Hypertension, blood pressure, cognition and cerebral blood flow in the cohort of "Men born 1914"

Reinprecht, Faina

2006

Department of Health Sciences, Division of Geriatric Medicine
Malmö University Hospital, Lund University, Sweden 2006

Hypertension, blood pressure, cognition and cerebral blood flow in the cohort of "Men born 1914"

Faina Reinprecht

FACULTY OF MEDICINE
Lund University

Printed in Sweden
Media Tryck, Lund 2006
ISBN 91-85559-21-0

In memory of my mother and father
and to my family,
my husband and my son.

Abstract

”Men born 1914” is a population-based cohort study of the epidemiology of cardiovascular disease. Five hundred men born in 1914 were examined at the age of 68, 185 of them being re-examined at 81 years of age. Examination included medical and psychological investigation, ultrasonographic measurement of the carotid arteries, 24-hour ambulatory blood pressure monitoring, measurement of regional cerebral blood flow, and assessment of cardiovascular risk factors. Although risk factors for stroke and dementia have been identified, little is known about their influence on cerebral perfusion in the non-demented elderly. Ischemic cerebrovascular disease is usually a consequence of atherosclerosis and is the commonest cause of stroke. It is well known that hypertension plays a major etiological role in the development of cerebrovascular disease, ischemic heart disease, and cardiac failure. Active treatment of hypertension substantially reduces the risk of these complications. Little is known of how diurnal variations in blood pressure level influence cerebral perfusion in the very elderly. High blood pressure has often been discussed as a risk factor for cerebrovascular disorders and vacular dementia. Although much research has been done on elevated blood pressure, including its treatment and prevention, very little attention has been paid to low blood pressure, diurnal variation in blood pressure and orthostatic hypotension. A high prevalence of orthostatic hypotension in the elderly has been reported. It is well known that a fall in blood pressure can lead to cerebral hypoperfusion. It may also play a decisive role in the development of cerebrovascular insufficiency, i.e. of cerebral blood flow being inadequate in relation to the metabolic needs of the brain tissue. Haemodynamically, vascular insufficiency can develop through a drop in tissue perfusion in relation to vascular resistance. The resultant decrease in cerebral blood flow can give rise to ischemic hypoxia. The decrease in cerebral blood flow is usually caused by a reduction in systemic circulation. Cardiac arrest, cardiac arrhythmia, heart failure, occlusion or stenosis of the carotid arteries, and antihypertensive treatment are conditions in which the systemic circulation may fall off, jeopardizing the cerebral circulation as a whole and causing ischemic-hypoxic lesions in vulnerable areas. Four studies within the framework of this overall investigation were carried out within the thesis as a whole.

Study I showed hypertension to be a potential risk factor for the development of carotid artery stenosis (CAS). In the ”Men born in 1914” cohort, the proportion of men with CAS changed noticeably during the period up to the 13 year follow-up. Of the 148 men with normal carotid blood flow at 68 years of age, there were only 12 who at the re-examination at 81 years of age in 1995-96 showed no signs of CAS, whereas 136 men, or 93% of the surviving study cohort, had developed it. A significantly higher proportion of the men with hypertension than those without were found to have developed carotid stenosis. A higher proportion of occurrence of hypertension was noted in the men with bilateral CAS than in the others. The proportion of those having hypertension was smaller for the men with unilateral CAS than in those with bilateral carotid artery stenosis. At follow-up there were 14 of 136

men (10%) with CAS who had experienced an incident stroke or transient ischemic attack (TIA) and that all of them were found among men with CAS. No significant differences for other major cardiovascular risk factors (diabetes, hyperlipidemia, obesity, alcohol consumption and lack of physical activity) were noted.

Study II showed hypertension in late midlife and high diastolic blood pressure (DBP), in particular, to be associated with a decline in cognitive functioning in the men when they became elderly. DBP but not hypertension (HT) examined by tertiles at 68 years of age, was found to be inversely related to verbal (Paired Associates and Synonyms) and spatial functioning (Block Design and Benton Visual Retention Test), and speed (Digit Symbol Substitution) at 81 years of age, but only spatial functioning to be related to SBP at 68 years. High blood pressure at baseline examination, especially with regard to DBP with an accompanying decrease in DBP, was found to be inversely related to both speed performance and spatial functioning in psychometric tests taken 13 years later.

Study III showed significant associations between blood pressure (BP) levels and cerebral blood flow (CBF), especially at night. DBP at night was found to be correlated with CBF in the temporal right medial ($p=0.012$) and the left medial ($p=0.039$) regions. DBP during the days was also found to be correlated with CBF in the right medial temporal region ($p=0.025$). Stratified analyses indicated subjects with a high DBP (>70 mmHg) during the day to show a stronger association between CBF and mean DBP at night in the right medial temporal region than subjects with a lower daytime DBP ($r=0.323$, $p=0.009$). No such association for any of the CBF areas was found for subjects with a low DBP during the day (<70 mmHg). Analyses of the correlations between CBF in the different regions and the mean DBP and SBP, respectively, showed there to be a significant negative correlation for the frontal regions between CBF and DBP at night and for the left frontal region between CBF and SBP at night. The associations found between CBF and low BP could indicate an increase in the nocturnal risk of cerebral ischemia.

Study IV showed an extreme fall in nocturnal DBP in this cohort of elderly men to be correlated with focal changes in CBF and an associated increase in BP. The relative fall in DBP at night was negatively correlated with CBF in the temporal medial, temporal lateral, and parietal inferior areas in both hemispheres. Analyses of the office SBP at follow-up showed that subjects showing an increase in SBP to have a higher frequency of an extreme dip in nocturnal DBP than subjects did who showed a decrease in longitudinal SBP (Chi-Square 3.652; $p=0.056$), irrespective of the blood pressure level or the prevalence of hypertension, before and after the last follow-up.

In conclusion, an extreme fall in blood pressure at night in a cohort of elderly men was found to be associated with focal changes in cerebral perfusion, which in turn was correlated with an increase in blood pressure over an extended period of time and resulting damage to vascular autoregulation.

List of publications

This thesis is based on the following papers, referred to in the text by their respective Roman numerals:

I Faina Reinprecht, Sölve Elmståhl, Lars Janzon, Flemming Hansen. Incidence and progression of carotid artery stenosis in elderly men: Thirteen-year follow-up of the population cohort "Men born in 1914". International Journal of Angiology 2002;11:132-138.

II Faina Reinprecht, Sölve Elmståhl, Lars Janzon and Lena André-Petersson. Hypertension and changes of cognitive function in 81-year-old men: a 13-year follow-up of the population study "Men born in 1914", Sweden. Journal of Hypertension 2003;21:57-66.

III Faina Reinprecht, Johan Axelsson, Arkadiusz Siennicki-Lantz, Sölve Elmståhl. Low nocturnal blood pressure is associated with reduced cerebral blood flow in the cohort "Men born 1914". Submitted 2006.

IV Arkadiusz Siennicki-Lantz, Faina Reinprecht, Johan Axelsson, Sölve Elmståhl. Cerebral perfusion in the elderly with nocturnal blood pressure fall. Submitted 2006.

Reprints of the articles are made with permission from the publishers.

Contents

Abbreviations

ABPI	Ankle-Brachial Pressure Index
ABPM	24-hour Ambulatory Blood Pressure Monitoring
AD	Alzheimer's disease
BP	Blood Pressure
CBF	Cerebral Blood Flow
CAS	Carotid Artery Stenosis
CVD	Cerebrovascular disease
DBP	Diastolic Blood Pressure
HT	Hypertension
ICD	International Classification of Diseases, Injuries and Cause of Death
MABP	Mean Arterial Blood Pressure
MCI	Mild Cognitive Impairement
MMSE	Mini-Mental State Examination
PAD	Peripheral Arterial Disease
rCBF	Regional Cerebral Blood Flow
ROI	Region Of Interest
SBP	Systolic Blood Pressure
SPECT	Single Photon Emission Computed Tomography
TIA	Transient Ischemic Attack
VD	Vascular dementia
WAIS	Wechsler Adult Intelligence Scale

Introduction

”Men born in 1914” is a prospective cohort study of the epidemiology of cardiovascular disease. A health investigation of men residing in the city of Malmö, Sweden who were born in 1914 was carried out in 1968-69. Since then, several epidemiological studies of these men have been conducted of [1, 2]. Two important aims of the studies have been to quantify the extent to which the men developed disease states in the arteries of the lower extremities [3, 4], and to explore possibilities of employing a non-invasive investigative method easy to handle and able to provide quantitative information on the distribution of blood flow in the carotid arteries. Diseases of the internal carotid artery in particular have been discussed, in recent studies [5, 6] in terms of their being an important factor in the pathogenesis of transient ischemic attack (TIA) and stroke.

Atherosclerosis and cerebrovascular disease (CVD) are common conditions in the elderly. In about 50% of the cases, ischemic CVD is due to artheromas in the large or medium-sized arteries, which can cause thrombi or emboli, and in about 25% of the cases to intracranial small vessel disease. Acute cerebral events are caused by cardioembolic disease in about 20% and in about 5% of cases are due to rare cause. Thus, about 75% of the ischemic strokes and TIAs that occurs are the embolic or thrombotic consequences of atherosclerosis that affects the large or medium-sized arteries going to the brain or the small intracranial vessels [7].

Atherosclerosis

Atherosclerosis is a synonym for hardening of the medium and large-sized muscular and elastic arteries, including the coronary arteries, the aorta, the carotids and major arteries supplying the brain, the extremities and the internal organs. At present, atherosclerosis is the principal cause of cardiovascular diseases, which in turn are the leading cause of death both in the United States and in Europe [8]. Nevertheless, atherosclerosis is still to be regarded as a complex of uncertain etiology, several hypothetical explanations of its pathogenesis having been advanced, not all of these being mutually exclusive. Currently, the response-to-injury theory, supported by numerous pathophysiological observations in humans and animals, is rather well accepted generally. This theory considers atherosclerosis to be an inflammatory disease in which “injury” to the endothelium is the initiating event in atherogenesis. This injury, which can be due to various metabolic or environmental factors such as hypercholesterolemia, hypertension, or cigarette smoking, results in structural and/or functional alternations in endothelial cells and changes in the nature of the protective barrier normally provided by them. These changes in endothelial cell function can result in a critical sequence of cellular and humoral interactions such as the activation and adhesion of leukocytes, platelets and other cells, inducing an inflammatory reaction and culminating in the initiation and formation of atherosclerotic lesions. Endothelium is more permeable when injured permitting such plasma constituents

as lipoproteins, growth factors and cytokines more ready access to the arterias wall. All of these cellular and humoral factors have been found to be strongly involved in the initiation of atherosclerosis and the proliferation of smooth muscle and other connective tissue cells, with the subsequent formation of early and advanced atherosclerosis lesions, such as fatty steaks and fibrous plaques [9, 10]. The outcome of the cerebral lesions can be affected by the vascular anatomy of the brain, the autoregulatory capacity of the cerebral vessels, an imbalance of monoamine neurotransmitters, intracranial small vessels disease, haemorheological conditions and the degree of carotid artery stenosis.

The brain is supplied with blood by the internal carotid and vertebral arteries, which anastomose at the base of brain via the circle of Willis, from which the anterior, middle and posterior arteries arise, these winding upwards around the cerebrum and forming the leptomeningeal plexus on the surface of the brain. Branches of the leptomeningeal arteries penetrate the cerebral parenchyma perpendicularly, converging on the ventricular system [11]. These vessels can be classified as being paramedian, short circumferential or long circumferential arteries. The paramedian and short circumferential arteries supply the grey subcortical nuclei, and the long circumferential arteries the cortex and white matter. The leptomeningeal arteries have numerous connections among themselves. These are almost always located in the border areas between the main cerebral arteries. This region, despite its abundant blood supply, is often afflicted with watershed lesions due to variations in the number, size, and location of the anastomoses, as well as to local arterial disease or to the considerable distance from the heart. The deeper grey and white matter structures are generally supplied with blood by the nonanastomosing penetrating vessels (ventriculopetal arteries). Besides these ventriculopetal arteries, there are also nonanastomosing ventriculofugal arteries that originate from the choroidal arteries of the ventricles. The subcortical watershed areas, because of the absence of anastomoses there, are more vulnerable to ischemia than the anastomosing cortical areas, although the danger of it in connection with the latter areas has been emphasized to a greater degree. Due to the increasing interest shown in white matter changes, i.e., in leukoariosis, however, the subcortical watershed region will probably attract greater attention in the future.

Cerebral autoregulation

Cerebrovascular insufficiency [12] refers to an overall hindrances to the flow of blood in the cerebrovascular system. It can be defined as an inadequacy of blood flow in relation to the metabolic needs of the brain tissue, though not a complete deprivation of blood slow there. Haemodynamically, vascular insufficiency develops when the tissue perfusion pressure drops in relation to the vascular resistance. The resultant decrease in cerebral blood flow gives rise to ischemic hypoxia. The decrease in cerebral blood flow is usually caused by a reduction in systemic circulation. The outcome of cerebral lesions can be affected by the vascular anatomy of the brain [11], the autoregulatory capacity of the cerebral vessels [13, 14], imbalance in the monoamine neurotransmitters, the degree of stenosis of the carotid artery, a disease condition of the small intracranial vessels, and the presence of haemorheological conditions.

The association between low BP, especially at night and lowered rCBF could be explained as being produced by insufficient cerebral autoregulation, this leading to an extensive reduction in cerebral perfusion and to subsequent ischemic damage. The autoregulation of rCBF is effective over a wide range of arterial blood pressures but has both a lower, and an upper, pressure limit. Under normal conditions, these limits are a MABP of about 70 and 140 mmHg, respectively. It is possible that this capacity decreases with age [13]. The underlying autoregulatory mechanisms are poorly understood, but three possibilities have emerged. According to myogenic theory [15], the smooth muscles respond directly to variations in blood pressure. Recently, an endothelially-derived relaxing factor [16] and endothelially-derived contracting factor [17] were discovered. These may be of importance for the local regulation of the lumen of the vessels. Another possibility is that the local accumulation of various substances with vasoconstrictor effects, such as serotonin [18, 19], and substances possessing vasodilator capacity, such as bradykinin and histamine, affect the vascular tone [20]. A third possibility is that autonomic, neurogenic factors control the vascular tone. The last alternative includes not only local vasomotor effects but also a remote impact, such as that of diaschisis. Diaschisis appearing as a bilateral reduction in hemispheric blood flow has been reported in patients with unilateral cerebral infarcts [21, 22]. It has been suggested that all three mechanisms may play a role in a given case. If the blood pressure decreases below 60 mmHg, autoregulation fails to work, the subcortical white matter in particular running the risk of being destroyed, whereas the regions of grey matter remain better preserved. Under circumstances of complete ischemia, the grey matter becomes more heavily involved. The neurotransmitter metabolism of the grey matter is extremely sensitive to even very short periods of hypoxia. Although the autoregulation adapts to long-standing hypertension, the small vessels gradually become affected structurally, with the development of atherosclerosis and the further reduction in their autoregolatory capacity through hyalinosis. In addition, in patients with long-standing hypertension the risk of hypotensive white matter lesions is increased, even at apparently normal blood pressure levels [14, 23].

The relationships between the development of atherosclerosis and cerebrovascular disease, as well the role of cardiovascular risk factors here has been reported in many earlier studies [24-36]. In the Western countries, atherosclerosis is the most serious risk factor in connection with cerebrovascular disease It is the major cause of illness and death from coronary heart disease, as well as of ischemic cerebrovasclular disease, TIA, stroke and vascular dementia, of carotid artery disease and of ischemia of the lower limbs.

Transient ischemic attack (TIA)

A TIA is a clinical syndrome characterized by acute loss of focal cerebral or monocular functioning, the symptoms lasting for less than 24 hours. It is thought to be due to inadequate cerebral or ocular blood supply as a result of an arterial thrombosis or an embolism associated with arterial, cardiac or haematological disease [37]. Stroke is preceded by TIA in about 10% of the causes [38]. The actuarial risk of stroke is about 11,6% during the first year after a TIA and approximately 5,9 %/year during each

of the four years thereafter, although the actuarial risk of death, stroke or myocardial infarction during the first 5 years after TIA is approximately 8,4%/year [39].

Stroke

A stroke is a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms either lasting more than 24 hours or leading prior to this to death, their having no apparent cause other than their being of vascular origin [40]. More than 4 million people worldwide suffer a stroke each year. An estimated 500.000 of these persons are in Western Europe. Stroke is the third leading cause of death after ischemic heart disease and cancer, not only in developed countries, but also worldwide [41], and is the leading cause of disability in industrialized countries [42]. With age, there is an exponential increase in the incidence of stroke, and the overwhelming majority of ischemic strokes occur in those over 65 years of age [43]. The stroke risk more than doubles with each decade past the age of 55 [44].

Carotid artery disease

A number of cross-sectional studies have examined the degree to which changes in the carotid artery represent risk factor for TIA/stroke. It has been found that plaque structure, and not stenosis of the carotid artery is the most important factor for the development of stroke [24, 25]. Recent studies have also shown that asymptomatic carotid artery disease is associated with an increased risk of ischemic stroke, the annual stroke risk being about 1.3% in those with stenosis of less than 75%, and 3.3% in those with stenosis of more than 75% [45].

Dementia

Dementia has presumably been an element of ageing throughout human history, the occurrence of it having often been regarded as simply a part of normal ageing. It was not until the end of nineteenth century that evidence of abnormal brain degeneration was found in older people. Dementia is a syndrome of global cognitive decline that can have many causes, both genetic and environmental factors being considered to be involved [46]. The prevalence of dementia is not known precisely but is estimated to be about 0.5% in the 60 to 65-year age. Epidemiological studies have shown there to be a high correlation between age and dementia disorders. The prevalence of such disorders seems to about double with each 5-year advance in age then, approximately 40% of those reaching 90 years of age suffering from moderate to severe dementia [47]. The occurrence of vascular dementia (VD), one of the major subtypes of it, has been found to often be linked with the presence of such vascular risk factors and disorders as hypertension, CVD (e.g, white matter lesions, as well as both clinical and silent stroke), and diabetes mellitus [47]. The current view is that the development of VD is due not to chronic ischemia but essentially to the accumulation of defects from large and small infarcts. The general mechanism underlying these brain lesions

is that of arteriosclerosis. The majority of cerebral infarcts have been reported to be caused by occlusive arteriosclerotic lesions, i.e., thromboembolism [47-49].

Low blood pressure levels, an impaired circadian rhythm and disturbed autonomic cardiovascular reactivity have also been observed in Alzheimer patients, but the pathogenesis of these variations is unknown.

Hypertension

It is well known that hypertension predisposes one to different types of both intra- and extracerebral arterial lesions, that can cause cerebrovascular damage [50].

The overall prevalence of hypertension, defined as SBP≥160 mmHg and DBP≥90 mmHg, is estimated to be nearly 50% in persons 70 years of age and older [51].

It was demonstrated in the Framingham study [33] and the Evans County study [34] in the early 1970s, that hypertension is a major risk factor for stroke. The risk of stroke is also directly related to high blood pressure levels within the normal range. Hypertension in turn is related to the development of ischemic cerebral disease and dementia. The role of high blood pressure, not only as a risk factor for stroke, but also as an etiologic factor in its development, is supported by extensive clinical trials [35, 36, 52, 53] in which a reduced incidence of stroke has been demonstrated following antihypertensive treatment.

Many earlier studies, both prospective and cross-sectional, support the link between elevated blood pressure and cognitive deterioration. The most convincing evidence thus far of such a relationship was obtained in a set of prospective studier in the 1960s, at a time when antihypertensive treatment was still infrequent. The most important of these studies were ones based on a reanalysis of the Framingham data reported originally by Farmer et al. [54, 55] and Elias et al. [56]. Evidence was obtained for a negative association between high blood pressure levels under conditions of few if any of participants involved taking antihypertensive medication, and cognitive performance as measured 12- 14 years later. Elevated blood pressure (both systolic and diastolic, the two being analysed separately) was predictive of lower composite neuropsychological performance scores and lower results for attention and memory [54, 55]. An early longitudinal study [57] showed negative correlations between DBP and several of the WAIS subscales, although no adjustment was made for age, education or antihypertensive therapy. The authors suggested that, ”the basis for the cognitive decline associated with aging should be considered secondary to some pathologic process and not merely as a normal aging process”. Results of other studies following BP measures longitudinally point in the same direction.

Population-based studies have reported similar relationships between cognitive performance and both SBP and DBP [58, 59]. The Swedish longitudinal study of 70- year old men showed that high diastolic blood pressure could predict later im-

pairment of psychomotor speed as measured by the Trail Making Test, although only in untreated men, but failed to show systolic hypertension to be related to later impairments in performance [58]. In the Honolulu-Asia Aging Study, elevated midlife systolic but not diastolic blood pressure was found to be associated with a higher risk of poor cognitive performance in late life [59]. Various cognitive functions differ in the pattern of association with blood pressure shown. One explanation for this might be that these cognitive functions differ in their vulnerability. This is supported by the fact that an age-related decline is more pronounced in performance speed functions than in verbal functions, for example. Accordingly, when studying cognitive functions, different tests are needed due to differences in the type of changes overtime that occur.

Changes in blood pressure

Changes in blood pressure appear to be an important indicator of the risk of cognitive decline. As already indicated, the Western Collaborative Group is longitudinal study conducted by Swan and co-workers [60] concerning effects of blood pressure changes reported impaired verbal function among participants with a high SBP≥140 mmHg in midlife. A subgroup showing a decrease in SBP at a follow-up displayed a reduction in speed performance instead as measured by the Trail Making Test, whereas those with an increased in SBP showed lower verbal performance. It has been reported that a decline in SBP with age can often be attributed to dementia-producing illness or to cardiac insufficiency, cross-sectional studies also having shown blood pressure to be lower in patients with clinically manifest dementia than in healthly controls [61, 62].

One study showed that individuals who developed dementia between the ages of 79 and 85 years had higher systolic and diastolic blood pressures at ages 70 and 75 than patients who did not develop dementia [63]. The authors suggested that a previously elevated blood pressure level might increase the risk of dementia, as well as of Alzheimer`s disease. The mechanisms underlying hypertension-related cognitive changes are complex and are not yet fully understood. Few studies have included patients receiving antihypertensive treatment. The potential positive effect of blood pressure levels being lower than 140 mmHg is still under debate [50]. It can only be speculated whether hypertension causes end organ damage that reduces blood pressure. The possible negative effects of drug-induced hypotension on cognitive functioning as a result of hypertensive treatment might also be considered.

Low blood pressure

Low BP levels can also be thought to be a cause of low levels of cognitive functioning. In a longitudinal study, it was found that in elderly patients (aged 65-102) an office SBP<130 mmHg increased the risk of cognitive decline over a 6-year period as compared with a reference group having SBP values of 130-139 mmHg [50]. Others studies have found a low SBP (<130 mmHg) in the elderly to be associated with increased mortality and with cerebral white matter lesions [64-66].

The development of a non-invasive device for ambulatory BP monitoring enabled us to assess both diurnal variations in BP and high BP levels in clinical practice [67].

Abnormal patterns of diurnal BP variations have been reported to be associated with both clinically overt and silent target organ damage and to be a predictor of subsequent cardiovascular events independent of high BP levels [68, 69]. The possibility of hypotension posing a potential risk of silent brain ischemia has also been suggested.

Data from the Kungsholmen Project in Sweden showed elderly persons with blood pressure levels of less than 130 mmHg to have a higher risk of cognitive impairment at follow-up 40 months later, a poorer functional status and higher mortality [70, 71]. Low blood pressure was also suggested to be an early correlate of a dementing process [72]. In the same study population, severe systolic hypertension was found to be a risk factor for developing dementia within a period of 3 years, subjects, whose systolic blood pressure decreased during follow-up being more likely to develop dementia, including that of the Alzheimer type. Lower blood pressure values, impaired circadian rhythm and disturbed autonomic cardiovascular reactivity have also been observed in Alzheimer patients, although the pathogenesis of these variations is unknown [62, 73, 74].

The amplitude of the fall in nocturnal blood pressure is decreased in the elderly, as well as in hypertensive patients with cerebrovascular lesions, with dementia due to vascular disease and with left ventricular hypertrophy [75]. The question of whether non-dipping represents the cause or the effect of end-organ damage and whether the dipping condition is beneficial or harmful to patients with cerebro- and cardiovascular disorders is still unresolved.

Kobrin et al. [76] reported in 1984 that six of 14 elderly patients whose nocturnal blood pressure fell to normotensive levels showed clinical evidence of cardiovascular complications, including one case of cerebrovascular disease, whereas all seven elderly patients whose blood pressure increased to levels at night similar to those measured in the office showed clinical evidence of cardiovascular complications, including two cases of cerebrovascular disease.

O'Brien et al. [77] reported further that when over 100 hypertensive patients were divided into "dippers", defined as showing a noctural systolic and diastolic blood pressure reduction of 10/5 mmHg or more, and "nondippers", as showing less than 10/5 mmHg, the "nondippers" showed a significantly higher prevalence of stroke (5/21, 24%) than the dippers did (3/102, 3%), there being no appreciable differences in age, sex, body weight, or daytime blood pressures.

Orthostatic hypotension

Orthostatic or postural hypotension is an important cause of distress and disability, and can severely affect the quality of life, especially in the elderly. It is arbitrarily de-

fined as a fall of more than 20 mmHg in systolic BP upon standing up from the supine rest position [78]. The prevalence of orthostatic hypotension is around 30% in people over 75 years of age [79]. Low blood pressure and orthostatic hypotension are common findings in demented patients, Passant et al. having shown that in 39 patients with Alzheimer's disease (AD) the blood pressure (especially in the late stage) was lower than what had previously been described in elderly persons of similar age [80]. This lower blood pressure is in agreement with results of other studies of patients with AD [62, 81], in which systolic values of around 130 mmHg have been reported.

Certain diseases of the autonomic nervous system can lead to orthostatic hypotension. The primary forms of autonomic failure involved include pure autonomic failure, the Shy-Drager syndrome, and autonomic failure associated with Parkinson's disease. These primary forms are rather unusual but can results in profound orthostatic hypotension. The secondary form (associated with peripheral neuropathy) can be seen in a variety of disorders such as diabetes mellitus, amyloidosis, multiple sclerosis and vitamin B12 deficiency. Autonomic dysfunction has also been suggested as a possible complication in dementia of the Alzheimer type [62, 82, 83] and in vascular dementia [84]. There is still uncertainty, however, concerning the severity of postural blood pressure changes in very old persons both with and without dementia. A five-year longitudinal study of healthy elderly women by Elmståhl et al. showed that at follow-up those with orthostatic hypotension during tilting at baseline had reduced cognitive function as measured by EEG as compared with women without orthostatic hypotension [85]. This might possibly indicate postural hypotension to contribute to brain damage.

Studies reporting reduced relative frontal blood flow during the tilting of healthy elderly persons [80, 86] and of demented patients with orthostatic hypotension (OH) as compared with those without OH [81] have suggested a "tardive" autonomic system to be a cause of the reduced autoregulatory reserve in pathologically affected brain arterioles. The authors in question also considered the possibility of activation of the sensory-motor systems that are involved in standing and the increased motor awareness this produced to be factors possibly responsible for the redistribution of brain blood flow in these subjects.

Neurotransmitter disturbances in the cholinergic, noradrenergic and serotoninergic systems have been found in the brain in patients with AD [87], similar deficiencies also having been described in vascular dementia [88]. Several of these neurotransmitter systems are involved as vasoconstrictor-and/or vasodilator agents in the regulation of the blood circulation.

Cognition and aging

Normal aging and pathologic aging are distinct from one another. Many of the changes in cognitive functioning that occur are gradual and develop starting in early adulthood, suggesting that the cognitive changes that occur may be part of a normal

developmental process. However, the definition of healthy normal aging does not entirely solve the problem of identifying truly healthy elderly individuals. Because of compensatory changes within a neuron population or the redundancy found in neuronal circuits, biochemical and/or structural changes in the normal aging brain may not necessarily be accompanied by functional deficits. The individuals in question may show no cognitive deficits and yet have entered a premorbid state of impending dementia, escaping correct classification. This is reflected in the observation that many elderly individuals with age-associated memory deficits show further detoriation over time, whereas others remain stable.

Already in 1967, Horn and Cattell demonstrated that intellectual ability can be classified in terms of two general types: on the one hand fluid intelligence, representing the ability to maintain a span of immediate awareness, to deal with conceptual information and conceptual attainment tasks, and ability in the areas of reasoning, abstracting and mentally flexibility, and on the other hand crystallized intelligence, representing verbal comprehension, vocabulary and fund of knowledge [89]. The authors were able to show in a reliable way that measures of fluid intelligence show decrements with age, whereas measures of crystallized intelligence are largely unaffected by age. In others studies it has been shown that crystallized mental abilities increase up to the sixth or seventh decade of life and may only decrease in late old age, whereas fluid mental abilities, in contrast, generally show a continuous linear decline beginning in early adulthood, there possibly being an acceleration of it in late old age [90, 91].Studies of brain-damaged patients with selective memory impairment have demonstrated convincingly that some forms of long-term memory depend on the integrity of the medial temporal lobe [92-94]. The medial temporal lobe system consists of the hippocampal formation, together with the adjacent anatomically related parahippocampal, entorhinal and cortical areas. The medial temporal lobe has widespread reciprocal connections with the associative neocortex, as well as with subcortical structures. Abnormalities in these brain structures are related to various vascular diseases and cardiovascular risk factors. They can be seen as often representing a clinical syndrome of intellectual decline produced by ischemic, hypoxic brain lesions.

Methods of assessing cognition

Many methods of examining or describing cognitive functioning are available. The surrounding world is perceived through different modalities of the individual. Cognition refers to how this information is processed. Because cognition is such a multifaceted concept, a complete battery of tests is needed in order to measure it adequately. Tests of perceptual speed, verbal ability, spatial ability and reasoning are just a few examples of cognitive dimensions for which specific tests have been constructed, tests that could be included in such a test-battery. The Wechsler Adult Intelligence Scale (WAIS) is one of the most well known test-batteries [95].

Five tests of cognitive ability are included in the psychological examination carried out here: The Synonyms test was chosen as representative of crystallized ability

(verbal ability); the performance level on this test is presumed, as in the case of, many others tests of verbal skills, to be relatively unchanged throughout life [96], The Block Design test (Swedish version), chosen here to represent visuospatial and constructional ability is very similar to the Block Design test that belongs to The Wechsler Adult Intelligence Scale; it is a test in which age effects are prominent and scores tend to be lowered by a brain injury of any kind, The Paired Associates test used to measure immediate verbal memory is considered especially sensitive to left-sided brain laesions, and also to depressive syndromes [97], The Digit Symbol Substitution test is a performance speeded test measuring several cognitive abilities, such as psychomotor speed, visual-motor coordination, concentration, and cognitive flexibility; this test is considered to be one of the Wechsler Adult Intelligence Scale tests, most sensitive to brain dysfunction generally, through its measuring various abilities of a less specific character. The Benton Visual Retention Test, finally, is a test used for measuring immediate visual and spatial memory; it is a test sensitive both to aging and to brain dysfunction.

CBF and aging

Studies of the aging of the human brain often involve only small numbers of subjects of arbitrarily selected age, without the developmental and aging pattern as a whole being considered. Normal aging is associated with the degeneration of specific neural systems, and data generally shows there to be an impairment of global CBF with age. The findings obtained suggest advancing age to have differential effects on cerebral perfusion, affecting certain areas in the frontal, parietal, temporal and occipital lobes at different brain levels [98].

Brain atrophy, changes in the white matter, and silent infarctions, frequently detected in the elderly by use of computer tomography and magnetic resonance imaging, are correlated with vascular risk factors and cognitive decline [99]. There is still no clear evidence of the manner in which the presence of vascular diseases affects brain function in the non-demented elderly. Thus far, few studies appear to have investigated the distribution of changes in white matter in elderly patients and possible relationships of such changes to systemic blood pressure expressed as rCBF. The rCBF method is presented as being sensitive in detecting cerebral changes related to stroke and dementia [62, 80, 81]. Results of the single photon emission computed tomography (SPECT) method have also been shown to be highly correlated with the cerebral blood flow ratio as estimated by positron emission tomography (PET) [86, 98]. Although cerebral atrophy with the accompanying increase in size of the ventricle system could introduce misleadingly low rCBF estimates in regions close to the ventricles, these regions have been selected for examination here on the basis of previous studies using both rCBF and CT [92, 99].

Aims of the separate studies

The aims of the various studies conducted are as follows:

Paper I

To investigate the prevalence and distribution of the level of stenosis in the carotid artery at 81 years of age, the progression of stenosis with the advance in age from 68 to 81 years, and its possible association with such cardiovascular risk factors as hypertension, lipids, smoking, alcohol consumption and diabetes.

Paper II

To examine the association of systolic and diastolic BP and the diagnosis of HT in cognitive functional terms in a population of healthy elderly men, and to determine changes in verbal, spatial and speed performance and attention accounted for by BP status while controlling for lifestyle factors, education and manifestations of vascular disease.

Paper III

To investigate the association in healthy elderly men between blood pressure levels and both diastolic and systolic, day and night, as determined by 24-hour ambulatory blood pressure monitoring (ABPM) and disturbances in CBF expressed as rCBF.

Paper IV

To investigate, in a cohort of elderly men, relations between changes in blood pressure levels, both SBP and DBP at night, extreme nocturnal in BP fall, as determined by 24-hour ambulatory blood pressure monitoring (ABPM), and cerebral blood flow (CBF) expressed as rCBF.

Material and Methods

Population

The ”Men born in 1914” study is a prospective population study that has been underway since 1968. The cohort includes all men residing in Malmö, Sweden born in even months in the year 1914. Of the 809 men of this category invited to participate, 703 agreed to take part in 1968-69. In 1982-83, the 465 participants still living in Malmö, together with 95 new residents there from the same cohort, were invited to participate in a new examination, in which 500 took part. The examination included measurements of carotid blood flow and of circulation in the leg, lipid analysis and assessment of smoking habits and of alcohol consumption, see Figure 1.

In 1995-96, at the most recent follow-up of the cohort, 281 men were found to be still alive and were invited to participate again. A total of 186 men (66%) agreed to take part in this new investigation. The examinations conducted previously were repeated on this occasion. One man, who filled out the questionnaire but declined to take part in the clinical investigation, was excluded because of incomplete data, our analysing the data then in **studies I** and **II** of 185 men.

In the following year (1996-1997), the men were contacted again and were asked to participate in a cerebral blood flow (rCBF) examination and in ambulatory blood pressure monitoring (ABPM). During that year, 10 out of the 185 men who had participated in the 1995-1996 study turned out to have died. ABPM was performed on 136 men, CBF on 129 men, and 108 of the men took part in both. Eleven of the men were excluded because incomplete ABPM through their showing an accumulated deficit of 6h or more during daytime and/or of 3h or more during nighttimes (10.00 pm to 06.00 am) or more than 3h of consecutive deficit during the day or at least 2h during the night. In **studies III** and **IV**, 97 men were included in the final analysis.

Questionnaire and health examination

A letter of invitation was sent out in January 1995 to the 281 survivors who had participated previously, the 186 who agreed being sent a written questionnaire to fill out at home. The first part of the questionnaire included sociodemographic variables (marital status, education and social class). Marital status was dichotomised into two groups: unmarried and non-cohabitant and married or cohabitant. Education was divided into four categories: 4-6 years, 7-9 years, 10-13 years and >14 years of education. Classification in terms of social class was based on data on earlier profession, work tasks and position. Social class III included ”blue-collar” workers and social class II ” white-collar” workers at the low to medium level. Social class I comprised subjects in leading positions; professionals with university degrees and owners of business enterprises with employees [100, 101].

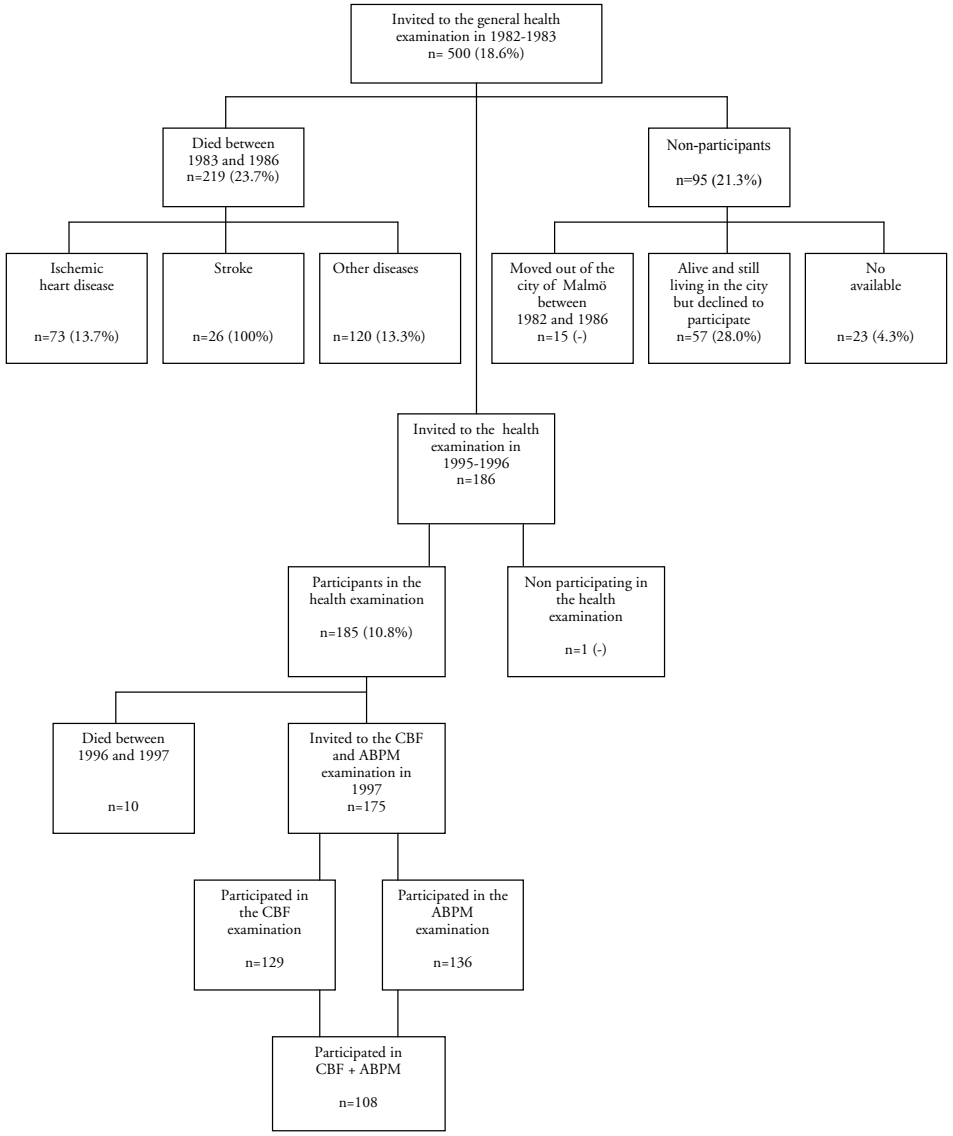

Figure 1. *Participation of the cohort "Men born 1914" in the prospective study. The prevalence of stroke at baseline and the incidence of stroke during the 13-year follow-up are given in percent in parentheses.*

The second part of the questionnaire was made up of questions concerning prescribed medicines, tobacco consumption, alcohol intake, physical activity, health status and history of previous ischaemic heart disease. Ischaemic heart disease was defined in terms of the subject either having fulfilled the diagnostic criteria of angina pectoris according to the Rose Questionnaire or having been hospitalised because of myocardial infarction (MI), or both [102]. Smoking habits were categorised into three groups: non-smokers (those who had never smoked regularly or had smoked less than 1g of tobacco/day during less than 1 year), ex-smokers (previous smokers who had stopped smoking at least 1 month prior to the investigation) and current

smokers (those who had smoked at least 1g of tobacco/day or had given up smoking less than 1 month prior to the investigation). Alcohol intake was measured in g/day. The men were divided into the following four groups according to their alcohol consumption: 0g/day, 0-19 g/day, 20-39 g/day and >40 g/day [103].

Physical activity was classified into three categories: low level of physical activity (mostly sedentary activities such as reading and watching TV), moderate level of physical activity (>4 hours/week of walking, cycling, light gardening) and high level of physical activity (>3 hours/week of swimming, running, heavy gardening) [104].

Laboratory analyses

At the previous examination in 1982-83, laboratory analyses included measurement of blood glucose, cholesterol and triglycerides under fasting conditions. Fasting blood glucose level was analysed by standard method and was expressed in mmol/l. Diabetes mellitus was defined as a fasting blood glucose level >7 mmol/l or medication for diabetes mellitus [105].

Plasma lipid, cholesterol and triglycerides levels were analysed by standard methods and were expressed in mmol/l. Hypercholesterolaemia was defined as cholesterol >6,5mmol/l [106] and hypertriglyceridaemia as triglycerides >2,3 mmol/l [107]. Hyperlipidaemia was defined as the presence of hypercholesterolaemia and hypertriglyceridaemia.

BMI

BMI was calculated as weight (in kg)/height (in m2). Obesity was defined as BMI >28 [108].

Mortality rate

Data on mortality and cause of death data were obtained from the Mortality Register at the Swedish National Bureau of Statistics [109]. The causes of death were coded in accordance with the International Classification of Diseases, injuries and cause of death (ICD), eighth revised version [110].

Cerebrovascular event rate

Information on incident stroke during 1982-1995 among the 80 out of 95 non-participants for whom information was available was retrieved from medical records. There were 15 of the former subjects, all of them non-participants, who moved out of the city of Malmö during 1982-1995. Stroke was defined according to the ICD-9 classification (430,00-438,99). Transient ischaemic attack (TIA) was defined according to the WHO definition as being a temporary cerebral dysfunction, rapid in onset and lasting less than 24 hours.

Ultrasonographic methods

Continuous-wave Doppler

The ultrasonographic examination of the carotid arteries at 68 years of age was made by use of the continuous-wave Doppler method Dopsan 1050 (Carolina Medical Electronics, Inc., King, NC, USA). This instrument operates with a 5 MHz transducer attached to a position-sensitive arm. The probe consists of a dual-crystal lens-focusing transducer. This is directed at the carotid artery at an angle of 60° from the longitudinal body axis. The Dopsan display is divided into two parts. On the upper part, it is possible to follow the real-time fast Fourier transformation spectrum. An image of the vessel is presented on the lower part of the display with a color-coded image of the frequencies. This makes it possible to determine at what point along the carotid artery the doppler signals have been obtained. All examinations were stored on videotape. Examination was conducted with the patient in a supine position after ten minutes of rest. Measurements were made on the common carotid artery 2 cm beneath the bifurcation, and in the proximal internal carotid artery from the point of the vessel where the most abnormal doppler signals were found and 2 cm distal to the obstruction. The maximum frequency of the Doppler shift (MFS) is closely related to the extent of stenosis. The error of a single determination was 0.40 kHz [5]. The MFS from the proximal part of the internal carotid artery increased as the degree of stenosis increased. On the average, an MFS of 3,1 kHz corresponded to a reduction in diameter of 30% and 6,1 kHz corresponded roughly to a reduction in diameter of 60%. If no doppler signals could be obtained in the proximal and distal parts of the internal carotid artery, the vessel was diagnosed as being totally occluded. In order to improve the accuracy of the method, computer-processed spectral analysis with use of digital printout was employed.

Duplex method

When the subjects were 81 years of age, their carotid arteries were examined using a Duplex method. All the Duplex examinations were carried out with the patient in a semi-supine position in a dental chair. Use was made of the an Acuson XP 10 computed sonography system (Acuson, Mountain View, California, U.S.A.), together with a 7 MHz B-mode real-time linear scanner in which a 5 MHz pulsed and color-coded Doppler was employed. The pulsed Doppler was used to identify the common carotid artery (CCA), the internal carotid artery (ICA), and the external carotid artery (ECA), from the characteristic Doppler signals of each. The vessels were visualised in several sagittal and transverse planes, the presence or absence of plaques being noted. The color-coded Doppler was also used to locate areas in the ICA of high flow velocity, the are of maximum flow velocity being sought and the flow velocity there being measured by means the pulsed Doppler. The angle between the flow direction and the Doppler signal was checked carefully, always being kept below 65°. The degree of stenosis in the ICA was determined from the peak systolic velocity according to the equation: $y = 0.54 \times e^{0,021.x}$ where y = the peak systolic velocity in the ICA in m/s, and x = the degree of stenosis expressed as the percentage of reduc-

tion in diameter (diameter reduction in percent = [**b-a**] x100, where **a** is the smallest diameter in the stenotic zone and **b** is the diameter of the normal CCA proximal to the stenosis). A Doppler shift of 1 kHz corresponds to a flow velocity of 0.31 m/s. A stenosis of less than 30% does not lead to an increase in the flow velocity. The degree of stenosis was considered to be less than 30% when no plaques were present, when the vessels were not severely diseased as judged from the B-mode picture, and when the peak systolic velocity was within normal limits (below 1 m/s). Whenever the ICA was patent, but the peak systolic velocity was 4.4 m/s or more, the degree of stenosis was estimated to be 99%.

Carotid artery disease was defined as a maximum frequency shift (MFS) >3.1 kHz (corresponding to a stenosis of more than 30% of the cross-sectional diameter of the internal carotid artery lumen) or either unilateral or bilateral occlusion of the carotid artery [111-113]. The degree of carotid stenosis was considered significant and was used for purposes of analysis when it was 30% or more. Carotid artery stenosis (CAS) was defined as a stenosis more than 30% or occurrence of plague, and the peak systolic velocity was within normal limits (below 1m/s).

A high level of diagnostic accuracy of the continuous-wave Doppler, when compared to angiography of carotid arteries, was found (with 94.6% sensitivity and 90.7% specificity) to detect stenosis above or equal to 30% [114]. A previous study of the B-mode ultrasonography showed a high degree of reproducibility of lumen diameter of the common carotid artery with reported inter-observer difference 0.4 ± 0.3 mm, r=0.90 and intra-observer difference 0.2 ± 0.2 mm, r=0.92 [115].

Resting systemic blood pressure

The medical examination included blood pressure measurement. Systolic and diastolic blood pressure in the upper arm was measured sphygmomanometrically after 15 min of rest, with the subject in a sitting position, making use of a calibrated mercury manometer and a standard rubber cuff (12x35 cm). Hypertension was defined as a systolic and diastolic brachial blood pressure of more than 160/90 or use of medication for hypertension [116].

Ankle-brachial blood pressure recording

The recording system for ankle-brachial blood pressure recording consisted of pulse sensors (mercury-in-Silastic strain gauges) placed on the big toes and the thumbs, two Wheatstone bridges with an amplifier for recording changes in the resistance of the strain gauges, and blood pressure cuffs (18x60 cm for measuring the ankle systolic blood pressure and 12x35 cm for measuring the upper arm systolic blood pressure), a pressure transducer (Siemens-Elema EMT 746 with amplifier EMT 311) for recording cuff pressures, and a six-channel ink-jet recorder (Siemens-Elema; Mingograph). Duplicate recordings were made with the subject in a supine position, the arithmetic average being obtained used. An ankle-brachial pressure index (ABPI)

was calculated for each leg, by dividing the ankle systolic pressure by the highest upper arm systolic pressure value [117].

Peripheral arterial disease (PAD) was defined as an ABI<0.90 in one or both legs. Subjects with an ABI>0.90 in both legs were considered to be free from PAD [118].

Measures of cognitive functions

The psychological investigation was performed on each of the two occasions involved, at the age of 68 and of 81 years, by one and the same clinical psychologist it's lasting for about ninty minutes each time. The examination included the five tests of cognitive capacity listed below, as well as the Mini Mental State Examination (MMSE) at the follow-up, and a standardised interview concerning the individual's quality of life both times [119].

Synonyms (Srb1)

Synonyms is a test on general verbal ability. The subject is presented a list of 30 words, each followed by five words, one of which should be chosen as being the correct synonym for the first word, the maximum score being 30 [96]. The performance level on this test is assumed to be relatively stable throughout life.

Block Design (Srb3)

The Block Design is a Swedish test of visuospatial and constructional ability. It is very similar to the Block Design test, which is part of The Wechsler Adult Intelligence Scale (WAIS). A printed design is shown to the individual, whereupon he or she is asked to assemble wooden blocks in order to produce a pattern identical with a printed design. Each design has time limits and bonuses are also given for fast performances, the maximum score being 42[95]. The test is sensitive to age and to brain injury of any kind of [97].

Paired Associates

This Swedish test is a test of immediate verbal memory. A list of 3x10 pairs of words is read to the individual, who at the same time can read them him-/herself. The list of words is then removed and the individual is shown a list of the stimulus words (in changed order) and asked when presented a given response word to respond with present the correct associated word. The maximum score is 30 [95]. This test is regarded as especially sensitive to left-sided brain lesions and also to depressive syndromes [120].

Digit Symbol Substitution Test

The Digit Symbol SubstitutionTest is a speed-performance test measuring several cognitive abilities, such as psychomotor speed, visual-motor coordination, concentration, and cognitive flexibility. The subject is asked to copy symbols that are paired with digits according to a coding key, which remains visible throughout the test. Speed is an

important component of the test, the subject being asked to copy as many symbols as possible during a 90-second period. The maximum score is 90. This test is considered in the Wechsler Adult Intelligence Scale to be one of the most sensitive tests of all to brain dysfunction, largely because at it measuring many non-specific abilities [95].

Benton Visual Retention Test

This is a frequently used test of immediate visual and spatial memory. A drawing of a geometrical design is shown for a period of ten seconds to the individual, who is then asked to immediately copy the design from memory. The test includes ten designs of increasing complexity. There are two parallel scoring systems for the test but here only the system in which all correctly copied designs are scored was used. The maximum score is 10. This test is sensitive to ageing as well as to brain dysfunction [121].

Zung Self-Rating Depression Scale

The Zung Self-Rating Depression Scale is a commonly used scale for the detection of depressive symptoms [122]. It consists of 20 items, a four-point grading system ranging from ”little or none of the time” to “most of or all of the time”. The 20 scores are converted to an index in which 1.00 represents the most severe level of depression. Although the scale is usually self-administered, in the present study it was administered by a psychologist.

Cerebral blood flow measurement

Cerebral blood flow measurement was performed with single photon emission computed tomography (SPECT). The radiopharmaceutical used for estimating perfusion was ^{99m} Tc-labelled hexamethylpropylene amine oxime (^{99m}Tc HMPAO; Ceretec®, Amersham Int.) [123, 124]. Masurement was carried out one hour after intravenous injection of 800MBq of this substance. The subject was placed in a prone position on the gamma camera couch; the person’s head being fixed by use of a vacuum cushion. Examination was performed under resting conditions, with normal lighting and a normal level of background noise. A triple-headed gamma camera system (Siemens Multispect 3, Siemens, USA) with fan-beam low-energy collimators was employed. Acquisition was at 360º (rotation, 64 views, 20s/view, in a 128x 128 matrix, and a zoom factor of 1.23). The energy window was a 15% window centered over the 140 keV peak. Image processing included the reconstruction of 10 transaxial slices each, 1 cm thick, from 1 cm below the orbitomeatal line and upwards.The regions of interest (ROI:s) were delineated in each slice by use of a standardized set of free-dimensional regions. The ROI:s were positioned and scaled to the recorded SPECT slices, based on the external borders of each slice. They included the cerebellum, the occipital area, and in each cortical hemisphere the frontal orbital, lateral and medial regions, the superior and the inferior parietal region, and the medial and lateral temporal regions. The value obtained for each ROI was quantified as a percentage of the mean cerebellar concentration of the kit.

Ambulatory Blood Pressure Monitoring

Monitoring the ambulatory blood pressure requires use of a mercury sphygmomanometer. In the present case a Micro AM Recorder, Model KI5600 (Kontron Instruments) was employed [125], the accuracy of which was confirmed by simultaneous measurements with a standard mercury sphygmomanometer, ambulatory readings being accepted if they were within 10 mmHg of the standard method. Programming of the intervals was conducted as follows: three reading at 20 min intervals during the day (from 06.20 am to 09.40 pm) and at 60 min intervals at night (from 10.00 pm to 06.00 am). The Research Department of Malmö University Hospital fitted the monitors to the subjects. Regarding physical activity, only advice that was necessary for obtaining accurate readings was given. Because of the need of monitoring the subject for 24h, the data had to be collected in the subject's private environment. There were no restrictions on physical activity other than what was necessary to obtain accurate readings. Subjects were excluded because of insufficient recording quality if the daytime recordings showed deficits either for >3 consecutive hours or >6 hours altogether, or if the nighttime recordings showed deficits for >2 consecutive hours or for >3 hours altogether. A mean value for DBP and SBP at night and during the day, respectively, was calculated and was divided into tertiles.

The nocturnal blood pressure fall was calculated relatively to daytime blood pressure using the formula: (daytime BP-night time BP) x100/daytime BP. The subjects were divided into three groups on the basis of noctural systolic and diastolic fall (in %) as follows: the highest tertile subgroup defined as diastolic extreme-dippers (DBP fall>14%) or systolic extreme-dippers (SBP fall>10,5%), the median and lowest tertile subgroups being combined into a single group.

Statistical analyses

SPSS 6.1 was used for all the analyses.

In **study I** use was made of three non-parametric tests- Kruska-Wallis test, Chi-square test and Mann-Whitney U-test- for studying cardiovascular risk factors pertaining to carotid artery stenosis and analysing differences between the groups. A linear regression model was used to adjust for covariates.

In **study II** the total group was divided into tertiles through the dividing up of both DBP and SBP at baseline, the Kruska-Wallis test being used to test differences between tertiles in terms of the cognitive-test results. Changes in DBP and SBP were obtained by subtracting pressure levels at follow-up from levels at baseline, the differences being divided then into tertiles. Spearman rank correlation coefficients were calculated to test for trends in blood pressure levels, partial correlation being employed to adjust for hypertensive treatment. Significance levels were calculated at $p<0.05$. Multiple regression analyses were used to determine the remaining effect of the independent variables DBP and SBP, respectively, categorised in terms of tertiles,

and of HT on the cognitive functions in question, located as the dependent variables following adjustments. The first model included education, marital status, smoking, alcohol intake, hyperlipidemia, and physical activity at age 68 years as categorical variables, the second model including carotid artery stenosis, ischaemic heart disease and ABPI, (yes/no), as intermediate factors. The definitions were those given above. All the variables included in the two models, except for ischaemisc heart disease, showed a significant univariate correlation with the dependent variables.

In **study III** a mean value of DBP at night was calculated and was likewise divided into tertiles. The lowest tertile was compared with the others, differences in the mean value of rCBF being tested using the Mann-Whitney U-test. Spearman rank correlation coefficients were used to study the rCBF in different regions, as well as mean DBP and SBP at night.

In **study IV** the CBF values were dealt with in terms of median and range. Relations between CBF and percentage of fall in noctural blood pressure were studied using Spearman correlation test coefficients. Chi-square tests were used to analyse relations between the categorial CBF and ABPM variables. The analyses of differences were studied by means of the Mann-Whitney U-test.

Results

The main findings in paper I

The aim of **study I** was to investigate the prevalence and distribution of various levels of stenosis of the carotid artery at 81 years of age, the progression of stenosis with advancing age and its possible association with such known cardiovascular risk factors as hypertension, lipids, smoking, alcohol consumption and diabetes.

The original cohort, consisting entirety of men, born in even months in the year 1914 and residing in Malmö, Sweden had previously been examined at the age 68 years and were re-examined here at the age 81 years. These men underwent at the age of 68 years an ultrasonographic examination of their carotid arteries, conducting using a continuous-wave Doppler. When the men were 81 years of age, their carotid arteries were examined again using a Duplex method. Of the 185 men of age who were 81 years old at that time, there were 148 of them who had had normal carotid artery blood flow at 68 years of age and 37 of them who had had CAS then. At the re-examination when they were 81 years old, 12 (8%) of the 148 men involved still had normal carotid artery blood flow, whereas there were 136 of them who had developed CAS, see Table 1; thus 93% of the total study cohort had CAS at 81 years of age. There were 105 (77%) of the 136 men who had developed bilateral CAS and 31 (23%) who had developed unilateral CAS. The 20 cases of incident stroke/TIA were distributed as follows: six cases of stroke (16%) occurring already at the age of 68 among the 37 men with CAS, eleven cases of stroke (11%) occurring first by the age of 81 among the men with bilateral CAS, 3 cases of stroke (10%) by the age of 81 among the men with unilateral CAS, there being no cases of stroke by the age of 81 among in men without CAS.

Table 1. *Incidence of carotid artery stenosis (CAS) in right and left vessel in 148 men initially without CAS at the age of 68, and re-examined at the age of 81.*

	Age 81 years					
	Degree of CAS (%)					
	No CAS	**0-29%**	**30-49%**	**50-69%**	**70-100%**	**Total**
CAS of right artery	12	16	116	3	1	148
CAS of left artery	12	15	115	6	-	148

At 81 years of age, 4.4% of the men showed no significant stenosis (<30%) of the right carotid vessel, 77% showed a moderate CAS of al (30 to 49%) and 18.6% showed a dense or a high degree of stenosis of al (>50%). The corresponding proportions of CAS in the left vessel were 7.7%, 74.3% and 18.0%, respectively. The proportion of CAS at 68 years of age was higher among the men who had later died prior to the follow-up (29%) as compared with the participants at the re-examination (20%) and the non-participants (17%), p<0.01.

The rate of progression during the period up to the 13-year follow-up among the 37 men who already had CAS in either one or both vessels at the age of 68 years, showed the degree of stenosis in the right carotid artery to increased from less than 30% to a moderate level (30- 49%) of CAS in 16 of 17 men, 8 of the 14 men developing the same degree of CAS on the left side. Of the 13 men with moderate (30-49%) CAS on the right side, only one developed a dense (50 -69%) stenosis. Few of the men developed a high degree of stenosis (> 70%), only 2.8% of them of the right carotid artery and 8.5% of them of the left carotid artery.

Table 2. *A 13-year follow-up of 148 men without carotid artery stenosis (CAS) at 68 years of age. Degree of CAS at 81 years of age and relationship to cardiovascular risk factors at 68 years. Corresponding data are given for deceased men with and without CAS at 68 years of age. (BMI= body mass index).*

Variable at 68 years	**81 years of age**			**Deceased between 1983-96**	
	No CAS at 81 yrs	**Unilateral CAS at 81 yrs**	**Bilateral CAS at 81 yrs**	**No CAS at 68 yrs**	**CAS at 68 yrs**
Number of subjects	12	31	105	144	61
Hypertension, yes (%)	50.0	35.5	64.8	70.6	77.0
Diabetes mellitus, yes (%)	8.3	3.2	2.9	10.4	8.3
Smoking habits (%)					
non-smoker	41.7	25.8	23.8	15.4	4.9
former smoker	41.7	45.2	42.9	44.8	50.8
current smoker	16.7	29.0	32.4	39.9	44.3
Hyperlipidaemia					
cholesterol >6.5 mmol/l and triglycerides >2.3 mmol/l	33.3	32.3	34.3	33.3	41.7
Obesity BMI >28	16.7	16.1	17.1	22.7	20.0
Alcohol consumption					
no intake	50.0	29.0	24.8	24.5	26.7
1-19g/ day	8.3	3.2	5.7	9.1	10.0
20-39g/ day	8.3	12.9	9.5	6.3	10.0
> 40g/ day	33.3	54.8	59.0	60.1	53.3
Physical activity					
low	0.0	0.0	1.0	10.6	11.7
moderate	75.0	71.0	77.1	74.6	83.3
high	25.0	29.0	21.9	14.8	5.0

Cardiovascular risk factors for the development of stenosis were studied in the 136 out of the 148 men without a previous CAS at age 68 who had developed CAS by the time of the follow-up. The proportion having hypertension at the age of 68 was less in men who showed unilateral CAS at the follow-up (n=31) than in those with bilateral CAS (35.5 % and 64.8%, $p<0.013$); see Table 2. Hypertension was also more frequent in the men with bilateral CAS at the follow-up (n=105) than in these with no CAS or with unilateral CAS (n=43), 64,8% and 39,5% respectively, $p<0.005$. No significant differences were found for the other cardiovascular risk factors investigated in the surviving men with and without CAS at 81 years of age. More high consumers of alcohol were noted among men who developed CAS (n=136) than among the others men, although this difference was not statistically significant ($p=0.06$). Hypertension at the age of 68 remained an independent risk factor for CAS in a regression model when the men were divided into the groups of no CAS, unilateral and bilateral CAS, and after adjustment for smoking habits, obesity, hyperlipidemia, alcohol consumption, social class and education. Hypertension was also more common among the deceased who had CAS at 68 years of age than among the survivors who had CAS at 81 years of age, 84% vs 54%, $p<0.001$.

The distribution of cardiovascular diseases and sociodemographic variables in the men who were healthy at the age 68 years but who developed CAS at 81 years was also studied. Peripheral arterial disease, defined as ABI less than 0.90 in one or both legs, was more prevalent in the men who developed bilateral CAS (n=105), occurring in 8.6% of them, than in the others, none of whom developed it ($p<0.05$).

The main findings in paper II

In this study, the relationship between both systolic and diastolic blood pressure and the diagnosis of hypertension as well as cognitive functioning was examined in a general population of 185 healthy men 81 years of age.

HT was noted for 93 of the men (50.3%), the remaining 92 men being normotensive at follow-up. Hypertension (HT) was defined as a systolic and a diastolic brachial blood pressure ≥160 mmHg and ≥90, respectively, or the taking of medication for hypertension. Seventy-nine of the 185 men (42,7%) had hypertension (HT) both at 68 and at 81 years of age, 14 of the others (7.6%) first having developed HT by 81 years of age, the 34 additional men (18.4%) remaining normotensive at follow-up. The cognitive functioning (verbal, speed performance and visuospatial test results) at the age of 81 years, assessed in 160 of the men, did not differ between groups with respect to present or current diagnosis of HT.

The DBP results at baseline were divided into tertiles. Seventy-five (40%) of the 185 men had a DBP ≥95 mmHg at 68 years. At 81 years, the lowest mean scores on the Paired Associates Test was noted in the men who had had the highest DBP scores at 68 years of age, see Table 3. Spatial and verbal performance on the Benton Visual

Table 3. Mean cognitive levels at 68 and 81 years of age by tertiles of diastolic blood pressure recorded at 68 years. Spearman correlation coefficients (r), are given and p for trend. DBP, diastolic blood pressure; SBP, systolic blood pressure; MMSE, Mini Mental State Examination.

	DBP at 68 years of age					
	<90 mmHg n=56	**≥90-<95 mmHg n=54**	**≥95 mmHg n=75**	**p- value**	**r**	**p for trend**
SBP at 68 years	137±15.8	149±14.1	166±18.7	0.000	*0.52*	0.000
DBP at 68 years	81±5.1	90±0.0	101±6.0	0.000	-	-
SBP at 81 years	141±14.6	143±15.2	146±14.9	0.128	*0.11*	0.141
DBP at 81 years	80±5.4	83±5.7	84±6.8	0.003	-	-
Antihypertensive treatment (%)	8.9	7.4	33.3	0.000	*0.17*	0.000
Cognitive function at 81 years:						
Synonyms (n=160)	21.1±5.3	19.2±5.3	18.4±6.1	0.441	*-0.23*	0.008
Block Design (n=170)	15.5±6.4	13.8±6.0	13.5±5.2	0.411	*-0.11*	0.213
Paired Associates (n=168)	15.5±6.5	16.6±5.5	13.0±5.8	0.004	*-0.18*	0.033
Digit Symbol Substitution (n=154)	30.6±9.5	27.8±10.3	26.1±9.6	0.059	*-0.15*	0.091
Benton Visual Retention (n=141)	4.8±1.6	4.4±1.6	4.1±1.6	0.178	*-0.19*	0.029
MMSE (n=184)	28.0±3.6	27.5±3.3	27.3±4.1	0.089	*-0.07*	0.359
Cognitive function at 68 years:						
Synonyms (n=181)	22.3±6.0	21.9±5.3	20.4±6.0	0.128	*-0.16*	0.056
Block Design (n=184)	21.7±6.6	22.1±5.7	21.3±5.4	0.501	*-0.11*	0.188
Paired Associates (n=180)	19.80±5.4	19.4±4.4	17.8±5.3	0.086	*-0.26*	0.003
Digit Symbol Substitution (n=183)	39.4±10.9	38.0±10.8	36.2±11.1	0.180	*-0.15*	0.091
Benton Visual Retention (n=184)	6.2±1.5	5.9±1.5	5.9±1.5	0.488	*-0.17*	0.051

Table 4. Change of diastolic blood pressure from 68 to 81 years of age divided in tertiles in relation to cognitive function. Spearman correlation coefficients (r), are given and p for trend. DBP, diastolic blood pressure; SBP, systolic blood pressure; MMSE, Mini Mental State Examination.

	Change of DBP from 68 to 81 years of age					
	Decreased DBP≥15mmHg n=62	**Decreased DBP<15mmHg n=77**	**Increased DBP≥0mmHg n=46**	**p- value**	**r**	**p for trend**
SBP at 68 years (mmHg)	164±21.0	151±16.7	137±14.7	0.000	*-0.50*	0.000
DBP at 68 years (mmHg)	100±7.8	90±5.7	83±7.4	0.000	*-0.70*	0.000
SBP at 81 years (mmHg)	142±15.3	143±13.9	146±16.1	0.000	*0.12*	0.110
DBP at 81 years (mmHg)	80±6.3	82±5.5	86±5.7	0.000	*0.37*	0.000
Antihypertensive treatment (%)	29%	16%	13%	0.062	*-0.16*	0.027
Cognitive function at 81 years:						
Synonyms (n=160)	18.9±5.9	18.5±5.7	21.7±4.9	0.01	*0.16*	0.038
Block Design (n=170)	13.1±5.8	14.5±5.0	15.1±7.1	0.29	*0.11*	0.143
Paired Associates (n=168)	13.6±6.3	14.6±5.4	17.0±6.6	0.01	*0.21*	0.006
Digit Symbol Substituition (n=154)	25.2±9.7	28.8±9.7	30.1±10.1	0.07	*0.19*	0.021
Benton Visual Retention (n=141)	4.3±1.7	4.2±1.5	4.8±1.7	0.33	*0.09*	0.281
MMSE (n=184)	27.0±4.6	27.8±2.4	28.0±4.1	0.02	*0.19*	0.009
Cognitive function at 68 years:						
Synonyms (n=181)	20.4±6.1	21.4±5.7	22.9±5.7	0.06	*0.17*	0.021
Block Design (n=184)	21.1±5.6	21.6±5.6	22.5±6.5	0.25	*0.12*	0.102
Paired Associates (n=180)	18.3±5.4	18.4±4.4	20.5±5.6	0.04	*0.15*	0.043
Digit Symbol Substitution (n=183)	35.1±10.7	38.6±10.8	39.7±11.7	0.05	*0.18*	0.017
Benton Visual Retention (n=184)	5.8±1.6	6.1±1.3	6.0±1.7	0.65	*0.04*	0.569

Retention Test and results on the Paired Associates Test both correlated negatively with the DBP results divided into tertiles. Similar relations between DBP and cognition as assessed at 68 years of age were noted for verbal functioning but not for spatial or speed performance. After adjustment for antihypertensive treatment, the DBP results at 68 years of age divided into tertiles was found to be associated with spatial functioning, in terms of Block Design ($p=0.04$, $r= - 0.15$) and with speed performance, in terms of Digit Symbol Substitution ($p=0.02$, $r= -0.19$) at 81 years of age.

A decrease in DBP in terms of tertiles from 68 to 81 years of age was found to be associated with a lower levels of cognitive functioning on Synonyms, Paired Associates, Digit Symbol Substitution and the MMSE at 81 years of age. The mean DBP level at 68 years was 100 mmHg in the group in which DBP was reduced by ≥15 mmHg, these men also showing significantly lower cognitive functioning than the others already at 68 years of age, on the Synonyms, Paired Associates and Digit Symbol Substitution tests, see Table 4.

SBP ≥160 mmHg was noted in sixty-nine out of the 185 men (37%) at 68 years of age. The cognitive levels found at 81 years of age was not found to differ between the groups with respect to their SBP levels at 68 years of age. Only the Benton Visual Retention Test at follow-up was negatively correlated with the earlier SBP level found at 68 years of age, divided into tertiles. This association with results of the Benton Visual Retention Test was not noted at 68 years of age. No assiociation was found between changes in SBP or in cognitive functioning from 68 to 81 years of age although the mean increase in SBP in the highest tertile was 11 mmHg, whereas the DBP in this group was unchanged.

A multiple regression model was used to examine the influence of possible confounders, such as lifestyle factors, education and arteriosclerotic manifestations on the associations that were noted between the hypertension diagnosis, DBP, SBP and cognitive functioning. The first model included education, marital status, social class, smoking, alcohol intake, hyperlipidemia, and physical activity at the age of 68 years as confounding factors. The association between DBP, divided into tertiles, and the spatial Block Design Test results ($p=0.026$) remained following these adjustments, whereas the univariate associations with Digit Symbol ($p=0.06$) and Paired Associates ($p=0.14$) obtained previous were not significant here. The Block Design Test results were also negatively associated with SBP, see Table 5. A decrease in DBP from 68 to 81 years, controlled for the same confounders, was found to be associated with a lower functioning in speed performance (Digit Symbol), spatial functioning assessed by the Block Design Test and verbal functioning tested by Paired Associates ($beta=0.16$; $p=0.04$) at follow-up, see Table 5. The intermediate effect of arteriosclerotic manifestations on the noted associations between blood pressure and cognitive functions was tested in a second multiple regression model. The negative relations of DBP and SBP to spatial functioning (Block Design) remained, as well as the associations between changes in DBP at follow-up and spatial functioning, speed performance (Digit Symbol) and Paired Associates results ($beta=0.18$; $p=0.03$) after

Table 5. Cognitive functions at age 81 years by blood pressure levels at the age of 68 years and change of blood pressure between 68 to 81 years. Diastolic (DBP) and systolic (SBP) blood pressure by tertiles and differences of DBP and SBP by tertiles and hypertension (HT) are adjusted for confounders[1] and possible intermediates[2] in two multiple regression models. Standardised beta coefficients are given.

		First model[1]				Second model[2]			
Cognitive test[3]	**Predictor**	**β**	**95% CI for B**		**p-value**	**β**	**95% CI for B**		**p-value**
Block Design	DBP	-0.176	-2.35	-0.15	0.026	-0.173	-2.34	-0.13	0.029
(n=168)	SBP	-0.155	-2.45	-0.08	0.042	-0.160	-2.45	-0.08	0.037
	HT	-0.151	-3.53	0.13	0.052	-0.143	-3.53	0.13	0.069
	Change of DBP	0.158	0.01	2.41	0.046	0.156	0.01	2.41	0.049
	Change of SBP	0.076	-0.57	1.67	0.314	0.073	-0.57	1.67	0.334
Benton Visual	DBP	-0.155	-0.67	0.05	0.087	-0.146	-0.65	0.06	0.189
Retention	SBP	-0.186	-0.77	-0.04	0.031	-0.184	-0.77	-0.04	0.107
(n=140)	HT	-0.152	-1.06	0.07	0.088	-0.117	-3.53	0.13	0.189
	Change of DBP	0.214	-0.17	0.60	0.269	0.111	-0.14	0.62	0.211
	Change of SBP	0.117	-0.10	0.59	0.168	0.103	-0.14	0.57	0.228
Digit Symbol	DBP	-0.160	-3.97	0.08	0.059	-0.137	-3.64	0.35	0.106
Substitution	SBP	-0.107	-3.59	0.71	0.188	-0.125	-3.76	0.44	0.120
(n=152)	HT	-0.105	-5.33	1.17	0.209	-0.097	-5.10	1.30	0.242
	Change of DBP	0.176	0.16	4.46	0.036	0.172	0.11	4.32	0.039
	Change of SBP	0.095	-0.77	3.13	0.235	0.102	-0.68	3.20	0.202

[1]The multiple regression model included education, merital status, social class, smoking habits, alcohol intake, hyperlipidemia, and physical activity.

[2]The second model included confounders in the first model and occurrence at baseline of carotid artery stenosis, ischemic heart disease and ABPI <0.90.

[3]Synonyms and MMSE were not associated to DBP, SBP or HT in the model and these data are not shown. Paired Associates was only associated to changed DBP.

adjustments were made for ABPI, ischaemic heart disease, carotid artery stenosis and the same confounders as included in the first model.

Separate analysis of the Δ values for cognitive functioning between 68 and 81 years of age as the dependent variables, on the one hand, and DBP, SBP and HT, on the other, in the regression model revealed a significant association between Δ Block Design and DBP, adjusted for the same confounders and intermediates as above, beta=0.18 (CI 0.12; 2.04; p=0.027). Similar results were found when antihypertensive treatment was adjusted for (beta=0.19, p=0.025). Depressive mood as assessed by the Zung self-rating depression scale did not show any significant differences between the three blood pressure groups.

The main findings in paper III

The present cohort study demonstrates an association between blood pressure (BP) levels and rCBF, especially at night.

A group of 185 men were examined both at the age of 81 and at follow-up, the subjects being contacted and asked to participate in a cerebral blood flow (rCBF) examination and in 24-hour ambulatory blood pressure monitoring (ABPM), 108 of the men taking part in both. Eleven men were excluded due to insufficient recording quality, 97 men being included in the final statistical analysis.

Mean DBP and SBP during the day were 76±10 mmHg and 131±12 mmHg, respectively, the mean DBP and SBP during the night being 68±11 mmHg and 121±13 mmHg, respectively. The mean level of DBP at night in the lowest tertile (DBP<61 mmHg) was 56.9±3.2 mmHg and for the lowest tertile of SBP (SBP< 115 mmHg) at night was 59.2±5.8 mmHg DBP, see Table 6.

for the temporal right (p=0.012) and the left medial (p=0.039) regions. Similar findings were noted for DBP and SBP during the day. The mean value of DBP during the day was correlated with rCBF in the temporal right medial region (p=0.025), see Table 7.

After the analyses were stratified for DBP during the day, subjects with high DBP (>70 mmHg) during the day showed a stronger association between rCBF in the right temporal medial region and mean DBP at night (r=0.323, p=0.009) than subjects with a low DBP (<70 mmHg) during the day, see Figure 2.

Of the 32 subjects having a low DBP at night (<61 mmHg), there were 11 (34%) who had a DBP during the day >70mmHg. Thus, simply measuring the blood pressure during the day was unable to identify a third of the subjects who showed low DBP at night.

Table 6. Mean blood pressure levels at night at 81 years of age for diastolic blood pressure (DBP) and systolic blood pressure (SBP), divided into tertiles. The findings are based on 24-hour ambulatory blood pressure monitoring. Standard deviations are given in parentheses.

	DBP tertiles at night			SBP tertiles at night		
Range	**low**	**middle**	**high**	**low**	**middle**	**high**
	<61 mmHg	**61-70 mmHg**	**>70 mmHg**	**<115 mmHg**	**115-125 mmHg**	**>125 mmHg**
n	*32*	*33*	*32*	*32*	*31*	*34*
Mean DBP night	56.9 (3.2)	65.8 (2.9)	79.9 (7.9)	59.2 (5.8)	67.5 (6.8)	75.4 (11.4)
Mean DBP day	66.8 (6.5)	74.4 (5.8)	85.4 (8.6)	69.4 (8.5)	74.7 (7.2)	82.0 (10.9)
Mean SBP night	111.1 (10.0)	120.5 (9.8)	130.9 (9.9)	106.7 (5.43)	120.8 (3.4)	134.2 (7.3)
Mean SBP day	123.0 (9.9)	130.0 (11.2)	138.6 (10.5)	120.0 (7.9)	129.4 (6.9)	141.6 (9.9)

Table 7. Spearman rank correlation coefficients (rs) between cerebral blood flow in different regions (CBF), on the one hand, and mean diastolic blood pressure (DBP) and mean systolic blood pressure (SBP), respectively, on the other, at night and during the day.

	DBP				SBP			
	DBP night		DBP day		SBP night		SBP day	
CBF region	**r_s**	**p-value**	**r_s**	**p-value**	**r_s**	**p-value**	**r_s**	**p-value**
Frontal lobe								
right	-0.211	0.034	-0.114	0.255	-0.114	0.257	-0.057	0.569
left	-0.242	0.015	-0.105	0.298	-0.215	0.031	-0.146	0.146
Temporal lobe								
right medial	0.249	0.012	0.222	0.025	0.193	0.053	0.200	0.045
right lateral	0.088	0.381	0.066	0.511	0.041	0.686	0.086	0.390
left medial	0.206	0.039	0.180	0.072	0.200	0.045	0.227	0.023
left lateral	0.045	0.657	-0.086	0.394	0.008	0.937	-0.011	0.914
Parietal lobe								
right	0.093	0.354	0.022	0.829	0.117	0.243	0.061	0.543
left	-0.032	0.752	-0.104	0.301	-0.028	0.782	-0.072	0.477
Occipital lobe	0.096	0.340	0.052	0.606	0.090	0.371	0.072	0.472

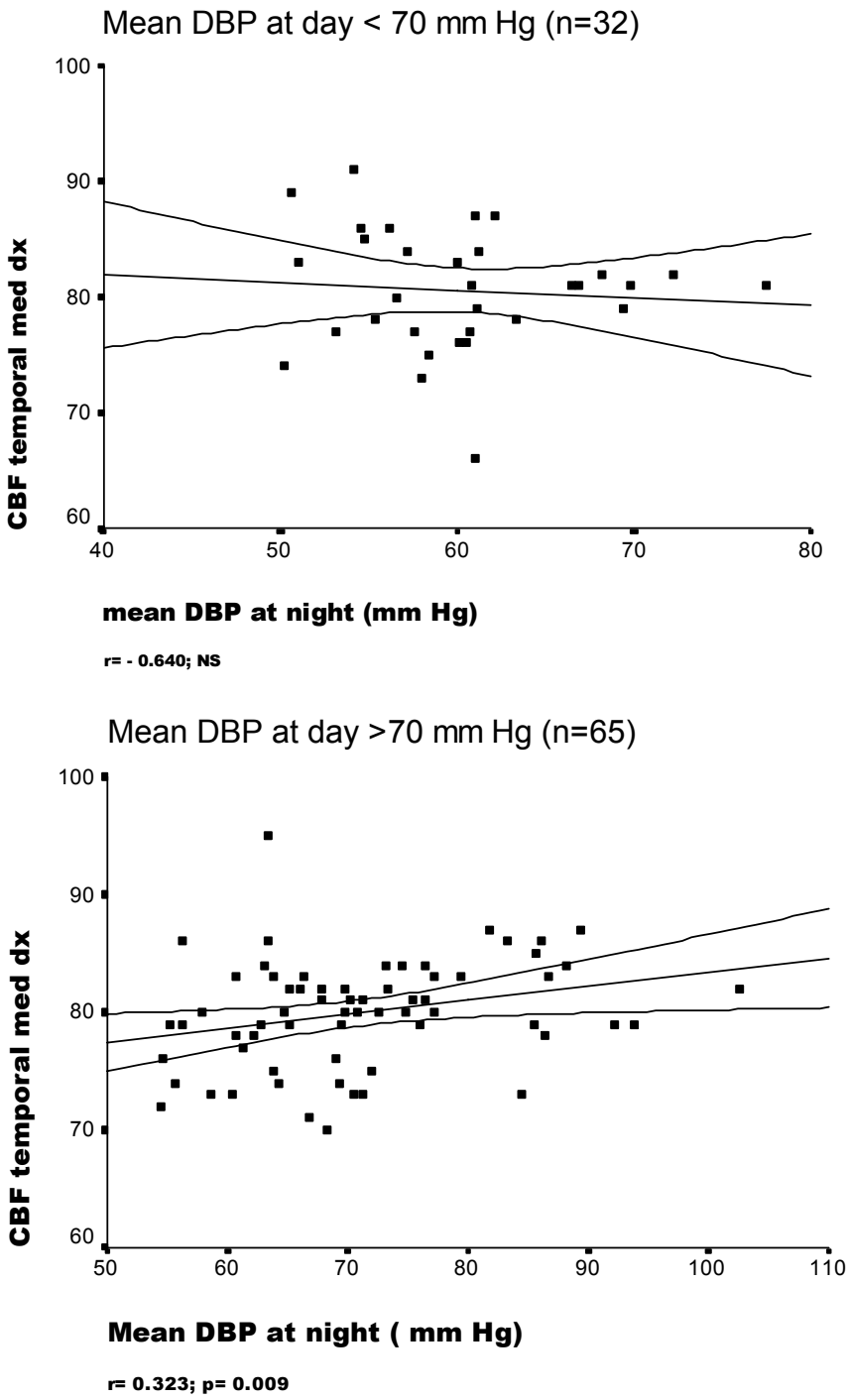

Figure 2. *Positive association between mean DBP at night and cerebral blood flow in the temporal medial right region in subjects with high DBP during the day (>70 mmHg).*

Mean rCBF levels for the temporal regions were not found to differ when the 21 subjects with a low DBP at night (<61 mmHg) and a low DBP at day (<70 mmHg) were compared with the corresponding 11 subjects who had a high DBP during the day (>70 mmHg), although the former group had a numerically higher rCBF. The levels of rCBF among the 65 subjects with a high DBP during the day (>70 mmHg) were significantly lower in the right and left temporal medial regions in those with a low DBP at night (DBP<61 mmHg; n= 11) than in the others (DBP>61 mmHg; n= 54). No significant difference between the right and left temporal medial regions in terms of rCBF was noted in relation to DBP at night in the subgroup with low DBP during the day.

A analysis of the correlation between rCBF in different regions and the mean SBP both during the day and night, given in tertiles, showed there to be a significant negative correlation between them in the left frontal region regarding SBP at night. A positive correlation between them was noted in the left medial temporal region regarding SBP during the day.

The main findings of paper IV

In this study, relations in the elderly population between nocturnal blood pressure, including both SBP and DBP, were measured especially the fall in nocturnal blood pressure fall and changes in cerebral blood flow (CBF). Of the 185 men who were examined at the age of 81, ninety-seven of them who had undergone both CBF measurement and ambulatory BP monitoring were included in the study. In this group of men, SBP was found to decrease at night in 85 of them and to increase at night in the other 12. Similar results were noted for DBP, which decreased at night in 84 of the subjects and increased at night in the remaining 13. A negative correlation was noted between the relative fall in DBP at night and CBF in the temporal medial, temporal lateral, and parietal inferior regions of both hemispheres, see Figure 3.

The relative fall in SBP at night was not found to be correlated in any way with regional CBF. During the 14 years prior to the last follow-up, the office SBP was found to have increased in 31 (32%) of the subjects.

The difference between the office SBP during the 14 years prior to the last follow-up showed there to be higher proportion of subjects with increasing office SBP in the age period of 68-82 years among the nocturnal extreme DBP-dippers than among the subjects with decreasing longitudinal office SBP ($p=0.056$). A significant correlation was noted between a continued nocturnal DBP fall and the differences in office SBP between the ages of 68 and 82 years ($r=0.199$; $p=0.05$). Analysis of the correlation between CBF and nocturnal fall in DBP was repeated by use of partial correlations, controlling for the difference in office SBP between the ages of 68 and 82 years. The correlations were found here to no longer be significant, except for one region, the temporal lateral lobe of the left hemisphere. In the 31 subjects showing an increase in office SBP during the 14-year period, no significant difference in the prevalence of hypertension was found between the extreme-dippers and the rest of population.

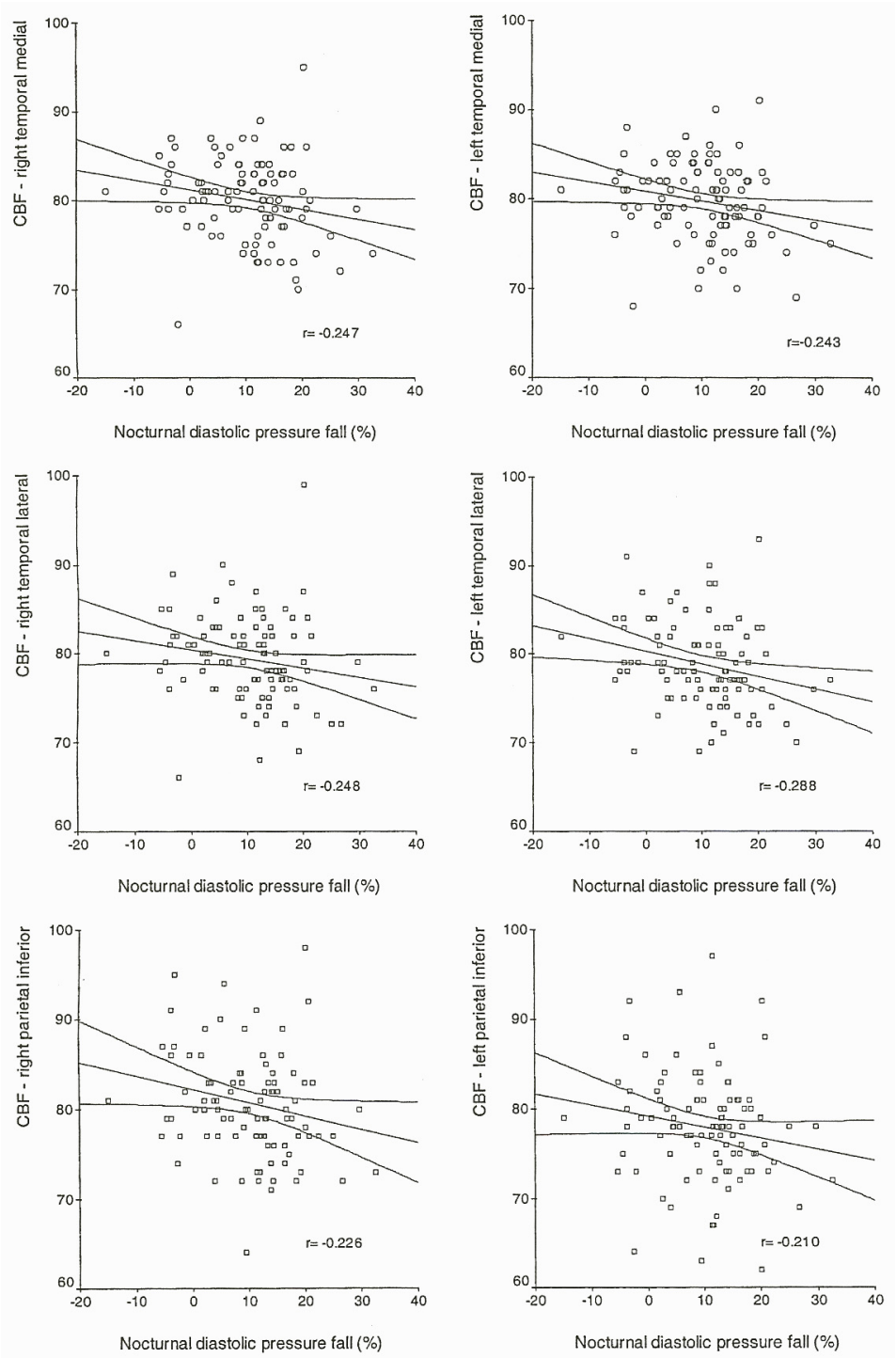

Figure 3. *Distribution of the individual CBF values in relation to nocturnal fall in DBP.*

Discussion

The present studies extend and confirm previous findings of an association being found in the elderly between blood pressure levels, on the one hand, and arteriosclerotic vessel diseases, cerebrovascular diseases, cognition and cerebral circulation. It is hoped that the findings of the present studies can contribute to a better understanding of the complex relationship between blood pressure levels and risk of cognitive decline in the healthy elderly population. Hypertension was shown to be a major risk factor for the development of CAS. It was also shown that the development of CAS increases with age and that by 81 years of age nearly everyone in the group had developed CAS (93%).

Support was also obtained for the hypothesis that high BP is associated with poor cognitive performance, in terms of spatial function in particular. High blood pressure at the baseline examination, especially DBP and the decrease in it, was found to be inversely related to speed performance and to spatial functioning on psychometric tests taken 13 years later. Nocturnal blood pressure levels also influenced cerebral blood circulation and were correlated with rCBF. Analysis of the correlations between rCBF in the different regions and the mean DBP at night showed significant correlations of this sort for right temporal and left medial regions. Abnormalities in these brain structures, which are related to vascular diseases and cardiovascular risk factors, can be seen as a clinical syndrome of intellectual decline produced by ischemic and hypoxic brain lesions. Negative correlations were also obtained between the relative fall in DBP at night and CBF in the medial temporal, lateral temporal and inferior parietal regions of both hemispheres but not between CBF in these or any other regions and the relative fall in SBP at night. The difference in office SBP values between the beginning and of the 14-year period prior to the last follow-up showed there to be a higher proportion of subjects with increasing office SBP during the age period of 68-82 years among the nocturnal extreme DBP-dippers than among the subjects with a decreasing longitudinal office SBP.

Population

The dissertation is based on four studies in which use was made of data from the population study "Men born in 1914". In a population study a high level of participation is important, since a low rate of participation can invalidate the results, due to the selection bias that the lack of data on the non-participants can cause. Although "Men born in 1914" is fairly small numerically as compared with many other population studies, it is a very rigorous study using basically the same methodology throughout to a large extent. Five hundred men participated in the examination at the age of 68 and 185 of them were re-examined at 81 years of age. Thus, 37% of the original cohort were participants in both **study I** and **study II**. There were 97 of the 185 original subjects who, reaching the age of 82, underwent cerebral blood flow (rCBF) examination and ambulatory blood pressure monitoring (ABPM). Thus,

19.4% of the original cohort were participants in **study III** and in **study IV**. Subjects were not excluded through use of any other selection principle. No confounding of age was present since all participants were born the same year and they were also from the same urban area. However, the restriction to male subjects in the present studies could limit generalisation of the results to elderly female subjects, even if the men participating are representative of the men of their age in the community. Selective mortality in the population studied cannot be excluded, however. A selective mortality between 1982 and 1995 could affect the results, since it is probable that subjects in whom atherosclerosis had progressed farthest did not reach the follow-up in the years 1995-96. This could result in a possible underestimation of the risk due to blood pressure effects, for example. In the cohort (n=500) at 68 years of age, 24% had CAS (n=118). As expected, more men who died between 1982 and 1996 had initially had CAS (29%) than was the case for the men who were re-examined (20%). However, similar proportions of men who had CAS were noted in the participants (20%) and in the non-participants (17%). Furthermore, the incidence of stroke between 1982 and 1995 was higher among the non-participants than among the participants, 21.3% and 10.8%, respectively. The fact of only one subject being diagnosed as having dementia suggests there to be a selection towards cognitively more intact persons, perhaps more willing to participate or capable of participating in the study, which means that cognitive performance in the study was defined relative to a group probably healthier than normal for their age. The study results thus seem valid for an elderly population of men with no diagnosis of dementia.

One of the major reasons for the growing interest in blood pressure changes and atherosclerosis as risk factors in relation to cognitive decline is that they represent condition that can be treated, its thus being possible in this way to reduce forms of cognitive decline that have dementia as an end point. Blood pressure, measured at the age of 54 in our cohort was significantly higher in the men who died of cardiovascular disease during the 13 years until follow-up than among those who survived ($p<0.001$). The overall prevalence of hypertension, defined as SBP≥160 mmHg and DBP≥90 mmHg, is estimated to be nearly 50% in persons aged 70 years and older [55]. A similar prevalence of hypertension could be noted in our cohort at the age of 81.

Discussion of methods

Ultrasonographic methods

In **study I**, the examination included ultrasonographic measurment of the carotid arteries and the assessment of cardiovascular risk factors, performed on 185 men. Ultrasonographic examination of the carotid arteries was conducted by use of the continuous-wave doppler method at 68 years of age and of the duplex method at 81 years of age. The maximum frequency for the Doppler shift (MFS) is closely related to the extent of stenosis [5]. MFS from the proximal part of the internal carotid artery increased with increasing degrees of stenosis. On the average, an MFS of 3,1 KHz corresponds to a 30% reduction in vessel diameter of and one of 6,1 KHz

roughly to a reduction in diameter of 60%. If no doppler signals could be obtained in the proximal and distal parts of the internal carotid artery, the vessel was diagnosed as being totally occluded. When the subjects were 81 years of age, the carotid arteries were examined using a Duplex method. The color-coded Doppler was used to localise areas of high flow velocity in the ICA, the maximum flow velocity then being sought and being measured carefully using a pulsed Doppler. A Doppler shift of 1 kHz corresponds to a flow velocity of 0.31 m/s. The degree of stenosis was considered to be less than 30% if no plaques were present and the peak systolic velocity was within normal limits (below 1 m/s). Whenever the ICA was patent but the peak systolic velocity was 4.4 m/s or more, the degree of stenosis was estimated to be 99 %. The ultrasonographic technique has limitations in assessing mild stenosis due to the fact that stenosis of less than 30% does not lead to an increase in flow velocity. Carotid artery disease was defined as a maximum frequency shift (MFS) >3.1 kHz (corresponding to a stenosis of more than 30% of the cross-sectional diameter of the internal carotid artery lumen), or occlusion of the carotid artery either unilaterally or bilaterally. Previous studies have shown that spectral analysis increases the usefulness of continuous-wave doppler method in the diagnosis of carotid artery disease [114, 126]. A high diagnostic accuracy of the continuous-wave Doppler, when compared to angiography of the carotid arteries, was found [with 94.6% sensitivity and 90.7% specificity] to detect stenosis of 30% or more [124]. A previous study of the B-mode ultrasonography showed there to be a high degree of reproducibility of the lumen diameter of the common carotid artery with a reported inter-observer difference of 0.4 ± 0.3 mm, r=0.90 and an intra-observer difference of 0.2 ± 0.2 mm, r=0.92 [115].

A few of the men also had a less pronounced stenosis at re-examination, which could indicate the regression of symptoms, although it is more likely to represent misclassification, due to the high level of reproducibility of the method. However, since a high reproducibility and validity of the method have been reported previously, the changes noted probably represent progression of the disease.

Hypertension and measures of office BP

In **study I** office BP levels at baseline were used to examine the association between stenosis of the carotid artery and BP. Office BP at baseline was measured by a sphygmomanometer with the individual in a sitting position after 15 minutes of rest. Blood pressure measurement at follow-up was performed while the subject was in the prone position. Three pressures were recorded, each to the nearest 5 mmHg, the mean of these assessments being calculated.

Hypertension was defined as a systolic and diastolic brachial blood pressure >160 mmHg and >90, respectively, or the subject's receiving medication for hypertension. **Study I** confirms elevated blood pressure being the principal risk factor for the development of CAS. The role of high blood pressure, not only as a risk factor but also as an etiologic factor in the development of stroke, is supported by results from large clinical trials [33-36] in which a reduced incidence of stroke was demonstrated

after antihypertensive treatment was given. Hypertension being a potential risk factor for the development of CAS and other ischemic cerebral diseases was supported by the findings of the present study. However, the area is still one involving controversy, due to a considerable extent to the relative lack of studies focusing on an elderly population. Even if no controlled clinical trials have clearly shown there to be benefits in treating elderly persons with an SBP of 140-159 mmHg, the recommendations of the European Society of Hypertension together with European Society of Cardiology (ESH-ESC) [127], the Joint National Committee on Prevention, Detection Evaluation, and Treatment of High Blood Pressure (JNC) [128] and WHO [129] are that one lower the SBP at least to a level below 140 mmHg, based to a considerable extent on extrapolations from studies of younger persons. Both ESH-ESC and JNC appear to be positive to this regime in their reports, also in regard to elderly persons over 80 years of age, whereas WHO states that no conclusions can be drawn as yet concerning the antihypertensive treatment of the very elderly. In the elderly, there have been shown to be benefits of antihypertensive drug treatment if repeated measurements of SBP are 160 mmHg or higher [130].

In **study II** the association of blood pressure levels, changes in blood pressure and cognitive performance levels at 68 and 81 years of age, respectively, in a male cohort was analysed. The separate measurement of office DBP and SBP at baseline was used to examine the association between cognitive functioning and both systolic (SBP) and diastolic (DBP) blood pressure, as well as changes in office DBP and SBP, viewed separate from one another, their both being divided into tertiles [(DBP: lowest tertile-<90 mmHg, middle tertile-≥90-<95 mmHg, highest tertile- ≥95 mmHg); (SBP: lowest tertile-<140 mmHg, middle tertile-≥140-<160 mmHg, highest tertile-≥160 mmHg)], and differences between the tertiles in terms of the cognitive tests that were given being examined. Changes in DBP and SBP were obtained by subtracting these two pressure levels at follow-up from the levels at baseline, the differences being divided into tertiles ((DBP decreased ≥15 mmHg or <15 mmHg and DBP increased ≥0 mmHg); (SBP decreased ≥15 mmHg or <15 mmHg and SBP increased ≥0 mmHg)).

During the last few decades the association between blood pressure and intellectual functioning has been the focus of many research projects [54-59]. Although considerable numbers of large population studies have been conducted, the assumed association is not fully understood. Recent studies [54-56], both prospective and cross-sectional, give added support to the link between blood pressure level and cognition. Mixed results concerning the relationship between blood pressure level and cognitive functioning have been presented in previous studies [54-56, 58, 59]. The Framingham Study [56] found elevated blood pressure in midlife to be associated with lower cognitive functioning in late life evidence was obtained for a negative association between blood pressure levels, few if any of the participants studied taking antihypertensive medication, and cognitive performance measured 12-14 years later. Higher blood pressure (both systolic and diastolic, analysed separately) was predictive of lower performance in terms of a composite neuropsychological performance

score and measures of attention and memory [131]. Similar results were obtained in the Honolulu-Asia Aging Study [59]. Another study showed diastolic hypertension, but not systolic hypertension, to be related to lower performance on a free- recall memory test in 2433 elderly subjects in the Iowa Aging Study [132]. These findings were confirmed in a Swedish population-based cohort study of 70-year old men followed from 50 to 70 years, when cognitive functions were assessed by the Mini-Mental State Examination and the Trail-Making Test. High diastolic blood pressure at baseline predicted later impairment of cognitive performance, also after men with a previous stroke were excluded [58]. **Study II** confirms elevated blood pressure being a risk factor for impaired cognitive functioning. Support was obtained for the hypothesis that hypertension, particularly high DBP in late midlife, is associated with a decline in spatial cognitive performance in elderly men.

Elevated blood pressure is an important risk factor for stroke and vascular dementia [133]. Few studies have addressed the problem of decreasing blood pressure in the elderly and the fact that cognitive functioning also shows age-related changes that could influence interpretation of the possible effects of high blood pressure on cognition. A 15-year follow-up study showed that individuals who developed dementia between the ages of 79 and 85 years had higher systolic and diastolic pressures at the ages of 70 and 75 than patients who did not develop dementia [63]. The authors suggested that previously elevated blood pressure levels can increase the risk of dementia, and also of Alzheimer`s disease. These findings were confirmed in **study II**, in which it was shown that changes in DBP (a decrease) between 68 and 81 years of age, handled as tertiles, were associated with lower levels of cognitive functioning at 81 years. The mean DBP level at 68 years of age was 100 mmHg in the group with a reduction in DBP of ≥15 mmHg, these men also having significantly lower levels of cognitive functioning at 81 years of age, as measured in terms of verbal, speed performance and visuospatial tests than others subjects did. The question of whether high blood pressure, as a risk factor for cerebrovascular disease, causes cognitive decline, or the observed decline in blood pressure in the elderly is the effect of cerebrovascular damage, remains to be answered. The mechanisms underlying hypertension-related cognitive changes are complex and are not fully understood and few studies have included patients receiving antihypertensive treatment. The increased risk of cognitive decline in subjects with low SBP found in cross-sectional studies can be attributed to a reduction in blood pressure in patients with concomitant diseases that also influence cognition. One longitudinal study, the EPESE study, reported a non-linear association between DBP and SBP and memory functions [134]. The group there in which SBP was lower than 130 mmHg performed less well than participants above this level did. The present hypertension guidelines focus on cardiovascular disease risk factors, the blood pressure levels between 130 and 139 mm Hg and between 85 and 89 mmHg being considered to be high-normal levels [116]. A recent follow-up study in connection with the Framingham Heart Study concluded that high-normal blood pressure is associated with an increased risk of cardiovascular disease [50]. Thus far, little is known about the possible effects on cognitive functioning of lowering blood pressure to these levels in the elderly. In fact, participants whose SBP

had increased showed no difference in verbal or spatial performance compared with others. This also highlights the limitations of cross-sectional studies of the elderly. Subjects with low blood pressure may have previously been exposed to HT. The potential positive effect of blood pressure levels being lower than 140 mmHg is still under debate [50].

We found no association between changes in SBP between 68 and 81 years of age and cognitive functioning, although the mean increase in SBP in the highest tertile was 11 mmHg, whereas the DBP in this group was unchanged.

Measures of cognitive functioning

In **study II** a neuropsychological test battery consisting of five psychometric tests was administered to all subjects in order to evaluate their cognitive performance. The psychological investigation at baseline, carried out by a clinical psychologist was repeated in an almost identical manner by a second clinical psychologist at follow-up. Scoring and administration were performed strictly according to the test manuals. To measure verbal performance, two tests were employed: Synonyms, a standard Swedish verbal intelligence test, and Paired Associates (Cronholm-Molander Paired Associates Test), a verbal short-term memory test. To assess perceptual and logical processing or reviewing ability and flexibility, the Digit Symbol Substitution Test was employed. To assess spatial ability, two tests were used: the Block Design Test and Benton Visual Retention Test, the latter test also assessing spatial short-term memory. It appears that the group being studied here in terms of its cognitive performance consisted of persons healthier than average for their age, especially since only one man was diagnosed as having dementia. The majority of subjects were examined neuropsychologically by use of the five psychological tests referred to earlier (Synonyms n=160, Block Design n=170, Paired Associates n=168, Digit Symbol n=154 and Benton Visual Retention test n=141). At the age 81 years, some of the men did not complete all of these tests. However, the men whose tests were incomplete and had only been assessed at the age of 68 years, their numbers ranging from 14 men for the Block Design to 43 men for the Benton Visual Retention test, had similar results at baseline to the men with complete test results. The mean scores were as follows: Synonyms 18.4±6.1, Block Design 20.7±8.0, Paired Associates 18.5±5.4, Digit Symbol 38.3±11.2 and Benton Visual Retention Test 5.9±1.5. Synonyms and DBP reached a significance level of $p=0.028$. The pattern of associations between blood pressure (DBP and SBP) and cognitive functioning at baseline was basically the same for subjects who responded at follow-up and those who did not. No significant differences between the non-responders and responders were found concerning the relationship between the various tests, on the one hand, and the tertiles of the DBP and SBP measures obtained for the subjects at 68 years of age, on the other. However, few longitudinal studies have described changes in cognition in the very old or other detrimental effects of hypertension. To our knowledge, there has been no such study as yet focusing on subjects of this high age level. The lack of any association being found between cognitive function and BP in previous studies could

be explained by the fact that the age-related decline differs from one type of cognitive function to another and that some tests are probably more sensitive in assessing abilities in terms of concentration, attention and spatial functions than MMSE, for example, is a test concerned with several cognitive functions and often used to assess cognitive impairment. This was also supported by findings in the present study of no association being found between MMSE scores and either DBP or SBP. The mixed results found in the literature could also be explained by the fact that most studies have used only a few neuropsychological tests or tests involving composite variables. The use of only composite variables to assess cognitive functioning does not seem justified. In the present study the neuropsychological examination involved five tests of cognitive ability referred to. Knowledge of the reference values for normal cognitive levels for the elderly is lacking what has been studied has been simply the associations found between BP levels and cognitive functioning. The results of cognitive functioning could be influenced by depressive mood. No differences in mean level of the Zung self-rating depression scale were noted between subjects divided in the three blood pressure groups and depressive feelings seems unlikely as a confounder for the findings in this study.

Ambulatory blood pressure monitoring

Ambulatory blood pressure (BP) was monitored during a 24-hour period, using non-invasive equipment (Micro AM-5600, Kontron Instruments), microphonic criteria together with an oscillometric backup system being employed. The accuracy of the recorders was confirmed by simultaneous measurements by a standard mercury sphygmomanometer, ambulatory readings being accepted if they were within 10 mmHg of results the standard method gave. Programming of the intervals involved was performed in terms of three readings at 20 min intervals being obtained during a day (from 06.20 am to 09.40 pm) and at 60 min intervals at night (from 10.00 pm to 06.00 am). The criteria for the exclusion of measurements of low quality were defined. Subjects with missing data pertaining to more than 6h altogether during the day or to more than 3h at night, or showing more than 3h of consecutive deficit during the day or 2h or more at night were excluded. To our knowledge, in previous studies MABP during the day and at night were calculated, but participants with missing data were not excluded. The limits for missing data selected were arbitrary, but if a greater number of participants had been included, the mean calculated levels during the night might have been falsely high. Incomplete registration of BP at night could reduce assessments of circadian variability. In the present study 32% of the participants had complete registration of their data, 34% and 26%, respectively, having missing data in terms of 1 or 2 entries being missing. A mean value for DBP and SBP, separately during the day and at night were calculated and were divided into tertiles: [(DBP-tertiles at night: low<60 mmHg, medium 61-70 mmHg, high >70 mmHg); (SBP-tertiles at night:low<115 mmHg, medium 115-125 mmHg, high>125 mmHg)]; [(DBP-tertiles during the day: low<70 mmHg and high>70 mmHg); (SBP-tertiles during the day: low<115 mmHg and high>115 mmHg)] and were used to study of rCBF in different regions. Mean SBP and DBP at night did not differ between

these groups, the variability being expressed as SD (range of mean DBP at night 66-71mmHg for groups without missing data or for 1, 2 and 3 missing entries).

In **study III** we analysed the association between blood pressure levels, both systolic and diastolic, day and night, assessed by 24-hour ambulatory blood pressure monitoring (ABPM) and as regional cerebral blood flow (rCBF) disturbances in the cohort of men born in 1914. Blood pressure normally displays a circadian rhythm involving a slight nocturnal drop. Both ”non-dipping” and ”extreme dipping” have been shown to be associated with cerebrovascular disease [68, 69]. There are few studies dealing with this in a very elderly population, however, although there are reports of circadian variation diminishing in upper age groups [135, 136]. No previous studies have examined variations in blood pressure at night as a possible risk factor in the cerebral circulation of the elderly. Mean levels of BP at night were calculated, their relation to rCBF being examined. It is possible that transient drops to low BP levels might not be registered, since BP was only measured hourly at night, so that the circadian variability could well be underestimated [69, 136]. However, low mean BP levels at night could be a more important indicator of cerebral ischemia than episodic changes in blood pressure levels are. Such findings indicate that continuous blood pressure recording is of special value in studying the relation between cerebral functioning and variations in blood pressure. Previous studies of patients with hypertension have reported that non-dipping during the night represents a risk for cerebrovascular disease[76]. Consistent variations in blood pressure occur as a result of diurnal rhythms, with the highest pressures being in the morning and the lowest during sleep [67]. Blood pressure in some patients with essential hypertension is known to remain elevated throughout the night. These patients, whose 24 h blood pressure does not follow the normal diurnal pattern but remains high at night, are likely to suffer more cerebrovascular complications as well as other atherosclerotic cardiovascular diseases than those whose blood pressure falls at night. An explanation for the present finding could be that the MABP for these men were at normal levels. However, the prevalence of cardiovascular disease was more prominent in the group that showed low DBP levels at night, which might indicate disturbed autoregulation.

Definition of extreme-dippers

Blood pressure (BP) normally displays a circadian rhythm involving a slight nocturnal drop. It is still unknown how the nocturnal BP fall influences cerebral circulation. In **study IV** the relation between the fall in nocturnal blood pressure and changes in cerebral blood flow in elderly men was examined. For the individual data, relative day-to-night changes in BP were calculated using the mean daytime and nighttime BP values: (daytime mean BP – nighttime mean BP) x 100/daytime BP. The 97 men were divided on the basis of their fall in nocturnal systolic and diastolic BP (%) into three groups through the highest tertile subgroup being defined as diastolic extreme- dippers (DBP fall>14%), or systolic extreme-dippers (SBP fall>10,5 %), whereas the median and the lowest tertiles subgroups were dealt with as a single group. The relative fall in DBP at night, but not the relative fall in SBP at night, was

found to be negatively correlated with CBF in the medial temporal, the lateral temporal and the inferior parietal regions of both hemispheres. Studies of brain-damaged patients with selective memory impairment have convincingly demonstrated that some forms of long-term memory ability depend on the integrity of the medial temporal lobe. The medial temporal lobe has widespread and reciprocal connection with the associative neocortex as well as with subcortical structures. Abnormalities in these brain structures are related to vascular diseases and cardiovascular risk factors and can be seen as constituting a clinical syndrome of intellectual decline produced by ischemic and hypoxic brain lesions. The difference between the offices SBP during 14 years prior to the last follow-up showed there to be a higher proportion of subjects with increasing office SBP during the age span of 68-82 years among the nocturnal extreme DBP-dippers than among subjects with a decreasing longitudinal office SBP. It is known that blood pressure tends to decrease over time in the very elderly. In the cohort of men 81 years of age, there were 2/3 of them who showed a decrease in SBP and 1/3 of them who showed an increase in SBP during the period of observation. In the 31 subjects showing an increase in office SBP over the 14 years, there were no differences in the prevalence of hypertension between extreme-dippers and the remainder of the group. It can be suggested that the minority showing an increase in SBP have a pathological autoregulation of blood pressure, even if they fail to develop hypertension. A low level of CBF can reflect degenerative or ischemic changes and local dysfunction. These findings indicate a possible relationship between silent brain changes and an extreme fall in blood pressure at night. However, low BP levels at night could be a more important indicator of cerebral ischemia than episodic changes in blood pressure levels are. Such findings indicate that continuous blood pressure recording is of special value in studying the relation between cerebral functioning and blood pressure variations with the aim of identitying individuals at risk for possible cerebral ischaemic lesions.

Cerebral blood flow

Cerebral blood flow measurement was performed with single photon emission computed tomography (SPECT) one hour after the intravenous injection of 800MBq of ^{99m} Tc-hexamethylpropyleneamine oxime (^{99m}Tc HMPAO; Ceretec®, Amersham Int.) [123, 124]. Subjects were placed in a prone position on the gamma camera couch, their head being fixed by use of vacuum cushion. Examination was performed under resting conditions, lighting and background noise being of normal level. Image processing included reconstruction of 10 transaxial slices, 1 cm thick, from 1 cm below the orbitomeatal line and upward. Regions of interest (ROI:s) were delineated in each slice by the use of a standardized set of three-dimensional regions. The ROI:s were positioned and scaled to the recorded SPECT slices based on the external borders of each slice. They included the cerebellum, the occipital area, and in each hemisphere the cortex of the frontal orbital, lateral and medial regions, the superior and inferior parietal regions, and the medial and lateral temporal regions. The value measured in each ROI was expressed as a percentage of the mean cerebellar count density. The ”large” regions were used for analysis. The large lobular ROI were cre-

ated by merging several small ROIs into a single lobular ROI in order to reduce the amount of multiple statistical testing needed. In **study III** the ROIs used for cerebral blood flow estimation were as follows: [frontal lobe (right and left), temporal lobes (right medial and right lateral and left medial and left lateral), parietal lobe (right and left) and occipital lobe]; in **study IV** the ROIs used for cerebral blood flow estimation were the followings: [frontal lobe (right and left), temporal lobes (right medial and right lateral and left medial and left lateral), parietal lobes (right inferior and superior and left superior and inferior) and occipital lobe]. The rCBF method has been found to be sensitive in detecting cerebral changes related to stroke and dementia [62, 80, 81]. The single photon emission computed tomography (SPECT) method has also shown high correlations with cerebral blood flow ratio as estimated by means of positron emission tomography (PET) [86, 98]. Cerebral atrophy with an increase in the size of the ventricular system could introduce false, low estimates of rCBF in regions close to the ventricles. The regions employed were chosen in accordance with previous studies using both rCBF and CT [92, 99]. Another limitation of the method is that of artefacts due to movements of the head during examination. In the present studies examinations were performed under resting conditions using a vacuum cushion to minimize errors of this sort. If small multiple ROIs are used for statistical analyses, the risk of false positive results increases due to the multiple comparison phenomenons. Thus, the number of ROIs has been limited in order to reduce Type 1 errors, large lobular ROIs being employed in the studies. An unwanted consequence of using large ROIs is that minor vascular changes go undetected. As regards ^{99m}Tc HMPAO, the cerebellum is frequently used as a stable reference region, since it is unaffected by most cerebrovascular and degenerative diseases [123].

Discussion of the results

Normal aging is associated with the degeneration of specific neuronal systems. Brain atrophy, white matter changes and silent infarction, frequently detected in the elderly by computer tomography and magnetic resonance imaging, are correlated with vascular risk factors and with cognitive decline [99]. There is general consensus that hypertension is an important risk factor for the occurrence of cerebrovascular disease. The role of high blood pressure, not only as a risk factor but also as an etiologic factor in the development of stroke, is supported by large clinical trials in which a reduced incidence of stroke after antihypertensive treatment has been given has been demonstrated [33, 34]. However, hypertension is also related to the development of atherosclerosis, ischemic cerebrovascular disease and dementia. The association between hypertension and increased risk of stroke could be mediated both by haemorrhagic stroke and by tromb-embolic stroke through the development of CAS. The result of long-term exposure to vascular risk factors, including hypertension, has been associated with the development of atherosclerotic disease in which small infarctions or alterations in blood flow are assumed to have negative consequences for cerebral circulation [35]. The marker of artherosclerosis in the large arteries is carotid stenosis. Hypertension as a potential risk factor for the development of CAS was supported in the present study, which is among the few to use non-invasive testing to evaluate the

prevalence and progression of carotid arterial disease in an elderly population. To our knowledge, there are a few previous longitudinal studies of the degree of progression of CAS in the elderly.

In **study I** it was shown that in the cohort "Men born in 1914" (n=185), the proportion of men with CAS changed noticeably during the 13 years to follow-up, where at 68 years of age 37 of the men had CAS. Of the 148 men with normal carotid blood flow at 68 years of age, only 12 were lacking in any signs of CAS at the re-examination in 1995-96, whereas 136 of them had developed it by the time of the follow-up, 93% of the surviving study cohort having CAS at 81 years of age. It was noted that 14 of the 136 men (10%) having CAS had experienced an incident stroke or TIA during the period to follow-up and that these occurred only in men who had CAS.

The results show there to be a significantly higher proportion of men with hypertension who developed carotid artery stenosis than those who did not in accordance with previous studies [27, 31, 32].

In the population-based Framingham Heart Study, information concerning a sample of 429 men and 661 women was studied who underwent B-mode ultrasound measurements of the carotid artery. Their mean age was 75 years, and each had attended most of the biennial clinic examinations given over the 34 years prior to the carotid ultrasound study. CAS (25% or more) was present in 189 of the men (44%) and 226 of the women (34%). High systolic blood pressure, high cholesterol levels, and smoking were associated with an increased risk of CAS in this elderly population [32]. The lower prevalence of CAS in the men in that study as compared with our data, 44% versus 93%, could partly be explained by the lower age of that group. In another study, the Russian Population Study, which included 529 subjects, 343 men and 186 women, aged 36-84 years a 9.4% prevalence of dense carotid artery stenosis (more than 50%) was reported in men who were 75 years of age or older [32]. This prevalence was similar to our findings of 7.7% dense CAS in the left side of the total cohort. The prevalence and degree of carotid artery stenosis in that study were significantly correlated with age, hypertension and smoking, but not with diabetes, hyperlipidemia or obesity. In the study by Muluk and co-authors, systolic hypertension also turned out to be one of the major predictors of the progression of CAS [27].

However, this area is still one involving controversy, due to a considerable extent to the relative lack studies focusing on elderly subjects.

Our findings confirm elevated blood pressure being the principal risk factor for the development of CAS. This seems to be true as well for the very old. In the present study it was shown that the development of CAS increases with age and that almost all the subjects developed CAS by 81 years of age (93%). However, the majority of the men developed a moderate stenosis, defined as one of <50%, only few of them developing a high degree of CAS. Only a slight progression was noted among the survivors who had already had CAS at 68 years of age. The risk of developing a high

level of CAS (i.e. a stenosis level>70%) among those surviving to the age of 81 appeared to be low, since less than 9% had it at re-examination. The proportion having CAS at baseline was in accordance with results of a recent longitudinal study of the progression of CAS involving 1004 subjects with a mean age of 65 in which an 18% occurrence of CAS was reported (15 to 49%). This was in accordance with the 16% at baseline in the present study. In that study, 88.5% of the carotid arteries assessed showed progression at follow-up [27].

The present study also dealt the association of cardiovascular risk factors such as hypertension, lipids, smoking, alcohol consumption and diabetes with the progression of CAS with advancing age. A higher proportion of hypertension was noted in men with bilateral CAS than in the other men. The proportion of men with hypertension was less in those with unilateral CAS than in those with a bilateral carotid artery stenosis. No significant differences for other major cardiovascular risk factors were noted (diabetes mellitus, hyperlipidemia, obesity, alcohol consumption and lack of physical activity). The lack of correlation between CAS and these factors might be explained by the low power of the study. The selective mortality of the population studied here cannot be excluded. A selective mortality between 1982 and 1995 could affect the results, since it is probable that the subjects in whom the atherosclerosis was most advanced did not reach follow-up in 1995-96. However, no major differences in these risk factors were noted between the men with and those without CAS, except for the results connected with smoking habits. In the cohort (n=500) at 68 years of age, 24% had CAS (n=118). As expected, more of the men who died during the period to follow-up, or between 1982 and 1996, had CAS initially (29%) than did those who were re-examined (20%). However, the proportions of men with CAS were similar for participants (20%) and non-participants (17%).

Blood pressure as measured at the age of 54 in our cohort was significantly higher among the men who died of cardiovascular disease during the 13 years to follow-up than among those who survived ($p<0.001$). Smoking was also more common at age 54 among those who died before 1982 [5]. Previous analyses revealed no relationship between CAS at age 68 and known cardiovascular risk factors at age 54. At the examination at age 54 it was found that the men with an occlusion also had higher blood pressure and higher lipid values than those not showing signs of carotid artery disease [5]. Furthermore, the incidence of stroke between 1982 and 1995 was higher among the non-participants than the participants, 21.3% and 10.8%, respectively.

Continuous-wave Doppler technique has limitations in assessing mild stenosis due to the fact that stenosis below a 30% level leads to no increase in flow velocity.

The relationship between blood pressure levels and decline in cognition has been discussed previously. Some previous studies have shown hypertension to be a risk factor for the development of cognitive impairment. Several theories seek to explain the association between hypertension and impaired cognitive functioning. One theory assumes that high blood pressure disturbs cerebral perfusion, with altered metabolism

as a consequence [56, 131]. Hypertension might also represent a risk for clinically silent stroke and may also be associated with leukoariosis, which has been shown to be related to poor cognitive functioning [137]. Many studies, both prospective and cross-sectional, support the link between blood pressure and cognition. The most important ones are those based on the reanalysis of the Framingham data originally reported by Farmer et al. [54, 55] and Elias et al. [56]. Evidence was obtained for a negative association between blood pressure levels, at a time when few if any participants were taking antihypertensive medication, and cognitive performance measured 12-14 years later. Higher blood pressure (the systolic and diastolic were analysed separately) was predictive of lower performance in terms of a composite neuropsychological performance score including Benton, Digit Span Backword and Logical Memory [54-56]. The chronicity of hypertension was inversely related to performance on a verbal memory test in the same study [131]. In our study we found support for the hypothesis that high BP is associated with poor cognitive performance, visuospatial tests being related to hypertension and to blood pressure levels, but not to chronicity. Cognitive functioning (verbal, speed performance and visuospatial tests) at the age of 81 years, assessed in 160 men, did not differ between groups with respect to a present or a current diagnosis of HT. This might be explained by the small sample size, but numerically lower scores on all but one of the tests were noted in the group of men who showed hypertension already at baseline.

In a community-based study, high SBP and DBP was a predictor of reduced cognitve functioning, significant differences being found in learning (immediate recall and retention). Cases were defined for persons aged 40-79 years as DBP≥100 mmHg or SBP≥180 mmHg, or drug treatment for hypertension at the time of the interview [138]. A study of 25 elderly patients with mild to moderate hypertension aged 62 to 78 years (hypertension being defined as DBP≥95 mmHg with a SBP≥165 mmHg) and 25 age-matched controls showed impairment on the part of the hypertensives in Digit Symbol, attention and Paired Associates, using tests similar to those employed in the present study [139]. In the Honolulu-Asia Aging Study, elevated midlife systolic, but not diastolic, blood pressure was found to be associated with a higher risk of poor cognitive performance late in life [59]. Another study showed diastolic hypertension, but not systolic hypertension, to be related to lower performance on free-recall memory test in 2433 elderly subjects from the Iowa Aging Study [132]. Similar findings were reported in a Swedish population based cohort study of 70-year old men, followed from 50 to 70 years, when cognitive functions were assessed by use of the Mini-Mental State Examination and the Trail-Making Test. High diastolic blood pressure at baseline predicted later impairment in cognitive performance, also after men with the history of a previous stroke were excluded [58]. This finding was confirmed in the present study, diastolic hypertension being found to be related toa decline in cognitive functioning. Seventy-five out of the 185 (40%) men had a DBP ≥95 mmHg at 68 years of age. At 81 years, the lowest mean score on the Paired Associates Test was that of the men who had had the highest DBP values at 68 years of age. Spatial and verbal performance, assessed by the Benton Visual Retenion and the Paired Associates test were found to be negatively correlated with DBP, divided

up by tertiles. Similar trends between DBP and cognition assessed at 68 years were noted for verbal but not for spatial or speed performance functions. After adjustment for antihypertensive treatment, DBP at 68 years divided into tertiles was found to be associated at 81 years with spatial functioning, Block Design ($p=0.04$, $r= - 0.15$) and speed performance, Digit Symbol Substitution ($p=0.02$, $r= -0.19$), whereas cognitive functioning at 81 years of age did not differ between groups with respect to their SBP levels at 68 years of age. Only spatial functioning at follow-up was negatively correlated with SBP at 68 years, divided into tertiles. Similar finding were obtained already at 68 years of age. The mixed findings obtained in earlier studies could be explained by the fact that in most of these studies have only a few neuropsychological tests or composite tests were employed, often not controlled for possible confounding factors, such as education, gender, alcohol use and smoking habits [56] or that they involved very selected populations. It appears that the pattern of association to blood pressure is not the same for different cognitive functions. One explanation might be that cognitive functions differ in their vulnerability to decline. This is supported by the fact that the age-related decline in speed performance functions is more pronounced than that in verbal functions, for example. Thus, in studying cognitive functions a variety of tests are needed. Swan and co-workers analyzed the effects of SBP on cognition over a period of several decades [60]. They found different risk panoramas associated with high SBP levels over long periods of time on the one other hand, and decreased SBP levels, on the other. They reported impaired verbal functioning in participants with a SBP≥140 mmHg in midlife. The subgroup showing a decrease in SBP during the period to follow-up displayed reduced performance speed instead, as measured by the Trail Making Test, whereas those showing an increase in SBP had lower performance on Paired Associates, a verbal memory test. This finding was not confirmed in the present study, in which no association was found between changes in SBP between 68 and 81 years of age and cognitive functioning. However, the findings for DBP obtained in the present study were similar. Changes in DBP (a decrease) between 68 and 81 years of age, examined by tertiles, was found to be associated with a lower level of cognitive functioning at 81 years than earlier. The mean DBP level at 68 years was 100 mmHg in the group whose DBP was reduced by ≥15 mmHg (the mean change in DBP was 20mmHg), these men also having significantly lower cognitive functioning at 81 years of age as expressed by results on verbal, speed performance and visuospatial tests that the others did. Also, after adjustment for antihypertensive treatment, DBP by tertiles at 68 years was found to be associated with the level of spatial functioning and speed performance at 81 years. This highlights the limitations of cross-sectional studies of the elderly. Subjects with low blood pressure may previously have been exposed to HT. One of the major reasons for the growing interest in blood pressure and atherosclerosis seen as risk factors for cognitive decline is that the conditions in question can be treated effectively, its being possible with treatment to counteract the cognitive decline that has dementia as its point.

The mechanisms underlying hypertension-related cognitive changes are complex and not fully understood. Also few patients receiving antihypertensive treatment have been included in studies in this area. In several studies, elevated blood pressure has

been found to be a risk factor for the development of vascular dementia [48, 140]. One study also showed that individuals who developed dementia between the ages of 79 and 85 years had higher systolic and diastolic pressures at the ages of 70 and 75 than those who did not develop dementia. The authors of that study suggested that earlier elevation of blood pressure could increase the risk of dementia, and also of Alzheimer`s disease [63].

It has been also reported that a decline in SBP with age can be attributed to dementing illness or to cardiac insufficiency, cross-sectional studies having shown that blood pressure is lower in patients with clinically manifest dementia than in healthly controls [62, 65]. An increased risk for cognitive decline in subjects found to have low SBP in cross-sectional studies was attributed to a reduction in blood pressure in patients who had a concomitant diseases that also affected cognition. The EPESE study, a longitudinal one, reported there to be a non-linear association between DBP and SBP, on the one hand, and memory functions, on the other [134]. The group in which SBP lower than 130 mmHg performed less well than participants above this level did. The present hypertension guidelines focus on the risk of cardiovascular disease and on blood pressure levels of between 130 and 139 mm Hg and between 85 and 89 mmHg, respectively, which are considered to be high-normal levels [116]. A recent follow-up study of the Framingham Heart Study concluded that high-normal blood pressure levels are associated with an increased risk for cardiovascular disease [50]. Little is known thus far about the possible effects on cognitive functioning of blood pressure being lowered to these levels in the elderly. One can only speculate on whether hypertension causes end organ damage that reduces blood pressure. The possible effect on cognitive functioning of treatment of hypertension in the form of drug-induced hypotension might also be considered. In the elderly, there have been shown to be benefits of antihypertensive drug treatment if repeated measurements of SBP are at level of 160 mmHg or higher [130], certain support for this approach has also been obtained in controlled clinical trials concerned with cognitive impairment [141, 142].

Normal BP has a diurnal variation, the lowest levels being during night. However, low BP levels at night could also be a more important indicator of cerebral ischemia than episodic changes in blood pressure levels are. Such findings indicate that continuous blood pressure recording is of particular value in studying relations between cerebral functioning and variations in blood pressure Other mechanisms that have been discussed could also contribute to the development of cerebrovascular insufficiency, specifically those in which the cerebral blood flow is inadequate in relation to the metabolic needs of the brain tissue. Several conditions such as heart disorders and hypotension may lead to hypoperfusive lesions in parts of the brain that are more vulnerable than others. Cerebral perfusion directly related to cardiac output and cardiac abnormalities may thus lead to cerebral hypoperfusion. Cardiac infarctions in the aged, as well as heart rhythm disorders and stenosis of the carotid artery have been pointed out as being important risk factors [143].

It is well known that hypertension predisposes persons to different types of both intra- and extracerebral arterial lesions that can cause cerebrovascular damage [144-147].

Few studies have addressed the problem of a decrease in blood pressure in the elderly and the fact that there are also age-related changes in cognitive functioning that can influence the interpretation of possible effects of high blood pressure on cognition. This is especially true of cross-sectional studies. The question of whether high blood pressure, as a risk factor for cerebrovascular disease, causes cognitive decline, or whether instead the observed decline in blood pressure in the elderly is the effect of cerebrovascular damage, remains to be answered. In a cross-sectional study, causal conclusions cannot readily be deduced, only the concurrent presence of low blood pressure and low level of cognitive functioning in such findings. In recent study, Paran and co-workers [148] reported findings of this sort pertaining to home BP in 70-85 year olds without dementia, persons with various systemic diseases being excluded. Subjects with mild hypertension were found to perform better on different cognitive tests. There has been shown to be a correlation between dementia and concurrent low BP [149, 150]. In cases in which there is a cerebral degenerative disease which causes the lowering of BP, the latter seems to be an early marker for it.

Normal ageing is associated with the degeneration of specific neural systems, functional imaging data generally showing there to be impairment of global CBF with increasing age. Finding of this sort suggest that advancing age has a differential effect on cerebral perfusion, affecting certain areas in the frontal, parietal, temporal and occipital lobes located at different levels [98]. Brain atrophy, changes in white matter, and silent infarctions, frequently detected in the elderly by compute tomography and magnetic resonance imaging, are correlated with vascular risk factors and with cognitive decline [99].

There is still no evidence regarding the way in which the presence of vascular diseases affects brain functioning in the non-demented elderly. Thus far, to our knowledge, there are few studies which have investigated the distribution of changes in white matter in elderly persons and possible relationships of these to systemic blood pressure as expressed by rCBF [80, 86]. It is still unknown how diurnal variations in blood pressure levels, calculated from individually defined times of the day and night are correlated with changes in rCBF in the very elderly population. It is well established that regional cerebral blood flow (rCBF) mirrors brain-metabolic activity and provides information concerning the functional level of the cerebral cortex. No previous studies have examined variations in blood pressure within the framework of the 24-hour ABPM, especially that at night, as a risk factor for problems of cerebral circulation in the elderly. In **study III** the association between blood pressure level, both diastolic and systolic, day and night, followed by 24-hour ambulatory blood pressure monitoring (ABPM), and regional cerebral blood flow (rCBF) disturbances expressed as rCBF in a cohort of men born 1914 was investigated. In **study IV** the relationship between fall in blood pressure at night and cerebral blood flow (CBF) changes in the same population generally were examined, where 185 men were studied at baseline and 108 of them were found to fulfill both CBF, which was performed using ^{99m} Tc- HMPAO SPECT and 24-hour ABPM, eleven of the men being excluded due to incomplete ABPM.

Nocturnal blood pressure levels were shown in that study to influence cerebral circulation and to be correlated with rCBF patterns in very elderly men. The mean DBP at night in tertiles was found to be correlated with rCBF in the right temporal ($p=0.012$) and left medial ($p=0.039$) regions. Also, DBP during the day was found to be correlated with rCBF in the right medial temporal region ($p=0.025$). When analyses were stratified for DBP during the day, subjects with high DBP (>70 mmHg) during day showed a stronger association in this respect between the right medial temporal region and mean DBP at night ($r=0.323$, $p=0.009$) than did subjects with a lower daytime DBP. These regions are especially vulnerable to ischemic damage. No association of this sort was noted for subjects with a low DBP during the day (<70 mmHg). An analysis of the correlation between rCBF in different regions and mean SBP during the day and night by tertiles showed there to be a significant negative correlation between rCBF in the left frontal region and SBP at night. A positive correlation was also obtained for the left medial temporal region and SBP during the day. In previous studies the association in the elderly of nocturnal and postprandial hypotension and the presence of lacunae was also observed [81, 98]. A J-shaped curve between blood pressure and stroke morbidity has also been noted [151]. Low blood pressure and orthostatic hypotension is a common finding in demented patients, especially in the late stage, their also showing reduced levels of rCBF [80].

We also found in **study IV** a negative correlation between rCBF and the relative fall in DBP at night. The relative fall in diastolic BP at night was negatively correlated with rCBF in the medial temporal, lateral temporal, and inferior parietal brain areas. The difference between the office SBP at the beginning and the end of 14-year prior to the last follow-up showed there to be a higher proportion of subjects with an increasing office SBP level during the age period of 68-82 years among the nocturnal extreme DBP-dippers than among subjects with a decreasing longitudinal office SBP ($p=0.056$). A significant correlation was obtained between values for the nocturnal fall in DBP and the differences in office SBP between the ages of 68 and 82 years ($r=0.199$; $p=0.05$).

Previous studies of brain-damaged patients with selective memory impairment have convincingly demonstrated that some forms of long-term memory depend on the integrity of the medial temporal lobe [92-94]. The medial temporal lobe system consists of the hippocampal formation, together with the adjacent anatomically related parahippocampal, and entorhinal cortices. The medial temporal lobe has widespread reciprocal connections with the associative neocortex as well as with subcortical structures. Abnormalities in these brain structures are related to vascular diseases and cardiovascular risk factors. They can be seen as representing a clinical syndrome of intellectual decline produced by ischemic and hypoxic brain lesions. The correlation between the fall in DBP and a low temporal and inferior parietal rCBF has not been described previously. Contrary to magnetic resonance studies, CBF expresses not only major morphological changes, which in a population with low incidence of stroke are rare, but also a metabolic and functional decline. In our study, blood pressure related decrease in CBF was observed in the temporal and inferior parietal areas. Studies of non-demented populations have reported hypoperfusion in these areas in Age-associ-

ated Memory Impairment [152], and Mild Cognitive Impairment [153] predicting conversion to dementia. The course of the degeneration that occurs in dementia, from the temporal up to the parietal lobe, has been described earlier [154]. The vulnerability of the temporal lobe to the effects of changes in BP has been reported, not only for subjects with a very high SBP in particular, who have a high risk for dementia, but also for persons using antihypertensive drugs, the risk for dementia being highest in those who have an extremely low DBP (≤65) [155]. A high DBP level has be found to predict hippocampal atrophy five years later in persons untreated for hypertension [156]. Conversely, in persons treated for hypertension, a low DBP has been found to be associated with more severe atrophy. In our study, a fall in nocturnal blood pressure can be an early sign of disturbed vasoregulation in subjects who have had high BP values previously. A mild decrease in CBF in extreme dippers who are non-demented and who have a low incidence of overt stroke can reflect the presence of dysfunctional brain tissue in a border zone between stroke and dementia.

Previous studies of patients with hypertension have reported that non-dipping during the night constitutes a risk for cerebrovascular disease, in contrast to what was found in the present study [76]. Consistent variations in blood pressure occur as a result of diurnal rhythms, the highest pressures being in the morning and the lowest during sleep [67]. The blood pressure in some persons with essential hypertension is known to remain elevated throughout the night. These persons, whose 24 h blood pressure level does not follow the normal diurnal pattern but remains high at night, are likely to suffer more cerebrovascular complications as well as other atherosclerotic cardiovascular diseases than those whose blood pressure falls at night do. An explanation for the present findings could be that the MABP among these men were within normal levels. However, the prevalence of cardiovascular disease was more prominent in the group with low DBP at night, which could be indicative of disturbed autoregulation.

Our results show also there to be a higher proportion of increasing SBP over the 14-year period involved, in the subgroup showing an extreme DBP dip. It is known that blood pressure tends to decreases over time in the very elderly. In the subject population as a whole, 2/3 of the subjects had a decrease in SBP during the observation period. It can be suggested that the minority (1/3) with an increasing SBP have a pathological autoregulation of their blood pressure, even if they are normotensive.

The association found between a low rCBF in vulnerable areas such as in the temporal regions and a low DBP at night was noted among the subjects with a high DBP during the day (>70 mmHg). This indicates the usefulnass of ambulatory monitoring in efforts to identify possible risk groups. A clinical finding here is that the third of the subjects that had a low DBP at night had normal or high DBP levels during the day, subjects who could only be identified by a 24 h ambulatory blood pressure monitoring. A surprising finding was the lack of association between rCBF and DBP at night in subjects with a low DBP at day. One explanation might be that this group has fewer vascular risk factors such as hypertension and less myocardial infarction

and angina pectoris, which could hypothetically affect cerebral autoregulation. The association between low BP, especially at night, and low rCBF could possibly be explained by there being an insufficient cerebral autoregulation, which can lead to an extensive reduction in cerebral perfusion and to subsequent ischemic damage [68]. The autoregulation of rCBF is effective over a wide range of arterial blood pressures, but it has both a lower and an upper pressure limit. Under normal conditions, these limits are a MABP of about 70 and 140 mmHg, respectively [157]. It is possible that this capacity decreases with age [13]. The underlying autoregulation mechanisms are poorly understood, although three possibilities have emerged. As previously mentioned three different mechanisms for regulation of vessel's tone has been suggested: myogenic, neurohumoral and neurogenic theories [15-22]. Neurotransmitter metabolism in the grey matter is extremely sensitive to even short periods of hypoxia. Although this autoregulation adapts to long-term hypertension, the small vessels gradually become affected structurally, the development of atherosclerosis and hyalinosis further reducing their autoregulatory capacity. In addition, in patients with long-term hypertension, the risk of hypotensive white lesions is increased, even at apparently normal blood pressure levels.

In our study the mean level at night for the lowest tertile was 56 mmHg. Although interpretation of the results of the present study is limited to men, there is no reason to believe that autoregulation differs in terms of gender.

Since the association found between rCBF and low BP could indicate an increased risk for nocturnal cerebral ischemia, further longitudinal studies are needed to analyse cognitive functioning and the risk of vascular dementia in connection with low blood pressure at night.

Conclusions

1. The development of CAS increases with age, almost everyone having developed CAS (93%) by 81 years of age according the present results. High blood pressure is the principal risk factor for the development of CAS. A higher proportion of hypertension was noted in the men who developed bilateral CAS, 64.8% (n =105) as compared with the others 39.5% (n=43), $p<0.005$. Less hypertension was noted in the men with unilateral CAS (n=31) than in those with bilateral CAS (n=105), the figures being 35% and 65% respectively, $p< 0.013$. No significant differences for other cardiovascular risk factors were noted. However, the majority of the men developed a moderate stenosis, defined as <50%, and only few of them developed a high degree of CAS. These results do not support the need for a follow-up of CAS from a clinical point of view.

2. High blood pressure at baseline examination, especially high DBP as a decrease in DBP, was associated with a decline in cognitive functioning according to psychometric tests given 13 years later. High DBP at 68 years was inversely related to verbal, spatial, and speed performance at 81 years. Only spatial functioning was related to SBP at 68 years. Changes in DBP (a decrease) from 68 to 81 years was associated with lower cognitive functioning at 81 years on verbal, spatial, and speed performance tests. The mean DBP level at 68 years was 100 mmHg in the group in which DBP was reduced by ≥15 mmHg, these men also having shown significantly lower cognitive functioning on verbal, spatial, and speed performance tests already at 68 years as compared with the others. Both DBP and SBP appeared to be risk factors for cognitive decline in visuospatial functioning, when analyses were controlled for possible confounding factors such as education and lifestyle factors in a multiple regression model. On the other hand, the remaining association between blood pressure and cognition could indicate that a hypothetical prevention of hypertension at late midlife might have an independent impact on cognition in 80-year olds. However, this is still an area of controversy, due to a considerable degree to the relative lack of studies focusing on the elderly population. Even if no controlled clinical trials have shown there to be benefits from treating elderly persons with an SBP at 140-159 mmHg, the recommendations of the European Society of Hypertension together with European Society of Cardiology (ESH-ESC), the Joint National Committee on Prevention, Detection Evaluation, and Treatment of High Blood Pressure (JNC) and WHO are to lower the SBP to below 140 mmHg at least, largely based on extrapolations from studies of younger people. Both ESH-ESC and JNC appear in their reports to view this regime in positive terms, also in relation to elderly persons over 80 years of age, whereas WHO feels that no conclusions can be drawn yet concerning antihypertensive treatment of the very elderly. In elderly, there are shown to be benefits of antihypertensive drug treatment if repeated measurements of SBP indicate it to be 160 mmHg or higher.

3. The nocturnal blood pressure levels influence cerebral circulation and are correlated with the rCBF pattern in very elderly men. A significant association was found between blood pressure (BP) levels and rCBF, especially at night. Analysis of the correlation between rCBF in different regions and mean DBP at night revealed significant correlations for the right temporal and left medial regions. Also the DBP levels during the day were correlated with temporal right medial region. These regions are especially vulnerable to ischemic damage. When the analyses were stratified for DBP during the day, subjects with a high DBP (>70 mmHg) during the day showed stronger associations between right medial temporal region and mean DBP at night than subjects with a lower daytime DBP. Analysis of the correlations between rCBF in the different regions and the mean SBP during the day and at night showed there to be significant negative correlations for the left frontal region with SBP at night. A positive correlation was obtained for the left medial temporal region and SBP during the day. The association between low rCBF in vulnerable areas such as the temporal regions and low DBP at night noted in subjects with a high DBP during the day (>70 mmHg) indicates the usefulness of ambulatory monitoring in identifying possible risk groups. One clinical finding is that a third of the subjects with low DBP at night had normal or high DBP levels during the day and that these persons could only be identified by a 24h ambulatory blood pressure monitoring. A surprising finding was the lack of association between rCBF and DBP at night among subjects with low DBP during the day. One explanation might be that this group has fewer vascular risk factors such as hypertension and less myocardial infarction and angina pectoris that could hypothetically affect cerebral autoregulation. The association noted between rCBF and low BP might indicate an increased risk of cerebral ischemia. Further longitudinal studies are needed to analyse cognitive functioning and the risk for vascular dementia apparently related to low blood pressure at night.

4. The relative fall in diastolic BP at night was negatively correlated with CBF in the medial temporal, lateral temporal, and parietal inferior brain areas. During the prior 14 years, office systolic BP had increased in 31 (32%) of the subjects. This group had a higher frequency of extreme nocturnal diastolic BP dip than subjects with decreasing longitudinal systolic BP. One explanation for this might be that the fall in nocturnal blood pressure can be an early sign of disturbed autoregulation in subjects with previously high BP values. It is known that blood pressure decreases over time in the very elderly. In our population as a whole, 2/3 of the subjects showed a decrease in SBP during the period of observation. This suggests that the minority (1/3) that shows an increase in SBP has some pathology in pressure autoregulation even if they are normotensive. Further longitudinal studies are need to better explain the mechanisms by which an increase in longitudinal blood pressure increase in the very elderly disturbs their vascular autoregulation, and to show whether a dip in nocturnal blood pressure leads to a vascular cognitive decline or to higher frequency of stroke.

Populärvetenskaplig sammanfattning

Flertal studier talar för att såväl vaskulär demens som demens av Alzheimers typ är relaterade till blodtrycksnivå tidigare under livet. En studie har visat att redan blodtrycket vid 50- årsåldern är relaterat till kognitiva (intellektuella) funktioner vid 70-års ålder. En annan studie har visat att hypertoni i 70-årsåldern föregår utveckling av demens i ålder 80-85 år. I gruppen av dementa som var 85 år gamla hade blodtrycket varit högt när de var 70 år men sjunkit till normal nivå vid 85 års ålder. Förekomst av demens ökar kraftigt i högre åldrar och förklarar nedgång i kognitiva funktioner. Kognitiv nedsättning utan demens är vanligt och åldersrelaterad minnesstörning (Mild Cognitive Impairement, MCI) är en av flera klassificeringar.

Kognitiva funktioner är ett samlingsbegrepp för minne och högre tankeprocceser som kan beskrivas med olika neuropsykologiska och neurofysiologiska metoder. Nedgången i dessa funktioner som rör språk, logik, rumsuppfattning och minne ses både vid normalt åldrandet och vid demens, stroke och åldersrelaterad minnesstörning.

Befolkningsstudier har visat att problemlösning och uppfattningsförmåga ofta försämras snabbare än språkliga funktioner mellan 75 till 85 års ålder. Förändringarna i dessa funktioner kan vara uttryck för åderförkalkning (arterioskleros), ett tidigt tecken på vaskulärt betingad sjukdom eller degenerativ sjukdom, t ex Alzheimers demens. Även om uppkomst delvis är klarlagd för vissa sjukdomstillstånd, finns en stor variation av rubbningar i hjärnans funktioner i samband med åldrandet som inte kan förklaras av kända riskfaktorer.

Högt blodtryck är en känd riskfaktor för demens men också för MCI hos äldre. Samband finns beskrivet mellan högt blodtryck och stroke, syrebrist förändringar i hjärnans vita substans och bristande funktion av blod-hjärnbarriären. Förändringar i hjärnan pga syrebrist är ofta konsekvens av arterioskleros och är bland de vanligaste orsaker till stroke. Det är välkänt att hypertoni är en väletablerad riskfaktor för stroke och hjärtkärlsjukdomar på grund av syrebrist.

Flera studier har visat att även lågt blodtryck i systemkretsloppet, hypotoni är relaterad till förekomst av demens och är förenad med ökad förekomst av hjärnskador och dödlighet hos äldre. Sambandet finns beskrivet mellan blodtrycksfall vid uppresning (ortostatism) och hjärnfunktioner. Hos friska och dementa individer sågs en lokal sänkning av blodgenomblödning i pannlober i stående då ortostatiskt test utfördes, mest uttalad hos dem med lågt blodtryck vid uppresning.

Det är välkänt att blodtrycksfall leder till sänkning av hjärnans genomblödning och är en riskfaktor för att utlösa en hjärnskada på grund av syrebrist. Kunskapen är begränsad om hur förändringar av blodtryck under dygnet påverkar hjärnans blodcirkulation. Dygnsvariationer i blodtrycket och nedsatt hjärnfunktion har under senare tid fått ökad uppmärksamhet. Individer utan normalt nattligt blodtrycksfall, så kallade ”non-dippers”, har högre grad av hjärnförändringar än så kallade ”dip-

pers". Non-dippers har också tecken på ortostatisk hypotoni, dvs lågt blodtryck vid uppresning, som kan tyda på bristande autoreglering, självreglering av blodtrycksnivåer. Även så kallade "extrema nattliga dippers" uppvisar ökad förekomst av hjärnskador, mätt med blodflödestekniken, där mekanismen kan också vara bristande autoreglering. Följande frågor är fortfarande obesvarade:

- Vilket inflyttande har blodtrycksförändringar över tid på förekomst av skador i hjärnans genomblödning och nedsatt hjärnfunktion hos äldre, och kan en bristande autoreglering av blodtryck öka hjärnans sårbarhet för episoder av lågt blodtryck?
- Vilken roll spelar utveckling av åderförkalkning (arteriosklerос) för hjärnans autoreglering av blodtryck?

Den avhandling baseras på en prospektiv, longitudinell studie, uppföljningen av en och samma grupp män "1914- års män" i Malmö som har pågått sedan 1968; 185 män, födda jämn månad 1914, har undersökts vid 68 och 81 års ålder med samma metodik, läkarundersökning inklusive blodtryck, ultraljudsundersökning av halsartärer (carotider), arm- ankel index, lipidstatus, sociodemografi, livstilsvanor samt neuropsykologisk undersökning. Vid 81 års ålder har vissa män även undersöktes med regionalt cerebralt blodflöde och 24-timmars blodtrycksmätning.

Neuropsykologisk undersökning omfattade fem kognitiva funktionstester som mätte intellektuell förmåga: Srb1 test-ordförståelse, synonyms test för bedömning av språklig förmåga, Srb3 test - Block Design- snabbhetstest för bedömning av rumsuppfattning, Paired Associates test- ordpartest, Digit Symbol Substitution Test- CWT-prestationstest och Benton Visual Retention Test för bedömning av kognitiv förmåga och minnesfunktion.

Syftet med avhandlingen var att studera hur de överlevande männens cirkulation, kognitiva funktion och minnesfunktion samt förändringar i hjärnans cirkulation har förändrats från 68 års ålder till 81 års ålder samt identifiera eventuella riskfaktorer för dessa förändringar.

Syftet med det första arbetet var att studera insjuknande i och förekomst av förträngning av halspulsåder (a.carotisstenos) och studera betydelsen av hjärtkärlsjukdomarnas riskfaktorer för utveckling av a.carotisstenos samt identifiera riskfaktorer för dessa förändringar i halsblodflöde som hade ägt rum hos män från 68 års ålder till 81 års ålder. Studiens resultat antydde att av samtliga, kända, riskfaktorer för hjärtkärlsjukdom var enbart hypertoni riskfaktor for utveckling av arteria carotisstenos. En högre andel av män med dubbelsidig a.carotis stenos hade högt blodtryck jämfort med övriga män. Sambandet saknades mellan utveckling av a.carotis stenos och förekomst av andra hjärtkärl sjukdomar (kärlkramp, infarkt eller stroke). Hos män som utvecklade dubbelsidig a.carotis stenos noterades förekomst av andra manifestationer av åderförkalkning, fönstertittarsjukdom, i högre utsträckning, än i den andra gruppen som saknade a.carotisstenos. I den här studien har man visat att 93% av 81-åriga män har utvecklat a.carotisstenos och att hypertoni är riskfaktor för utveckling av detta tillstånd.

I studie II studerades om högt blodtryck (HT), det höga systoliska (SBP) och diastoliska (DBP) samt förändringar i blodtryck vid 68 års ålder hade något samband med nedgång i kognitiva funktioner som hade ägt rum mellan 68 och 81 års ålder. Det noterades att inte enbart högt blodtryck utan även blodtrycksnivå, särskilt DBP vid 68 års ålder kan inverka negativt på kognitiv funktion upp i 81 års ålder. Studiens resultat antydde att förhöjda blodtrycksnivåer vid 68 års ålder kunde ha ett samband med större nedgång i kognitiva funktionstester, som mätte rumsuppfattning (visuell-spatial förmåga) och visuell minne.

Målet i den tredje studien var att undersöka sambandet mellan blodtrycksnivåer, SBP och DBP, på natten och på dagen undersökt med 24-timmars blodtrycksregistrering och regionalt hjärnblodflöde (rCBF) hos men vid 81 års ålder. I den studien noterades att det finns klart sambandet mellan blodtrycksnivåer och regionalt hjärnblodflöde, speciellt på natten. Låg DBP på natten visade samband med lägre genomblödning i hjärnområden belägna centralt (rCBF) i tiningsområden. Dessa områden är speciellt sårbara för episoder av lågt blodtryck. Individer med hög DBP på dagen (>70mmHg) visade starkare samband mellan rCBF i höger centrala tinninglob och medelnivå av DBP på natten jämfört med individer som hade lågt DBP på dagen (<70 mmHg). Dessa individer upptäcks således endast genom undersökning med 24-timmars blodtrycksregistrering. Det noterade sambandet mellan rCBF och lågt BP på natten kan antyda att lågt BP på natten kan utgöra risk för nattlig syrebrist i hjärnan och kan vara en riskfaktor för hjärnskada utlöst av syrebrist.

I den fjärde studien noterades ett liknande samband, då vi studerade förändringar i blodtryck, blodtrycksfall och regionalt hjärnblodflöde (CBF). Relativt diastoliskt blodtrycksfall (DBP) på natten, dvs jämförelse med tryck nattetid i förhållande till tryck dagtid, hade negativt samband med hjärnblodflöde i båda tinnings- samt bakre hjässloberna. Det fanns inget samband mellan relativt systoliskt blodtrycksfall (SBP) på natten och regionalt hjärnblodflöde. Analyser av systoliskt blodtryck (SBP) visade att individer med stigande SBP under den 14 år långa uppföljningen hade högre frekvens av extrem DBP fall på natten vid 81 års ålder jämfört med individer som uppvisade sjunkande SBP under uppföljningstiden. Således, extremt BP fall på natten förefaller att orsaka försämrat hjärnblodflöde och detta fynd kan ha betydelse för uppkomst av hjärnskador på basen av nattlig syrebrist och är möjligen resultatet av störd autoreglering av hjärnans blodflöde.

Ackowledgements

I would like to express my deepest and sincerest gratitude to all those, named and unnamed, who have helped or supported me to complete my work and make this thesis possible.

My sincere gratitude goes to colleagues, nurses and friends who have supported and helped me during this work. Especially, I would like to thank the following:

Professor Sölve Elmståhl, my tutor for excellent supervision, continuous advice, enthusiasm, personal support, and never ending support throughout the thesis.

Professor Lars Janzon, my co-tutor, for his interest in my work and who has introduced me to the field of epidemiology.

Registered Nurse Eva Robertsson for a long time of the great support, cooperation, power of initiative and her never-ending kindness.

Berit Mattisson for her expert secretarial and excellent work with the technical assistance.

Clinical psychologist Lena André-Petersson for co-operation with the psychological data collection at the follow-up study of ”Men born in 1914”.

My co-authors and co-workers Flemming Hansen, Arkadiusz Siennicki-Lantz, Johan Axelsson for sharing work and experience.

Mats Persson Lintrup for support during the work and excellent work with the final layout of this thesis.

Last but not least, my family, especially my parents for their never-ending love, encouragement and support throughout my life.

References

1. Hanson BS. *Social network, social support and health in elderly men : a population study (dissertation)*. Community Medicine. Lund: Lund University, 1988.
2. Hedblad B, Juul-Moller S, Svensson K, et al. Increased mortality in men with ST segment depression during 24 h ambulatory long-term ECG recording. Results from prospective population study 'Men born in 1914', from Malmo, Sweden. *Eur Heart J* 1989;10(2):149-58.
3. Isacsson SO. Venous occlusion plethysmography in 55-year old men. A population study in Malmo, Sweden. *Acta Med Scand Suppl* 1972;537:1-62.
4. Janzon L. The effect of smoking and smoking cessation on peripheral circulation and fibrinolysis. A population study in 59-year-old men. *Acta Chir Scand Suppl* 1974;451:1-45.
5. Jungquist G, Nilsson B, Ostberg H, et al. Carotid artery blood flow velocity related to transient ischemic attack and stroke in a population study of 69-year-old men. *Stroke* 1989;20(10):1327-30.
6. Sterpetti A, Schultz R, Feldhaus R, et al. Ultrasonographic features of carotid plaque and the risk of subsequent neurologic deficits. *Surgery* 1988;104(4):652-60.
7. Warlow C, Dennis M, van Gijn J, et al. *Stroke: a practical quide to management.* Malden, MA: Blackwell Science (UK), 1996 p. 190-257.
8. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997;337(19):1360-9.
9. Ross R. The pathogenesis of atherosclerosis--an update. *N Engl J Med* 1986;314(8):488-500.
10. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362(6423):801-9.
11. Van den Bergh R, Van der Eecken H. Anatomy and embryology of cerebral circulation. *Progr. Brain Res.* 1968;30:1-25.
12. Obrist W. *Cerebral physiology of the aged: influence of circulatory disorders. Aging and dementia.* New York: Plenum Press, 1972 p 117-133.
13. Wollner L, McCarthy S, Soper N, Macy D. Failure of cerebral autoregulation as a cause of brain dysfunction in the elderly. *Br Med J* 1979;1(6171):1117-8.
14. Paulson O, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2(2):161-92.

15. Edvinsson L, MacKenzie E, McCulloch J. Autoregulation. In: Edvinsson L, MacKenzie E, McCulloch J, eds. *Cerebral blood flow and metabolism.* New York: Raven Press, cop, 1993:553-598.

16. Furchgott R, Zawadzki J. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288(5789):373-6.

17. Vanhoutte P. *Relaxing and contracting factors: biological and clinical research.* Clifton, N.J.: Humana Press, 1988.

18. Thompson J, Wei E, Kontos H. Inhibition by ketanserin of serotonin induced cerebral arteriolar constriction. *Stroke* 1984;15(6):1021-4.

19. Rusch N, Chyatte D, Sundt TJ, Vanhoutte P. 5-hydroxytryptamine: source of activator calcium in human basilar arteries. *Stroke* 1985;16(4):718-20.

20. Wahl M, Unterberg A, Baethmann A, Schilling L. Mediators of blood-brain barrier dysfunction and formation of vasogenic brain edema. *J Cereb Blood Flow Metab* 1988;8(5):621-34.

21. Lou H, Edvinsson L, MacKenzie E. The concept of coupling blood flow to brain function: revision required? *Ann Neurol* 1987;22(3):289-97.

22. Lavy S, Melamed E, Portnoy Z. The effect of cerebral infarction on the regional cerebral blood flow of the contralateral hemisphere. *Stroke* 1975;6(2):160-3.

23. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. *Circulation* 1976;53(4):720-7.

24. O'Leary D, Polak J, Kronmal R, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke* 1992;23(12):1752-60.

25. Fitzgerald D, O'Farrell C. Prognostic value of ultrasound morphology in carotid atherosclerosis. *Int Angiol* 1993;12(4):337-41.

26. Geroulakos G, Domjan J, Nicolaides A, et al. Ultrasonic carotid artery plaque structure and the risk of cerebral infarction on computed tomography. *J Vasc Surg* 1994;20(2):263-6.

27. Muluk S, Muluk V, Sugimoto H, et al. Progression of asymptomatic carotid stenosis: a natural history study in 1004 patients. *J Vasc Surg* 1999;29(2):208-14; discussion 214-6.

28. Jungquist G, Nilsson J. Increased body weight in men after the age of 55 is a risk factor for internal carotid artery stenosis: an epidemiological study of men aged 69. *Clin Physiol* 1994;14(1):71-7.

29. Bots M, van Swieten J, Breteler M, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet* 1993;341(8855):1232-7.

30. Salonen R, Tervahauta M, Salonen J, Pekkanen J, Nissinen A, Karvonen M. Ultrasonographic manifestations of common carotid atherosclerosis in elderly eastern Finnish men. Prevalence and associations with cardiovascular diseases and risk factors. *Arterioscler Thromb* 1994;14(10):1631-40.

31. Wilson P, Hoeg J, D'Agostino R, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med* 1997;337(8):516-22.

32. Harer C, Gusev E. Asymptomatic cervical artery stenoses in Moscow. *Acta Neurol Scand* 1996;93(4):286-90.

33. Kannel W, Wolf P, Verter J, McNamara P. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham study. *Jama* 1970;214(2):301-10.

34. Heyman A, Karp H, Heyden S, et al. Cerebrovascular disease in the biracial population of Evans County, Georgia. *Arch Intern Med* 1971;128(6):949-55.

35. Kannel W, Wolf P, Dawber T. Hypertension and cardiac impairments increase stroke risk. *Geriatrics* 1978;33(9):71-7, 81-3.

36. Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. Hypertension Detection and Follow-up Program Cooperative Group. *Jama* 1982;247(5):633-8.

37. Hankey G, Slattery J, Warlow C. Transient ischaemic attacks: which patients are at high (and low) risk of serious vascular events? *J Neurol Neurosurg Psychiatry* 1992;55(8):640-52.

38. Sandercock P, Warlow C, Jones L, Starkey I. Predisposing factors for cerebral infarction: the Oxfordshire community stroke project. *Bmj* 1989;298(6666):75-80.

39. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990;21(6):848-53.

40. Hatano S. Variability of the diagnosis of stroke by clinical judgement and by a scoring method. *Bull World Health Organ* 1976;54(5):533-40.

41. Murray C, Lopez A. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;349(9063):1436-42.

42. American Heart Association. *Heart and Stroke Statistical Update.* Dallas, Tex: American Heart Association, 1998.

43. Sacco R. Risk factors and outcomes for ischemic stroke. *Neurology* 1995;45(2 Suppl 1):S10-4.

44. American Heart Association. *Heart and Stroke Facts: Statistical Supplement 1995.* Facts. Dallas: American Heart Association, 1995.

45. Norris J, Zhu C, Bornstein N, Chambers B. Vascular risks of asymptomatic carotid stenosis. *Stroke* 1991;22(12):1485-90.

46. Fratiglioni L, Rocca W. Epidemiology of dementia. In: Boller F, Cappa S, eds. *Handbook of neuropsychology. Vol. 6, Aging and dementia.* Amsterdam: Elsevier, 2001:193-215. 2 ed.

47. Jorm A, Korten A, Henderson A. The prevalence of dementia: a quantitative integration of the literature. *Acta Psychiatr Scand* 1987;76(5):465-79.

48. Erkinjuntti T, Hachinski V. Rethinking vascular dementia. *Cerebrovasc Dis* 1993;3:3-23.

49. Erkinjuntti T, Rockwood K. Vascular dementia. *Semin Clin Neuropsychiatry* 2003;8(1):37-45.

50. Vasan R, Larson M, Leip E, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345(18):1291-7.

51. Skoog I, Gustafson D. Hypertension and related factors in the etiology of Alzheimer's disease. *Ann N Y Acad Sci* 2002;977:29-36.

52. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet* 1980;1(8181):1261-7.

53. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *Jama* 1970;213(7):1143-52.

54. Farmer ME, Kittner SJ, Abbott RD, Wolz MM, Wolf PA, White LR. Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: the Framingham Study. *J Clin Epidemiol* 1990;43(5):475-80.

55. Farmer ME, White LR, Abbott RD, et al. Blood pressure and cognitive performance. The Framingham Study. *Am J Epidemiol* 1987;126(6):1103-14.

56. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol* 1993;138(6):353-64.

57. Schultz NR, Jr., Elias MF, Robbins MA, Streeten DH, Blakeman N. A longitudinal study of the performance of hypertensive and normotensive subjects on the Wechsler Adult Intelligence Scale. *Psychol Aging* 1989;4(4):496-9.

58. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension* 1998;31(3):780-6.

59. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *Jama* 1995;274(23):1846-51.

60. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. *Stroke* 1998;29(11):2334-40.

61. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. *Bmj* 1996;312(7034):805-8.

62. Elmståhl S, Petersson M, Lilja B, Samuelsson S, Rosen I, Bjuno L. Autonomic cardiovascular responses to tilting in patients with Alzheimer's disease and in healthy elderly women. *Age Ageing* 1992;21(4):301-7.

63. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996;347(9009):1141-5.

64. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *Jama* 1999;281(5):438-45.

65. Guo Z, Viitanen M, Winblad B. Low blood pressure and five-year mortality in a Stockholm cohort of the very old: possible confounding by cognitive impairment and other factors. *Am J Public Health* 1997;87(4):623-8.

66. Räihä I, Tarvonen S, Kurki T, Rajala T, Sourander L. Relationship between vascular factors and white matter low attenuation of the brain. *Acta Neurol Scand* 1993;87(4):286-9.

67. Pickering T, Harshfield G, Devereux R, Laragh J. What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension* 1985;7(2):171-7.

68. Shimada K, Kawamoto A, Matsubayashi K, Nishinaga M, Kimura S, Ozawa T. Diurnal blood pressure variations and silent cerebrovascular damage in elderly patients with hypertension. *J Hypertens* 1992;10(8):875-8.

69. Watanabe N, Imai Y, Nagai K, et al. Nocturnal blood pressure and silent cerebrovascular lesions in elderly Japanese. *Stroke* 1996;27(8):1319-27.

70. Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. *Am J Epidemiol* 1997;145(12):1106-13.

71. Guo Z, Viitanen M, Winblad B. Clinical correlates of low blood pressure in very old people: the importance of cognitive impairment. *J Am Geriatr Soc* 1997;45(6):701-5.

72. Guo Z, Viitanen M, Winblad B, Fratiglioni L. Low blood pressure and incidence of dementia in a very old sample: dependent on initial cognition. *J Am Geriatr Soc* 1999;47(6):723-6.

73. Landin K, Blennow K, Wallin A, Gottfries CG. Low blood pressure and blood glucose levels in Alzheimer's disease. Evidence for a hypometabolic disorder? *J Intern Med* 1993;233(4):357-63.

74. Wang SJ, Liao KK, Fuh JL, et al. Cardiovascular autonomic functions in Alzheimer's disease. *Age Ageing* 1994;23(5):400-4.

75. Carmona J, Amado P, Vasconcelos N, et al. Long-term (four years) follow-up of patients with treated nocturnal hypertension assessed by ambulatory blood pressure monitoring. *Rev Port Cardiol* 2001;20(2):135-50; discussion 153-4.

76. Kobrin I, Oigman W, Kumar A, et al. Diurnal variation of blood pressure in elderly patients with essential hypertensionw. *J Am Geriatr Soc* 1984;32(12):896-9.

77. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988;2(8607):397.

78. Mathias C, Bannister R. Investigation of autonomic disorders. In: Bannister R, Mathias C, eds. *Autonomic failure: a textbook of clinical disorders of the autonomic nervous system.* Oxford, England: Oxford University Press, 1992:255-90. 3 ed.

79. Steen B. Ortostatiska blodtrycksreaktioner hos 70-åringar och 75-åringar. En populationsstudie. *Forskning och Praktik* 1980;12(3):47-48.

80. Passant U, Warkentin S, Minthon L, Faldt R, Edvinsson L. Cortical blood flow during head-up postural change in subjects with orthostatic hypotension. *Clin Auton Res* 1993;3(5):311-8.

81. Passant U, Warkentin S, Karlson S, Nilsson K, Edvinsson L, Gustafson L. Orthostatic hypotension in organic dementia: relationship between blood pressure, cortical blood flow and symptoms. *Clin Auton Res* 1996;6(1):29-36.

82. Vitiello B, Veith RC, Molchan SE, et al. Autonomic dysfunction in patients with dementia of the Alzheimer type. *Biol Psychiatry* 1993;34(7):428-33.

83. Jhee SS, Sramek JJ, Wardle TS, Cutler NR. Orthostasis in Alzheimer disease: a retrospective analysis. *Alzheimer Dis Assoc Disord* 1995;9(4):243-6.

84. Yamamoto T, Shimazu K, Tamura N, Watanabe S, Hamaguchi K. Autonomic nervous functions in Alzheimer type and multi-infarct dementia--a hemodynamic study. *Rinsho Shinkeigaku* 1990;30(9):1020-2.

85. Elmståhl S, Rosen I. Postural hypotension and EEG variables predict cognitive decline: results from a 5-year follow-up of healthy elderly women. *Dement Geriatr Cogn Disord* 1997;8(3):180-7.

86. Warkentin S, Passant U, Minthon L, et al. Redistribution of blood flow in the cerebral cortex of normal subjects during head-up postural change. *Clin Auton Res* 1992;2(2):119-24.

87. Pomara N, Deptula D, Singh R. Pretreatment postural blood pressure drop as a possible predictor of response to the cholinesterase inhibitor velnacrine (HP 029) in Alzheimer's disease. *Psychopharmacol Bull* 1991;27(3):301-7.

88. Schneider LS, Lyness SA, Pawluczyk S, Gleason RP, Sloane RB. Do blood pressure and age predict response to tacrine (THA) in Alzheimer's disease? A preliminary report. *Psychopharmacol Bull* 1991;27(3):309-14.

89. Horn JL, Cattell RB. Age differences in fluid and crystallized intelligence. *Acta Psychol (Amst)* 1967;26(2):107-29.

90. Sliwinski M, Buschke H. Cross-sectional and longitudinal relationships among age, cognition, and processing speed. *Psychol Aging* 1999;14(1):18-33.

91. Christensen H. What cognitive changes can be expected with normal ageing? *Aust N Z J Psychiatry* 2001;35(6):768-75.

92. Parnetti L, Lowenthal DT, Presciutti O, et al. 1H-MRS, MRI-based hippocampal volumetry, and 99mTc-HMPAO-SPECT in normal aging, age-associated memory impairment, and probable Alzheimer's disease. *J Am Geriatr Soc* 1996;44(2):133-8.

93. Tulving E. Organization of memory: Quo vadis? In: Gazzaniga M, Bizzi E, eds. *The cognitive neurosciences.* Cambridge, Massachusetts: MIT Press, 1995:839-47.

94. Squire L, Knowlton B. Memory, hippocampus and brain systems. In: Gazzaniga M, Bizzi E, eds. *The cognitive neurosciences.* Cambridge, Massachusetts: MIT Press, 1995:825-37.

95. Wechsler D. *Wechsler Adult Intelligence Scale-Revised.* San Antonio, TX: The Psychological Corporation, 1981.

96. Dureman I, Kebbon L, Österberg E. *Manual till DS-batteriet.* Stockholm: Skandinaviska testförlaget, 1971.

97. Lezak M. *Neuropsychological assessment.* New York: Oxford University Press, 1995. 3 ed.

98. Krausz Y, Bonne O, Gorfine M, Karger H, Lerer B, Chisin R. Age-related changes in brain perfusion of normal subjects detected by 99mTc-HMPAO SPECT. *Neuroradiology* 1998;40(7):428-34.

99. Mantyla R, Aronen H, Salonen O, et al. Magnetic resonance imaging white matter hyperintensities and mechanism of ischemic stroke. *Stroke* 1999;30(10):2053-8.

100. Swedish National Central Bureau of Statistics. *Swedish socioeconomic classification. Reports on statistical coordination: 4 (In Swedish).* Stockholm, 1982.

101. Carlsson G. *Social mobility and class structure.* Lund, Sweden: Gleerups, 1958.

102. Rose G, Blackburn H. Cardiovascular survey methods. *World Health Organization Monograph series 56.* Geneva: World health organization, 1968:162-5.

103. Royal College of Psychiatrists. *Alcohol: Our Favourite Drug.* London: Tavistock, 1986.

104. Grimby G, Wilhelmsen L, Björnstorp P, Saltin B, Tibblin G. Habitual physical activity, Aerobic power and blood lipids. In: Pernow B, Saltin B, eds. *Muscle metabolism during exercise : proceedings of a Karolinska institutet symposium held in Stockholm, Sweden, September 6-9, 1970.* New York: Plenum Press, 1971:469-81.

105. Carroll J, Smith N, Babson A. A colorimetric serum glucose determination using hexokinase and glucose-6-phosphate dehydrogenase. *Biochem Med* 1971;4(2):171-80.

106. Roeschlau P, Bernt E, Gruber W. Enzymatic determination of total cholesterol in serum. *Z Klin Chem Klin Biochem* 1974;12(5):226.

107. Wahlefeld W. Triglycerides: determination after enzymatic hydrolysis. In: Bergmeyer H, ed. *Methods of enzymatic analysis.* New York: Academic Press, 1974:18-31. English 2 ed.

108. Bray GA. Definition, measurement, and classification of the syndromes of obesity. *Int J Obes* 1978;2(2):99-112.

109. Swedish National Bureau of Statistics. *Swedish mortality classification. Reports on statistical coordination 1984-89.* Örebro: SCB Förlag, 1991.

110. World health organization. *Manual of the international statistical classification of diseases, injuries and causes of death, based on the recommendations of the eighth Revision conference, 1965, and adopted by the nineteenth World health assembly.* Geneva: World health organization, 1969.

111. Krause H, Segard M, Carey P, Bernstein EF, Fronek A. Doppler power frequency spectrum analysis in the diagnosis of carotid artery disease. *Stroke* 1984;15(2):351-8.

112. Poli A, Tremoli E, Colombo A, Sirtori M, Pignoli P, Paoletti R. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. A new model for the quantitation and follow-up of preclinical atherosclerosis in living human subjects. *Atherosclerosis* 1988;70(3):253-61.

113. Margitic SE, Bond MG, Crouse JR, Furberg CD, Probstfield JL. Progression and regression of carotid atherosclerosis in clinical trials. *Arterioscler Thromb* 1991;11(2):443-51.

114. Norrving B, Jungqvist G, Olivecrona H, Cronqvist S, Nilsson B. Non-invasive detection of carotid bifurcation disease by continuous-wave Doppler with spectral analysis. *Acta Neurol Scand* 1985;72(2):203-9.

115. Persson J, Stavenow L, Wikstrand J, Israelsson B, Formgren J, Berglund G. Noninvasive quantification of atherosclerotic lesions. Reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. *Arterioscler Thromb* 1992;12(2):261-6.

116. 1986 guidelines for the treatment of mild hypertension: memorandum from a WHO/ISH meeting. *J Hypertens* 1986;4(3):383-6.

117. Gundersen J. Segmental measurements of systolic blood pressure in the extremities including the thumb and the great toe (dissertation). *Acta Chir Scand Suppl* 1972;426:1-90.

118. Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. *Int J Epidemiol* 1988;17(2):248-54.

119. Steen G, Hagberg B, Johnson G, Steen B. Cognitive function, cognitive style and life satisfaction in a 68-year-old male population. *Compr Gerontol [B]* 1987;1(2):54-61.

120. Cronholm B, Molander L. Memory disturbances after electroconvulsive therapy. I. Conditions 6 hours after electroshock treatment. *Acta Psychiatr Neurol Scand* 1957;32(3):280-306.

121. Benton A. *The Revised Visual Retention Test: Clinical and Experimental Applications.* New York: Psychological Corporaton, 1974. 4 ed.

122. Zung WW. A Self-Rating Depression Scale. *Arch Gen Psychiatry* 1965;12:63-70.

123. Yonekura Y, Tsuchida T, Sadato N, et al. Brain perfusion SPECT with 99mTc-bicisate: comparison with PET measurement and linearization based on permeability-surface area product model. *J Cereb Blood Flow Metab* 1994;14 Suppl 1:S58-65.

124. Elmståhl S, Siennicki-Lantz A, Lilja B, Bjunö L. A study of regional cerebral blood flow using 99mTc-HMPAO-SPECT in elderly women with senile dementia of Alzheimer's type. *Dementia* 1994;5(6):302-9.

125. Verdecchia P. Prognostic value of ambulatory blood pressure : current evidence and clinical implications. *Hypertension* 2000;35(3):844-51.

126. Jungquist G, Olivecrona H, Kendrup I, et al. Spectral analysis with digital presentation of C-W Doppler signals in the evaluation of carotid stenosis. *Clin Physiol* 1986;6(4):319-27.

127. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21(6):1011-53.

128. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-52.

129. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens* 1999;17(2):151-83.

130. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355(9207):865-72.

131. Elias PK, D'Agostino RB, Elias MF, Wolf PA. Blood pressure, hypertension, and age as risk factors for poor cognitive performance. *Exp Aging Res* 1995;21(4):393-417.

132. Wallace RB, Lemke JH, Morris MC, Goodenberger M, Kohout F, Hinrichs JV. Relationship of free-recall memory to hypertension in the elderly. The Iowa 65+ Rural Health Study. *J Chronic Dis* 1985;38(6):475-81.

133. Strandgaard S, Paulson OB. Hypertensive disease and the cerebral circulation. In: Laragh J, Brenner B, eds. *Hypertension: pathophysiology, diagnosis, and management.* New York, N.Y.: Raven Press, 1990:399-416.

134. Cervilla JA, Prince M, Joels S, Lovestone S, Mann A. Long-term predictors of cognitive outcome in a cohort of older people with hypertension. *Br J Psychiatry* 2000;177:66-71.

135. O'Sullivan C, Duggan J, Atkins N, O'Brien E. Twenty-four-hour ambulatory blood pressure in community-dwelling elderly men and women, aged 60-102 years. *J Hypertens* 2003;21(9):1641-7.

136. Jumabay M, Ozawa Y, Kawamura H, et al. Ambulatory blood pressure monitoring in Uygur centenarians. *Circ J* 2002;66(1):75-9.

137. Viitanen M, Guo Z. Are cognitive function and blood pressure related? *Drugs Aging* 1997;11(3):165-9.

138. Battersby C, Hartley K, Fletcher AE, et al. Cognitive function in hypertension: a community based study. *J Hum Hypertens* 1993;7(2):117-23.

139. Kalra L, Jackson SH, Swift CG. Psychomotor performance in elderly hypertensive patients. *J Hum Hypertens* 1993;7(3):279-84.

140. Loeb C, Meyer JS. Vascular dementia: still a debatable entity? *J Neurol Sci* 1996;143(1-2):31-40.

141. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;163(9):1069-75.

142. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352(9137):1347-51.

143. Sulkava R, Erkinjuntti T. Vascular dementia due to cardiac arrhythmias and systemic hypotension. *Acta Neurol Scand* 1987;76(2):123-8.

144. Reinprecht F, Elmståhl S, Janzon L, Hansen F. Incidence and progression of carotid artery stenosis in elderly men: Thirteen-year follow-up of the population cohort "Men born in 1914". *Int J Angiol* 2002;11:132-8.

145. Astrup J, Siesjo B, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke* 1981;12(6):723-5.

146. Starr J, Whalley L. Senile hypertension and cognitive impairment: an overview. *J Hypertens Suppl* 1992;10(2):S31-42.

147. Starr J, Whalley L, Inch S, Shering P. Blood pressure and cognitive function in healthy old people. *J Am Geriatr Soc* 1993;41(7):753-6.

148. Paran E, Anson O, Reuveni H. Blood pressure and cognitive functioning among independent elderly. *Am J Hypertens* 2003;16(10):818-26.

149. Skoog I, Andreasson LA, Landahl S, Lernfelt B. A population-based study on blood pressure and brain atrophy in 85-year-olds. *Hypertension* 1998;32(3):404-9.

150. Hogan DB, Ebly EM, Rockwood K. Weight, blood pressure, osmolarity, and glucose levels across various stages of Alzheimer's disease and vascular dementia. *Dement Geriatr Cogn Disord* 1997;8(3):147-51.

151. Nakamura K, Oita J, Yamaguchi T. Nocturnal blood pressure dip in stroke survivors. A pilot study. *Stroke* 1995;26(8):1373-8.

152. Siennicki-Lantz A, Lilja B, Elmstahl S. Cerebral perfusion deficits in age-associated memory impairment. The role of tobacco smoking. *Aging Clin Exp Res* 2002;14(2):108-16.

153. Hogh P, Madsen Sjo N, Gade A, Waldemar G. Temporal lobe hypoperfusion in isolated amnesia with slow onset: a single photon emission computer tomography study. *Dement Geriatr Cogn Disord* 2004;18(1):15-23.

154. Brun A, Englund E. Regional pattern of degeneration in Alzheimer's disease: neuronal loss and histopathological grading. A. Brun & E. Englund. Histopathology 1981; 5; 459-564. *Histopathology* 2002;41(3A):37.

155. Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L. Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Arch Neurol* 2003;60(2):223-8.

156. den Heijer T, Launer L, Prins N, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005;64(2):263-7.

157. Strandgaard S, Olesen J, Skinhoj E, Lassen N. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* 1973;1(5852):507-10.