Vascular risk factors, atherosclerosis, cerebral white matter lesions and cerebral perfusion in a population-based study

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Abstract. We studied risk factors for cerebral vascular disease (blood pressure and hypertension, factor VIIc, factor VIIIc, fibrinogen), indicators of atherosclerosis (intima-media thickness and plaques in the carotid artery) and cerebral white matter lesions in relation to regional cerebral blood flow (rCBF) in 60 persons (aged 65–85 years) recruited from a population-based study. rCBF was assessed with single-photon emission tomography using technetium-99m *d,l*-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO). Statistical analysis was performed with multiple linear regression with adjustment for age, sex and ventricle-to-brain ratio. A significant positive association was found between systolic and diastolic blood pressure and temporo-parietal rCBF. In analysis with quartiles of the distribution, we found a threshold effect for the relation of low diastolic blood pressure (≤60 mmHg) and low temporo-parietal rCBF. Levels of plasma fibrinogen were inversely related to parietal rCBF, with a threshold effect of high fibrinogen levels (>3.2 g/l) and low rCBF. Increased atherosclerosis was related to low rCBF in all cortical regions, but these associations were not significant. No consistent relation was observed between severity of cerebral white matter lesions and rCBF. Our results may have implications for blood pressure control in the elderly population.

Key words: Vascular risk factors – Atherosclerosis – Cerebral white matter lesions – Cerebral blood flow – Elderly population

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Introduction

Several studies have related the presence of vascular risk factors to changes in regional cerebral blood flow (rCBF). An overall CBF decrease was reported in persons with vascular risk factors compared to age-matched controls without these risk factors [1] and some authors have suggested an association of vascular risk factors with CBF, including hypertension [2], whole blood viscosity [3] and smoking [4]. Clinical indicators of atherosclerosis have also been linked to decreases in rCBF [5, 6]. However, few reports are available on the relation between indicators of vascular risk and atherosclerosis and rCBF in the general population.

The reported frequency of cerebral white matter lesions in the elderly on magnetic resonance imaging (MRI) scans varies around 25% [7–9] and these lesions may be associated with cognitive impairment of subcorticofrontal functions in a random sample of non-demented elderly subjects [10]. Reductions in CBF investigated with positron emission tomography (PET) and the xenon-133 inhalation technique have been reported in elderly individuals with severe white matter abnormalities [11, 12]. Others, however, did not find a significant relation between periventricular white matter lesions on MRI and CBF measured with the ^{133}Xe inhalation technique [13–15]. Since subjects included in some of these studies were selected on the basis of presence or absence of cardiovascular risk factors, these inconsistent results leave open the question of whether, in the general population, lesions in cerebral white matter are associated with decrements of rCBF in cerebral grey matter.

In this study, we investigated in a population-based sample the association of rCBF, measured with single-photon emission tomography (SPET) using technetium-99m *d,l*-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO), and vascular risk factors, including thrombogenic factors, indicators of atherosclerosis and cerebral white matter lesions on MRI.

Materials and methods

Subjects. This study is based on a population-based study (The Rotterdam Study) [16] for which all persons of 55 years and over from the suburb of Ommoord in Rotterdam were eligible, including institutionalized persons. The response rate of the main study was 79% and written informed consent was obtained for participation in this study as well as the SPET investigation. Subjects for the present study were recruited from a group of 111 persons randomly selected as a stratified sample of persons from 65 to 85 years old who participated in an MRI study (response rate 87%) [9]. In this MRI study three persons were excluded because they had a pacemaker or metal prostheses or clips, one because he was suffering from a major psychiatric disorder and two because they were wheelchair-bound. An additional 21 persons were excluded from the SPET study because they had a neurological disorder with a known effect on rCBF, including a history of transient ischaemic attacks (TIAs) or stroke, Parkinson's disease or dementia, including Alzheimer's disease (employing a careful screening for dementia [17] and NINCDS-ADRDA criteria) [18]. Twenty-four of the 90 eligible persons refused participation and one died before the SPET study could be performed. Five scans were not available for technical reasons and a total of 60 subjects were included in the present study.

Measurements. At a home interview, information was obtained from subjects on current health status, medical history, drug prescriptions and actual use, and smoking behaviour by a trained interviewer using a computerized questionnaire. Subjects were divided into three groups of smoking behaviour: current smokers, former smokers and those who had never smoked. A history of cerebrovascular event was considered positive when the diagnosis had been made by a physician and the diagnosis of myocardial infarction was based on ECG.

At the research centre several measurements were performed as part of the baseline data collection. The average of two blood pressure measurements, separated by a count of the pulse rate, taken in the sitting position at the right upper arm with a random-zero sphygmomanometer was used for the analysis [19]. Hypertension was defined as systolic blood pressure of ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg, and/or by the use of antihypertensive drugs for the indication hypertension. The collection of blood samples and subsequent procedures, and determination of serum total cholesterol, high-density lipoprotein cholesterol, plasma fibrinogen levels, factor VIIc and factor VIIIc activity, have been described in detail previously [9].

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear array transducer using a Duplex scanner (ATL Ultramark IV, Advanced Technology Laboratories, Bethel, Washington, USA), according to the Rotterdam Study scanning protocol [20]. The distance between the lumen-intima interface and the media-adventitia interface of the far wall represents the intima-media thickness [21]. The interfaces of the distal common carotid artery were marked with a cursor over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. The average of the intima-media wall thickness of each of three frozen images stored on video tape was taken as a measure for the current wall thickness of the distal common carotid artery. In addition, for each subject the total intima-media wall thickness was calculated as the average of the left and right side. Results from a reproducibility study on intima-media thickness measurements have been described elsewhere [22]. The carotid artery was also evaluated for the presence of atherosclerotic plaques, defined as focal widening relative to adjacent segments, with protrusion into the lumen composed either of only calcified deposits or of a combination of calcification and non-calcified material. A reproducibility study for the assessment of plaques in the carotid bifurcation showed moderate agreement [23].

SPET. Regional CBF studies were performed with ^{99m}Tc-HMPAO, prepared by adding 1110 MBq freshly eluted sodium pertechnetate to a vial containing freeze-dried 0.5 mg *d,l*-HMPAO, 7.6 μg stannous chloride dihydrate and 4.5 mg sodium chloride (Ceretec). From this mixture, 740 MBq was intravenously administered within 15 min after preparation. SPET scanning was carried out 10–20 min later. Data acquisition was performed with either a single-headed rotating gamma camera (Orbiter by Siemens) with a low-energy all-purpose collimator (n = 36), or a three-headed rotating gamma camera (Prism 3000 by Picker; n = 24). Total acquisition angle was 360°, 60 projections of 30 s each, with a 64×64 matrix and spatial resolution for tomographic images of approximately 12 mm for the Siemens camera (estimated by the calculation of the full-width at half-maximum for 99mTc using an air distance between the object and rotating collimator of 15 cm), and a 128×128 matrix and approximately 7 mm spatial resolution for the Picker camera, as estimated by the manufacturer. We reconstructed transversal (parallel to orbitomeatal line) slices, after correction for attenuation, by calculation of the geometric means. The geometric mean was calculated giving weight to each variable relative to the distance to the outer cortex.

Regions of interest. Regions of interest (ROIs) were drawn by a standardized procedure on a personal computer with GAMMAPC 1.41 software (Dr. O. Nickel, Department of Nuclear Medicine, University of Mainz, Germany), as described previously [24, 25] The matrix of images acquired with the Picker camera was reduced from 128×128 to 64×64. The reference slice included one cerebellar hemisphere that contained a pixel with the highest counts of the entire cerebellum. After drawing a region by hand roughly around this hemisphere, the computer precisely defined a subregion within this region, with activity higher than 70% of the maximum value in this slice. The boundary of this reference region corresponded to the anatomical boundary of the cerebellum with reference to an anatomical atlas [26]. The mean activity of this ROI in counts per pixel was regarded as the reference value and all other slices in a linear colour scale were set relative to this value. The ROIs corresponding to frontal, temporal, temporo-parietal and parietal cortices were drawn by hand, in all slices, with reference to an anatomical atlas [26]. The temporo-parietal region was defined as the transition area of the temporal and parietal cortex where no reliable differentiation between these two areas could be made. The outer border of these ROIs was placed at the first line of pixels with a fast decline in activity, assuming that this reflects the transition from brain tissue to cerebrospinal fluid. The inner border was set to a fixed distance of 2 cm from the outer border to approximate the area of grey matter in the brain. With this method our intra-observer variability in terms of mean counts per pixel in a specific ROI was 0.8%. With the exception of the outermost slices, all slices were included in the analysis. Normalized rCBF was defined as the average counts per pixel within an ROI divided by that of the cerebellar reference slice and multiplied by 100 (percentage). The average of right and left ROIs was used for all cortical regions, since no differences between right and left ROIs were found.

Magnetic resonance imaging. MRI scans of the brain were performed with a 1.5-T Philips Gyroscan. T2-weighted axial images

were obtained using multiple-slice spin-echo sequences with a repetition time of 2000 ms and an echo time of 50 and 100 ms. The total volume of the ventricles and corresponding total brain volumes were measured according to a previously described procedure [10]. The perimeters of the entire brain and of the ventricles were identified on each axial slice containing the lateral ventricles, with the use of a light table and transparent paper. The areas were measured in pixel percentages by means of an IBAS 2000 (Zeiss-Kontron) and summed over all slices. The volume of the lateral ventricles was expressed as a percentage of the total brain volume (ventricle-to-brain ratio) [27, 28].

The presence and severity of white matter lesions were defined as described previously [10]. In short, a distinction was made between white matter lesions directly adjacent to the ventricles (periventricular lesions) and punctate or confluent lesions at some distance from the ventricles (focal lesions). Punctate lesions were dichotomized at fewer than five and five or more lesions [8]. Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal. The overall severity of white matter lesions was graded as follows. Normal scans (grade 0, no/slight white matter lesions) showed no or slight periventricular hyperintensity (small caps or pencil-thin lining), fewer than five focal lesions and no confluent lesions. Abnormal scans with moderate periventricular hyperintensity (caps on both anterior and posterior horns of the lateral ventricles, corpus only partly involved, not irregularly extending into the deep white matter), five or more focal lesions, or both, but no confluent lesions, were classified as grade 1 (moderate white matter lesions). Abnormal grade 2 scans (severe white matter lesions) showed severe periventricular hyperintensity (irregularly extending into the deep white matter or marked areas of hyperintensity completely surrounding the lateral ventricles) or confluent lesions. For comparison of persons with and without cerebral white matter lesions, persons with grade 1 and grade 2 scans were combined.

Statistical analysis. The relations between various individual variables (vascular risk factors, indicators of atherosclerosis and cerebral white matter lesions) and normalized rCBF were examined with multiple linear regression analysis, with adjustments for age, sex, type of SPET camera and ventricle-to-brain ratio [29]. When a significant relation was found, an additional analysis was performed with quartiles of the distribution, using indicator variables [29]. The relation between cerebral white matter lesions and rCBF was also analysed for trend, using the variable grade of severity as an independent and rCBF as a dependent variable. For analyses with factor VIIc activity, subjects taking anticoagulant medication at the time were excluded. Regression coefficients [with 95% confidence interval (CI)] are reported as a measure of the strength of the association between putative determinants and rCBF.

Table 1. Subject characteristics[a]

	65–75 years (n = 33)	76–85 years (n = 27)	All subjects (n = 60)
Sex (men/women)	16/17	12/15	28/32
CAMCOG[b]	94.2±6.8	90.3±8.7	92.5±7.9
MMSE[b]	28.7±1.2	27.5±2.0	28.2±1.7
Ventricle-to-brain ratio	7.0±1.9	8.3±1.6	7.6±1.9
Systolic blood pressure (mmHg)	132.2±19.3	142.3±18.1	136.7±19.3
Diastolic blood pressure (mmHg)	69.5±11.4	69.1±10.2	69.3±10.7
History of hypertension (n)	6	7	13
History of myocardial infarction (n)	1	5	6
Anticoagulant therapy (n)	2	3	5
Haematocrit (l/l)	0.41±0.04	0.40±0.04	0.40±0.04
Fibrinogen (g/l)	2.8±0.7	3.2±0.6	3.0±0.7
Factor VIIc (IU/l)	1.0±0.3	1.0±0.3	1.0±0.3
Factor VIIIc (IU/l)	1.9±0.7	2.1±0.7	2.0±0.7
Cholesterol (mmol/l)	6.5±1.5	6.5±1.2	6.5±1.3
HDL (mmol/l)	1.2±0.3	1.2±0.4	1.2±0.3
Intima-media vessel wall thickness (mm)	80.2±18.2	92.5±25.9	85.3±22.3
Plaques in either carotid bifurcation (n)	16	15	31
Frontal rCBF (%)	84.9±5.6	83.5±5.2	84.2±5.4
Parietal rCBF (%)	83.4±5.1	81.3±5.9	82.4±5.4
Temporo-parietal rCBF (%)	79.3±6.4	77.2±6.0	78.4±6.3
Temporal rCBF (%)	84.1±4.8	81.7±4.3	83.0±4.7
No/slight WML (n)[c]	28	18	46
Moderate WML (n)	3	5	8
Severe WML (n)	2	4	6

[a] Values are reported as mean ±SD

[b] Cognitive test from the Cambridge Examination for Mental disorders of the Elderly (CAMDEX) [49, 50] and Mini-Mental Status Examination (MMSE) [51]

[c] White matter lesions (WML). No/slight: <5 focal lesions, no/slight periventricular hyperintensities and no confluent lesions. Moderate: <5 focal lesions, moderate periventricular hyperintensities and no confluent lesions, *or* ≥5 focal lesions, no/slight/moderate periventricular hyperintensities, and no confluent lesions. Severe: confluent lesions and/or severe periventricular hyperintensities

Results

Characteristics of the study subjects are presented in Table 1. Twenty-three percent of the subjects had white matter lesions while 10% had severe white matter lesions.

Analysis of blood pressure, independent of the effect of age, showed that both diastolic and systolic blood pressure were positively associated with normalized values of rCBF in all cortical regions, and these relations were statistically significant for temporo-parietal rCBF (Table 2). High fibrinogen levels were related to low normalized rCBF in all cortical regions, and a statistically significant relation was observed for parietal rCBF (Table 2). The relation of fibrinogen and parietal rCBF persisted after adjustment for previous myocardial infarction. Since current smoking is associated with increased levels of fibrinogen, these analyses were adjusted for current smoking. Smoking itself, defined in three groups of smoking behaviour, was not related to rCBF.

A threshold effect was observed for the relation of diastolic blood pressure and temporo-parietal rCBF in the additional analysis with quartiles of the distribution. Subjects in the lowest quartile of the distribution of diastolic blood pressure (≤60 mmHg) had a significantly lower temporo-parietal rCBF than subjects above the 25th percentile (difference –5.1% rCBF; 95% CI:–8.4%,–1.8%) (Fig. 1). Similar results were observed when subjects using antihypertensive drugs were excluded. Presence of hypertension was associated with higher normalized rCBF in all cortical regions, but none of these relations were statistically significant (Table 2). Subjects in the highest quartile of the distribution of fibrinogen (>3.2 g/l) had significantly less parietal rCBF than subjects below the 75th percentile (difference –4.4% rCBF; 95% CI:–8.1,–0.7) (Fig. 2). No significant associations were found between factor VIIc, factor VIIIc and normalized rCBF (Table 2).

Measurements of the intima-media wall thickness of the carotid artery and plaques in either carotid bifurcation revealed lower normalized rCBF in all cortical re-

Table 2. Differences in rCBF in percentage relative to cerebellum according to levels of blood pressure, vascular risk factors, indicators of atherosclerosis and cerebral white matter lesions, adjusted for age, sex, ventricle-to-brain ratio and type of SPET camera[a]

	Normalized rCBF in percentage relative to cerebellum							
	Frontal		Parietal		Temporo-parietal		Temporal	
	Difference	(95% CI)	Difference	(95% CI)	Difference	(95% CI)	Difference	(95% CI)
Blood pressure								
Systolic blood pressure (per 10^{-1} mm Hg)	0.2	[–0.6, 1.0]	0.5	[–0.3, 1.3]	0.8	[0.1, 1.5]*	0.5	[–0.1, 1.1]
Diastolic blood pressure (per 10^{-1} mmHg)	0.1	[–1.3, 1.5]	0.6	[–0.6, 1.8]	1.7	[0.4, 3.0]*	0.6	[–0.5, 1.7]
Hypertension (with versus without)[b, c]	0.5	[–2.8, 3.8]	1.6	[–1.5, 4.7]	1.8	[–1.7, 5.3]	2.3	[–0.4, 5.0]
Thrombogenic factors								
Hematocrit (per standard deviation l/l)	–0.8	[–2.4, 0.9]	0.1	[–1.5, 1.6]	–0.5	[–2.2, 1.2]	–0.7	[–2.1,0.7]
Fibrinogen (per g/l)	–0.2	[–2.3, 1.9]	–2.0	[–3.9, –0.1]*	–1.5	[–3.7, 0.7]	–0.5	[–2.3,0.3]
Factor VIIc (per 10^{-1} IU/l)	5.8	[–1.6, 13.2]	4.2	[–2.7, 11.1]	4.6	[–3.4, 12.6]	4.4	[–1.7, 10.5]
Factor VIIIc (per 10^{-1} IU/l)	0.4	[–1.8, 2.6]	–0.2	[–1.9, 2.3]	0.4	[–2.0, 2.8]	0.4	[–1.4, 2.2]
Plasma lipids								
Total cholesterol (per mmol/l)	0.0	[–1.1, 1.1]	0.2	[–0.8, 1.2]	0.1	[–1.1, 1.3]	–0.4	[–1.3,0.5]
HDL cholesterol (per 10^{-1} mmol/l)	0.3	[–3.8, 4.4]	0.1	[–3.8, 4.0]	–1.8	[–6.2, 2.6]	–1.6	[–4.1, 1.9]
Indicators of carotid atherosclerosis								
Intima-media vessel wall thickness (per 10^{-1} mm)	–0.2	[–0.9,0.5]	–0.5	[–1.1,0.1]	–0.5	[–1.2,0.2]	–0.2	[–0.8,0.4]
Plaques in either carotid bifurcation (without versus with)[d]	–2.2	[–5.4, 1.0]	–1.6	[–4.7, 1.5]	–1.7	[–5.2, 1.8]	–0.9	**[–3.8, 2.0]**
Cerebral white matter lesions (no/slight versus moderate/severe)[e]	–1.7	[–5.4, 2.0]	0.4	[–2.9, 3.7]	1.2	[–2.7, 5.1]	–0.4	[–3.5, 2.7]

* Significant relation between independent variable and rCBF ($P<0.05$)

[a] Multiple linear regression coefficients are with 95% confidence intervals (95% CI)

[b] Defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg, or use of antihypertensive medication

[c] Differences in % rCBF between persons with (n = 13) and without (n = 47) hypertension, respectively

[d] Differences in % rCBF between persons with (n = 31) and without (n = 16) plaques in either bifurcation of the carotid artery

[e] Differences in % rCBF between persons with no/slight cerebral white matter lesions (n = 46) and persons with moderate/severe cerebral white matter lesions (n = 14)

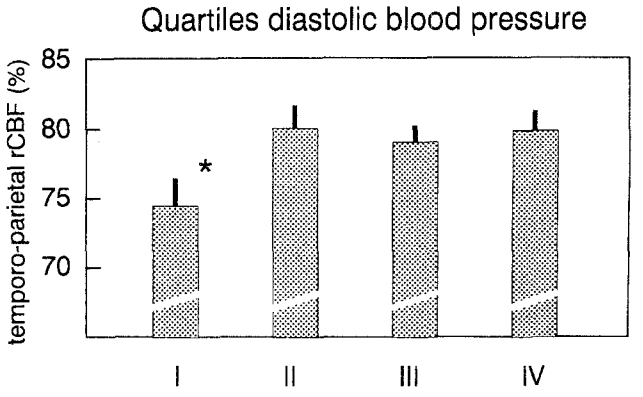

Fig. 1. Mean temporo-parietal rCBF values in percentage relative to cerebellum are shown for quartiles of diastolic blood pressure distribution. The 1st quartile is significantly different from the other quartiles with multiple linear regression, adjusted for age, sex, ventricle-to-brain ratio and type of SPET camera ($P<0.01$)

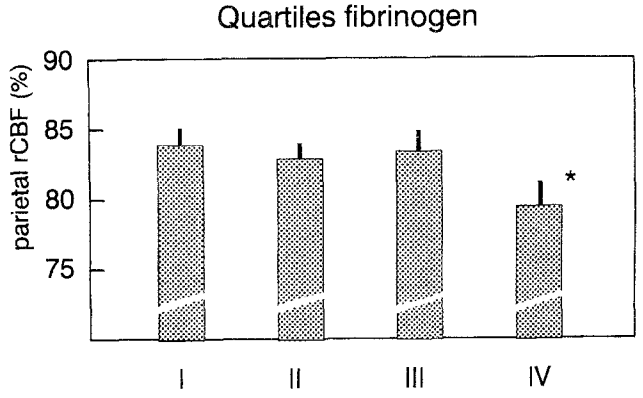

Fig. 2. Mean parietal rCBF values in percentage relative to cerebellum are shown for quartiles of fibrinogen distribution. The 4th quartile is significantly different from the other quartiles with multiple linear regression, adjusted for age, sex, ventricle-to-brain ratio and type of SPET camera ($P<0.01$)

gions, but the inverse associations were not statistically significant (Table 2). Also when these relations were examined on either the right or the left side, similar results were obtained.

No consistent patterns of rCBF change with the presence of cerebral white matter lesions could be detected (Table 2). In persons with moderate or severe white matter lesions a decrease was observed in frontal rCBF while a slight increase was present in temporo-parietal rCBF. Using analyses for linear trend, these changes were not statistically significant.

Discussion

We studied the relation of vascular risk factors, indicators of atherosclerosis, cerebral white matter lesions and rCBF in a sample from the general population aged 65–85 years. The distribution of various demographic and vascular characteristics under study was very similar in the 60 subjects studied with SPET in this study to that in all subjects included in the original population in the same age range. Analysis of the relation between blood pressure and rCBF corrected by age revealed that both diastolic and systolic blood pressure were associated with temporo-parietal rCBF. A threshold effect of low temporo-parietal rCBF was observed with diastolic blood pressure under 60 mmHg independent of the presence of hypertension. Increased atherosclerosis, indicated by measurements of the intima-media wall thickness of the carotid artery and plaques in the carotid bifurcation, was consistently associated with lower rCBF in all regions examined. However, these relations were not significant. Examination of thrombogenic factors in relation to rCBF showed that high levels of fibrinogen were independently associated with decreased rCBF in parietal cortex. In addition, no consistent relations between severity of cerebral white matter lesions and rCBF were observed.

The relation between blood pressure and temporo-parietal CBF in our study contrasts with results from previous studies, where no significant associations [30–33] or an inverse association [34] were found. Furthermore, hypertension has been associated with global CBF decrease [35], even in asymptomatic patients [2]. The discrepancies with results from our study are probably explained by differences in the study populations, since in previous studies few subjects over 65 years were included and persons were not selected from the general population. In addition, most of these studies used the ^{133}Xe inhalation method [2, 30–32, 34, 35] with a lower spatial resolution and reliability [36] than SPET with ^{99m}Tc-HMPAO. Moreover, no statistical adjustment for age was made in a multiple comparison model in these studies. The role of atherosclerosis in rCBF changes in the healthy elderly is hard to compare with results from other studies since no direct quantified measures of atherosclerosis were taken in previous studies [5, 6]. Indirect comparison is possible with those studies that have compared rCBF in persons with and without risk factors for vascular disease. The results of our study are in agreement with observations of reduced rCBF in those subjects with clinical evidence of atherosclerosis or increased vascular risk [5, 6] and with the finding that subjects with asymptomatic carotid artery disease have lower CBF values than asymptomatic subjects without abnormalities of the carotid artery [37].

The reduction in temporo-parietal rCBF in relation to blood pressure (the temporo-parietal region corresponding to the watershed area between the middle cerebral artery and the posterior cerebral artery) suggests that this region is most susceptible to changes in cerebral perfusion pressure, as previously reported [38]. In particular, our results are compatible with a shift of the lower limit of cerebral autoregulation to a higher pressure level in the elderly population [39–42]. Autoregulation is mainly a function of small arteries and arterioles [39, 43] and it has been suggested that atherosclerosis impairs the contractility of the muscle wall of these vessels [44]. It is

tempting to speculate, based on this hypothesis of altered cerebral autoregulation, that one should be wary of low blood pressure levels in the elderly population. Further studies are needed, however, to determine precisely the clinical relevance of low temporo-parietal rCBF as related to low blood pressure levels.

The relation of cerebral white matter lesions and CBF in cerebral grey matter has been investigated in both symptomatic and asymptomatic study populations. In asymptomatic individuals, not selected by presence or absence of vascular risk factors, no significant CBF differences between subjects with and without white matter lesions were found [13–15]. In asymptomatic subjects, selected by the presence of cerebrovascular risk factors, two studies reported significantly decreased CBF in all cortical regions [11, 32]. When symptomatic patients with atherosclerotic carotid artery disease were investigated, a global CBF reduction was observed in those with severe white matter lesions [12], and patients with vascular dementia of the Binswanger type showed decreased CBF compared to controls in frontal, temporal and parietal cortex [30]. With few reports available, these studies suggest that there is no, or only a weak inverse relation between cerebral white matter lesions and CBF in asymptomatic individuals that becomes stronger when this relation is examined in those with vascular risk factors and in symptomatic subjects. The absence of consistent rCBF changes in persons with moderate/severe cerebral white matter lesions in our study, where subjects were randomly sampled from the population and neurologically symptomatic individuals were excluded, fits well with these observations. Thus, together with data from previous studies, it appears that there are rCBF reductions related to cerebral white matter lesions in selected subjects with high risk of atherosclerotic vessel disease, as evidenced by the presence of vascular risk factors or by clinical symptoms, but not in those from the general population.

The inverse and independent relation of fibrinogen with parietal rCBF in our study is in agreement with the previously reported inverse relation of fibrinogen with global CBF in a heterogeneous sample of patients with vascular disease and controls [3] and in healthy persons over 45 years [45]. This is probably a result of lower blood flow velocity of the middle cerebral artery in subjects with high fibrinogen serum levels [46]. Further, the absence of some relations between indicators of vascular risk and rCBF fits well with previously reported results. Although Meyer et al. found a trend towards lower CBF values in normal subjects with elevated cholesterol and triglycerides, these relations were not significant [47]. A recent study showed that even long-lasting hypercholesterolaemia was not associated with alterations in CBF [48]. We found no significant alterations in rCBF as a function of haematocrit, which is consistent with a minimal relation of haematocrit with CBF in asymptomatic individuals as reported by Mathew et al. [34]. It appears that only in patients with cerebrovascular disease is decreased CBF observed with higher levels of haematocrit, and these patients were excluded from our study [3].

In conclusion, both systolic and diastolic blood pressure are related to rCBF in temporo-parietal cortex, possibly due to altered cerebrovascular autoregulatory function. These findings may have clinical relevance for blood pressure control in the elderly population. In addition, high levels of fibrinogen are related to low rCBF in parietal cortex, possibly due to decreased blood flow velocity of the middle cerebral artery. Finally, cerebral white matter lesions in a sample from the general population appeared not to be related to rCBF.

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