomly selected from the same population. Tthe study group

for this trial was selected from this cohort on the basis of at least three blood pressure readings of 140 and/or 90 mmHg or over, at annual examinations during seven to nine years of follow-up and no evidence of secondary hypertension. In this population the subjects thus selected match the norm for childhood hypertension as reported by the Task Force on Blood Pressure Control in Children.(14) Of 80 eligible, 42 young people with mildly elevated blood pressure, as previously defined, agreed to take part in this study. Two subjects were excluded because they refused to continue, once they were confronted with the diet. All other fourty completed the trial, 34 males and 6 females, age 18 to 28 years.

Protocol

During a two week lead-in period, blood pressure was measured at three occasions, two at the examination center and one at home. The subjects collected two 24-hour urine specimens and a blood sample was taken at the end of the lead-in period. The study group then entered into a randomised double-blind crossover study with "slow-sodium" tablets for six weeks (CIBA, 10 mmol sodium per tablet), six weeks with "slow-potassium" tablets (CIBA, 8 mmol potassium per tablet), and six weeks with matched placebos (CIBA), with a fixed dose of nine tablets a day. The subjects were randomly assigned to one of six possible sequences. All participants restricted their dietary sodium intake during the whole period of the trial (18 weeks). During the lead-in period they kept a food-diary, and at the end of this period everyone received individual dietary advice. They were also visited at home every three weeks by the study dietician. Tablets were provided for periods of three weeks and the number of tablets left over after these periods was recorded as an index of compliance. A local baker provided bread with 35% less salt for the normal price, and low-salt meat products and cheese were provided for free.

Measurements

Blood pressure was measured on the left arm with a random zero sphygmomanometer after 10 minutes of rest and before venipuncture. At each occasion six readings were made, three sitting and three supine, in time separated by a count of the pulse rate. The average of three subsequent readings was used in the analysis. During the trial the patients were seen at the examination center for blood pressure measurement every three weeks. Every sixth week a blood sample was obtained using an indwelling venous catheter with the

patient supine for 20 minutes. Two-dimensional echocardiograms were performed in supine left lateral decubitus position. The parasternal short axis, apical long axis and four chamber views were recorded for subsequent quantitative analysis. The modified Simpson-rule formula was used for the calculation of end-diastolic and end-systolic left ventricular volumes from three consecutive cardiac cycles.(15) End-diastolic minus end-systolic volume yielded stroke volume and cardiac output was obtained by multiplying stroke volume by heart rate. Serum and plasma samples were stored at -70°C. Plasma renin was determined by radioimmunoassay as the concentration of active enzyme,(16) and plasma catecholamines were measured using the COMT radioenzymatic method.(17) Mean urinary sodium, potassium and creatinine excretion was estimated from four 24-hour urine collections in each six-week period.

Data-analysis

The data were analysed in two ways. First, the effect of changes in sodium and potassium intake on the blood pressure were examined by comparing blood pressure at the end of the placebo period and at the end of the slow-potassium period with blood pressure at the end of the slow-sodium period. Second, changes in blood pressure were related to characteristics of the patients at baseline in order to identify subgroups of patients specifically susceptible to sodium restriction and potassium supplementation. The differences were tested using a t-test for paired observations. The results of this procedure are expressed as a one-tailed p-value (p1) for changes in blood pressure and a two-tailed p-value (p2) for other variables. A separate analysis revealed no treatment order effects.

Results

Baseline characteristics

These are summarized in table 6.1.1.

Electrolytes and body weight

Mean sodium excretion was 129 mmol/24h during the slow-sodium period, and fell to 57 mmol/24h during placebo, and to 69 mmol/24h during slow-potassium. The urinary sodium/potassium ratio was 1.7 in the slow-sodium period, and fell to 0.5 during slow-potassium. Serum sodium was unchanged during the intervention periods. Serum potassium was 0.23 mmol/l higher during high potassium/low sodium

intake than in the other periods ($p2 < 0.05$). Body weight remained stable during the intervention periods (Table 6.1.2).

Table 6.1.1. Baseline characteristics.

	Mean	SD
Age (yrs)	24	3
Body weight (kg)	77	11
Supine systolic BP (mmHg)	143	14
Supine diastolic BP (mmHg)	78	10
Pulse rate (beats/min)	68	10
24 h urinary sodium (mmol)	141	46
24 h urinary potassium (mmol)	71	22
24 h urinary creatinine (g)	1.67	0.38
Plasma noradrenaline (pg/ml)	302	140
Plasma adrenaline (pg/ml)	91	77
Plasma dopamine (pg/ml)	72	42
Plasma renin (u-units/ml)	12.1	6.5
Cardiac output (l/min)	4.8	2.0
Cardiac index (l/min/m2BSA)	2.7	1.1

Table 6.1.2. Effects of sodium restriction with slow-sodium, placebo or slow-potassium on urinary electrolyte excretion, body weight, pulse rate, plasma catecholamines, plasma renin, cardiac output and cardiac index.

	INTERVENTION PERIODS		
	Slow-sodium (normal sodium)	Placebo (low sodium)	Slow-potassium (low sodium/ high potassium)
24 h urinary sodium (mmol)	129±5	57±4 **	69±6 **
24 h urinary potassium (mmol)	77±4	74±3	131±6 **
Body weight (kg)	74.7±1.6	74.4±1.6	74.8±1.6
Pulse rate (beats/min)	70±2	68±2	70±2
Plasma noradrenaline (pg/ml)	220±18	239±19	225±21
Plasma adrenaline (pg/ml)	62±5	77±9	67±7
Plasma dopamine (pg/ml)	112±13	98±16	89±12
Plasma renin (u-units/ml)	14.5±1.3	17.0±1.4	17.0±1.6
Serum sodium (mmol/l)	143.3±0.5	142.6±0.5	142.8±0.6
Serum potassium (mmol/l)	3.77±0.04	3.76±0.03	4.00±0.05 *
Serum creatinine (mg/dl)	1.05±0.02	1.06±0.02	1.07±0.02
Serum cholesterol (mg/100ml)	184±6	184±5	183±5
Serum uric acid (mg/dl)	5.9±0.2	6.0±0.2	5.9±0.2
Cardiac output (l/min)	4.9±0.3	4.6±0.3	4.2±0.2 *
Cardiac index (l/min/m2BSA)	2.6±0.1	2.4±0.1	2.2±0.1 *

Results are given as mean ±SEM.
* $p2 < 0.05$, ** $p2 < 0.001$ with reference to the slow-sodium period.

Blood pressure

At the end of the sixth week of the slow-potassium period supine systolic pressure was 3.3 mmHg lower than after six weeks of slow-sodium ($p1 = 0.025$). There was no significant change in blood

pressure after six weeks of sodium restriction alone (Figure 6.1, Table 6.1.3). During the slow-potassium period the fall in blood pressure was already apparent, although not significant, at the third week. Diastolic pressure did not change significantly. Changes in sitting blood pressure followed the same pattern but failed to reach statistical significance.

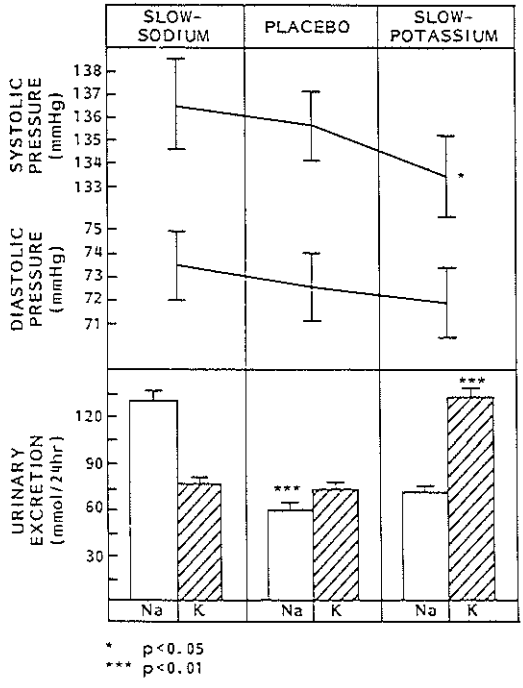

Figure 6.1. Mean systolic and diastolic blood pressure and 24 hour urinary electrolyte excretion on slow-sodium, placebo and slow-potassium.
* p1 = 0.025.

Table 6.1.3. Effects of sodium restriction with slow-sodium, placebo or slow-potassium on supine blood pressure.

	INTERVENTION PERIODS		
	Slow-sodium (normal sodium)	Placebo (low sodium)	Slow-potassium (low sodium/ high potassium)
Body weight (kg)	74.7±1.6	74.4±1.6	74.8±1.6
Supine systolic BP (mmHg)	136.5±2.0	135.7±1.5	133.2±1.9 *
Supine diastolic BP (mmHg)	73.3±1.5	72.5±1.6	71.9±1.5
Supine mean pressure (mmHg)	94.3±1.3	93.5±1.2	92.3±1.2

Results are given as mean ±SEM.

* p1 = 0.025 with reference to the slow-sodium period.

Renin and catecholamines

Plasma renin and catecholamines did not differ significantly between the three periods (Table 6.1.2). Baseline dopamine was inversely associated with the change in systolic blood pressure during placebo (coefficient of linear regression b= -0.4 pg/ml/mmHg, p2 = 0.001), and baseline plasma renin was positively associated with changes in diastolic pressure in this period of sodium restriction (b = 0.3 u-units/ml/mmHg, p2 = 0.12). Baseline plasma renin and catecholamines did not correlate significantly with changes in blood pressure during high potassium/low sodium intake.

Haemodynamic changes

Cardiac index was 0.4 l/min/m2BSA (p2 = 0.03) lower after the slow-potassium period as compared with the slow sodium period (Table 6.1.2). Differences in cardiac index between the slow-sodium and the placebo periods and between the slow-potassium and the placebo periods were not significant.

Discussion

The main findings of this study in young people with mildly elevated blood pressure are that moderate sodium restriction alone had no significant effect on blood pressure, but that blood pressure was reduced by a combination of sodium restriction and potassium supplementation, and that this was accompanied by a fall in cardiac index. Although an overall blood pressure lowering effect of moderate sodium restriction was not observed, the greater fall in pressure in subjects with low baseline dopamine than in those with high dopamine may indicate a characteristic of sodium sensitivity. Changes in blood pressure during the intervention periods were not significantly related to baseline plasma renin, adrenaline or noradrenaline levels. Also, blood pressure changes during sodium restriction were not related to changes in plasma renin or plasma catecholamines. This is at variance with previous findings that a pressure reducing effect of sodium restriction is associated with a concomitant stimulation of renin release.(18)

Although the antihypertensive effect of extreme sodium restriction are well documented, evidence for a pressure lowering action of moderate sodium restriction is equivocal.(3-8) Studies in which a blood pressure lowering effect of sodium restriction was observed included patients that were more hypertensive and had a higher salt intake to begin with, than negative studies.

Recently two controlled trials on potassium supplementation in

hypertensive patients were reported. One study showed no additive effect of potassium when combined with sodium restriction, whereas in a second one a significant fall in blood pressure was observed when potassium was supplied to diuretics treated hypokalemic hypertensive subjects.(19,20)

There is evidence for an antagonistic role for sodium and potassium in blood pressure regulation. Studies in rats showed potassium not only to lower blood pressure but to have an additional protective effect resulting in a longer life.(21) Several mechanisms have been postulated to account for the antihypertensive action of potassium. The diuretic properties of potassium are well established.(9) However, from our data we cannot demonstrate a marked diuretic effect as judged by changes in body weight. Also, potassium may modify the neural mechanisms that regulate blood pressure, or influence plasma renin concentration. We found no significant change in plasma renin and catecholamines, nor was the change in blood pressure related to a change in these hormones during potassium supplementation. Potassium may also affect peripheral resistance by changing intracellular ion concentrations, either directly or by alteration of sodium/potassium pump activities.(22) The fall in blood pressure during the period of high potassium/low sodium intake in our study was accompanied by a fall in cardiac index and an increase in serum potassium, whereas mean pulse rate and catecholamine levels remained unchanged. This observation is compatible with a direct effect of potassium on cardiac muscle cells.

The question whether the fall in blood pressure is the result of the increase of potassium intake solely, or of the combined sodium restriction/potassium supplementation cannot be answered on the basis of our data. Several studies have shown an inverse relation between the dietary sodium/potassium ratio and blood pressure.(23,24) The rice-fruit diet advocated by Kempner in 1944 as treatment of hypertension is known as a rather unpalatable rigid low-sodium diet. Often overlooked, however, is the relatively high potassium content of this diet, and the resulting considerable reduction of the sodium/potassium ratio. We found a difference in response to potassium supplementation between those showing a fall in systolic pressure on sodium restriction alone ($n = 20$), and those showing a rise ($n = 20$). The first group had a mean fall of 5.8 mmHg during combined sodium restriction/potassium supplementation, the second group a fall of 0.8 mmHg ($p2 = 0.15$). This appears to support the view that sodium and potassium should be considered together when studying their role in blood pressure regulation.

Treating high blood pressure by altering dietary intake of sodium and potassium is of special importance in young people.

"Tracking" studies of blood pressure in children and adolescents have shown that the predictive value of blood pressure increases with age and stabilizes at about 18 years of age.(25) Since hypertension may influence the relation between sodium, potassium and blood pressure by secundary structural alterations of the vessels or adaptation of pressure regulating mechanisms,(26) studying this relation in an early stage, i.e. in young hypertensives, might elucidate mechanisms involved in the aetiology of hypertension.

In conclusion, our observations suggest that moderate restriction of dietary sodium intake has little effect on the blood pressure of young subjects with mildly elevated blood pressure levels, but that the combination of moderate sodium restriction with high potassium intake may have an antihypertensive effect. This may, in part, be due to reduction of the cardiac index. Decreasing the dietary sodium/potassium ratio may prove to have a place in the early prevention of hypertension.

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6.2 CALCIUM SUPPLEMENTATION LOWERS DIASTOLIC BLOOD PRESSURE IN YOUNG PEOPLE WITH MILD HYPERTENSION

Introduction

There is evidence that alterations in calcium metabolism may be implicated in the early etiology of primary hypertension.(1,2) Recent studies have suggested that a low dietary calcium intake is associated with high blood pressure levels.(3-8) Hypertensive subjects appear to have elevated urinary calcium excretion,(9,10) and may have reduced serum ionized calcium levels.(11,12) An increased prevalence of hypertension has been observed in patients with primary hyperparathyroidism.(13) There is also evidence that levels of plasma parathyroid hormone may be elevated in hypertensive patients, thereby suggesting enhanced parathyroid gland function in primary hypertension.(10,14,15) A controlled intervention study of calcium versus placebo by Belizan and coworkers showed a blood pressure lowering effect of calcium in normotensive students.(16) In a randomized crossover study by McCarron and coworkers, supplementation with one gram of calcium for eight weeks resulted in a fall in blood pressure in hypertensive, but not in normotensive subjects.(17) The potential hypotensive action of calcium supplementation is of special importance in young subjects and patients with mildly elevated blood pressure levels, in whom the pharmacological approach to lower blood pressure is relatively unattractive.(18,19)

We conducted a double-blind randomized trial on the effect of supplementation with one gram calcium daily during a period of twelve weeks in 90 young people with mildly elevated blood pressure. We also studied the predictive value of a number of biochemical indicators of calcium metabolism for a blood pressure response to calcium supplementation.

METHODS

Population

From 1975 to 1980 all 5-19 year old residents of two districts of the Dutch town of Zoetermeer were invited to participate in a study of blood pressure and other cardiovascular risk indicators (the EPOZ study).(20) Blood pressure was measured in 4,649 out of 5,670 eligible subjects (82%). Of those initially examined, the children in the upper decile of the distribution of one or more cardiovascular risk indicators were selected for annual follow-up

together with a control group randomly drawn from the same population.(21) From this cohort of 1,597 children, subjects were selected when they had at least three annual blood pressure readings of 140 and/or 90 mmHg or over during seven to nine years of follow-up. Of 130 eligible, 90 youngsters (77 males) aged 16 to 29 years, agreed to participate in the present study. None of them had diagnosed secondary hypertension or was on antihypertensive medication.

Protocol

After a three week lead-in period during which blood pressure was measured twice and two 24 hour urine specimens were collected, the study group attended the examination center for baseline measurements. The subjects were randomly assigned to one of two groups, receiving either 4.17 g calcium-citrate, representing 1 g calcium, or a matched placebo containing cellulose, for a period of twelve weeks. All participants entered the trial within three weeks. Calcium and placebo were provided by way of three times three water-soluble powders a day. No dietary advice was given to the participants. During this period blood pressure was measured after six and twelve weeks, and four 24 hour urine specimens were collected at three week intervals. A venous blood sample was obtained at baseline and after twelve weeks.

Measurements

Blood pressure was measured on the left arm with a random zero sphygmomanometer,(21) by two trained paramedical observers who did not know what group the subjects were in. At each occasion a series of three readings was made, with the subject sitting, and the mean of these readings was used in the analysis. Before the three week lead-in period an estimate of dietary calcium intake was obtained by a dietitian using a standardized questionnaire. From this questionnaire, mean daily calcium intake was calculated using a computerized food composition table.(22) Compliance to intervention was evaluated by personal contact between staff and participants at three week intervals, and by monitoring of the number of powders used. Non-compliance was defined as cessation of use of powders for a period of more then seven consecutive days: five subjects receiving calcium and five receiving placebo fulfilled this criterion. Serum total calcium, magnesium, total protein, total cholesterol and creatinine, and urinary calcium, magnesium and creatinine were measured by standard laboratory methods. Serum ionized calcium was determined by use of a calcium-selective

electrode, with adjustments made for differences in serum pH (Radiometer).(23) Intracellular sodium and potassium levels were measured in erythrocytes by flame-spectrophotometry as described by Lijnen et al.(24) Plasma intact parathyroid hormone 1-84 (PTH) was determined with a recently developed two-step immunochemical method.(25) Plasma noradrenaline, adrenaline and dopamine were measured with a COMT radioenzymatic assay.(26)

Data analysis

Our data-analytic approach was threefold. First, the overall effect of calcium on blood pressure was examined by comparing the change in blood pressure from baseline levels after six and twelve weeks, between the calcium and the placebo group. Second, separate analyses were performed for the compliers, and for subgroups based on higher or lower than median plasma PTH, serum total calcium level and body weight at baseline. The latter analyses included all participants in the trial. Third, the relation between indices of calcium metabolism and blood pressure, at baseline and during calcium supplementation, were studied by linear regression of blood pressure on these variables. P-values for the effects of calcium on blood pressure are based on a one-tailed test of significance (p1), using a t-test for unpaired observations. The results of other statistical tests are expressed as two-tailed p-values (p2).

Results

Baseline characteristics

The baseline characteristics by treatment group are given in table 6.2.1. Within the total group both systolic and diastolic blood pressure at baseline increased with baseline plasma PTH: b = 2.3 mmHg/pmol/l (SE = 1.1, p2 = 0.05), and b = 2.2 mmHg/pmol/l (SE = 1.1, p2 = 0.05), respectively. PTH showed a significant decrease with serum ionized calcium (b = -8.2 pmol/mmol/l, SE = 3.0, p2 = 0.02), but not with serum total calcium (b = -1.1 pmol/mmol/l, SE = 0.9, p2 = 0.21). Blood pressure was not significantly related to serum ionized calcium, nor to serum total calcium.

Intervention effects on body weight and biochemical variables

Body weight after six and twelve weeks did not differ from baseline values in either group. Also, serum and intracellular electrolytes were not significantly different within and between treatment groups after twelve weeks of intervention (Table 6.2.2). Although plasma

PTH tended to fall more in the calcium treated group, this difference failed to reach statistical significance. 24 hour urinary calcium excretion during calcium supplementation was on the average 0.96 mmol/24 hour higher in the calcium treated group (SE = 0.35, p2 = 0.008). The urinary excretion of other electrolytes remained stable during the study. No serious adverse effects of the calcium powders were reported. Five participants had short periods of diarrhoea, two in the calcium and three in the placebo group.

Table 6.2.1 Baseline characteristics by treatment group.

	Placebo (n = 44)	Calcium (n = 46)
Age (years)	24.6 (3.2)	23.9 (3.1)
Male:female (nr)	38:6	39:7
Body weight (kg)	77.5 (11.4)	78.4 (13.3)
Systolic BP (mmHg)	143.2 (10.1)	143.2 (11.0)
Diastolic BP (mmHg)	82.8 (9.7)	83.3 (10.6)
Mean arterial pressure (mmHg)	103.0 (7.7)	103.2 (8.6)
Pulse rate (beats/min)	77 (14)	78 (12)
Calcium intake (mg/24h)	1267 (585)	1411 (883)
Serum total calcium (mmol/l)	2.36 (0.12)	2.37 (0.12)
Serum ionized calcium (mmol/l)	1.26 (0.03)	1.27 (0.03)
Serum magnesium (mmol/l)	0.88 (0.07)	0.88 (0.06)
Serum total protein (g/l)	78 (7)	77 (6)
Intracellular sodium (mmol/l)	5.91 (0.93)	6.21 (0.93)
Intracellular potassium (mmol/l)	91.9 (3.8)	92.3 (3.3)
Plasma PTH (pmol/l)	2.38 (1.14)	2.32 (0.83)
Plasma noradrenaline (pg/ml)	311 (139)	354 (163)
Plasma adrenaline (pg/ml)	64 (46)	68 (40)
Plasma dopamine (pg/ml)	92 (80)	89 (87)
Urinary calcium (mmol/24h)	3.87 (2.04)	4.50 (2.05)
Urinary magnesium (mmol/24h)	4.56 (2.43)	4.86 (2.21)
Urinary creatinine (g/24h)	1.86 (0.75)	1.79 (0.67)

Standard deviations between brackets.

Table 6.2.2 Body weight and biochemical variables after twelve weeks of intervention in the placebo and in the calcium group.

	Placebo	Calcium	p2
Body weight (kg)	77.7 (1.7)	78.8 (2.0)	0.67
Pulse rate (beats/min)	78 (2)	78 (2)	0.76
Serum total calcium (mmol/l)	2.40 (0.02)	2.43 (0.02)	0.47
Serum ionized calcium (mmol/l)	1.26 (0.01)	1.28 (0.01)	0.07
Serum magnesium (mmol/l)	0.85 (0.01)	0.83 (0.01)	0.18
Intracellular sodium (mmol/l)	6.28 (0.16)	6.51 (0.16)	0.31
Intracellular potassium (mmol/l)	89.3 (0.5)	89.6 (0.57)	0.70
Plasma PTH (pmol/l)	2.08 (0.11)	1.84 (0.12)	0.15
Plasma noradrenaline (pg/ml)	289 (15)	283 (12)	0.75
Plasma adrenaline (pg/ml)	54 (5)	47 (4)	0.25
Plasma dopamine (pg/ml)	101 (12)	117 (12)	0.34
Urinary calcium (mmol/24h)	3.71 (0.25)	4.67 (0.24)	0.008

Standard error of the mean between brackets.

Intervention effects on blood pressure

For the groups as a whole diastolic blood pressure was 3.1 mmHg (SE = 1.7) lower in the calcium treated group than in the placebo treated group after six weeks of calcium supplementation, and 2.3 mmHg (1.9) after twelve weeks (Table 6.2.3). Only small differences in systolic blood pressure were observed. When compliers were analysed separately, differences in diastolic blood pressure between the groups were 5.1 mmHg (1.8) after six, and 3.9 mmHg (2.0) after twelve weeks (Table 6.2.4). When all subjects were categorized according to baseline PTH levels, those with a higher than median plasma PTH level showed a 6.1 mmHg (2.5) greater fall in diastolic blood pressure after six weeks and 5.4 mmHg (2.3) after twelve weeks, compared to placebo, while there was no effect on blood pressure in the group with a lower than median PTH (Figure 6.2.1). When subjects were categorized according to their baseline serum total calcium levels, those with a lower than median serum total calcium had a fall in diastolic blood pressure of 6.5 mmHg (2.4) after six, and 4.8 mmHg (2.5) after twelve weeks, and no such changes were found in those with a higher than median baseline serum total calcium (Figure 6.2.2). Finally, the subjects were divided according to the median of body weight. In the group with a relatively large body weight the difference in systolic blood

Table 6.2.3 Blood pressure levels at baseline and after six and twelve weeks of intervention for the total group (n = 90).

	Baseline	6th week	12th week
Systolic BP (mmHg)			
Placebo	143.2 (10.1)	139.8 (9.5)	139.3 (10.0)
Calcium	143.2 (11.0)	138.8 (13.6)	138.9 (13.5)
P1*		0.29	0.43
Diastolic BP (mmHg)			
Placebo	82.8 (9.7)	81.1 (8.2)	80.7 (9.5)
Calcium	83.3 (10.6)	78.5 (12.3)	78.8 (9.9)
P1		0.04	0.11

Values are means, standard deviations between brackets.

* p1 values are given for differences from baseline between groups.

Table 6.2.4 Blood pressure levels at baseline and after six and twelve weeks of intervention for the compliant group (n = 80).

	Baseline	6th week	12th week
Systolic BP (mmHg)			
Placebo	143.7 (10.3)	140.3 (9.5)	140.3 (9.8)
Calcium	143.3 (11.0)	138.5 (13.8)	138.0 (13.7)
p1*		0.23	0.17
Diastolic BP (mmHg)			
Placebo	82.3 (9.9)	81.6 (8.0)	81.0 (9.8)
Calcium	83.3 (10.2)	77.5 (11.7)	78.2 (9.9)
p1		0.003	0.03

Values are means, standard deviations between brackets.

* p1 values are given for differences from baseline between groups.

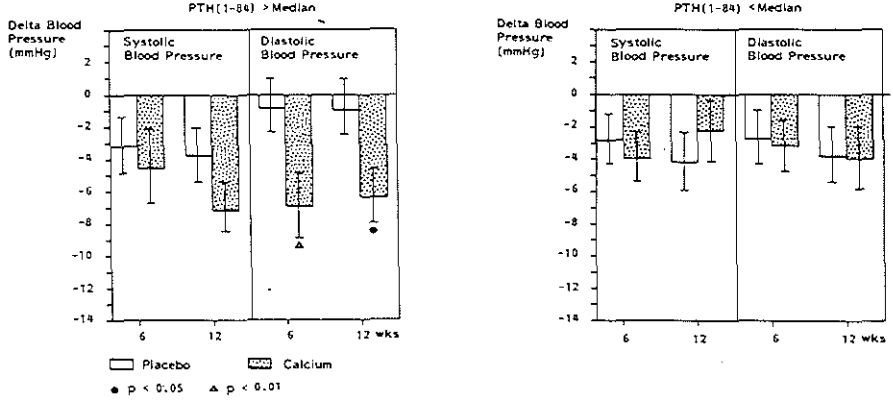

Figure 6.2.1. Difference in average fall in blood pressure between placebo and calcium treated subjects, in two subgroups according to the median of baseline plasma PTH.

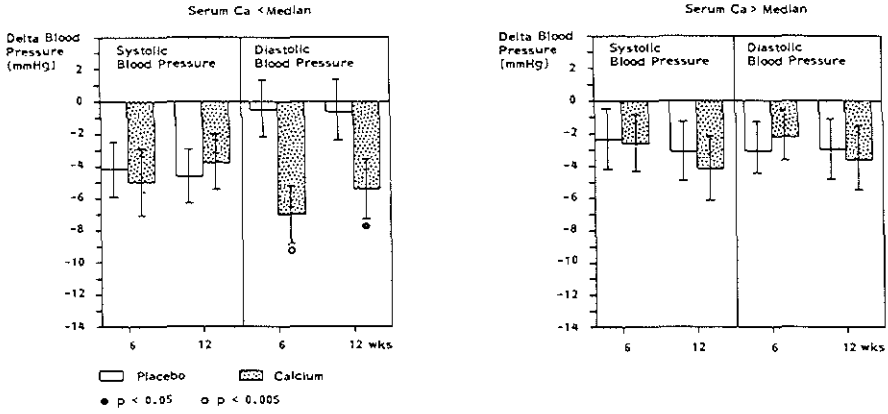

Figure 6.2.2. Difference in average fall in blood pressure between placebo and calcium treated subjects, in two subgroups according to the median of baseline serum total calcium.

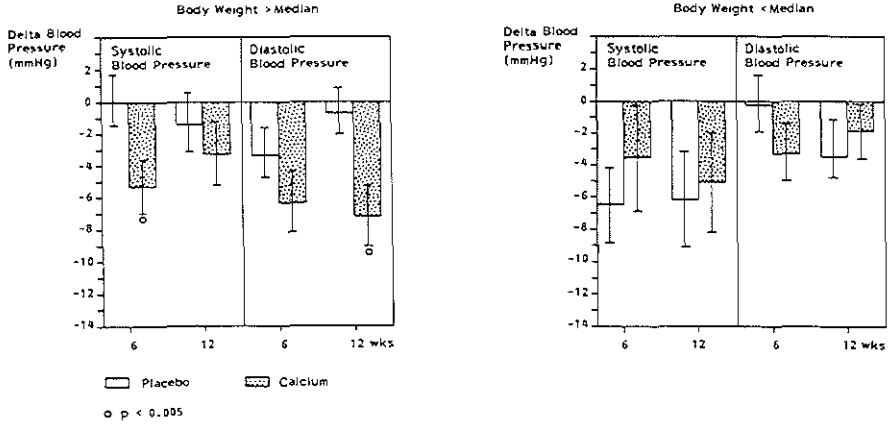

Figure 6.2.3. Difference in average fall in blood pressure between placebo and calcium treated subjects, in two subgroups according to the median of baseline body weight.

pressure was 5.3 mmHg (2.3) after six weeks, and 1.9 mmHg (2.7) after twelve, and in diastolic blood pressure 3.1 mmHg (2.5) and 6.5 mmHg (2.3), respectively (Figure 6.2.3). The change in plasma PTH during calcium supplementation was associated with the change in diastolic blood pressure during the trial in the calcium treated group (b = 5.3 mmHg/pmol.l-1, SE = 2.0, p2 = 0.01), but not in the placebo group (b = 0.2, SE = 1.1, p2 = 0.84). The difference between these regression coefficients was statistically significant (p2 = 0.04).

Discussion

These observations suggest that calcium supplementation may lower diastolic blood pressure in young people with persistently mildly elevated blood pressure levels, in particular in youngsters with low serum total calcium and/or high plasma PTH levels. Before we quote this as support for the hypothesis that altered calcium metabolism is implicated in early primary hypertension, some methodological issues have to be addressed.

The level of blood pressure in the study group is relatively low by clinical criteria for hypertension. These subjects are, however, much younger than the average patient attending a hypertension clinic. Moreover, blood pressure was assessed at multiple measurements in different years and the blood pressure levels in these youngsters were persistently in the upper range. In combination, these findings imply that these young subjects are at increased risk of developing severe hypertension in the future.27 The effect on diastolic blood pressure was greater in those compliant to the intervention than in the total group, and reductions in blood pressure tended to be larger after six than after twelve weeks. This is compatible with a reduced overall compliance towards the end of the intervention period. In our experience, the use of nine powders a day is an inconvenient way of supplying calcium. Oral calcium supplementation by one tablet a day would have been more appropriate, but it turned out to be impossible to obtain well matched placebos. Calcium in a dosage of one gram daily did not lead to any demonstrable side effects in this group. The individual increase in calcium intake in the calcium treated group cannot be determined reliably on the basis of urinary calcium excretion. This makes a dose response analysis of the effect of calcium supplementation impossible. In this study average daily calcium intake was increased by approximately 60%. Whether a greater or lesser increase in intake would result in similar blood pressure changes remains to be clarified.

The observation that calcium lowers diastolic blood pressure to a greater extent than systolic blood pressure is in agreement with the findings of Belizan et al.(16) in normotensive subjects. Mc Carron and coworkers,(17) however, observed a significant fall in systolic blood pressure in hypertensive patients but not in normotensive subjects. The effect of calcium supplementation appears to be restricted to subjects with a higher than median plasma PTH and/or a lower than median serum total calcium concentration. Furthermore, the change in diastolic blood pressure during the trial is positively associated with the change in PTH in the calcium treated group. This finding supports the view that

enhanced parathyroid gland activity may be implicated in primary hypertension.(9,14,15) A puzling finding is the apparent relation between body weight and response to calcium, an observation that cannot be readily explained by factors involved in obesity-associated hypertension.(28)

Several mechanisms may explain the effect of calcium on blood pressure. Intracellular calcium is the final determinant of the excitation contraction coupling and tonic contraction of the smooth muscle cell.(29) In hypertensive patients transcellular membrane calcium transport and binding kinetics may be changed and intracellular calcium may be higher as compared to normotensive controls.(7,30,31) Furthermore, in a study by Erne and coworkers a strong positive association was observed between intra-platelet calcium concentration and mean arterial pressure, in both normotensive and hypertensive subjects.(12) This links calcium directly to increased peripheral resistance and thereby to the main hemodynamic characteristic of primary hypertension.(32) Intracellular calcium may be controlled in part by the serum calcium concentration and by circulating PTH.(18,20) In this study no clear effects of increased calcium intake on the levels of serum total calcium and ionized calcium were observed. Although plasma PTH was not significantly reduced in the calcium treated group, the change in blood pressure within this group appeared to be related to the change in PTH. This suggests that PTH may mediate the effect of calcium on blood pressure. Whether the individual change in PTH on calcium supplementation in hypertensive subjects can be used to detect susceptibility to calcium merits further evaluation.

In conclusion, our findings are compatible with the view that a subgroup of hypertensive individuals exists, which is susceptible to calcium supplementation and is characterized by alterations in calcium metabolism indicative of a relative calcium need. An increase in daily calcium intake may be beneficial in young people with mild primary hypertension, in particular in subjects with increased plasma PTH and/or reduced serum total calcium levels.

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Chapter 7

NON-PHARMOCOLOGICAL INTERVENTION ON BLOOD PRESSURE IN THE YOUNG

7.1 Introduction

The concept that the roots of primary hypertension are to be found in childhood has become increasingly popular.(1,2) It has been recommended to measure an individual's blood pressure from the age of three on.(3) Although this recommendation may seem somewhat overenthousiastic, more and more children's blood pressures will be measured, and the finding of elevated blood pressure levels in a particular child or adolescent will inevitably lead to the question how to continue. During the past decades our understanding of the natural history of high blood pressure and its determinants has greatly expanded. Knowledge of the mechanisms involved is still limited, but there are some indications for rational ways of influencing blood pressure at an early stage. The question remains, whether intervention programs in children with elevated blood pressure will prevent the development of future hypertension. At present there is much debate regarding this question and the answer is likely to be dependent on the level of blood pressure and the age of the children involved.(4) In this chapter we will briefly discuss strategies of identifying children with potential primary hypertension. Several approaches to intervention and studies investigating their efficacy will be reviewed. Finally, we will come to some conclusion about the current status and directions for future research.

7.2 Blood pressure in children: Approaches and attitudes

Blood pressure rises in children from birth to after puberty, in virtually all populations in all parts of the world.(1,5,6) This rise in pressure is closely related to normal growth.(7) The question arises whether this rise is perhaps an inevitable consequence of maturation and therefore not susceptible to intervention at all. Although available data are scarce, it appears that at least part of the rise is determined by factors other than biological maturation.(8,9)

When it is accepted that children's blood pressure may be influenced, two approaches may be followed.(10) The "high risk" approach, aiming primarily at certain identified individuals with actual or potential elevated blood pressure and therefore with an increased risk for cardiovascular morbidity and mortality, or the "mass" or "whole population" approach aiming at a general shift of the distribution of blood pressure to lower levels. Moreover, as in adults, both strategies are not necessarily alternatives, but may form complementary means of preventing high blood pressure. In children and young adults, the lack of firm evidence relating blood

pressure levels to future hypertension and cardiovascular disease favours the mass strategy. However, in selected cases of subjects consistently in the highest percentiles of the distribution for their age and sex, individual treatment may be considered, depending on the possibilities of intervention.

The observation that blood pressure levels in childhood rise substantially, adds an attractive perspective to both of these two approaches. Apart from aiming at a reduction of the actual blood pressure level, the purpose of intervention in children and adolescents might be to prevent the blood pressure from rising in the future. To summarize the different approaches towards non-pharmacologic intervention on blood pressure in the young, four patterns may be discriminated.

1. The "high risk" approach, aiming at a lowering of actual blood pressure levels in young subjects at increased risk.
2. The "high risk" appraoch, aiming at preventing or limiting the rise in blood pressure with age in young subjects at increased risk.
3. The "whole population" approach, aiming at an overall shift of the blood pressure distribution in the young to lower levels.
4. The "whole population" approach, aiming at limiting the rise in blood pressure during growth and maturation.

In practice these different appraoches may not be as clearly separated, but as a means of delineating strategies of intervention this distinction may be profitable. In the following paragraphs we will follow this classification when discussing studies on non-pharmacologic intervention on blood pressure in children and young adults.

7.3 The "high risk" approach aiming at a reduction of blood pressure level

7.3.1 Who should be treated?

Since there is only sparce evidence available concerning cardiovascular end organ damage or mortality resulting from high blood pressure in children, the rationale for intervention on blood pressure levels in children is based on the concept that the level of blood pressure in childhood is related to the level of blood pressure later on in life. This view is known as the "tracking" phenomenon.(2,11) Tracking describes the stability of rank of an individual in the blood pressure distribution over time and may be expressed as a "tracking coefficient". There is considerable controversy about the magnitude of blood pressure tracking in childhood, although the degree of tracking in a series of studies

appears to be moderate.(12-17) This may be due to methodological difficulties in establishing tracking coefficients in populations, resulting in random error and an underestimation of the phenomenon. Several determinants of future blood pressure levels in children have been studied, but the actual blood pressure level appears to be the best, though relatively weak, predictor of future blood pressure. The predictive value is higher for systolic than for diastolic blood pressure and increases with age. Moreover, it has been suggested that the predictive value increases when based on multiple blood pressure readings on different occasions although this has not consistently been observed in different studies.

In measuring blood pressure in children the following guidelines may be considered. As a rule, a child's blood pressure must be interpreted relative to the blood pressure distribution of a reference group of the same age. Furthermore, the method of blood pressure measurement used, and the cirumstances under which the readings take place, should closely resemble those applied to the reference population.(18) At present there are no strong arguments to pay more attention to elevated diastolic than to elevated systolic blood pressure levels.(19) In general the increase in blood pressure with age is more pronounced for the systolic blood pressure and takes place to a greater extent in boys.

One may propose an algorithm as a means of selecting those at

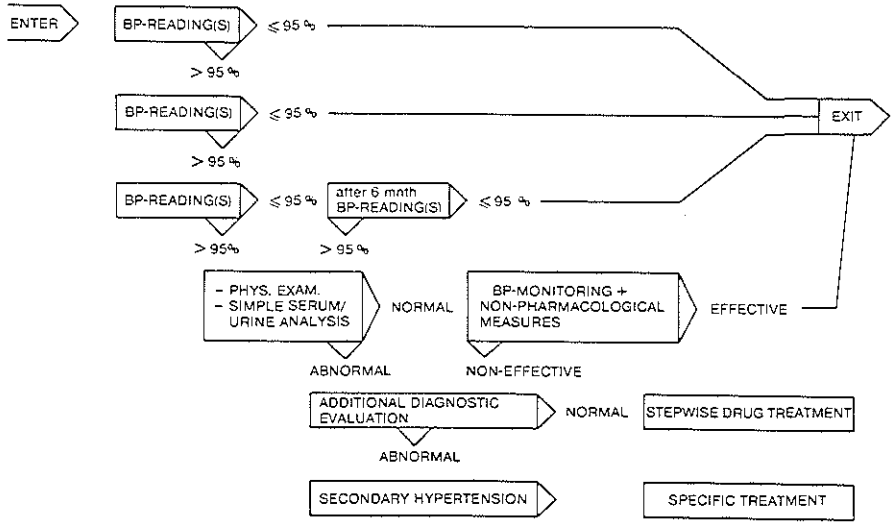

Figure 7.1. Algorithm indicating the various steps in the detection and management of children and young adults with elevated blood pressure levels.

risk and eligible for intervention. A schematic and rather arbitrary representation is presented in figure 7.1. The scheme is based on a relative measure of elevated blood pressure, i.e., a blood pressure level equal to or higher than the 95th percentile of the age and sex specific blood pressure distribution. In our view there is no rationale for the use of an absolute blood pressure level somewhere in this scheme above which further action is indicated, apart from confirmation to common clinical practice in adults. It can, however, be argued that an absolute blood pressure level as a cut-off point for increased risk is of value in practice and should therefore be used. For reasons of clarity of presentation we have refrained from this option in the algorithm. The use of multiple (3) readings to assess an elevated pressure not only may increase the predictive value, but also substantially reduces the number of subjects eligible for further evaluation.

7.3.2 How should be treated?

As stated by Oliver,(20) there is a great difference between removing a risk factor and introducing a new one such as prescribing a drug, and this is especially true for children. Since the risk-benefit ratio for drug treatment of hypertension in young subjects with mildly elevated blood pressure levels is unknown, the primary goal should be to find, and test, means of nonpharmacologic intervention.(21) Moreover, the mere existence of an elevated blood pressure in a child may constitute increased risk on cardiovascular disease half a decade later, but the identification of a young individual as a patient may have a serious impact on the rest of his or her life.(22) Therefore, when possible, intervention must form an integral part of a normal life style, including dietary habits. The objectives of any intervention in children can be either to lower an already elevated blood pressure level, or to prevent blood pressure from rising any further. In this review we will focus on the former, since experimental information on the latter in children with elevated blood pressure is virtually lacking. Furthermore, we may expect these two aspects to go together to some extent. There are several factors, related to the level of blood pressure, that may be changed in order to evoke changes in blood pressure. Evidence is accumulating that body mass and dietary factors are related to blood pressure levels, and there are some reports indicating a putative role of (lack of) physical activity, noise, the use of oral contraceptives and psychosocial stress.(23-28) There is, however, only limited information from trials in children and youngsters, in which the effect of changes in these factors is tested, thus some evidence needs to be inferred from studies in adults.(29)

Weight reduction

Evidence on the effect of reductions in body weight in hypertensive adults is inconclusive.(30-32) Moreover, methodological problems limit the possibilities of dissociating the effect of weight reduction per se from changes in other factors, like salt intake, that might affect blood pressure.(33,34) The feasibility of weight reduction programs in children was studied by Brownell and associates in 42 obese adolescents, normotensive as well as with elevated blood pressure.(35) From this study it appeared that reductions in weight were larger when the mothers of the children studied were involved in the program. Also, significant falls in blood pressure were observed, although the lack of a control group makes the interpretation of this finding difficult. Future studies are needed to establish the value of weight reduction programs in children with elevated blood pressure. Until then it appears to be justified to pay attention to dietary habits and/or physical activity in overweight children with high blood pressure.

Dietary changes: Sodium and potassium

A multitude of dietary factors may affect blood pressure and they provide a number of ways for single or multiple intervention in subjects with elevated blood pressure.(36) Reduction of sodium intake to reduce high blood pressure is by far the most extensively studied of these factors. While the antihypertensive effects of extreme sodium restriction in severe hypertension are well documented, the effects on blood pressure of a more moderate reduction of sodium intake, to about 3 to 4 gram NaCl daily, are much debated.(37,38) In an analysis of thirteen randomized trials the hypotensive effect of a reduction in sodium intake appeared to be restricted to older patients with high blood pressure levels.(39) This may suggest that sodium restriction per se, is of limited use in young subjects with mildly elevated blood pressures. However, a subgroup of children and adolescents which is susceptible to sodium may exist. As this "sodium sensitivity" may be genetically determined, Watt and coworkers studied susceptibility to sodium restriction in youngsters from hypertensive parents.(40) No effects on blood pressure were observed after four weeks on a low sodium diet. Contrary to this, an open study by Skrabal et al. suggests the opposite.(41) There are some indications that the intracellular sodium concentration may relate to sodium sensitivity.(42) In addition, plasma catecholamine levels, and in particular dopamine, may give a lead to the efficacy of sodium restriction in an individual.(43) To provide a definite answer to the question who

will respond to sodium restriction and who will not, clearly more studies are needed. Alternatively, not the sodium intake by itself but the dietary sodium to potassium ratio may determine the fall in blood pressure on intervention.(44) The effect of sodium restriction in combination with potassium supplementation was studied in fourty young people with persistent mildly elevated blood pressure levels.(43) Blood pressure fell significantly after six weeks of intervention and was accompanied by a fall in cardiac output. This finding is in agreement with an earlier study by Khaw and Thom in twenty young normotensive males.(45) Moreover, on the basis of analyses of the relationship between total body sodium and potassium with blood pressure levels, Lever and coworkers have suggested that potassium is particularly implicated in the early stage of primary hypertension, whereas sodium may play a part later on in life.(46) These observations look promising, but further studies are needed to assess the safety and efficacy of increases in potassium intake, whether or not in combination with sodium restriction.(47,48) Furthermore, one has to be aware of the risk that changes in one dietary constituent result in concurrent changes in other components as well. For example, a sodium restricted diet may also reduce calcium and vitamin B intake as an unintended consequence.(49)

Dietary changes: Calcium

Another component of the diet of which a relative shortage in the diet has been associated with blood pressure level, is calcium.(50) In a study by Belizan and collaborators, supplementation with one gram calcium daily resulted in a significant fall in mean diastolic blood pressure of normotensive young adults.(51) In a study in ninety young subjects with mildly elevated blood pressure levels, a fall in diastolic blood pressure was observed after twelve weeks of calcium supplementation.(52) This effect appeared to be most prominent in subjects with relatively low serum calcium and/or high plasma parathyroid hormone levels. The latter finding may provide a way to identify subjects who are sensitive to increases in dietary calcium. In a recent study which compared hypertensive and normotensive youngsters from the same population, raised plasma parathyroid hormone levels were observed in hypertensive subjects.(53) Although further experimental evidence for a beneficial effect of calcium in children and young adults with elevated blood pressure needs to be awaited, these first investigations look promising.(54)

Other dietary factors

Although several other dietary constituents, like magnesium,(55) poly-unsaturated fatty (PUFA),(56) alcohol,(57) coffee,(58) and trace elements,(59) have been implicated in the aetiology of hypertension, very limited experimental evidence, in particular in young subjects, is available on the blood pressure lowering potential of these factors. Studies on the effect on blood pressure of magnesium supplementation are equivocal and have only been conducted in middle-aged hypertensive patients.(60,61) In a study by Stern and associates in adolescents with elevated blood pressures, a diet rich in PUFA resulted in a fall in systolic and diastolic blood pressure.(62) The same was reported in studies in adults.(63,64) The use of alcoholic drinks to a total amount of more than 40 grams of alcohol per day may induce elevation of blood pressure in adults. No sufficient data are available to estimate the contribution of alcohol to blood pressure in youngsters, nor on the effects of lowering alcohol intake on blood pressure levels. The same holds true for coffee use. Although trace elements may affect blood pressure at very high doses, this appears to be of little relevance under physiological circumstances.(59)

Increasing physical activity

Both physical fitness and physical activity may be associated with blood pressure level.(23) From studies in adults, it appears that isotonic excercise may reduce blood pressure in hypertensive subjects.(65) A program of excercise training in hypertensive adolescents significantly lowered systolic and diastolic blood pressure during the study.(66) The effect, however, was not sustained after the program had stopped. In a study by Duncan and coworkers aerobic excercise for sixteen weeks reduced both systolic and diastolic blood pressure in mildly hypertensive patients.(67) The hypotensive action of the program was most pronounced in subjects with elevated plasma adrenaline levels. As plasma catecholamine levels may be elevated in a subgroup of young hypertensive subjects,(68) this may indicate a way of selecting youngsters with elevated blood pressure in whom a benefit of increases in physical activity might be expected.

Behavioural modification

Irrespective of the exact part played by psychological stress in the aetiology of high blood pressure,(69) behavioural factors may be used to reduce elevated blood pressure levels.(70) In particular,

relaxation therapy by biofeedback and yoga techniques have gained substantial interest and evidence from studies in humans is suggestive that this approach may show favourable results in hypertensive subjects.(71,72) However, studies in children and adolescents are lacking. As with physical activity, it might be suggested that sympathetic nervous system activity is associated with a response to behavioural intervention.(73) In this area, more studies in younger subjects are clearly indicated.

7.4 The "high" risk approach aiming at reducing the rise in blood pressure

No studies have been conducted thus far that specifically addressed the question whether a further rise in blood pressure may be limited in children at increased risk, i.e., with persistently elevated blood pressure levels. As has been mentioned, it is often very difficult to clearly discriminate between an effect on the actual level and the potential change of blood pressure on intervention. In particular, when a given intervention shows to reduce blood pressure levels, this implies an effect on blood pressure slope at the same time. The reverse, however, may not be true. When a particular measure fails to affect blood pressure levels, an effect of the same intervention on the change in blood pressure over time can not be ruled out unless the groups under study are followed up for a considerable period. The latter has, for obvious practical reasons, seldomly been accomplished. Because a significant reduction in blood pressure rise in high risk youngsters may have a beneficial effect on blood pressure levels later on in life, this potential of non-pharmacologic intervention clearly merits further investigation.

7.5 Shifting the distribution of blood pressure levels: The "whole population" approach

The whole population approach is of great interest when aiming at prevention of cardiovascular disease by influencing blood pressure in childhood. As indicated by Blackburn et al. the distribution of risk factors, like hypertension, and their associate lifestyles suggests that an unfavorable environment encourages the maximal exhibition of susceptible phenotypes in the population.(74) A preventive strategy based on this concept attempts to create the most favourable environment possible. Thus, the concept that "nurture", much as in combination with "nature", influences blood pressure, means by definition that intervention is applied at best as early as possible, i.e., in childhood. Although some would favor a more selective appraoch to achieve an effective control of

cardiovascular disease,(75) at least it appears justified to stimulate a healthy lifestyle at an early age. Which factors may be succesfully influenced to reduce blood pressure levels in children is, however, not yet very clear.

The efficacy of the whole population approach in intervening on risk factors for cardiovascular disease is in general evaluated in groups of subjects without increased risk, e.g. in normotensive individuals. There are limited data from intervention studies in normotensive children and adolescents. Some investigators have studied the effect of a single factor on blood pressure in normotensive children. In agreement with studies in adults,(76) intervention trials on a reduction in sodium intake in normotensive children and adolescents show virtually no effect on blood pressure.(41,77,78) It may, however, be that a low sodium intake may show an effect only after a prolongued period of time. As discussed in the previous paragraphs, there are some indications that increased intake of dietary calcium or potassium may reduce blood pressure in normotensive adolescents.(46,51) In addition, a reduction of body weight may affect blood pressure also in children with normal blood pressures.(36) Intuitively, a mass approach to blood pressure reduction calls for multiple intervention aiming at the combined effect of several changes in lifestyle and dietary habits that may be integrated in normal (school-) children's lifes. Data on multiple intervention in children, as in adults, are inconclusive. Puska and associates did not observe an average fall in blood pressure due to intervention after two years, while in New York Walter and associates reported significantly lower blood pressure levels after one year of multifactorial intervention.(79,80)

7.6 The "whole population approach aiming at shifting the distribution of blood pressure rates of increase

In children, more than in adults, the whole population approach has an interesting additional perspective, namely to prevent the blood pressure from rising, or to limit its rate of increase. Partly because of logistic and methodological difficulties, studies on this subject are very scarce. In the Netherlands Hofman and coworkers studied the role of sodium intake in the developement of blood pressure during the first six month of life in a double blind randomised trial.(81) This observation not only provides a rationale for intervention aiming at a reduction of rise, but also offers experimental evidence for an aetiological role of dietary sodium in the development of elevated blood pressure. The effects of changes

in other determinants of blood pressure rise have not been formally tested.

7.7 Conclusion and directions for future research

The measurement of blood pressure levels in children is becoming increasingly common. It is, however, still insufficiently clear to what extent children's blood pressures are related to blood pressure later on in life and in particular to hypertension. Nevertheless, it appears to be justified to pay extra attention to those children and adolescents persistently in the upper part of their age and sex specific blood pressure distribution ("high risk" approach). In addition, it may show to be beneficial to encourage a "non-hypertensiogenic" lifestyle, including dietary advices, for the young population at large ("whole population" approach). However, it has to be noted that this benefit, albeit plausible, is not yet firmly established. Therefore, there is little justification for agressive strategies to achieve this goal.

Several means of non-pharmacological intervention may be used in young mildly hypertensive subjects. Unfortunately, the intervention that is the most studied, restriction of sodium intake, appears to be of little merit in the young.(40) A number of other factors have been less extensively studied and, therefore, still have the benefit of the doubt.

Promising effects of dietary changes have been suggested for increases in potassium and/or calcium intake, and an increase in the proportion of polyunsaturated fatty acids in the diet. Calcium supplementation may show to be most effective in those expressing a relative calcium need, as indicated by indices of calcium metabolism. The excessive use of alcoholic drinks, and perhaps of coffee, should be disencouraged. The efficacy of sodium restriction appears to be limited. Future studies may, however, clarify the significance of certain characteristics suggested to be associated with sodium sensitivity.

Weight reduction and increase in physical activity may be aimed for in obese children and adolescents with elevated blood pressure. Relaxation procedures and behavioural modification have shown promising results in hypertensive adults. It is conceivable that this type of intervention is most effective in youngsters with elevated plasma catecholamines indicative of raised sympathetic nervous system activity. These children and young adults may also be susceptible for the hypotensive action of physical activity programs.

When non-pharmacological treatment is applied to evaluate its efficacy or to clarify mechanisms involved, the modification of only

one factor is generally pursued. However, in medical practice the before mentioned approaches may well go in combination.

Approaches to shift the blood pressure distribution in children to lower levels may follow the same lines of intervention as in children at increased risk. However, even more than in children and young adults with elevated blood presssure, changes in lifestyle and dietary habits should be easily integrated in normal life. Therefore, these advices will presumably result in a so-called "prudent" diet, low in saturated fatty acids and with sufficient amounts of potassium and calcium, with moderate use of sodium, alcohol and coffee. Furthermore, in obese subjects weight reduction is advisable, as is regular physical activity in these and other children. There are indications that a limited sodium intake may reduce the rise in blood pressure early in life. This observation argues against the addition of extra sodium salts to baby food.

From this review it may be clear that further studies are needed in a number of ways. Firstly, the relative contribution of dietary and other factors to blood pressure levels is still insufficiently established. Secondly, there are only limited data on the efficacy of changes in diet, body weight, physical activity and psychological and social factors in children and young adults with or without elevated blood pressure. Thirdly, apart from the blood pressure lowering potential of a certain intervention, attention should be given to its effect on the rate of change of blood pressure over time.

Future studies should aim at longer periods of intervention and evaluate the predictive value of genetic and other factors for a blood pressure response to a specific intervention. Moreover, the use of double blind procedures to increase validity of results should be encouraged. Also, because ultimately the purpose of intervention on blood pressure is to reduce cardiovascular risk, the effect of non-pharmacological treatment on other risk indicators, like serum cholesterol levels, should be monitored. It should be noted that, in particular in children, modifaction of a dietary factor may result in imbalances in the intake of other, valuable, dietary constituents. Finally, still more information is needed on determinants of future blood pressure levels in children, other than the actual level of blood pressure. In addition, long term follow-up of children and young adults may assess and quantify the risk associated with high blood pressure at a young age.

To summarize, data are needed for a more adequate selection of young subjects at increased risk, for further clarification of the efficacy of non-pharmacological intervention both for the young population as a whole and for individuals at increased risk, and

finally for assessment of the predictive value of certain characteristics for a specific means of intervention.

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Chapter 8

SUMMARY

The studies presented in this thesis were conducted in a population of young, non-hospitalized subjects. This opportunity was presented by the availability of a large cohort of children and young adults that had been followed up for more than seven years as part of the Epidemiologic Preventive Organization Zoetermeer (EPOZ study), and of which a large body of data on blood pressure and other characteristics could be used. The basic theme of the studies was to elucidate mechanisms involved in the early pathogenesis of primary hypertension, with special emphasis on the role of dietary electrolytes. (chapter 1)

The effect of changes in electrolyte intake in youngsters with elevated blood pressure was studied in two randomized trials. The scientific concept of the randomized trial is of primary importance in evaluating the effect of a certain characteristic, like electrolyte intake, on another characteristic, like blood pressure. Randomization garantuees internal validity of a study with regard to potential sources of bias. In addition, blinding of participants and investigators for the type of intervention during the trial reduces the possibility of distortion of the results by information bias. Randomization may be accomplished by random assignment of individuals to a certain treatment, the parallel-group design, or by randomization of treatment periods within an individual, the crossover design. Both methods were applied in studies presented in this thesis. (chapter 2)

The main haemodynamic characteristic of hypertension in adults is an increase total peripheral resistance. In early hypertension, the situation is less clear. Several investigators have suggested that a high cardiac output state exists in young subjects with elevated blood pressure. This, however, could not be confirmed by a number of other studies, including the one presented in this thesis. A major discrepancy between the former and the latter studies is that the latter used non-invasive methods to assess cardiac output, whereas the former studies used invasive techniques. This could account for a difference in stress response between hypertensive and normotensive subjects within the various studies leading ot the inconclusive findings. In our view, elevated blood pressure at all ages is asociated with elevated peripheral resistance. Furthermore, significantly elevated plasma catecholamine levels may be present in a subgroup of young primary hypertensive subjects. This would indicate altered sympathetic nervous system activity in the early phase of hypertension. (chapter 3)

Of all dietary factors related to blood pressure, electrolytes have gained major interest. In particular a putative role of sodium intake in the aetiology of high blood pressure has been the subject of many studies. The magnitude of an effect of sodium on blood

pressure is, however, still unclear. Moderate reduction of sodium intake appears to be of limited use in those most eligible for non-pharmacologic treatment, namely young subjects with mildly elevated blood pressure. Data on the relationships between potassium and calcium and blood pressure are more limited. Increased intake of potassium and calcium may be associated with lower levels of blood pressure. Moreover, supplementation of these electrolytes may have an hypotensive effect in both subjects with normal or elevated blood pressure. The mechanism by which electrolytes exert their effect on blood pressure is likely to reside, in part, on a cellular level. The final consequence of alterations in cellular electrolyte homeostasis would then be an increase in the contractile state of vascular smooth muscle cells, leading to a raised circulatory resistance and consequently to elevated blood pressure. (chapter 4)

Plasma levels of catecholamines, plasma renin and cardiac output were studied in fourty young hypertensive individuals and an equal number of normotensive subjects, matched for age and gender. To eliminate selection bias both groups were drawn from the same population. A strictly standardized protocol of measurements assured that hypertensive and normotensive groups were treated similarly during the study. The findings in this study indicate that hypertensive and normotensive subjects do not differ significantly with regard to plasma renin levels, or cardiac output and cardiac index. Also, pulse rates were similar between the groups. However, mean plasma noradrenaline, adrenaline and dopamine were all significantly higher in the hypertensive group. Furthermore, the "normal" interrelation between noradrenaline, adrenaline and blood pressure appeared to be altered in hypertensive subjects.

In two additional studies in groups of hypertensive and normotensive individuals, increased levels of plasma intact parathyroid hormone, and reduced serum total calcium concntration were observed in hypertensive groups, compared to normotensive reference groups. These findings support the hypothesis that altered calcium metabolism may be implicated in early primary hypertension. (chapter 5)

The main investigations of this thesis are formed by two intervention studies on changes in electrolyte intake and blood pressure. (chapter 6)

In a double blind randomized crossover trial, the effect on blood pressure was studied of moderate sodium restriction and combined sodium restriction and potassium supplementation in fourty young subjects with mildly elevated blood pressure. In this study, six weeks of reduced sodium intake showed no significant effect on blood pressure. However, when combined with potassium supplementation, a significant fall in systolic blood pressure was

observed. The change in blood pressure in the high potassium/low sodium period was accompanied by a fall in cardiac index. The latter finding may indicate a mechanism where by alterations in dietary sodium/potassium ratio may affect blood pressure.

In a subsequent double blind randomized trial the effect of calcium supplementation versus placebo was evaluated in two groups of hypertensive youngsters. Supplementation with one gram of calcium daily significantly lowered diastoilic blood pressure. The hypotensive action of calcium was most prominent in subjects with relatively high plasma parathyroid hormone levels and/or relatively low serum total calcium levels. This observation is compatible with the view that a subgroup of hypertensive individuals exists, susceptible to calcium supplementation characterized by biochemical indications of a relative calcium need.

In the final chapter of this thesis, ways of non-pharmacological intervention in young subjects are discussed. Several approaches may be followed. The "whole population" approach, aims at either a downward shift of the distribution of blood pressure levels, or an average reduction in the rate of increase of blood pressure at an early age. Alternatively or in combination, one might attempt to identify those individuals at increased risk for cardiovascular disease, as judged by their blood pressure, and lower either their blood pressure level or their blood pressure rate of increase, the "high risk" approach. Non-pharmacological intervention in youngsters as well as in older age groups may act by changing body weight, dietary habits, or physical activity, or by behavioural modification. Experimental evidence on the efficacy of these interventions in the young is, however, very limited. Further studies are needed, with special emphasis on long-term effects of non-pharmacological intervention on blood pressure characteristics in the whole young population as well as in high risk groups. In addition, the predictive value of certain biochemical and other characteristics for a specific means of intervention in an individual needs to be further clarified. (chapter 7)

Chapter 9

SAMENVATTING

De onderzoekingen die in dit proefschrift beschreven worden werden uitgevoerd in een populatie van jongeren die niet in een ziekenhuis opgenomen waren. Deze mogelijkheid werd geboden door de beschikbaarheid van een cohort kinderen en jong volwassenen die sinds meer dan zeven jaar deelnamen in een vervolgonderzoek als onderdeel van het Epidemiologisch Preventief Onderzoek Zoetermeer (EPOZ). Van deze jongeren was een groot aantal gegevens over ondermeer de bloeddruk beschikbaar. Het voornaamste doel van de onderzoekingen was het inzicht te vergroten in de mechanismen die een rol spelen in de vroege pathogenese van primaire hypertensie, met speciale aandacht voor electrolyten in de voeding. (hoofdstuk 1)

In twee interventie onderzoekingen werd de invloed van verandering in electrolyt inname op de bloeddruk nagegaan bij jongeren met een verhoogde bloeddruk. Het gerandomiseerde onderzoek, de "randomized trial", vormt een belangrijke manier om op ondubbelzinnige wijze het effect van veranderingen in een factor, zoals electrolyt inname, op een andere factor, zoals de bloeddruk, vast te leggen. Het aselect toewijzen van de deelnemers in een onderzoek aan de onderzoeksgroepen (randomiseren) waarborgt de interne validiteit van een onderzoek. Daarnaast wordt door het dubbel blind uitvoeren van het onderzoek het optreden van informatie bias voorkomen. Aselecte toewijzing kan plaatsvinden tussen twee groepen, parallele groepen onderzoek , of tussen verschillende elkaar opvolgende interventie perioden, het cross-over onderzoek. Beide methoden werden toegepast bij onderzoekingen beschreven in dit proefschrift. (hoofdstuk 2)

Hypertensie bij volwassenen wordt hemodynamisch gekenmerkt door een toegenomen totale perifere weerstand. Bij vroege primaire hypertensie is de situatie minder duidelijk. Door verscheidene onderzoekers is verondersteld dat bij jongeren met een verhoogde bloeddruk sprake is van een toegenomen hartminuut volume. Dit is echter door ander onderzoek, waaronder onderzoek beschreven in dit proefschrift, niet bevestigd. Een belangrijk verschil tussen deze twee waarnemingen wordt gevormd door de toepassing van invasieve methoden om het hartminuut volume te bepalen in de eerste groep onderzoekingen, terwijl in de tweede groep gebruik werd gemaakt van niet invasieve technieken. Een verschil in reactie op invasief onderzoek, stress-respons, tussen hypertensieve en normotensieve jongeren zou het verschil in bevindingen geheel of ten dele kunnen verklaren. Waarschijnlijk hangt hoge bloeddruk op elke leeftijd samen met een verhoogde perifere weerstand. Tevens is, met name op jonge leeftijd, sprake van significant verhoogde plasma catecholamine spiegels. Dit zou kunnen wijzen op een veranderde activiteit van het sympatisch zenuwstelsel in de vroege fase van primaire hypertensie. (hoofdstuk 3)

Van de elementen van de voeding waarvan een verband met de bloeddruk verondersteld is hebben met name electrolyten veel aandacht gekregen. Vooral de rol van natrium in de ontwikkeling van hypertensie is het onderwerp van veel onderzoek geweest. De mate van het effect van natrium op de bloeddruk is echter nog onvoldoede duidelijk. Matige natrium beperking als maatregel ter verlaging van een verhoogde bloeddruk blijkt van beperkt belang juist in die gevallen waar niet medicamenteuze behandeling aangewezen lijkt, namelijk bij jongeren en patienten met een matig verhoogde bloeddruk. Veel minder gegevens zijn voorhanden aangaande het verband tussen kalium en calcium en de bloeddruk. Een verhoogde inname van deze electrolyten lijkt echter samen te gaan met een lagere bloeddruk. Daarnaast leidt verhoging van de inname van kalium en calcium mogelijk tot verlaging van de bloeddruk zowel bij normotensieve als hypertensieve personen.

De wijze waarop electrolyten de bloeddruk kunnen beinvloeden lijkt onder andere te verlopen via mechanismen op cellulair niveau. Het uiteindelijke gevolg van veranderingen in electrolythuishouding zou dan een toename van de contractietoestand van de gladde spiercel in de vaatwand zijn, met als gevolg een toename van de perifere weerstand en verhoging van de bloeddruk. (hoofdstuk 4)

Plasma spiegels van catecholaminen en renine en het hartminuutvolume werden onderzocht bij veertig jongeren met een verhoogde bloeddruk en veertig normotensieve jongeren van gelijke leeftijd en geslacht. Beide groepen jongeren waren afkomstig uit dezelfde bronpopulatie en werden onderzocht volgens eenzelfde protocol om de invloed van verstorende variabelen zoveel mogelijk te beperken. De twee groepen bleken gelijke plasma renine spiegels te hebben en ook het hartminuut volume verschilde niet. Er werden echter grote verschillen gevonden in de gemiddelde plasma noradrenaline, adrenaline en dopamine concentraties die allen hoger waren in de hypertensieve groep. Daarnaast leek het "normale" verband tussen deze catecholaminen en de bloeddruk veranderd bij de jongeren met een verhoogde bloeddruk.

In twee volgende onderzoekingen in vergelijkbare groepen normotensieve en hypertensieve personen werden verhoogde plasma bijschildklierhormoon en verlaagde serum totaal calcium spiegels gevonden in de hypertensieve groep. Deze bevindingen ondersteunen de veronderstelling dat veranderingen in de calciumhuishouding een rol spelen in vroege primaire hypertensie. (hoofdstuk 5)

De voornaamste deel van dit proefschrift wordt gevormd door twee interventie onderzoekingen naar de invloed van veranderingen in electrolyt inname op de bloeddruk. (hoofdstuk 6)

In een dubbelblind gerandomiseerd cross-over onderzoek werd het effect van een verlaging van de natrium inname, al dan niet

gecombineerd met een verhoging van de kalium inname, nagegaan bij veertig jongeren met een matig verhoogde bloeddruk. In dit onderzoek bleek zes weken natriumbeperking geen significante verlaging van de bloeddruk te veroorzaken. De combinatie van een lage natrium inname en een verhoogde kalium inname leidde echter tot een verlaging van de bloeddruk die samen bleek te gaan met een verlaging van het hartminuutvolume. Deze bevinding vormt een aanwijzing over de wijze waarop veranderingen in dietaire natrium/kalium ratio de bloeddruk kunnen beinvloeden.

Vervolgens werd een dubbelblind gerandomiseerd onderzoek uitgevoerd, waarbij het effect van extra calcium versus een placebo werd vergeleken in twee groepen hypertensieve jongeren. Dagelijkse inname van een extra hoeveelheid van een gram calcium bleek de diastolische bloeddruk te verlagen. Dit effect was het meest uitgesproken bij diegenen met relatief lage plasma bijschildklierhormoon spiegels en/of een relatief hoge serum totaal calcium concentratie. Deze bevinding is in overeenstemming met de hypothese dat een deel van de personen met verhoogde bloeddruk geveolig is voor een verhoging van de calcium inname en dat deze groep gekenmerkt wordt door biochemische aanwijzingen van een relatief calcium tekort.

Het laatste hoofdstuk van dit proefschrift bespreekt de mogelijkheden van niet medicamenteuze beinvloeding van de bloeddruk op jonge leeftijd. Hierbij kunnen verschillende benaderingen gekozen worden. De "bevolkings" aanpak streeft ernaar de bloeddruk verdeling in een bevolking in z'n geheel naar lagere waarden te verschuiven of de toename van de bloeddruk met de leeftijd in een bevolking gemiddeld te verlagen. Daarnaast kan, al of niet in combinatie met de eerste aanpak, gekozen worden tot het opsporen van personen met een verhoogd risico op hartvaatziekten op basis van een verhoogde bloeddruk en kan geprobeerd worden deze bloeddruk te verlagen. De tweede aanpak wordt de "hoog risico" benadering genoemd. Niet medicamenteuze beinvloeding van de bloeddruk kan plaatsvinden via een verlaging van het lichaamsgewicht, verandering van voedingsgewoonten, toename van de lichamelijke activiteit of beinvloeding van het gedrag. Experimenteel onderzoek naar de effectiviteit van deze vormen van bloeddrukverlaging is echter nog maar zeer beperkt verricht. Verder onderzoek, met speciale aandacht voor de lange termijn gevolgen van niet medicamenteuze beinvloeding van de bloeddruk op jonge leeftijd, is noodzakelijk zowel voor de "bevolkings" als de "hoog risico" aanpak. Daarnaast verdient de voorspellende waarde van biochemische en andere karakteristieken nader aandacht. (hoofdstuk 7)

If therefore some may apt to think that I have sometimes too far indulged conjecture, in the inferences I have drawn from the events of some experiments; they ought to consider that it is from these kinds of conjectures that fresh discoveries first take their rise; for tho' some of them may prove false, yet they often lead to further and new discoveries.

Stephen Hales
Haemastatics (1733)

EPILOOG

Dit proefschrift is het resultaat de inspanning van vele anderen naast de auteur. Ik wil dan ook dit slotwoord gebruiken om al diegenen te bedanken die bijgedragen hebben aan de totstandkoming van dit werk.

Een aparte plaats wordt hierbij ingenomen door de deelnemers aan het onderzoek. Ik heb veel geleerd van de grote bereidwilligheid en inzet van vele Zoetermeerse jongeren die vrijwillig deelnamen aan het onderzoek en daarvoor zelfs hun dieet ingrijpend hebben willen wijzigen.

Daarnaast dank ik de medewerkers van het instituut Epidemiologie in Zoetermeer en Rotterdam. Zo er al sprake kan zijn van een ideale werkomgeving dan wordt die hier dicht benaderd. Jullie allen zijn van grote invloed geweest op het in dit proefschrift beschreven werk. Zowel door jullie stimulerende aanwezigheid als door de daadwerkelijke hulp bij het uitvoeren ervan. Zonder anderen tekort te willen doen wil ik een paar personen apart noemen.

Prof. Hans Valkenburg, die er in slaagt binnen zijn afdeling zoveel verschillende individuen in eigenzinnige samenwerking zo creatief te laten functioneren. Ik dank je voor de steun en begeleiding bij mijn werk aan dit proefschrift. Bert Hofman, vanaf mijn eerste schreden in de epidemiologie hebben je positieve invloed en vertrouwen mij zeer geinspireerd, ik hoop dat we nog veel samen kunnen werken. Ria Rijneveldshoek, Alix Bruens en Joke Jansen zijn de stuwende en onmisbare krachten achter het veldwerk geweest. In Rotterdam hebben Jolanda Bekker en Leo Muller de soms chaotische administratieve en computertechnische verlangens van de auteur op onnavolgbare wijze weten te verwerken. Van de vele laboratorium medewerkers die in en buiten de afdeling Epidemiologie hun bijdrage hebben geleverd dank ik met name Janet Drop en Rene Vermeeren. Hans Eggink maakte en analyseerde tijdens vaak langdurige avondsessies de voortreffelijke echocardiografische opnamen.

Dit proefschrift vormt slechts een volgende stap in een opleiding die nooit volledig zal zijn. Ik dank mijn ouders voor hun eigen bijdrage in mijn vorming en de vanzelfsprekendheid waarmee zij mij lieten studeren. Tijdens mijn studie zijn veel mensen van invloed geweest. Het waren Prof. Peter Biersteker en Prof. Dr. E.J. Dorhout Mees die mijn interesse voor de fysiologie en pathofysiologie van nieren en hypertensie wekten.

Sjoukje, bedankt voor jouw bijdrage die zich niet laat samenvatten in een laatste zin.

ABOUT THE AUTHOR

Rick Grobbee was born on March 24th, 1957 in Zwolle, the Netherlands. He passed his secondary school exam in 1975 at the "Marianum" in Groenlo. In the same year he started studying art at the Academy of Art in Rotterdam. This study was in part continued in the years thereafter by courses at the Academy of Art "Artibus" in Utrecht. In 1976 he commenced his medical training at the State University in Utrecht. In 1978 a course in electronic music was followed at the Department of Sonology of the the same University. During his medical studies he participated in a number of committees installed to evaluate and restructure the medical curriculum. In December 1983 he obtained his medical degree and started a training in Epidemiology at the Department of Epidemiology of the Erasmus University Rotterdam (Head: Prof. Dr. H.A. Valkenburg). Then also the investigations described in this thesis were set out. In 1984 he was selected as a fellow to attend the 17th International Teaching Seminar on Cardiovascular Epidemiology and Prevention, organized by the Council of Epidemiology and Prevention, International Society and Federation of Cardiology. In February 1986 he started specialist training in Internal Medicine (Supervisor: Prof. Dr. A. Struyvenberg) at the Department of Internal Medicine St. Elisabeth Hospital Amersfoort (Head: Dr. D. Bonte). He is a member of the Netherlands Society of Hypertension and the European Society of Cardiology Working Group on Epidemiology and Prevention.