A Population-Based Study on Blood Pressure and Brain Atrophy in 85-Year-Olds

Ingmar Skoog, Lars-Arne Andreasson, Sten Landahl, Bodil Lernfelt

Abstract—In the general population, mean systolic and diastolic blood pressure increases up to age 75 years but decreases thereafter. The brain has a role in blood pressure regulation; it is not clear whether the cerebral changes that occur with aging contribute to the decline in blood pressure in the very elderly. We examined a population-based sample of 484 85-year-old persons (344 nondemented and 140 demented, 61 with Alzheimer’s disease, 65 with vascular dementia, and 14 with other types of dementia) with a neuropsychiatric examination and blood pressure measurements. Dementia was diagnosed according to the criteria proposed in the Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised. Brain atrophy was measured by CT of the brain. In the nondemented group, frontal (r = −0.23, P = 0.008) cortical atrophy and bifrontal ratio (r = −0.20, P = 0.013) were associated with lower systolic blood pressure, and frontal (r = −0.23, P = 0.010) and parietal (r = −0.24, P = 0.008) cortical atrophy and bifrontal ratio (r = −0.23, P = 0.006) with lower diastolic blood pressure. Systolic blood pressure was lower in subjects with Alzheimer’s disease and vascular dementia, and diastolic blood pressure was lower in those with vascular dementia compared with the nondemented. Systolic (r = −0.27, P < 0.001) and diastolic (r = −0.10, P = 0.020) blood pressure was negatively correlated to dementia severity. In the demented subjects, frontal cortical atrophy was correlated to lower diastolic blood pressure (r = −0.21, P = 0.043). Our findings suggest that age-related changes in brain structure may contribute to the decrease in blood pressure in the very elderly and that low blood pressure in dementia disorders is mainly a secondary phenomenon. (Hypertension. 1998;32:404-409.)

Key Words: blood pressure, cerebral atrophy, epidemiological methods, Alzheimer’s disease, dementia, vascular

In western populations, mean systolic blood pressure rises with advancing age, at least up to age 75 years, while mean diastolic blood pressure rises until the ages of approximately 55 to 65 years. After the age of 75 to 80 years, a decrease in mean blood pressure levels has been observed.1–3 The reason for the decrease in blood pressure in the highest age groups has not been fully clarified, but it has been suggested that selective mortality in individuals with high blood pressure, age-related impairment of left ventricular function, and changes in body mass, body composition, and endocrine and metabolic function may play a role. With increasing age, the prevalence of cerebral disorders such as Alzheimer’s disease and vascular dementia increases,4 but cerebral changes also occur in normal aging.5 Several brain areas suggested to have a role in blood pressure regulation6–8 are affected in Alzheimer’s disease9 and in normal aging.1,5 Brain disorders may thus also contribute to the decrease in blood pressure observed in the very elderly.10 In line with this hypothesis, we recently reported from a 15-year longitudinal population study that a decline in blood pressure occurred in the years before dementia onset,11 and Guo et al12 reported that blood pressure was lower in individuals aged >75 years with Alzheimer’s disease or vascular dementia compared with the non-demented. Whether the decline in blood pressure observed in the very elderly is related to organic brain changes in the nondemented elderly as well is unclear. To further elucidate this relationship, we studied blood pressure in relation to brain atrophy measurements determined by CT of the brain and in relation to Alzheimer’s disease and vascular dementia in a representative sample of 85-year-old persons as part of the Longitudinal Gerontological and Geriatric Population Studies in Gothenburg.11,13–15

Methods

Subjects

All 85-year-old persons born between July 1, 1901, and June 30, 1902, and registered for census purposes in Gothenburg, Sweden, were invited to take part in a health survey. Persons living in both the community and at institutions were included. A systematic subsample, comprising every second person from the sample, was examined by a psychiatrist in the subject’s home (n = 494). The sample has been described in detail previously.11 Nonparticipants and participants were compared with regard to gender, marital status, 3-year mortality rate, and registration as psychiatric outpatient or inpatient in Gothenburg. No significant

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differences were found with regard to these factors. Ten individuals (3 nondemented, 7 demented) had no blood pressure recordings, leaving 344 nondemented and 140 demented (61 with Alzheimer’s disease, 65 with vascular dementia, and 14 with other types of dementia). Informed consent was obtained from all subjects and/or their relatives, and the study was approved by the Ethics Committee for Medical Research at Göteborg University. All procedures were in accordance with institutional guidelines.

Examinations
The examinations included medical history and a physical examination performed by a geriatrician, a neuropsychiatric examination and a telephone interview with a close informant performed by a psychiatrist, an ECG, a chest x-ray, a battery of blood tests, and CT of the brain. The examinations were semistructured. Cognitive function in nondemented individuals was measured with the Mini-Mental State Examination (MMSE), a simple instrument measuring global cognitive function with a maximum score of 30. Spontaneous activity and ambulatory capacity were rated according to the Gottfries-Bråne-Steen Scale. Medical records from psychiatric and geriatric institutions and outpatient departments in Gothenburg were examined by a psychiatrist.

Casual blood pressure was measured in the right arm with the subject in the seated position after 5 minutes of rest using a mercury manometer. Systolic and diastolic blood pressures were registered to the nearest 5 mm Hg. Diastolic blood pressure was defined as Korotkoff phase V. Orthostatic hypotension was defined as a decline of ≥20 mm Hg in systolic blood pressure or ≥10 mm Hg in diastolic blood pressure within 3 minutes of standing after 5 minutes of rest in the supine position. All the blood pressure measurements were made without knowledge of the results from the neuropsychiatric and CT examinations. During a house call, a registered nurse interviewed the subjects regarding their social and living conditions, their need for social and medical care, and their drug consumption. The prescribed and actually taken drug doses were registered and classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The right sylvian fissures, the minimum width of the bodies of the lateral ventricles at the waist, and the width of the third ventricle. Ratios for a to d were determined by dividing the obtained values by the width of the brain at the level of the measurement, giving the following ratios: bifrontal ratio, bicaudate ratio, sylvian fissure ratio, and sella media ratio. The rating procedure was carried out separately for the cortical and ventricular studies.

Statistical Analyses
Fisher’s exact test and t test were used to test the hypothesis of no difference between the groups. Pitman’s permutation test was used to test correlations. Adjustments for gender and treatment with antihypertensive drugs were performed in all analyses. Adjustments for gender, dementia, and treatment with antihypertensive drugs were made in the analyses of the total group. An ordinary stepwise multiple regression analysis was used to adjust for gender and body mass index (BMI) in the nondemented group.

Results
Blood Pressure in Relation to Brain Atrophy
In the nondemented group, the presence of frontal and parietal cortical atrophy and an increased bifrontal ratio was significantly correlated to lower systolic and diastolic blood pressure (Table 1). In the demented group, the presence of frontal atrophy was related to lower diastolic blood pressure.

Antihypertensive Treatment
Drugs classified as antihypertensive (diuretics, β-blockers, and other antihypertensive drugs) were prescribed less often for demented individuals than nondemented (46 of 147 versus 164 of 347; odds ratio, 0.5; 95% confidence interval, 0.3 to 0.8; P = 0.001). Those given these drugs did not differ from other individuals regarding mean systolic and diastolic blood pressure either in the total group or when demented and nondemented individuals or men and women were considered separately.

Among nondemented individuals, the strength of the correlations between blood pressure and cerebral atrophy did not differ between those treated and not treated with antihypertensives, except for the correlation between systolic blood pressure and bifrontal ratio (not treated with antihypertensives, r = 0.30, P = 0.008; treated, r = −0.08, P = 0.532).

In the demented group, there were correlations only between cortical atrophy and blood pressure in those not treated with antihypertensive drugs. In this group, lower diastolic blood pressure was correlated to frontal (not treated with antihypertensives, r = 0.31, P = 0.011; treated, r = 0.01, P = 0.964), parietal (not treated, r = −0.29, P = 0.017; treated, r = 0.05, P = 0.814), and occipital cortical atrophy (not treated, r = −0.31, P = 0.012; treated, r = 0.12, P = 0.541), and lower systolic blood pressure was correlated with occipital cortical atrophy (not treated, r = −0.23; treated, r = −0.04). There was a similar difference between treated and not treated demented
Blood Pressure and Brain Atrophy

TABLE 1. Correlation (r) Between Systolic and Diastolic Blood Pressure and Cerebral Atrophy in 85-Year-Olds

<table>
<thead>
<tr>
<th>Cerebral Atrophy</th>
<th>Nondemented (n=133)</th>
<th>Demented (n=99)</th>
<th>All Subjects (n=232)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal atrophy</td>
<td>-0.18*</td>
<td>-0.23†</td>
<td>-0.13</td>
</tr>
<tr>
<td>Temporal atrophy</td>
<td>-0.08</td>
<td>-0.17</td>
<td>-0.13</td>
</tr>
<tr>
<td>Parietal atrophy</td>
<td>-0.23†</td>
<td>-0.24†</td>
<td>-0.12</td>
</tr>
<tr>
<td>Occipital atrophy</td>
<td>-0.09</td>
<td>-0.03</td>
<td>-0.18</td>
</tr>
<tr>
<td>Central atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bifrontal ratio</td>
<td>-0.20*</td>
<td>-0.23†</td>
<td>0.03</td>
</tr>
<tr>
<td>Bicaudate ratio</td>
<td>-0.01</td>
<td>0.07</td>
<td>-0.07</td>
</tr>
<tr>
<td>Third ventricle width</td>
<td>-0.01</td>
<td>-0.16</td>
<td>-0.07</td>
</tr>
<tr>
<td>Sylvian fissure ratio</td>
<td>-0.14</td>
<td>-0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>Sella media ratio</td>
<td>-0.07</td>
<td>-0.11</td>
<td>0.06</td>
</tr>
</tbody>
</table>

In analysis of the total group, dementia was a background factor. Gender and antihypertensive treatment were background factors in all analyses.

Correlation (r) tested with Pitman’s permutation test. *P<0.05, †P<0.01.

Blood Pressure in Relation to Dementia

Systolic and diastolic blood pressures were lower in demented than in nondemented 85-year-olds and decreased with dementia severity (Table 2). Blood pressure was lower in both Alzheimer’s disease and vascular dementia groups than in the nondemented group. Dementia severity was correlated to lower systolic blood pressure in Alzheimer’s disease (r=-0.22, P<0.0001) and in vascular dementia (r=-0.19, P<0.0001) and to lower diastolic blood pressure in vascular dementia (r=-0.11, P=0.019) but not in Alzheimer’s disease (r=-0.05, P=0.351).

Reduced Ambulatory Capacity and Spontaneous Activity

Reduced ambulatory capacity (defined as an inability to move independently) was found in 7 of 338 (2.1%) nondemented individuals and in 33 of 139 (23.7%) demented individuals. Among nondemented individuals, those with a reduced ambulatory capacity had lower mean±SD systolic (132.9±22.9
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that age-related changes in brain structure may contribute to frontal and parietal cortical areas, and in central frontal areas, we found that cerebral atrophy (ie, neuronal degeneration) in individuals with reduced spontaneous activity had lower systolic blood pressure than other individuals (139.9 ± 26.2 versus 153.1 ± 22.7; P = 0.002), while diastolic blood pressure did not differ between the groups (76.5 ± 13.0 versus 77.1 ± 12.0; P = 0.770).

At least 1 of these symptoms was found in 17 of 344 (4.9%) nondemented individuals and in 2 of 41 (4.9%) mildly demented, in 21 of 49 (42.9%) moderately demented, and in 39 of 50 (78.0%) severely demented individuals. Adjustment also for spontaneous activity and ambulatory capacity did not change the correlations between blood pressure and brain atrophy. After the adjustment, low systolic blood pressure was associated with dementia (P = 0.006), severity of dementia (r = -0.11, P = 0.019), Alzheimer’s disease (P = 0.006), and other dementias (P = 0.045) but not with vascular dementia (P = 0.732). Diastolic blood pressure was not associated with dementia, dementia severity, or type of dementia after the adjustment for spontaneous activity and ambulatory capacity.

**Blood Pressure in Relation to MMSE Score in Nondemented Individuals**

In nondemented individuals (n = 308), lower systolic blood pressure was related to lower scores on the MMSE (r = 0.12, P = 0.042). No relationship was found between MMSE scores and diastolic blood pressure (r = 0.02, P = 0.685) in nondemented individuals.

**Orthostatic Hypotension**

Orthostatic hypotension, defined as a systolic blood pressure fall of ≥20 mm Hg within 3 minutes of standing after 5 minutes in the supine position, was found in 67 of 333 (20.1%) nondemented and in 19 of 86 (22.1%) demented subjects. A diastolic blood pressure fall of 10 mm Hg or more was found in 44 of 332 (13.3%) nondemented and in 14 of 86 (16.3%) demented subjects. The frequency of orthostatic hypotension did not differ among different severities or different types of dementia.

**Discussion**

We found that cerebral atrophy (ie, neuronal degeneration) in frontal and parietal cortical areas, and in central frontal areas, was correlated to lower blood pressure in a representative sample of nondemented 85-year-old persons; this suggests that age-related changes in brain structure may contribute to the decrease in blood pressure observed in the very elderly, emphasizing the important role of the central nervous system in blood pressure regulation. We also confirmed previous reports that systolic and diastolic blood pressure is lower in individuals with manifest Alzheimer’s disease and vascular dementia than in nondemented individuals and that blood pressure decreases with dementia severity. These findings are supported by reports that blood pressure declines in the years preceding dementia onset and further declines during the course of Alzheimer’s disease. The hypothalamus, the insular cortex, the medial prefrontal cortex, the locus coeruleus, the parabrachial nucleus, the pons, and the medulla oblongata are involved in central blood pressure regulation. Several of these areas are affected in Alzheimer’s disease and in normal aging. Burke et al reported a strong correlation between the number of C1 neurons in the medulla oblongata and blood pressure in Alzheimer patients. In our study, frontal atrophy was associated with lower blood pressure in both nondemented and demented individuals. Prefrontal areas are thought to be involved in blood pressure regulation, but frontal convexity lesions may also lead to a presentation of apathy and inertia, a state that could be regarded as the opposite to that of stress, which is correlated to increased blood pressure. In our study, we found that reduced spontaneity and ambulatory capacity were related to lower blood pressure. It is thus possible that reduced activity in individuals with brain atrophy may explain the association with low blood pressure. However, although reduced activity influenced the correlation between low blood pressure and severity of dementia and vascular dementia, it did not explain the correlation between blood pressure and cerebral atrophy.

The relationship between blood pressure and cognitive function/dementia may be age dependent. Although most cross-sectional studies in groups of younger and middle-aged individuals report a lower cognitive performance in hypertensives compared with normotensives, studies in the elderly report less conclusive results. In line with this, the Rotterdam Elderly Study reported that blood pressure was negatively correlated to cognitive performance before age 75 years, whereas there was a positive correlation above that age. The latter was similar to our finding in nondemented 85-year-olds. This may explain why 2 previous brain imaging studies performed in clinical samples of elderly persons who were younger than those in our study, reported an association between hypertension and indices of brain atrophy.

The relationship may also be time dependent. The Honolulu-Asia Aging Study reported that low performance in psychometric tests in the population was correlated to higher systolic blood pressure 25 years before the measurement of cognitive function, and the Framingham Study reported that low cognitive performance was correlated to higher blood pressure measured 12 to 14 years before testing. At the time of testing, cognitive performance was not correlated to blood pressure levels, and in the very elderly there was even a tendency for low blood pressure to be associated with low cognitive performance. In line with these results, a recent study reported that both systolic and diastolic blood pressures were increased 10 to 15 years before the onset of
both Alzheimer’s disease and vascular dementia. However, blood pressure declined in the years before dementia onset. Thus, although previously high blood pressure seems to precede the onset of dementia and cognitive decline by many years, low blood pressure is often associated with already manifest dementia, at least in the very elderly. It is possible that the subtle cognitive impairment and the brain atrophy reported in middle-aged and younger elderly hypertensives are early subclinical manifestations of a dementia process, before the brain lesions reach a threshold causing dementia and low blood pressure.

Although we believe that the low blood pressure found in individuals with dementia and cerebral atrophy is secondary to the brain lesions, one should not exclude the possibility that low blood pressure may cause lesions in the brain. Systemic hypotension associated with reduced cerebral blood flow may give rise to a spectrum of ischemic neuronal lesions in vulnerable areas of the brain. Although the frequency of orthostatic hypotension was similar in demented and non-demented individuals in our study, we cannot exclude the possibility that delayed orthostatic hypotension might have contributed to or caused dementia or reduced ambulatory capacity. Delayed orthostatic hypotension, starting after >10 minutes of standing, is common in individuals with dementia. However, it is not clear whether the frequency differs from that in normal elderly persons. Overtreatment with antihypertensive drugs has thus been suggested to increase the risk of brain damage and dementia in the very old. In our study, however, individuals with dementia used antihypertensive medications less often than did nondemented individuals. Although this may be due to recall bias in demented individuals, the registration of drug consumption was based on both subjective and objective information obtained by a registered nurse during the house call. The findings are also supported by our longitudinal data, which showed that during an observational period from age 70 to 85 years, those who developed dementia after age 80 were given antihypertensives to a lesser extent before this age than those not developing dementia. Overtreatment with antihypertensives was thus not the cause of the low blood pressure in demented individuals.

Some limitations of the study have to be considered. It has to be emphasized that linear measurements and subjective ratings are rather crude ratings of cortical atrophy. However, if anything, this should decrease the possibility of finding differences between the groups. A second limitation is that only about half of those invited to have a CT scan accepted. However, this is not a low response rate for such an examination in a population study. Furthermore, those who participated did not differ from those not participating regarding a number of factors, including mean blood pressure levels. Third, it has to be emphasized that differential survival may be of importance in cross-sectional studies at these high ages. If the combination of high blood pressure and cerebral atrophy is lethal, it may contribute to the relationships reported here. Fourth, there is a possibility that unrecognized confounders may account for the observed relationships. One such possibility is difference in BMI. Although this was not relevant in the nondemented group, we cannot exclude that this possibility may partly explain the results in the demented group, due to insufficient information regarding BMI in this group.

In summary, we found that cerebral atrophy was associated with lower blood pressure in a population-based sample of non-demented 85-year-old persons. Lower blood pressure was also associated with increasing severity of dementia. Our findings emphasize the intriguing relationship between the brain and blood pressure and suggest that low blood pressure is mainly a secondary phenomenon in dementia disorders.

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