CEREBRAL HEMODYNAMIC INDICES

MEASURED BY MEANS OF

TRANSCRANIAL DOPPLER

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measured by means of

transcranial Doppler

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gemeten met behulp van

transcraniële Doppler

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GENERAL INTRODUCTION

HISTORY

Christiaan Huijgens, Dutch physicist, mathematician and astronomer who lived between 1629 and 1695 formulated his theory of the nature of light in "Traité de la Lumiere (1692). In this monologue, he defined the kinematics of wave propagation, better known as the "Huijgens' principle", on which the development of the transducer for ultrasonic imaging, presently the most versatile and widely used imaging technique, is based.

Some confusion has been risen concerning the name of the famous Doppler descendant, as Alec Eden put it nicely in his famous letter,[1] but it was the Austrian physicist Christian Andreas Doppler (1803-1853) *(see appendix for a unique photograph)* and not, as stated many times, his older brother Johann Christian Doppler, who described and explained color shifts in the visible light of double stars in 1842 in *Über das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels* (On the coloured Light of Double Stars and Certain Other Stars of the Heavens) while working in Prague. This basic assumption, also called the *Doppler frequency shift*, has proven valid for most other waveforms, including (ultra)sound. With the proposition of the Doppler shift in medical science, it was possible to obtain information on the blood flow velocity and its direction. Introduced by Miyazaki and Kato, Doppler ultrasound was used routinely in neurological and neurosurgical practice to record the blood flow velocity in the extracranial arteries supplying the brain, from 1965 on.[2] During the late nineteen sixties and seventies, the blood flow velocity in the intracranial vessels was only observed by Doppler techniques during neurosurgical procedures or in children with open fontanels, because the skull was always a severe obstacle to the penetration of ultrasound.

Aaslid and co-workers in 1982 introduced the range-gated noninvasive *transcranial* Doppler (TCD) ultrasound instrument with a frequency of 2 MHz and the skill to penetrate the thin bone of the temporal region, by using the so-called "ultrasonic window" technique.[3] With this approach, it was possible to insonate the middle, anterior, and posterior cerebral arteries. In order to try and quantify changes in the normal waveforms, Gosling and King introduced the pulsatility index (PI) in 1974, which is thought to represent cerebrovascular resistance.[4] Reactivity of cerebral vessels to CO_2 was observed in experimental studies in the newborn rhesus monkey in the early seventies.[5] The first TCD study in men that described the dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure was published in 1984.[6]

Since the early nineteen eighties, TCD became more easily available for both clinical practice and research. Technique and devices have undergone several improvements and significant changes. Nowadays, multi-channel instruments, allow for simultaneous bilateral insonation, are readily available. The ability to store data, even real-time information, and to produce hard copy results has also been improved and incorporated into TCD instruments. Other ultrasound techniques have made their entry into neurological and neurosurgial research. The value of TCD, as other neuro-ultrasound techniques, such as transcranial sonography (TCS), transcranial color-coded sonography (TCCS), tissue harmonic imaging (THI), contrast-enhanced three-dimensional power Doppler

(CE3DPD) and transcranial duplex (TCDu), in which the Doppler technique is combined with conventional B-mode imaging, in everyday clinical practice is still under investigation and subject of debate.

BASIC PRINCIPLES, TECHNICAL CONSIDERATIONS AND ADVANTAGES OF TCD

Basic principles

Ultrasound is an energy form with a frequency of more than 20,000 waves per second indicating that these frequencies rate above the audible range for humans. In the Doppler apparatus, electrical power is sent to the transducer crystal which converts it to acoustic energy. The emitted beam can produce short pulses or packets of ultrasound. These acoustic pulses move away from the transducer at a known propagation speed for soft tissue. Subsequently, they collide with a moving object and reverberate to the transducer (see figure 1).

The *Doppler frequency shift* (Δf) describes the difference between transmitted and reflected frequencies. The magnitude of the *Doppler frequency shift* is directly related to the speed of the reflector (blood flow speed = v), transmitted incident frequency (f) and the propagation speed (c) through the following equation (1):

$$\Delta f = \frac{2 \cdot v \cdot f}{c}$$

Because the direction of the sound beam is not identical to the flow direction, correction for the apparent decrease in the *Doppler frequency shift* is needed by the cosine of the angle (α) of insonation through the following equation (2):

$$\Delta f = \frac{2 \cdot v \cdot f \cdot \cos\alpha}{c}$$

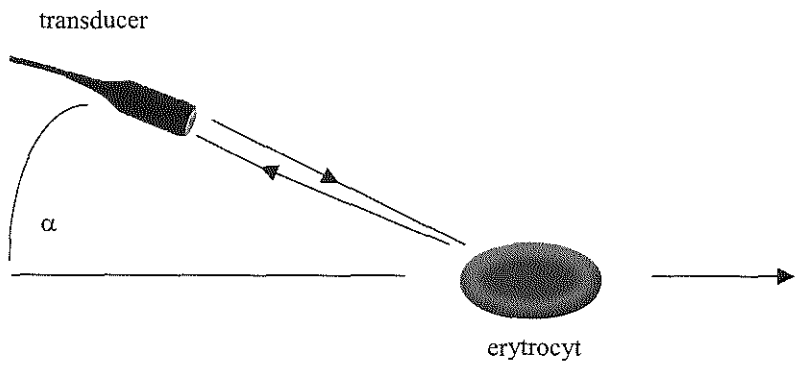

Figure 1

Technical considerations

During transtemporal measurements, the transducer is placed on the side of the head just cephalad to the zygomatic arch and immediately anterior and slightly superior to the tragus of the ear conch. A 0-30° angle (α) of insonation is assumed for blood flow velocity estimations during TCD examination. If the insonation angle exceeds 30°, uncorrected blood flow velocities are lower compared with corrected flow velocities and hence give rise to misinterpretation. Because TCD is a blind procedure, it is not possible to routinely correct for insonation angle errors, which are presumed to be small in anatomically normal brains.[7] On the other hand, it has been suggested that in approximately 25% of insonated arteries the insonation angle exceeds 30°.[8] Next to the angle correction, transcranial Doppler has others limitations and these should be taken into account when interpreting its findings.

First, inadequacy for the ultrasonic beam to penetrate the relatively thin bone of the temporal region of the skull, or window failure, is found in 5-20% of patients and other imaging procedures have to be used in these patients. In black and japanese subjects and also with advancing age, especially in postmenopausal women, the percentage of window failure can mount up to 40%,[9] and is considered to be one of the main disadvantages of transcranial Doppler. The explanation for this window failure lies in the fact that the skull has considerable effects on the geometry of the ultrasonic beam, varying from a simple shortening of the focal distance to complete disintegration of the sample volume caused by irregularities of the inner bony surface. The distortion effects of the temporal bone are variable and unpredictable. Part of these difficulties may be compensated for by either increasing the acoustic output of the instrument or improving the visibility of the intracranial vessels with echo-enhancing substances. When monitoring is essential and no temporal acoustic window is available, a transorbital approach for middle cerebral artery blood flow velocity recording is recommended as an alternative.[10] Second, like other ultrasound techniques, TCD is operator dependent and consequently, reproducibility of the results may vary. TCD reports appear to be highly reproducible when based upon the interpretation of qualitative data (Kappa: 0.95-1.00), whereas a moderate to good agreement is obtained when considering alterations in quantitative parameters (Kappa: 0.44-0.81).[11] For this reason, it has been advocated that TCD should be performed and interpreted by those with adequate background, training, and experience with the diagnostic modality. Even neurosonology certification for physicians and neurovascular laboratory accreditation are recommended. Finally, TCD examinations are time consuming and adequate and complete diagnostic examinations will cost approximately one hour, whereas examinations that include spectral analysis will last even at least an hour and a half longer.

Advantages

Although the above mentioned disadvantages can not be ignored, TCD has become a useful diagnostic tool in neurological research. TCD is noninvasive, puts no strain on the patient, can be repeated at bedside at any time and is considered to be cheap. The possibility of monitoring cerebral hemodynamics on both sides for a longer period of

time is thought to be one of the main advantages of TCD over other ultrasonic examinations, such as transcranial duplex.

Depending on emitted powers, thermal effects of focused ultrasound exposure of brain tissue have been described in an experimental setting, but it is generally accepted that exposure to ultrasound is a safe medical examination in humans.[12]

TCD MEASUREMENTS IN GENERAL

Transcranial Doppler examinations can be used for diagnostic, for functional measurements, and for monitoring during (cardio)vascular surgery. As the temporal bone window is used to insonate the anterior part of the circle of Willis, natural gaps in the human skull are used for other TCD examinations. The orbit at the front and the foramen magnum at the rear side of the skull are used to examine other parts of the basal cerebral arteries such as the ophtalmic artery and the vertebrobasilar arteries. TCD findings have been described even without using these natural gaps, for example in patients with acute thrombosis of the sagittal venous sinus.

Diagnostic measurements

Peak systolic, end diastolic and mean cerebral blood flow velocity (centimeters/second) and their directions can be registered and monitored in the basal cerebral arteries of both the anterior and posterior circulation on both sides if needed *(see appendix for an example of the waveform of the middle cerebral artery)*. Indices that are thought to be indicative for cerebrovascular resistance, such as the pulsatility index (PI = (peak systolic blood flow velocity - end diastolic blood flow velocity) / mean blood flow velocity) and resistance index (RI = (peak systolic blood flow velocity - end diastolic blood flow velocity) / peak systolic blood flow velocity), are generally computed automatically from the envelope of the Doppler spectrum using fast Fourier transformation.

Functional measurements

TCD may be used to study the dynamics induced by metabolic changes, or by focal brain activation. Changes of flow velocity in the middle cerebral artery, elicited by hemisphere-specific cognitive tests are detectable by unilateral or bilateral recordings, as this vessel perfuses about 80% of the cerebral hemisphere. It has been known for example, that flow velocity in the posterior cerebral artery increases significantly in response to light stimulation.[13] Recent observations show that functional TCD may be helpful for the detection of the determination of language dominance,[14] which may replace the Wada test in the future. Monitoring of patients with sleep apnea has revealed significant changes in intracranial flow. The common carotid artery compression tests may be performed in patients before carotid surgery, in order to obtain information whether the circle of Willis is functional or not and to determine if a shunt is indicated.

Cerebrovascular reactivity or cerebral vasomotor reactivity reflects this compensatory dilatory mechanism to a vasodilatory stimulus of the intracerebral arterioles,[15,16]

and is thought to provide a more sensitive hemodynamic index than the level of resting blood flow velocity.[17] The cerebrovascular reactivity can be assessed by measuring changes in flow velocities in response to acetazolamide injection, hyperventilation, CO_2 inhalation, or breath-holding. The CO_2 method of testing is preferred as there is less risk, the effect is stronger and there is greater certainty regarding which arterial segments are affected *(see appendix for example of normal cerebrovascular CO_2 reactivity registration).*[16] Cerebral vasomotor reactivity can be assessed in different intracranial vessels and it is still unknown whether this specific cerebral hemodynamic parameter is equal in different cerebral arteries, as it is recently suggested that the ophtalmic artery for example has a specific autoregulative response.[18]

Monitoring

TCD monitoring may generally take place during carotid procedures and cardiac surgery and may concern both flow velocity and spectral analysis. Using spectral analysis, high-intensity transient signals (HITS) or micro-embolic signals (MES) can be detected as abnormalities within the bloodstream which, for example, can be detected in patients with atrial fibrillation, cardiac prosthetic valve or carotid artery disease. Although Doppler techniques and software have undergone many improvements during the last years, it is still very difficult to determine the composition of HITS. There is strong evidence that transcranial Doppler can be used to detect cerebral microembolization, but the clinical usefulness of identifying the passage of microemboli into the cerebral circulation remains to be studied.

GENERAL CLINICAL APPLICATIONS

Many clinical practitioners including neurologists, neurosurgeons, anesthesiologists and pediatricians have been interested in the use of transcranial Doppler. TCD was first used to evaluate vasospasm following subarachnoid hemorrhage.[19] It has been suggested that for the individual patient, only low or very high middle cerebral artery flow velocities (i.e., <120 or more than 200 cm/s, respectively) reliably predict the absence or presence of clinically significant angiographic vasospasm and that intermediate flow velocities are not dependable and therefore should be interpreted with caution.[20] Nowadays TCD is routinely used as a diagnostic tool on both the neurological as the neurosurgical wards and on the neuro-intensive care unit for a variety of diagnoses, such as ischemic cerebrovascular disease, migraine, and stenoses and occlusions of main cerebral arteries. It has become a useful instrument in the evaluation of cerebral hemodynamics in carotid artery disease.[21,22] Also during several operations and procedures, such as carotid endarterectomy, carotid stenting and cardiac surgery, TCD has been frequently used as monitoring device. Even in space and aviation medicine, it has been used for scientific research.[23]

Serial TCD studies allow monitoring of venous hemodynamics and collateral pathways in patients with cerebral venous thrombosis, but normal venous velocities in serial

measurements, however, do not exclude a diagnosis of cerebral venous thrombosis.[24,25] Although determination of brain death by TCD should be carried out by an experienced investigator since unexpected collateral flow signals can be misinterpreted,[26] the application of TCD for the diagnosis of brain death is promising.[27] This seems especially the case in patients treated with central nervous system depressant drugs, in whom TCD may significantly reduce the time taken to confirm brain death, which may be important for organ donation. In this setting, it has been suggested that transcranial Doppler is even superior to brain scintigraphy.[28] Testing for cerebral circulatory arrest, TCD is given a type B recommendation.[16] Whether TCD data may allow for an assessment of the forces acting on the terminal vasculature of the brain in patients with elevated intracranial pressure (ICP) is still under debate. Statistically significant correlations have been found between elevated ICP on the one hand and lower blood flow velocity and elevated PI and RI in the middle cerebral artery on the other.[29] ICP B-waves parallel changes in the TCD signal (the so-called TCD B-waves equivalents), but the clinical relevance is questionable.[30] It is generally accepted that exact noninvasive measurement of ICP by TCD is impossible. Another interesting clinical finding was the recent observation in the thrombolytic treatment in ischemic stroke that ultrasonic energy transmission by TCD monitoring seemed to expose more clot surface to recombinant tissue plasminogen activator (rTPA) and facilitated thrombolysis.[31]

TCD examinations in children have been performed only few years after the introduction in the early nineteen eighties. The cerebral blood flow velocities increase rapidly during the first weeks and reach their maximum around the sixth year of life. The clinical applications of TCD in children cover diseases such as patent ductus arteriosus, perinatal brain damage, increased intracranial pressure, cerebral malformations, brain death, and stenoses and occlusions of main cerebral arteries. As many factors may influence the flow velocities in children, gestational age, birth weight and hematocrit should be taken into account before interpreting TCD findings in children.[32]

TCD data from the elderly, especially in the last decades of life, are scarce and when available, derived from hospital-based studies. These non population-based studies performed thus far, concerning cerebral hemodynamics measured by means of TCD in the elderly, were small by design and observed differences in cerebral hemodynamics between patients with various neurological disorders and their age and sex-matched controls. Occasionally, small non-population based studies have been performed in healthy and relatively young volunteers. These studies have focused mainly on the influence of normal ageing on the cerebral hemodynamic indices.[33-35] Ultrasonic investigations of the general population, using Doppler techniques, have already taken place. Cardiological studies for various diagnoses have been described, as well as screening procedures for carotid stenosis and atherosclerosis. Even screening for ovarian and endometrial cancer in asymptomatic postmenopausal women, using Doppler techniques, has been performed.

Transcranial Doppler examinations in population-based studies in general and in the elderly in particular have not been performed thus far. For the non hospital-based

studies in this thesis we used participants from a unique setting: The Rotterdam Study, which is a population-based prospective cohort study conducted in a suburb of Rotterdam, the Netherlands.

TCD data are available on a generous scale when it comes to various neurological disorders, such as carotid arterystenosis and cardiac valve disease, as described before. However, TCD has not been implemented yet as a standard neurological instrument in everyday practice.

Even in a frequently observed diagnosis as ischemic stroke, follow-up TCD data on cerebral hemodynamics are not available. As a result, it is not known whether the cerebral hemodynamic indices in both hemispheres are affected by unilateral hemispheric ischemia and whether alterations in hemodynamics occur only during the period of ischemia. It has still to be determined whether cerebral hemodynamic indices are associated with clinical outcome. Information on cerebral hemodynamics in patients with an infrequently observed clinical diagnosis as normal pressure hydrocephalus (NPH) is scarcely available and has not been examined prospectively. Whether cerebral hemodynamic indices are influenced by elevated intracranial pressure and whether cerebrospinal fluid shunt surgery alters hemodynamics is still under investigation. Furthermore, it is not known if cerebral hemodynamic indices are related to clinical performance in patients with NPH. For the hospital-based studies we used patients who were admitted to the neurological and neurosurgical wards of the University Hospital Rotterdam-Dijkzigt.

THIS THESIS

The first aim of our population-based study was to investigate the feasibility of TCD investigations in the elderly, with special attention to the cerebrovascular CO_2 reactivity measurements, as it is known that the administration of carbon dioxide by means of an anaesthetic mask during several minutes, although absolutely harmless, may be uncomfortable. Secondly, as reference values of the cerebral hemodynamic indices are scarce in the elderly, especially in the 8th-10th decade and the percentage of window failure in the elderly dutch population is not known, we wanted to obtain a global impression of the cerebral hemodynamics in the elderly non-hospitalized population in the Netherlands. Thirdly, we examined the relationship between age and sex and the cerebral hemodynamic indices. Fourthly, we investigated possible associations between the cerebral hemodynamic indices in the non-hospitalized elderly and laboratory, radiological and neuropsychological abnormalities.

We performed our TCD examinations within the setting of the Rotterdam Study. The Rotterdam Study is a prospective population-based cohort study among 7,983 participants aged 55 years and over (response 78%), which focuses on neurological, cardiovascular, endocrine and ophthalmologic diseases in the elderly. Baseline examination was performed from 1990-1993. From the third survey on (1997-1999), cerebral blood flow

velocity in the middle cerebral artery, pulsatility index and cerebrovascular CO_2 reactivity measurements by means of transcranial Doppler ultrasonography were incorporated in the study protocol.

Chapters 1 and 2 are based on the first 1,300 consecutive participants who visited the study research centre for the third survey in the period May 1997-June 1998. Chapters 1 and 2 involve 826 individuals. In chapter 1, the influence of age, sex and peripheral arterial disease on the cerebral hemodynamic parameters is described. Chapter 2 shows the influence of total cholesterol and high-density lipoprotein cholesterol on the cerebral vasomotor reactivity. Chapter 3 is based on 80 individuals that were randomly selected from the Rotterdam Scan Study. The Rotterdam Scan Study is a population-based study of causes and consequences of age-related brain changes as visible on MRI. In this chapter, the association between cerebral vasomotor reactivity and cerebral white matter lesions is clarified. Chapters 4 and 5 are based on 3,101 consecutive participants from the Rotterdam Study who visited the study research center during the third survey. Chapter 4 unravels the relationship between the cerebral hemodynamic parameters and cognitive decline and dementia. In chapter 5, the association between depressive disorders and cerebral hemodynamics in the elderly is described.

The clinical part of this thesis contains 2 chapters. We have limited the number of diagnoses and have preferred to examine patients with acute ischemic hemispheric stroke and normal pressure hydrocephalus. The aim of our clinical-based studies was to observe and record possible changes in cerebral hemodynamics, induced by ischemic stroke and normal pressure hydrocephalus. In chapter 6, alterations of the cerebral hemodynamic indices due to ischemic stroke are shown. In chapter 7, cerebral hemodynamics and changes in the indices are related to clinical performance in patients with normal pressure hydrocephalus both before and after cerebrospinal fluid shunt surgery.

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CEREBRAL HEMODYNAMIC INDICES IN THE ELDERLY

THE ROTTERDAM STUDY

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Abstract

Objective: Data on the relationship between age, sex, peripheral arterial disease and cerebral hemodynamics are scarce.

Methods: We examined the cerebral hemodynamic indices in 826 consecutive participants of the Rotterdam Study, a population-based study in the elderly, by means of transcranial Doppler. The presence of peripheral atherosclerosis was assessed by means of the ankle-to-brachial index.

Results: The end diastolic and mean cerebral blood flow velocity declined with increasing age: -0.4 cm/sec per year (95%CI -0.5; -0.3) and -0.3 cm/sec per year (95%CI -0.4; -0.2), respectively. The peak systolic cerebral blood flow velocity declined -0.4 cm/sec per year (95%CI -0.7; -0.2) in women only. The pulsatility index increased 0.01 per year (95%CI 0.01-0.02). Cerebrovascular CO_2 reactivity declined -0.4%/kPa per year (95%CI -0.6; -0.2). End diastolic, mean and peak systolic cerebral blood flow velocities were lower in men compared with women and their mean differences were 2.0 cm/sec (95%CI 0.9-3.1), 2.8 cm/sec (95%CI 1.4-4.4) and 4.6 cm/sec (95%CI 2.1-7.2), respectively. Pulsatility index was 0.02 (95%CI 0.00-0.04) higher in men compared with women. Adjustment for presence of peripheral arterial disease did not change the magnitude of these associations.

Conclusions: Our data show that there is an age associated decrease in cerebral blood flow velocities and cerebrovascular CO_2 reactivity and a concomitant increase in the pulsatility index. The contribution of peripheral atherosclerosis to these associations is limited. The relation between sex and the cerebral hemodynamic indices is equivocal.

INTRODUCTION

Physiologic aging is associated with changes in cerebral hemodynamics. Age-related changes in cerebral hemodynamics, measured by means of the N_2O technique, were already described by Schieve and Wilson in 1953.[1] After the introduction of transcranial Doppler in 1982, several small hospital-based studies have shown a decrease in cerebral blood flow velocity and a concomitant increase in pulsatility index with increasing age.[2-7] An age-related decrease in cerebrovascular CO_2 reactivity was reported in some studies,[8-13] but not in others.[2,14-16] Data on a population-based level among the very elderly are scarce. The underlying mechanism of age-associated changes in hemodynamic cerebral indices is probably diverse and may reflect a combination of decreased cerebral metabolic demands and structural changes in the blood vessels, such as alterations due to atherosclerosis.

Several studies have shown sex-related differences in human cerebral blood flow and revealed higher mean blood flow velocities for women than for men.[2-6] Recent studies of transcranial Doppler have shown that cerebrovascular reactivity was also higher in women compared with men.[13-15,17] How sex influences these non-invasive hemodynamic indices is still largely unknown, but sex-related differences in hormonal status and prevalence of atherosclerosis have been suggested.[3,6,7,17]

Whether peripheral arterial disease may attribute to age and sex related changes in cerebral hemodynamics is unknown. Most studies performed thus far were small and the participants were healthy and relatively young. Little information is available on the influence of age, sex, peripheral arterial disease and cerebral hemodynamics in the elderly, especially in the 8-10th decades of life.

We investigated the association between age, sex, peripheral arterial disease and the cerebral hemodynamic indices in 826 consecutive participants from a population-based study, the Rotterdam Study.

STUDY POPULATION AND METHODS

Study Population

This study is based on the Rotterdam Study, a prospective population-based cohort study among 7983 participants aged 55 years and over (response 78%), which investigates neurological, cardiovascular, endocrine and ophthalmologic diseases in the elderly.[18] Baseline examination was performed from 1990-1993. From the 2nd re-examination on (1997-1999), cerebral blood flow velocity, pulsatility index and cerebrovascular CO_2 reactivity measurements by means of transcranial Doppler ultrasonography were incorporated in the study protocol. The current analysis is based on the first 1300 consecutive participants who visited the study research center for the 2nd re-examination in the period May 1997-June 1998.

Transcranial Doppler Assessment

Transcranial Doppler ultrasonography monitoring was performed (Multi-Dop X-4, DWL,

Sipplingen, Germany) and the cerebral blood flow velocity (cm/sec) was measured in the middle cerebral artery on both sides if possible. End diastolic, peak systolic and mean cerebral blood flow velocity was recorded automatically. The pulsatility index was defined as (peak systolic cerebral blood flow velocity - end diastolic cerebral blood flow velocity) / mean cerebral blood flow velocity and was measured automatically with fast Fourier transformation. The pulsatility index values were determined in both middle cerebral arteries, over five cardiac cycles and their mean was used for the analyses. Cerebrovascular CO_2 reactivity measurements were done as follows: the cerebral blood flow velocity was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Participants were then asked to inhale a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes. Cerebrovascular CO_2 reactivity was defined as the percentage increase in mean cerebral blood flow velocity during inspiration of 5% CO_2 / the absolute increase in end-tidal CO_2 in the same time period (%/kPa). End-tidal CO_2 pressure (kPa) was recorded continuously with a CO_2 analyzer (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2.[19] Before and during the transcranial Doppler recordings, blood pressure was measured automatically (Dynamap, Datascope, Hoevelaken, The Netherlands) on the right arm in lying position. TCD-8 DWL special software (VMR-CO_2) was used. All transcranial Doppler data were stored on hard disk for off-line analysis.

Measurements of atherosclerosis

The presence of peripheral atherosclerosis in the arteries of the lower limbs was assessed by means of the ankle-to-brachial index. The ankle-to-brachial index, measured during baseline, was computed by measuring blood pressure in the tibial artery using an 8 Mhz continuous wave Doppler probe (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK) and a random zero sphygmomanometer, with the participant supine. Blood pressure was measured on the right arm by means of a random zero sphygmomanometer in sitting position. The ankle-to-brachial index was defined as the systolic blood pressure measured at both the left and right posterior tibial artery divided by the systolic blood pressure of the right arm. The lowest ankle-to-brachial index in either leg was used in the analyses. Subjects with an ankle-to-brachial index less than 0.9 were considered to suffer from peripheral arterial disease.[20]

Data analysis

Because all right and left hemodynamic indices were highly correlated, we used their mean for the analyses if both middle cerebral arteries could be insonated adequately. In case of one-sided window-failure, the contralateral cerebral hemodynamic parameter was used in the analyses.

We used analysis of covariance (ANCOVA) to evaluate age and sex-adjusted differences at baseline between participants with and without transcranial Doppler assessment. The means (SE) of the cerebral hemodynamic indices were calculated by sex-adjusted ANCOVA in strata of five years. Regression coefficients (95% confidence

interval CI) were calculated for the associations between age and sex and the cerebral hemodynamic indices with age and sex as determinants and the cerebral hemodynamic indices as outcome. Sex specific analyses were performed within strata of five years of age; differences between men and women for the cerebral hemodynamic indices were calculated, using ANCOVA adjusted for age.

In order to investigate whether the association between age and sex and the cerebral hemodynamic indices was due to vascular pathology, additional adjustments were done for the ankle-to-brachial-index as an indicator for peripheral arterial disease.

RESULTS

Adequate transcranial Doppler data were obtained in 826 of 1300 participants (63.5%). The other 474 participants had either window failure on both sides (n=328), difficulty to wear the dose-fitting mask (n=78), or difficulty to participate due to restlessness or discomfort (n=68). Characteristics of participants with and without transcranial Doppler are shown in Table 1. There was no difference in age at baseline between participating men and women with transcranial Doppler (66.5 years (SD 6.8) versus 66.2 years (SD 6.6) respectively). Except for diabetes and a history of peripheral arterial disease, vascular risk factors were significantly more frequent in participants who did not undergo transcranial Doppler examination compared with participants with transcra-

Table 1
Baseline characteristics (1990-1993) from participants in the study population with and without transcranial Doppler (TCD) examinations in 1997 and 1998.

	TCD N=826	No TCD N=474	*p* value*
Age (yrs)	66.4	68.2	
Sex (% women)	50	79	
Systolic blood pressure (mmHg)	135	137	0.02
Diastolic blood pressure (mmHg)	72	74	0.03
Hypertension† (%)	34	42	
Diabetes‡ (%)	5.5	6.6	
Body-mass-index (kg/m^2)	26.1	27.0	<0.001
Ankle-to-brachial-index	1.19	1.19	0.45
Peripheral arterial disease§ (%)	5.3	4.4	

Values represent means.
*p value was calculated with ANCOVA, adjusted for age and sex.
†Hypertension was defined as a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 95 mmHg or the use of blood pressure lowering drugs.
‡Diabetes was considered present if subjects used anti-diabetic medication or had a random or post-load serum glucose level above 11.0 mmol/l.
§Peripheral arterial disease was defined as ankle-to-brachial-index < 0.9

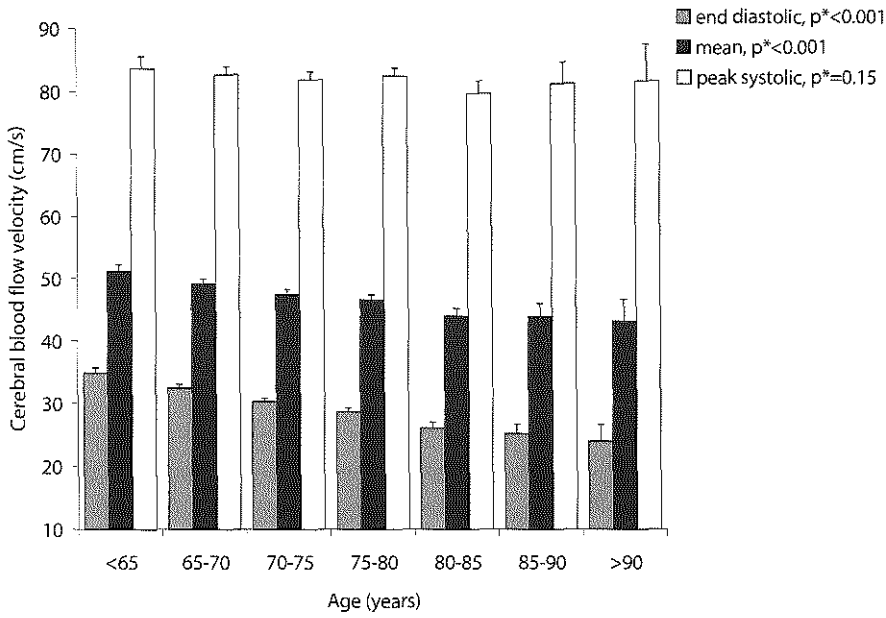

Figure 1
The association between age and end diastolic, mean and peak systolic cerebral blood flow velocity in cm/s (SE), adjusted for sex (n=826).
**p* value from the regression coefficient of age.

nial Doppler examination. The percentage in which transcranial Doppler measurements could be performed was higher in men compared with women.

Figure 1 shows that end diastolic and mean cerebral blood flow velocity declined with increasing age: -0.4 cm/sec per year (95%CI -0.5; -0.3) and -0.3 cm/sec per year (95%CI -0.4; -0.2, respectively). The peak systolic cerebral blood flow velocity declined also with aging albeit not statistical significantly: -0.1 cm/sec per year (95%CI -0.3;0.1). The pulsatility index increased 0.01 per year (95%CI 0.01;-0.02). Cerebrovascular CO_2 reactivity declined -0.4%/kPa per year (95%CI -0.6; -0.2). Additional adjustments for confounding peripheral arterial disease did not change the relation between age and the cerebral hemodynamic indices.

Table 2 shows the association between sex and the cerebral blood velocities by age categories. The inverse association between mean and peak systolic cerebral blood flow velocity and increasing age was significant only in women: -0.5 cm/sec per year (95%CI -0.7; -0.4) and -0.4 cm/sec per year (95%CI -0.7; -0.2), respectively. There was no sex difference between aging and end diastolic cerebral blood flow velocity, pulsatility index and cerebrovascular CO_2 reactivity. End diastolic, mean and peak systolic cerebral blood flow velocities were lower in men compared with women and their mean differences were 2.0 cm/sec (95%CI 0.9; -3.1), 2.8 cm/sec (95%CI 1.4; -4.4) and 4.6 cm/sec (95%CI 2.1; -7.2), respectively. The cerebral blood flow velocities were higher in men

Table 2
Cerebral blood flow velocities (cm/sec) by age and sex.

	Women				Men			
			Cerebral blood flow velocity*				Cerebral blood flow velocity*	
Age (years)	Number	End diastolic	Mean	Peak systolic	Number	End diastolic	Mean	Peak systolic
<65	48	37.3†	54.2†	88.0†	51	32.6	48.3	79.6
65-70	109	34.2†	51.6†	86.4†	90	30.4	46.4	79.4
70-75	93	30.8	48.5	84.0	108	30.0	46.7	80.1
75-80	99	30.0	48.3	85.4†	101	27.7	45.0	79.7
80-85	46	26.2	43.7	78.7	42	26.0	44.3	80.8
85-90	16	23.9	41.8	77.6	13	26.7	46.4	86.0
>90	2	23.2	41.8	89.3	8	24.1	42.7	79.7
Decline per year increase in age		−0.4‡	−0.5‡	−0.4‡		−0.4‡	−0.2	0.1

*Values represent means.
†$p < 0.05$ For age adjusted differences in cerebral blood flow velocity between men and women.
‡Values represent statistically significant regression coefficient.

Table 3
Pulsatility index (PI) and cerebrovascular CO_2 reactivity (VMR) [%/kPa] by age and sex.

		Total		Women		Men	
Age (years)	Total	PI	VMR	PI	VMR	PI	VMR
<65	99	0.89	2.9	0.87	2.7	0.91	3.0
65-70	199	0.97	2.9	0.95	2.7	0.98	3.1
70-75	201	1.02	2.5	1.03	2.4	1.01	2.5
75-80	200	1.11	2.3	1.10	2.4	1.11	2.1
80-85	88	1.16	2.1	1.13	2.2	1.19	2.0
85-90	29	1.22	2.1	1.19	1.9	1.24	2.2
>90	10	1.25	1.9	1.29	2.1	1.21	1.6
	Difference per year increase in age	0.01†	-0.4†	0.01†	-0.4†	0.01†	-0.4†

*Values represent means.
†Values represent statistically significant regression coefficient.

compared with women above 80 years of age but these differences did not reach statistical significance. Table 3 shows the association between sex and pulsatility index and cerebrovascular CO_2 reactivity by the different age categories. Pulsatility index was 0.02 (95%CI 0.00; -0.04) higher in men compared with women. There was no sex difference in cerebrovascular CO_2 reactivity in the different age categories. Although men had more frequent peripheral arterial disease compared with women (5.7% and 4.7%, respectively), the differences in cerebral hemodynamic indices between men and women did not change when we adjusted for peripheral atherosclerosis.

DISCUSSION

This is the first population-based study on cerebral hemodynamics assessed by means of transcranial Doppler. Our study shows a significant decrease in cerebral blood flow velocity and cerebrovascular CO_2 reactivity during normal aging and a concomitant increase in pulsatility index. We found that these age-related changes in cerebral hemodynamics continue up to the tenth decade of normal life, although we should emphasize the small number of participants in the age category above 90 years of age. Our findings also support sex-related differences in cerebral hemodynamics. Men had lower cerebral blood flow velocity compared with women up to age 80. An accompanying higher pulsatility index was found in men compared with women. No sex differences were found regarding cerebrovascular CO_2 reactivity. Additional adjustments for confounding peripheral arterial disease did not alter the relation between the cerebral hemodynamic indices and age and sex.

Before these findings can be accepted, some methodological issues need to be con-

sidered. First, transcranial Doppler was not assessed in twenty-six percent of all participants visiting the research center. However, this was a random sample of all eligible persons that visited the research center and it is unlikely that this has biased our results. Second, we failed to obtain adequate data in 36.5 percent of participants in whom we tried to assess cerebral hemodynamic indices, mainly due to window failure. This rate is in accordance with previous findings from clinical studies.[21,22] With advancing age, especially in postmenopausal women, the transtemporal window can be very small or non-existent.[23] In our study window failure was indeed more frequent in women and in older persons. Third, it is known that high grade internal carotid artery stenosis or occlusion may influence cerebral hemodynamics, especially cerebrovascular CO_2 reactivity. Due to the study protocol, carotid ultrasound data are not available in the second re-examination of the Rotterdam Study. However, it is very unlikely that high-grade internal carotid artery stenosis contributes to our findings, because previous results from the Rotterdam Study have shown a prevalence of only 0.5%-1.0% of high grade internal carotid artery stenosis or occlusion.[24]

We know from small studies in patients and healthy volunteers that the cerebral blood flow velocity at rest in the basal arteries of both anterior and posterior circulation decreases with age, accompanied by a concomitant increase in pulsatility index.[2-7] These findings were corroborated in studies that measured regional cerebral blood flow by means of the noninvasive ^{133}Xenon inhalation method.[9,25,26] Several investigators have reported a decline in cerebrovascular CO_2 reactivity with aging,[8-13] whereas other non-population-based studies showed little or no association between aging and a reduced cerebrovascular CO_2 reactivity.[1,2,14-16] Little information is available on cerebral hemodynamics in the very elderly, especially in the 8-10th decade.[4,6,11]

Several explanations for age-associated changes in cerebral hemodynamic indices have been suggested and in most of them atherosclerosis related factors play an important role.[7,27-29] However, the association between age and cerebral hemodynamics in our study remained similar after adjustment for an indicator of peripheral atherosclerosis. This suggests that the contribution of atherosclerosis to the observed association between cerebral hemodynamics and age and sex is limited. Other structural and biochemical changes in the cerebral vessels and vessel wall occurring with advancing age and changes in cerebral metabolism therefore likely contribute to these age-associated changes in cerebral hemodynamic indices.[26,30,31] Recent observations suggest that elevation of the hematocrit with advancing age may also influence several cerebral hemodynamic indices.[32,33]

Sex-related differences in human cerebral blood flow have been described by several investigators in several small and non population-based studies.[2-6,16,25] Most studies reveal statistically higher mean blood flow velocities for women than for men, although it is questioned whether this difference is limited to specific ages.[2,6,16] In our study, the sex differences in cerebral blood flow velocity were no longer manifest in ages above eighty years. The observed associations between sex and cerebral hemodynamics found in our study were not influenced by peripheral arterial disease. A possible explanation for higher cerebral blood flow velocity among women may be the difference in hormonal

status compared to men. This is supported by findings of others who found that premenopausal women had significantly higher cerebral blood flow values compared with age-matched men.[16,25] It is well known that estradiol levels are higher in postmenopausal men compared with women and this can brought forward as part of an explanation for these sex-differences in hemodynamics in the (very) elderly.[34] Another explanation may be the sex differences in cerebral metabolism, vessel lumen and hematocrit.[4,5,7,35] Results on sex-related differences in cerebrovascular CO_2 reactivity are somewhat controversial. In several recent studies, of CO_2 and acetazolamide enhanced transcranial Doppler ultrasound, women were found to have a higher cerebrovascular CO_2 reactivity than men,[13-15,17] whereas others could not find a significant difference.[2] In 100 healthy, nonsmoking volunteers, aged 20-70 years, Kastrup et al. found a significant decline in cerebrovascular CO_2 reactivity, assessed by means of CO_2-enhanced transcranial Doppler, during normal aging in women but not in men.[15] We found a borderline statistically significant reduction in cerebrovascular CO_2 reactivity in women and, in contrast with the findings of Kastrup et al., also a significant reduction in men. A possible explanation may be the relatively large number of participants, aged 70 years and over in our study and the difference in study design, ours being a population-based study.

In conclusion, our study shows a significant decline in cerebral blood flow velocity and cerebrovascular CO_2 reactivity and a concomitant increase in pulsatility index in the elderly, even in the 8-10th decade. The contribution of atherosclerosis to these associations is limited. Sex related differences in cerebral hemodynamic indices vary and exist particularly up to age 80. Future research should focus on the underlying mechanisms causing age and sex related changes in cerebral hemodynamics.

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CEREBRAL CO_2 REACTIVITY, CHOLESTEROL AND HIGH-DENSITY LIPOPROTEIN CHOLESTEROL IN THE ELDERLY

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Abstract
Cholesterol and its subfractions play a role in the development of atherosclerosis. Cerebral CO2 reactivity reflects the compensatory capacity of cerebral arterioles. We investigated the relation between total cholesterol, HDL, their ratio and cerebral CO_2 reactivity in 826 participants from the Rotterdam Study. Cerebral CO_2 reactivity increased significantly with increasing levels of HDL, and decreased significantly with an increasing total cholesterol/HDL ratio. This suggests that blood lipids may also affect smaller cerebral blood vessels.

INTRODUCTION

Cholesterol and its subfractions are associated with medium and large vessel atherosclerosis.[1] The relationship between blood lipids and cerebral small vessel atherosclerosis is less clear.[2] Cerebral CO_2 reactivity reflects the compensatory dilatory mechanism of the intracerebral arterioles.[3] The pathogenesis underlying changes in cerebral CO2 reactivity is largely unknown, but likely diverse. Impaired cerebral CO_2 reactivity due to occlusive carotid artery disease has been established.[4] Recent observations between lacunar infarcts and white matter lesions and a decrease in cerebral CO_2 reactivity support the notion that cerebral CO_2 reactivity reflects the function of the smaller intracerebral arteries.[5,6]

The association between blood lipids and cerebral CO_2 reactivity has never been examined in a population-based setting of elderly participants.

We have investigated the association between total cholesterol, HDL cholesterol, and their ratio and cerebral CO_2 reactivity in 826 participants from a population-based study, the Rotterdam Study.

METHODS

Study Population

This study is part of a prospective population-based study (the Rotterdam Study) among 7983 participants aged 55 years and over. Baseline examination was performed from 1990-1993. The current analysis is based on the first 1300 consecutive participants who visited the research center for the third survey in the period May 1997-June 1998.

Cholesterol

During baseline examination, total cholesterol and HDL cholesterol serum levels were measured by means of enzymatic methods. The cholesterol/HDL ratio was calculated.

Transcranial Doppler

From the third survey on (1997), transcranial Doppler (TCD) measurements were incorporated in the study protocol. TCD monitoring was performed (Multi-Dop X-4, DWL, Sipplingen, Germany) and mean cerebral blood flow velocity (CBFV) (cm/sec) was continuously measured in the middle cerebral artery (MCA) on both sides. The participants first breathed room air through an anesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Then they inhaled a mixture of 5% carbon dioxide in 95% oxygen for two minutes. End-tidal CO_2 pressure (kPa) was recorded continuously with a CO_2 analyzer (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2.[3] TCD-8 DWL special software (VMR-CO_2) was used. All TCD data were stored on hard disk for off-line analysis. Cerebral CO_2 reactivity was defined as the relative increase in CBFV during inspiration of 5% CO_2, divided by the absolute increase in end-tidal CO_2 in the same time period (%/kPa). The right and left cerebral CO_2 reactivity were highly correlated (r^2 =

0.99, $p<0.001$) and therefore their mean was used for the analyses if both MCAs could be insonated adequately.

Blood pressure

Blood pressure was measured automatically (Dynamap, Datascope, The Netherlands) before and during the TCD recordings.

Data analysis

In case of one-sided window-failure, the contralateral cerebral CO_2 reactivity was used. We used multiple linear regression analysis to assess the relation between total cholesterol, HDL and their ratio on the one hand and cerebral CO_2 reactivity on the other. Total cholesterol, HDL and their ratio were entered in the model both continuously and in tertiles of their distribution. All analyses were adjusted for age, sex and systolic blood pressure. Additional adjustments were done for diabetes mellitus, hypertension, body-mass-index and ankle-to-brachial-index.

RESULTS

Adequate TCD cranial Doppler data were obtained in 826 of 1300 participants (63.5%). The other 474 participants had window failure on both sides (n=328), difficulty to wear the dose-fitting mask (n=78), or difficulty to participate due to restlessness or an unpleasant feeling (n=68). Mean age of the participants with transcranial Doppler assessments was 66.4 years (SD 6.7) and 50% of them were men. Mean cerebral CO_2 reactivity was 2.5%/kPa (SD 2.2). Mean baseline level of total cholesterol was 6.8 mmol/l (SD 1.2) and mean baseline level of HDL cholesterol was 1.4 mmol/l (SD 0.4). Mean baseline total cholesterol/HDL ratio was 5.3 (SD 1.7). Except for diabetes and a history of peripheral arterial disease, vascular risk factors were significantly more frequent in participants in the study population without transcranial Doppler examination compared to the participants with transcranial Doppler examination (Table 1). Vascular risk factors and participants with a history of peripheral arterial disease were significantly more frequent in the Rotterdam Study as a whole compared to the study population, except for the body-mass-index. Both systolic and diastolic blood pressure increased during the period of hypercapnia ($p<0.001$ for both systolic and diastolic bloodpressure).

Cerebral CO_2 reactivity increased with increasing levels of HDL cholesterol (0.8%/kPa per 0.4 mmol/l HDL cholesterol; $p<0.001$). Figure 1 shows that participants with higher levels of HDL cholesterol had a higher cerebral CO_2 reactivity ($p_{trend}=0.04$). In addition, we found that cerebral CO_2 reactivity decreased with an increasing total cholesterol/HDL ratio (-0.1%/kPa per 1.7 cholesterol/HDL ratio; $p=0.01$). As shown in figure 2, participants with a lower total cholesterol/HDL ratio had a higher cerebral CO_2 reactivity ($p_{trend}=0.01$). There was no linear relationship between total cholesterol and cerebral CO_2

Table 1
Baseline characteristics (1990-1993) from participants in the study population with and without transcranial Doppler (TCD) examinations in 1998.

	TCD N=826	No TCD N=474	*p* value*
Age, y	66.4	68.2	<0.001
Sex, % men	50	79	<0.001
Systolic blood pressure, mm Hg	135	137	0.02
Diastolic blood pressure, mm Hg	72	74	0.03
Hypertension†, %	34	42	0.01
Diabetes‡, %	5.5	6.6	NS
Body-mass-index, kg/m^2	26.1	27.0	<0.001
Ankle-to-brachial-index	1.19	1.19	0.45
Peripheral arterial disease§, %	5.3	4.4	NS

Values represent means.
NS = nonsignificant.
**p* Value was calculated with ANCOVA, adjusted for age and sex differences between groups.
†Hypertension was defined as a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 95 mmHg or the use of blood pressure lowering drugs.
‡Diabetes was considered present if subjects used anti-diabetic medication or had a random or post-load serum glucose level above 11.1 mmol/l.
§Peripheral arterial disease was defined as ankle-to-brachial-index < 0.9

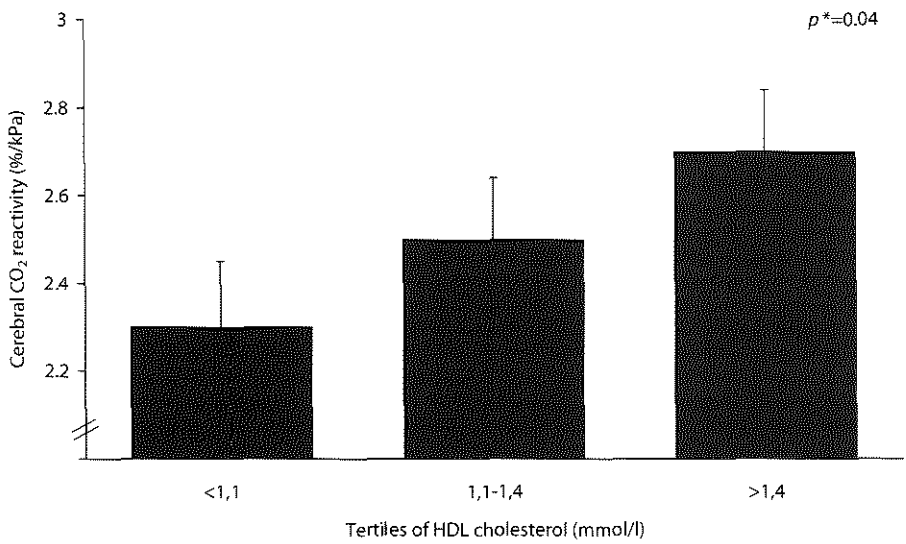

Figure 1
The association between tertiles of high-density lipoprotein (HDL) cholesterol and cerebral CO_2 reactivity (%/kPa) (SE), adjusted for age, sex and confounding vascular risk factors in the Rotterdam Study (n=826).
**p* Value was calculated in a test for trend

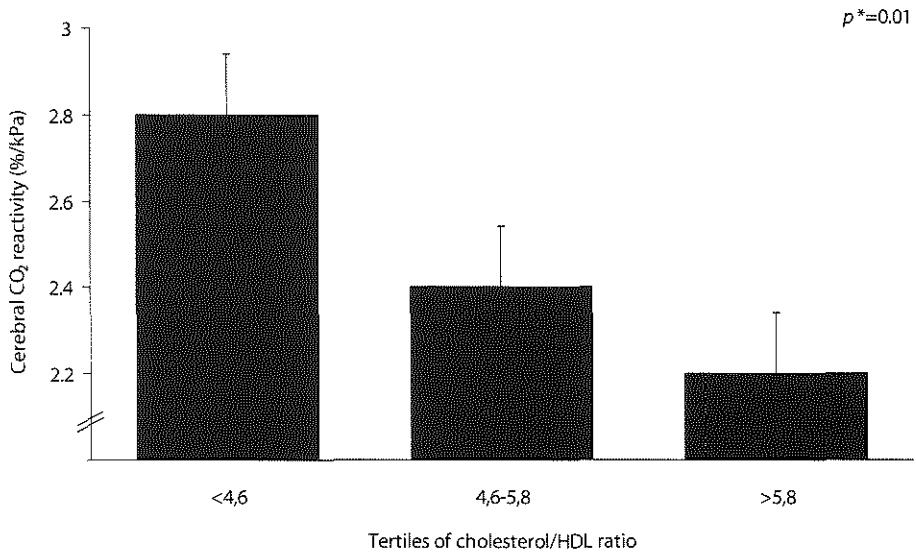

Figure 2
The association between tertiles of cholesterol/HDL ratio and cerebral CO_2 reactivity (%/kPa) (SE), adjusted for age, sex and confounding vascular risk factors in the Rotterdam Study (n=826).
**p* Value was calculated in a test for trend.

reactivity (-0.02%/kPa per 1.2 mmol/l total cholesterol; p=0.73). Additional adjustment for confounding vascular risk factors did not alter the magnitude of these associations.

DISCUSSION

We have found an association between HDL and the total cholesterol/HDL ratio and cerebral CO_2 reactivity, assessed by means of CO_2-enhanced transcranial Doppler, in a population-based cohort study of elderly participants. The association was independent of other vascular risk factors.

Cholesterol and its subfractions are associated with atherosclerosis of carotid arteries.[7] Conflicting data are available on the influence of blood lipids on the intracranial smaller vessels.[1,2] Increasing levels of HDL cholesterol prevent the development of atherosclerosis which may explain the positive association between HDL cholesterol and cerebral CO_2 reactivity we found in our study. Surprisingly, we found no relationship between total cholesterol and cerebral CO_2 reactivity. One explanation may be that our study was too small to detect an inverse relationship between total cholesterol and cerebral CO_2 reactivity.

The effect of hypercholesterolemia on the vessel wall, cerebral circulation and perfusion and cerebral CO_2 reactivity is not well defined and conflicting data have been reported.[8,9] Studies of the underlying mechanisms of altered cerebral CO_2 reactivity are

scarce. Impaired cerebral CO_2 reactivity in patients with carotid artery disease has been reported.[4] It is very unlikely that high grade internal carotid artery stenosis contributes to our findings. Although data from the Rotterdam Study are indirect evidence, results show a prevalence of only 0.5-1.0% of high grade internal carotid artery stenosis or occlusion.[10] Data on the prevalence of significant stenosis or occlusion of the carotid artery in a non-hospitalized elderly population are limited. Although blood pressure rose during the period of hypercapnia, it is unclear whether and how this affects flow velocity in the cerebral arteries. The inverse relation between atherosclerosis and cerebral CO_2 reactivity has been investigated in vitro in arterial segments obtained from rabbits with different stages of atherosclerosis. Acetylcholine induced and endothelium-dependent vasodilations were significantly impaired in the hypercholesterolemic animals, whereas this phenomenon was partially prevented by cholesterol lowering treatment with lovastatin. The authors concluded that lipoprotein accumulation in atherosclerotic arteries may alter vascular reactivity through changes in the vessel wall.[9] Rodriguez and co-workers investigated the effect of sustained, long-lasting and severe hypercholesterolemia on cerebral blood flow and cerebral CO_2 reactivity. Cerebral perfusion and cerebral CO_2 reactivity were maintained within the normal range in 15 consecutive subjects with familial hypercholesterolemia, although somewhat lower cerebral blood flow was found in these patients.[8]

There is growing interest in cholesterol and its subfractions and the occurrence of stroke. Current reports have suggested beneficial effects of cholesterol lowering drugs on the risk for stroke. It remains unclear whether this preventive effect lies in the protection against the development of medium and large vessel disease, small vessel disease, or a combination of these.

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CEREBRAL VASOMOTOR REACTIVITY AND WHITE MATTER LESIONS IN THE ELDERLY

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Abstract

Objective: The pathogenesis of white matter lesions is still uncertain but an ischemic-hypoxic cause has been suggested. Cerebral vasomotor reactivity reflects the compensatory dilatory mechanism of the intracerebral arterioles to a vasodilatory stimulus and provides a more sensitive hemodynamic index than the level of resting flow.

Methods: We determined the association between vasomotor reactivity and white matter lesions in 73 consecutive individuals from the Rotterdam Scan Study who also participated in the Rotterdam Study, a large population based prospective follow-up study of individuals aged 55 years and over. Vasomotor reactivity was measured by means of CO_2-enhanced transcranial Doppler and in all individuals axial T_1, T_2 and PD weighted MRI scans (1.5T) were obtained. White matter lesions were scored according to location, size and number by two independent readers.

Results: Vasomotor reactivity was inversely associated with the presence of deep subcortical and total periventricular white matter lesions (OR 0.5; 95%CI 0.3-1.1 and OR 0.7; 95%CI 0.4-1.1, respectively). A strong association was found between impaired vasomotor reactivity and periventricular white matter lesions adjacent to the lateral ventricular wall (OR 0.6; 95%CI 0.4-1.0; p=0.001). No association was found with periventricular white matter lesions near the frontal and occipital horns.

Conclusions: Our data confirm the association between vasomotor reactivity and white matter lesions and support the hypothesis that some white matter lesions may be associated with hemodynamic ischemic injury to the brain.

INTRODUCTION

White matter lesions are frequently detected on magnetic resonance imaging (MRI) in the elderly and the extent of these white matter lesions correlates positively with age[1,2] and several cerebrovascular risk factors.[3,4] The pathogenesis of these white matter lesions is still largely unknown[5,6] but a hemodynamic contribution has been suggested.[7-10] Cerebral vasomotor reactivity, or cerebrovascular reserve capacity, reflects the compensatory dilatory mechanism to a vasodilatory stimulus of the intracerebral arterioles,[11] and provides a more sensitive hemodynamic index than the level of resting blood flow.[12] The vasomotor reactivity can be estimated by means of CO_2-enhanced transcranial Doppler and has become a well established method for evaluating possible hemodynamic failure for instance in occlusive carotid artery disease.[13-18]

The association between vasomotor reactivity and white matter lesions has never been examined in a population based study among elderly individuals. In series of asymptomatic individuals and individuals with hypertension a decreased vasomotor reactivity has been found to be associated with periventricular lesions on MRI.[19,20] There are no reports on the relationship between vasomotor reactivity and subcortical white matter lesions.

We investigated the association between vasomotor reactivity and different subtypes of white matter lesions in 73 individuals selected from a population-based study.

STUDY POPULATION AND METHODS

For the current study eighty individuals were randomly selected from the Rotterdam Scan Study. The Rotterdam Scan Study is a population-based study of causes and consequences of brain changes as visible on MRI. Persons with dementia and contraindications for MRI were excluded. This study was carried out between July and September 1996 and based on the part of the cohort that also participated in the Rotterdam Study, which focuses on determinants of neurological, cardiovascular, endocrinal and ophthalmologic diseases in the elderly.[21]

Transcranial Doppler monitoring was performed (Multi-Dop X-4, DWL, Germany) and mean cerebral blood flow velocity was continuously measured in the middle cerebral artery on both sides if possible, as follows. The subject breathed air and 5% carbon dioxide through an anaesthetic mask, tightly fit over mouth and nose. End-tidal CO_2 pressure (mmHg) was recorded continuously with a CO_2 analyzer (Multinex, Datascope). Individuals first breathed room air, until a steady expiratory end-tidal CO_2 was obtained. Individuals were then asked to inhale a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes and the end-tidal CO_2 was recorded. End-expiratory CO_2 was assumed to reflect arterial CO_2.[11] TCD-8 DWL special software (VMR-CO_2) was used. All transcranial Doppler data were stored on hard disk for off-line analysis. Vasomotor reactivity was defined as the percentage increase in blood flow velocity occurring during inspiration of 5% CO_2, divided by the absolute increase in end-tidal CO_2 in the same time period (%/mmHg). The mean of the right and left vasomotor reactivity was used for the analy-

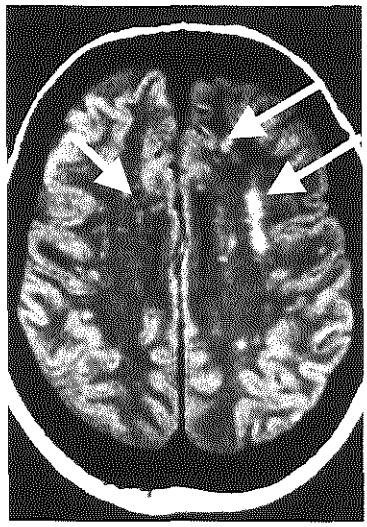

Figure 1
MRI example of deep subcortical white matter lesions. Arrows directing to various deep subcortical white matter lesions.

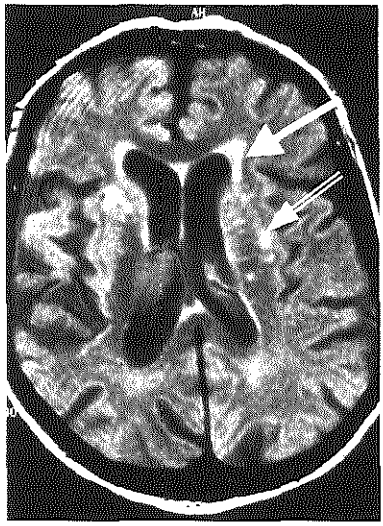

Figure 2
MRI example showing the distinction between periventricular white matter lesions (large closed arrow) and deep subcortical white matter lesions (smaller partially open arrow).

ses if both middle cerebral arteries could be insonated adequately. The one-sided vasomotor reactivity was used if a window-failure appeared on one side.

Each subject underwent cerebral MRI scanning using a 1.5 Tesla (T) Siemens Gyroscan. From each participant axial T_1 (TR 700ms, TE 14ms), T_2 (TR 2200, TE 80ms) and proton density (PD) (TR 2200, TE 20ms) weighted images were made. Slice thickness was 5mm, with a gap of 1.0mm. All MRI scans were examined independently by two experienced readers. White matter lesions were considered present if visible on both PD and T_2 weighted images and not on the T_1 weighted image. White matter lesions were distinguished into the deep subcortical (Figure 1) and those in the periventricular region (Figure 2). The number of deep subcortical white matter lesions was counted on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate a deep subcortical white matter lesions volume, the white matter lesions were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were scored semi-quantitatively per region (adjacent to the frontal horn or frontal capping, adjacent to the lateral wall of the lateral ventricles or bands and adjacent to the occipital horn or occipital capping) at a scale ranging from 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining) to 3 (large confluent white matter lesions). Total severity of periventricular white matter lesions was calculated by adding up the scores of the three separate categories (range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of a disagreement of more

than one point, a consensus reading was held; in all other cases the average of the two readers was calculated. Inter- and intra-rater studies showed a good to excellent agreement. Weighted kappa's were calculated with respect to scoring of the periventricular white matter lesions (weighted kappa between 0.79-0.90). Pearson's correlation coefficient were calculated for deep subcortical white matter lesions ($r^2 = 0.88$ for total volume of deep subcortical white matter lesions).

To assess the relationship between vasomotor reactivity and presence of white matter lesions, age and sex adjusted logistic regression was used. In these analyses vasomotor reactivity was used as a continuous variable and white matter lesions were dichotomized at the upper quintile. All analyses were performed using BMDP statistical software.[22] To detect a possible threshold, the association between tertiles of vasomotor reactivity and extent of white matter lesions was assessed using age and sex adjusted linear regression.

RESULTS

Combined TCD and MRI data were obtained in 73 individuals (91%). The other individuals had either window failure on both sides (n=4) or difficulties wearing the dose-fitting mask (n=3). MRI examination was tolerated well. Mean age of the study population was 70.2 years and 74% of all individuals were men. Except for age and sex, vascular risk factors were equally frequent in The Rotterdam Scan study as in The Rotterdam Study as a whole (Table 1). Mean vasomotor reactivity was 3.4 %/mmHg and ranged from

Table 1
Baseline characteristics from the study population and The Rotterdam Study.

	Study population N=73	Rotterdam Study N=7123	*p* value
Age (years)	70.2 (8.0)	72.8 (8.0)	0.003*
Sex (men)	74	41	< 0.0001*
Ankle-brachial-index	1.2 (0.02)	1.1 (0.003)	NS
Systolic blood pressure (mmHg)	138 (21.5)	139 (21.4)	NS
Diastolic blood pressure (mmHg)	74 (11.5)	74 (11.5)	NS
Hypertension	41	45	NS
Diabetes	5	8	NS
History of myocardial infarct	12	11	NS
History of stroke	3	3	NS
History of peripheral arterial disease†	7	11	NS

Values represent means (SD) or percentages
NS = non significant
* *p* value was calculated performing analysis of co-variance
† Peripheral arterial disease was defined as ankle-brachial-index < 0.9

0.8-6.3 %/mmHg with a normal distribution. A correlation coefficient of 0.94 was found between right and left vasomotor reactivity. Women tended to have a lower vasomotor reactivity than men: mean 3.0 versus 3.6 (p=0.4). Sixty-eight percent of the individuals had at least some periventricular white matter lesions and 86% at least some deep sub-

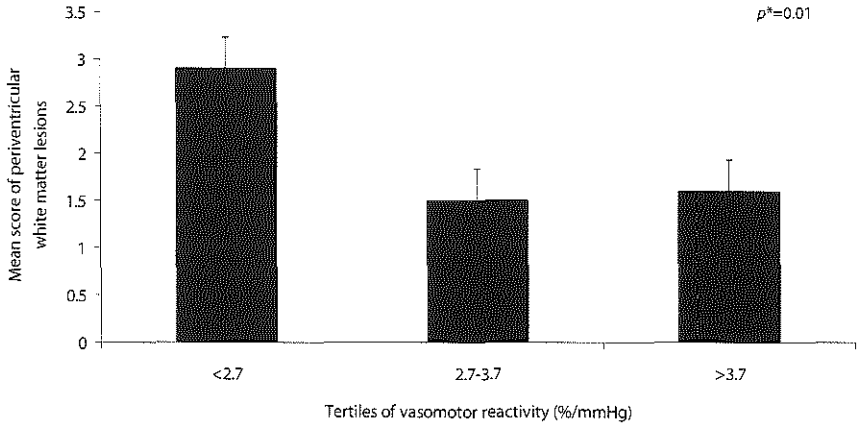

Figure 3
The association between tertiles of cerebral vasomotor reactivity (%/mmHg) and mean total score (SE) of periventricular white matter lesions, adjusted for age and sex.
*p Value was calculated in a test for trend.

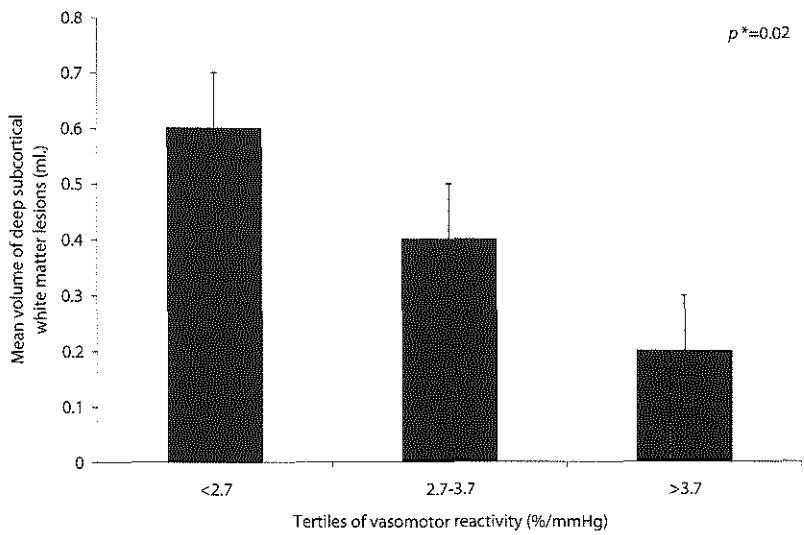

Figure 4
The association between tertiles of cerebral vasomotor reactivity (%/mmHg) and mean volume (SE) of total deep subcortical white matter lesions (ml.), adjusted for age and sex.
*p Value was calculated in a test for trend.

Table 2
The association between cerebral vasomotor reactivity (VMR [%/mmHg]) and white matter lesions (WML) per region (periventricular) and per size (deep subcortical).*

	VMR<2.7	VMR 2.7-3.7	VMR>3.7	$p^{\dagger}$
Frontal capping	0.9 (0.13)	0.4 (0.13)	0.6 (0.13)	0.06
Occipital capping	0.8 (0.14)	0.5 (0.14)	0.4 (0.14)	0.13
Bands	1.2 (0.13)	0.6 (0.13)	0.6 (0.13)	0.001
Large deep subcortical WML	1.2 (0.3)	0.5 (0.3)	0.2 (0.3)	0.02
Medium deep subcortical WML	0.3 (0.08)	0.3 (0.08)	0.2 (0.08)	0.20
Small deep subcortical WML	0.1 (0.02)	0.06 (0.02)	0.06 (0.02)	0.03

*Values represent mean score (SE) of periventricular and mean volume (SE) [ml.] of deep subcortical white matter lesions and are adjusted for age and sex.
† *p* values were calculated in a test for trend.

cortical white matter lesions. Fifty-seven percent of the individuals had periventricular white matter lesions adjacent to the lateral ventricular wall (bands).

Vasomotor reactivity was inversely associated with severe deep subcortical and total periventricular white matter lesions (OR 0.5; 95%CI 0.3-1.1 and OR 0.7; 95%CI 0.4-1.1 per 10% vasomotor reactivity, respectively). Figure 3 shows that individuals with higher vasomotor reactivity had a significantly lower mean score of total periventricular white matter lesions (p=0.01). As shown in Figure 4, individuals with higher vasomotor reactivity had also a significantly lower mean score of total deep subcortical white matter lesions volume (p=0.02).

Table 2 gives the mean score of white matter lesions in each periventricular region per tertile of vasomotor reactivity and provides the mean scores for deep subcortical white matter lesions for each size in the different vasomotor reactivity groups. Individuals in the lowest tertile of vasomotor reactivity were found to have the highest mean score of white matter lesions in all three periventricular regions, whereas individuals in the highest tertile of vasomotor reactivity had the lowest mean score. The inverse association between vasomotor reactivity and white matter lesions seemed strongest with periventricular white matter lesions adjacent to the lateral ventricular wall (p=0.001). Better vasomotor reactivity was associated with less deep subcortical lesions, irrespective of the size of the lesions.

DISCUSSION

This is the first study to show an association between vasomotor reactivity, assessed by means of CO_2-enhanced transcranial Doppler, and the presence and extent of white matter lesions in a population based study among elderly individuals. The results suggest that vasomotor reactivity is inversely associated with white matter lesions in the periventricular as well as in the deep subcortical regions. A strong association was

found between impaired vasomotor reactivity and periventricular white matter lesions adjacent to the lateral ventricular wall (bands) in particular.

There are few reports on the relationship between magnetic resonance white matter lesions, cerebral blood flow and the subject's ability to increase cerebral blood flow in response to hypercapnia. Most investigators have found no significant changes in resting cerebral blood flow in individuals with asymptomatic periventricular white matter lesions,[23,24] although one study with positron emission tomography showed that in such patients cerebral blood flow was low compared to the oxygen requirements of the (surrounding) healthy brain.[25] Others have found decreased cerebral blood flow values in areas of white matter lesions compared to areas with normal white matter.[23,25-27] For the detection of reductions in cerebral perfusion, measurements of resting cerebral blood flow alone may be insufficient. Cerebral perfusion may only be impaired in situations where there is increasing demand, due to failure of normal compensatory mechanisms. This can be estimated by the determination of vasomotor reactivity that provides a more sensitive hemodynamic index than the level of resting blood flow.[12]

In one study with asymptomatic individuals, the severity of periventricular white matter lesions was significantly and negatively correlated with a decrease in vasomotor reactivity and not with resting cerebral blood flow, which led the authors to suggest that the reduction of vasomotor reactivity is a more important hemodynamic marker in the pathogenesis of periventricular white matter lesions than is a decrease in the level of resting blood flow.[19] This inverse association between a decrease in vasomotor reactivity and the severity of white matter lesions was subsequently found in hypertensive patients with leukoaraiosis.[20]

In our study, we found an increased mean score of periventricular white matter lesions, as well as an increase in severe deep subcortical white matter lesions volume in individuals with the lowest vasomotor reactivity scores. A strong and inverse association was found between low vasomotor reactivity and bands which suggests that periventricular regions adjacent to the lateral ventricle wall harbor a circulatory borderzone and may have less microcirculatory anastomoses than the other periventricular zones. The relationship between cerebral hemodynamics and white matter lesions has not been fully explored. Hypoxia-ischemia, disturbances in the circulation of the cerebrospinal fluid and changes in the permeability of the blood brain barrier to macromolecules are thought to play an important role in the pathogenesis of white matter lesions.[7] Several arguments support the hypothesis that some types of white matter lesions may be the result of ischemic injury to the brain.[7-10] The region of the white matter immediately adjacent to the lateral ventricular walls receives its blood supply from the ventriculofugal vessels arising from the subependymal arteries, which originate either from the choroidal arteries or from terminal branches from the lenticulostriatal arteries.[7,25] Anastomoses between the vessels originating at the surface as well as those branching off the subependymal system are either scarce or absent, leading to a minimal overlap between the territories of the different end arteries.[28-31] This pattern of vascularization suggests that the periventricular white matter harbors an arterial borderzone, particularly susceptible to injury from systemic or focal decreases in cerebral blood flow,[7,32]

although this has been challenged by others.[33-35] Hypoperfusion can result either from arteriolosclerotic changes affecting the small intraparenchymal arteries and arterioles that are associated with aging and with stroke risk factors,[7,32,36,37] or by hemodynamic mechanisms in case these arteries are already maximally dilated, for instance in high grade carotid artery stenosis or occlusion, in which cerebral perfusion can become directly dependent of the systemic arterial blood pressure. This may explain the inability to increase focal blood flow in response to hypercapnia in these individuals. In the former, a drop in blood-pressure may result in hypoperfusion and ischemic changes to the deep white matter. It is very unlikely that high grade internal carotid artery stenosis contributes to our findings. Data on the prevalence of significant stenosis or occlusion of the carotid artery in a non-hospitalized elderly population are limited, but results from the Rotterdam Study show a prevalence of about 0.5-1.0%.[38] We therefore consider it unlikely that this will affect the association we found. An association between white matter lesions and atherosclerotic abnormalities in the carotid artery, the coronary arteries and in the peripheral vessels has already been established.[39] It is still unclear however, how different types of ischemia may induce selected structural changes of the white matter. We did not determine systemic blood pressure. Although systolic and diastolic blood pressure rise during a period of hypercapnia, it is still unclear whether and how this affects flow velocity in the cerebral arteries.

Future studies should elucidate the clinical and pathogenetic relevance of vasomotor reactivity in individuals with white matter lesions.

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CEREBRAL HEMODYNAMICS, COGNITIVE DECLINE AND DEMENTIA IN THE ROTTERDAM STUDY

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Abstract

Background: Transcranial Doppler (TCD) is a noninvasive tool to measure cerebral blood flow (CBF) velocity and cerebrovascular CO_2 reactivity in cerebral arteries. Clinical TCD studies have demonstrated a decrease in blood flow velocity in the proximal tract of the middle cerebral artery in patients with Alzheimer's disease. A reduced cerebrovascular CO_2 reactivity, indicating cerebral small vessel pathology, has been found in vascular dementia patients. It is unclear wether cerebral blood flow velocity and cerebrovascular CO_2 reactivity are decreased in persons with cognitive impairment.

Methods: We examined the association between cerebral hemodynamics, as measured by means of TCD, and dementia and cognitive performance in 2,107 participants of the Rotterdam Study, a large population-based study in the Netherlands.

Results: A total of 18 individuals were diagnosed with dementia. All cerebral hemodynamic parameters were lower in demented compared with non-demented persons (mean difference end diastolic CBF: 5.7 cm/sec, 95%CI: 2.0-9.7; peak systolic CBF: 14.0 cm/sec, 95%CI 5.2-22.8; mean CBF: 8.6 cm/sec, 95%CI: 3.4-13.8; cerebrovascular CO_2 reactivity: 0.2 %/kPa, 95%CI: -1.1-1.4). Among non-demented subjects those who had declined in the period before TCD assessment had the lowest CBF velocity and cerebrovascular CO_2 reactivity. Persons with low cognitive performance had a lower cerebrovascular CO_2 reactivity as well.

Conclusion: Our data suggest that cerebral blood flow velocity and cerebrovascular CO_2 reactivity are decreased in persons with dementia and are lower in persons with impaired cognitive performance.

INTRODUCTION

Transcranial Doppler ultrasonography (TCD) is a noninvasive tool to measure cerebral blood flow (CBF) velocity in cerebral arteries.[1] Neuroradiologic techniques including SPECT and PET have shown reductions of global and regional cerebral blood flow in patients with Alzheimer's disease.[2,3]

Furthermore, a decrease in blood flow velocity in the proximal tract of the middle cerebral artery in Alzheimer patients has been demonstrated in clinical TCD studies.[4-8] This association has not been examined in the general population. An abnormal cerebral blood flow and impaired vascular response to metabolic demand, indicating cerebral small vessel pathology,[9] have been observed in vascular dementia.[10,11] It is unclear whether cerebral blood flow and cerebrovascular CO_2 reactivity are causally related to cognitive decline and dementia or a consequence of neurodegenerative brain changes.

In this study, we examined the association between cerebral hemodynamics (including cerebral blood flow velocity and cerebrovascular CO_2 reactivity), measured by means of TCD, and cognitive decline and dementia, within the Rotterdam Study, a large population based study in the Netherlands.

DESIGN/METHODS

Study population

The study is based on the Rotterdam Study, a population based prospective cohort study that is ongoing since 1990.[12] TCD assessment was added to the core protocol for the second re-examination (1997-1999), in which 4,730 persons participated. Of these, 4,214 visited the study research centre. In 1,113 participants we were unable to perform TCD due to logistic reasons (no research assistant available). Adequate transcranial Doppler data were obtained in 2,107 of the 3,101 participants (67.9 %) in whom we tried to assess cerebral blood flow velocity and cerebrovascular CO_2 reactivity. The other 994 participants had window failure on both sides (n = 769), difficulty to participate due to restlessness or discomfort (n = 38) or data were lacking due to other reasons (n = 187).

Transcranial Doppler Assessment

Transcranial Doppler ultrasonography monitoring was performed (Multi-Dop X-4, DWL, Sipplingen, Germany) and the cerebral blood flow velocity (cm/sec) was measured in the middle cerebral artery on both sides if possible. End diastolic, peak systolic and mean cerebral blood flow velocities were recorded automatically. Cerebrovascular CO_2 reactivity measurements were done as follows. The cerebral blood flow velocity in the middle cerebral artery was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Participants were then asked to inhale a mixture of 5% carbon dioxide in 95% oxygen for two minutes. Cerebrovascular CO_2 was defined as the percentage increase in cerebral blood flow velocity occurring during inspiration

of 5% CO_2, divided by the absolute increase in end-tidal CO_2 in the same period (%/kPa). End-tidal CO_2 pressure (kPa) was recorded continuously with a CO_2 analyser (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2.[13] TCD-8 DWL special software (VMR-CO_2) was used. All transcranial Doppler data were stored on hard disk for off-line analysis.

Diagnosis of dementia

Dementia screening and diagnosis followed a three-step protocol, as described in detail elsewhere.[14] Briefly, all subjects were screened with a short test of cognition (Mini Mental State Examination (MMSE)[15] and the Geriatric Mental State schedule, organic level[16]). Screen positives underwent further cognitive testing, and an informant interview was obtained. Persons suspected of dementia were examined by a neurologist and underwent more elaborate neuropsychological testing. If possible an axial T1, T2 and coronal T1 cerebral MRI scan was made in order to assess hippocampal and cortical atrophy and to exclude other causes of dementia. Dementia diagnosis was made according to internationally accepted criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.[14,17-19]

Measurements of cognitive function

As part of the cognitive assessment the following neuropsychological tests were administered: the Dutch version of the 30-point Mini Mental State Examination;[15] an abbreviated Stroop test consisting of three subtasks[20] (in Part 1, the subject reads color names printed in black ink, in Part 2, the subject has to name the color of squares, in Part 3, the subject has to name the color in which the color names are printed and disregard their verbal content[21]); the Letter Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test;[22] and a verbal fluency test in which as many animals as possible had to be named within 60 seconds. The MMSE is a global cognitive test developed to use in dementia screening[15] and appeals mainly to cortical functions. The Stroop test and verbal fluency test are timed tasks that measure executive control functions (mental flexibility, vulnerability to interference, concept shifting), sustained attention and mental speed. The Letter Digit Substitution Task is used to assess complex scanning and visual tracking.[22]

The MMSE had been administered during previous examination rounds (1990-1993; 1993-1994) of the Rotterdam Study and the Rotterdam Scan study (1995-1996)[23] as well. Therefore, we were able to examine cognitive decline in the period preceding the TCD assessment (on average 6.5 years). We assumed a linear decline over time and calculated the rate of decline in MMSE for all participants with at least two measurements (n = 3,062) and who were still non-demented at time of the last MMSE measurement.

Data analysis

We used the mean of right and left hemodynamic parameters for the analyses if both middle cerebral arteries could be insonated adequately. In case of one-sided window-failure, the contralateral cerebral hemodynamic parameter was used in the analyses.

Differences in characteristics between persons with successful TCD measurements (n = 2,107) and without successful TCD measurements (n = 994) were compared using analysis of covariance adjusted for age and gender.

To assess the relation between hemodynamic parameters and cognitive function and dementia, we first compared these parameters between demented and non-demented persons. Next, we investigated within non-demented persons the cross-sectional relation between cerebral blood flow velocity and cerebrovascular CO_2 reactivity and cognitive test scores. Finally, we compared within non-demented persons the hemodynamic parameters between those who had declined on the MMSE in the preceding period and those who had not.

In the relation between hemodynamic parameters and dementia, hemodynamic parameters can be either determinant or outcome. Therefore, we assessed the relation between cerebral hemodynamic parameters and dementia by analysis of covariance with dementia as determinant and by logistic regression analysis where we used hemodynamic parameters as determinant and dementia as outcome. The relation between cerebral hemodynamic parameters and neuropsychological test performance was assessed by means of multivariate regression.

Neuropsychological test results were available on more than 99% of the subjects in this study. If data were missing because the person was cognitively unable to complete the test, rather than excluding him or her from the analyses, we assigned that person the worst score that was obtained among those who did complete the tests. Otherwise subjects were excluded from that particular analysis. The relation between hemodynamic parameters and cognitive decline was assessed by analyses of covariance and by logistic regression analysis. Individual rates of decline in MMSE scores were calculated based on at least two and maximal five MMSE scores with the use of a random effects model (SAS 6.12, PROC MIXED). We used all baseline and follow-up MMSE-measurements as outcome variable, time of measurement as independent variable with time at baseline examination as t=0, and the intercept and time of MMSE measurement as random effects.

The estimated fixed effect and the individual random effect were added to obtain the estimated slopes and intercepts of the individual MMSE scores. We defined cognitive decline as a decline of more than two standard deviations from the mean decline of the total non-demented population (0.20 points per year). All analyses were adjusted for age and gender. Additional adjustments were made for education, dichotomised in primary education or less and more than primary education.

RESULTS

Table 1 shows the characteristics of participants with and without adequate TCD measurements. Subjects without TCD measurements were on average older, more frequently female and had a higher systolic blood pressure compared to those with TCD measurements.

Table 1
Characteristics of participants in the study population with and without transcranial Doppler (TCD) examinations.

	TCD* (n = 2,107)	No TCD* (n = 994)	Adjusted difference† (95% CI)
Age (yrs)	71.2 (6.5)	73.6 (6.7)	2.4 (1.9;2.9)
Gender (%women)	46.7	78.2	31.6 (28.0;35.2)
Systolic blood pressure (mmHg)	142.9 (20.8)	145.7 (21.7)	1.8 (0.2;3.5)
Diastolic blood pressure (mmHg)	75.4 (11.2)	75.1 (11.1)	0.8 (-0.0;1.7)
Primary education or less (%)	25.1	34.3	1.9 (-1.6;5.5)
Dementia (%)	0.9	1.7	0.4 (-0.5;1.2)

* Values represent means (SD)
† Adjusted difference adjusted for age and gender

Of the 18 demented with TCD assessment (9 men and 9 women) 16 were diagnosed with Alzheimer's disease and 2 with vascular dementia. Dementia patients had either minimal (n = 12, Clinical Dementia Rating Scale = 1) or mild dementia (n = 6, Clinical Dementia Rating Scale = 2).[24] In 11 of the 18 dementia patients (61 %) we obtained MRI (9 Alzheimer's disease, 2 vascular dementia). Of the Alzheimer patients, 7 had moderate to severe atrophy and 2 patients had normal scans. Besides the atrophy, 3 patients had also mild white matter lesions.

Cerebral blood flow velocity was significantly lower in demented than in non-demented persons (Table 2). The risk of dementia decreased per 10 cm/s increase in cerebral blood flow velocity. Cerebrovascular CO_2 reactivity was lower in demented than in non-demented participants, but the difference was not statistically significant. When we repeated these analyses confined to patients with Alzheimer's disease, the results were virtually the same as for all dementia patients.

Non-demented participants with higher cerebral blood flow and cerebrovascular CO_2 reactivity tended to perform better on cognitive tests (Table 3). Additional adjustment for education did not essentially change the results.

Table 4 shows the comparison of blood flow velocities and cerebrovascular CO_2 reactivity between participants with and without cognitive decline in the period preceding TCD assessment. Persons with cognitive decline had lower cerebral blood flow velocities compared to those without cognitive decline. Mean cerebrovascular CO_2 reactivity was also lower in persons with than without cognitive decline (cerebrovascular CO_2 reactivity: 0.8 %/kPa; 95% CI: 0.2-1.4). The risk of cognitive decline decreased per 10 cm/s increase in cerebral blood flow velocity. Additional adjustment for education level did not change the results.

Table 2
Comparison of cerebral hemodynamic parameters in persons with and without dementia.

	No dementia* (n = 2,089)	Dementia* (n = 18)	Adjusted difference† (95% CI)	Odds ratio‡ (95% CI)
End diastolic cerebral blood flow velocity (cm/s)	32.5 (9.0)	22.0 (5.7)	5.7 (2.0;9.7)	0.31 (0.15-0.61)
Peak systolic cerebral blood flow velocity (cm/s)	86.5 (19.0)	70.0 (16.1)	14.0 (5.2;22.8)	0.62 (0.46-0.83)
Mean cerebral blood flow velocity (cm/s)	50.5 (11.6)	38.0 (8.6)	8.6 (3.4;13.8)	0.40 (0.24-0.68)
Cerebrovascular CO_2 reactivity (%/kPa)	3.9 (2.6)	2.9 (2.4)	0.2 (-1.1;1.4)	0.97 (0.76-1.22)

*Values represent means (SD)
†Adjusted difference (95% CI), adjusted for age and gender
‡Odds ratio (95% CI), adjusted for age and gender, per 10 cm/s increase in cerebral blood flow velocity

Table 3
Adjusted difference in test score by increasing cerebral blood flow velocity (per 10 cm/sec) and by increasing cerebrovascular CO_2 reactivity (per %/kPa)*

	Stroop (sec)			MMSE	Wordfluency (animals/min)	Letter Digit Substitution Task (letters/min)
	Part 2	Part 3	Part (3-2)			
Mean neuropsychological test result (SD)	24.5 (5.4)	62.5 (40.2)	38.1 (38.5)	27.9 (1.7)	21.4 (5.4)	27.6 (6.8)
Cerebral blood flow velocity (per 10 cm/s)						
– End diastolic	-0.34 (-0.61;-0.07)	0.51 (-2.50;1.51)	-0.17 (-2.12;1.77)	0.03 (-0.05;0.12)	0.14 (-0.13;0.41)	0.06 (-0.27;0.39)
– Peak systolic	-0.12 (-0.24;0.00)	0.08 (-0.82;0.98)	0.20 (-0.67;1.07)	0.01 (-0.03;0.04)	0.02 (-0.10;0.13)	0.05 (-0.09;0.20)
– Mean	-0.24 (-0.44;-0.04)	-0.12 (-1.63;1.40)	0.12 (-1.34;1.58)	0.02 (-0.05;0.08)	0.07 (-0.13;0.27)	0.07 (-0.17;0.32)
Cerebrovascular CO_2 reactivity (per %/kPa)	-0.04 (-0.13;0.05)	0.14 (-0.53;0.81)	0.18 (-0.45;0.83)	0.05 (0.02;0.07)	0.12 (0.03;0.20)	0.19 (0.08;0.29)

*Regression coefficient and 95% CI, adjusted for age and gender

Table 4
Comparison of cerebral hemodynamic parameters in persons with and without cognitive decline.*

	No cognitive decline¶ (n = 2,008)	Cognitive decline¶ (n = 81)	Adjusted difference† (95% CI)	Odds ratio (95% CI)
End diastolic cerebral blood flow velocity (cm/s)	32.6 (9.0)	29.2 (8.6)	1.9 (0.1;3.8)	0.73 (0.55-0.97)
Peak systolic cerebral blood flow velocity (cm/s)	86.7 (18.9)	80.6 (18.6)	5.3 (1.1;9.5)	0.85 (0.75-0.97)
Mean cerebral blood flow velocity (cm/s)	50.6 (11.5)	46.3 (11.2)	3.1 (0.6;5.6)	0.77 (0.62-0.95)
Cerebrovascular CO_2 reactivity (%/kPa)	3.9 (2.7)	2.9 (1.8)	0.8 (0.2;1.4)	0.86 (0.76-0.96)

*Cognitive decline defined as a decline of more than two standard deviations from the mean decline of the non-demented population
¶Values represent means (SD)
†Adjusted difference (95% CI), adjusted for age and gender
‡Odds ratio (95% CI), adjusted for age and gender, per 10 cm/s increase in cerebral blood flow velocity

DISCUSSION

We found in a large population-based study that cerebral blood flow velocity was not only significantly lower in persons with dementia, but also in non-demented persons with cognitive decline as compared to cognitively intact subjects. Likewise, the cerebrovascular CO_2 reactivity was significantly lower in persons with cognitive decline and in those with impaired cognitive performance and tended to be lower in dementia patients.

Before further discussing our findings we want to consider whether selection bias may have influenced our findings. First, since participants had to attend the research centre for TCD assessment, persons with severe dementia and persons with severe comorbidity are underrepresented in our study sample. The relatively healthy sample in our study may have attenuated the strength of the associations. Second, TCD was not assessed in 26 percent of all persons visiting the research centre. However, since this was a random sample of all eligible persons that visited the research centre it is unlikely that this has biased our results. Third, we failed to obtain adequate TCD data in 32 percent of participants in whom we tried to assess hemodynamic parameters, mainly due to window failure. This rate is in accordance with previous findings from clinical studies.[25,26] This could have biased our results if window failure were related to cognitive performance or dementia, which we consider unlikely.

To our knowledge, this is the first population-based study examining cerebral hemodynamic parameters in relation to dementia and cognitive decline. Some small, clinical studies suggested no differences in basal flow velocities between healthy controls and Alzheimer patients and lower flow velocities and diminished vasomotor responses in multi-infarct dementia patients.[6,11] It should be noted that these studies used highly selected Alzheimer patients to exclude confounding by vascular pathology. In our study, we were unable to evaluate differences between Alzheimer's disease and vascular dementia since we had only two vascular dementia patients in our sample.

The explanation for our finding that cerebral blood flow velocity is lower in dementia patients and persons with cognitive dysfunction compared to non-demented persons is still unclear. The reduced flow velocities may represent consequences of reduced metabolic needs due to neuronal tissue loss.[26,27] Neuroradiologic techniques including SPECT and PET have shown reductions of global and regional cerebral blood flow in subjects with Alzheimer's disease.[2,3,8,26] Flow abnormalities in persons with very mild dementia have also been found.[7] An alternative explanation is that a decline in cerebral blood flow velocity is a risk factor for dementia. A decrease in blood flow velocity results in decreased delivery of oxygen.[28] Hypoxia may affect cognitive function[29] and may cause ischaemic neuronal lesions in vulnerable areas of the brain,[30] especially in watershed areas.[30,31] Our observation that cerebral blood flow velocity was already lower in persons with cognitive decline, without dementia, does fit with both explanations. Follow-up studies with repeated assessments are needed to distinguish between these mechanisms.

Transcranial Doppler ultrasonography is one of the safest and most inexpensive as well as the most reliable techniques to evaluate cerebral arterial reserve capacity.[32] A

low vasomotor response may indicate small vessel pathology.[9] In our study, cerebrovascular CO_2 reactivity was lower in persons with cognitive decline or low cognitive performance, lending further support to the hypothesis of a role for vascular risk factors and vascular disease in the aetiology of cognitive decline and dementia. The fact that we did not find a significantly lower cerebrovascular CO_2 reactivity in persons with dementia may reflect lack of power. However, it is also possible that this was a group of relatively healthy and 'pure' Alzheimer patients who were free of vascular comorbity.

In conclusion, our study demonstrates that cerebral blood flow velocity is significantly lower in persons with dementia and cognitive decline than in persons with intact cognition. Also, cerebrovascular CO_2 reactivity was lower in persons with reduced cognitive function. Whether the lower blood flow velocity and vasomotor response are a cause or a consequence of dementia remains to be elucidated. Future research should include more non-invasive diagnostic tools to investigate cerebral hemodynamics, such as transcranial Doppler.

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CEREBRAL HEMODYNAMICS AND DEPRESSION IN THE ELDERLY

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Abstract

Background: Evidence from epidemiological and neuroimaging studies suggests that cerebrovascular disease is associated with depressive syndromes in the elderly. It is unclear whether cerebrovascular disease contributes substantially to the pathogenesis of late life depression.

Methods: In the present study we utilized transcranial Doppler ultrasonography to investigate the relationship between depressive disorders and cerebral hemodynamics in a population-based study. In 2093 men and women who participated in the Rotterdam Study we measured cerebral blood flow velocity and CO_2-induced vasomotor reactivity in the middle cerebral artery. All subjects were screened for depressive symptoms using the Center of Epidemiological Studies Depression Scale and subjects with a score of 16 or over had a psychiatric work-up. We controlled for age, gender, education, stroke and cognitive score.

Results: Subjects with depressive symptoms had reduced blood flow velocities (mean difference in mean flow: -2.7 cm/s; 95% CI: -4.9;-0.6) and lower vasomotor reactivity (mean difference: -0.6 %/kPa; 95% CI: -1.1;-0.06). Blood flow velocity was increasingly reduced along the worsening spectrum of the affective illness (mean difference of depressive disorders: -5.1 cm/s; 95% CI: -8.5;-1.6). The overall reduction in vasomotor reactivity, however, was accounted for by subjects with subclinical depressive symptoms.

Conclusions: Late life depression is associated with cerebral hemodynamic changes that can be assessed by transcranial Doppler ultrasonography. The observed reduction in cerebral blood flow velocity could be a consequence of reduced demand in more seriously depressed cases, whereas reduced CO_2-induced cerebral vasomotor reactivity reflects a possible causal factor for depressive symptoms.

INTRODUCTION

The "vascular depression" hypothesis postulates that in late life vascular pathology contributes significantly to the pathogenesis of depression.[1] Converging evidence from epidemiology, genetics and neuropsychology suggests that cerebrovascular changes may lead to depressive syndromes.[2-6] Strong evidence comes in particular from neuroimaging studies.[2,7] These studies have focused on MRI hyperintensities, but SPECT and PET have also been utilized to provide information on the function of the brain in depressive disorders.[8-10] Regional differences in cerebral blood flow between subjects with depressive disorders and controls have been reported.

With transcranial Doppler ultrasonography (TCD) one can assess hemodynamic changes resulting from cerebrovascular impairment.[11,12] Both changes in vasomotor reactivity and in blood flow velocities are commonly measured in the basal cerebral arteries by TCD. Vasomotor reactivity is reduced in patients with cerebral microangiopathy,[11] while changes in cerebral artery blood velocities reflect changes in cerebral blood flow and brain tissue perfusion.[13-15]

Most findings in research on vascular depression have been based on selected and small samples of older individuals. The generalizability of the vascular depression hypothesis to the majority of old people with depressive disorders is therefore unknown. The Rotterdam Study provides an opportunity to examine the relation between cerebral hemodynamics and depressive symptoms in a population-based sample of older adults.

We conducted this study to evaluate whether cerebrovascular impairment as measured by TCD is related to depression.

SUBJECTS AND METHODS

Subjects

The Rotterdam Study is a population-based prospective cohort study conducted in a suburb of Rotterdam, the Netherlands. It was designed to investigate chronic neurologic, cardiovascular, locomotor and ophthalmologic disorders.[16] The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus University Medical School. The original cohort consisted of 7983 subjects aged 55 years and over. The baseline examinations at the research center took place from 1990 to mid 1993 and the third examination was conducted between 1997 to 1999.

At the third examination both screening and diagnostic work-up for depression and TCD assessment were added. Screening for depressive symptoms was carried through during the home interview of this survey in which 4730 subjects participated. In 3101 consecutive participants we tried to perform TCD as part of the standard clinical investigation at the research center. No TCD measurement were carried out in the remainder due to logistical reasons or unavailability of a technician. In 990 (32%) subjects no TCD data were obtained. In most cases this was due to window failure on both sides (n=771) or difficulty to participate because of restlessness or discomfort (n=36). In 183 participants other reasons like ambiguous flow directions or lack of time prevented

the hemodynamic measurements. This rate is in accordance with previous findings in clinical studies.[13,17] Subjects in whom no TCD data were obtained were older ($p<0.001$) and more likely to be female ($p<0.001$). In addition, 18 subjects were excluded because they had no complete screening for depression. The present study group consisted of 2093 participants from which adequate depression and hemodynamic parameters were obtained.

Depression Assessment

Depressive disorders were assessed using a two step procedure. As a first step the Dutch version of the original Center for Epidemiology Studies Depression scale (CES-D) was completed by the participant during the home interview. The CES-D is a 20-item self-reported measure of symptoms experienced in the last week scored on a scale of 0 to 3 points. The criterion validity of the CES-D version is well established.[18] We used a score of $\geq$ 16 as a cut-off, which reportedly has a sensitivity of 100% for major depression in a random sample of older subjects in the Netherlands.[19] On the other hand the majority of those depressed according to the CES-D do not fulfil rigorous diagnostic criteria for DSM IV affective disorder. Therefore, screen positive subjects had a psychiatric work-up as a second step. They were evaluated with the Dutch version of the Present State Examination (PSE-10), a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry.[20] All interviews were conducted by two experienced clinicians. Psychiatric disorders were classified according to the DSM-IV criteria with an algorithm based on the PSE-10 scores. The diagnostic categories include minor depression as defined in the appendix of DSM-IV.

Of the 2093 subjects included in the analyses 116 (5.5%) were screen-positive for depression as measured by the CES-D. Psychiatric work-up was performed in 111 (95.6%) of these participants. Four subjects refused to participate in this evaluation, one screen positive subject could not be reached.

To define late-onset depression we used the data from the baseline interview with a physician. All subjects in the present analysis responded to the questions about psychiatric history. Cases who reported unipolar of bipolar depression before age 60 were considered as suffering from early onset depression.

Transcranial Doppler Assessment

Transcranial Doppler ultrasonography monitoring was performed (Multi-Dop X-4, DWL, Sipplingen, Germany) and the cerebral blood flow velocity (cm/sec) was measured in the middle cerebral artery on both sides if possible. End diastolic, peak systolic and mean cerebral blood flow velocity were recorded automatically. CO_2-induced cerebral vasomotor reactivity measurements were done as follows. The cerebral blood flow velocity was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Next, participants inhaled a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes. Cerebral vasomotor reactivity was defined as the percentage increase in cerebral blood flow velocity occurring during inspiration of 5% CO_2,

divided by the absolute increase in end-tidal CO_2 in the same period (%kPa). End-tidal CO_2 pressure (kPa) was recorded continuously with CO_2 analyzer (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2. TCD-8 DWL special software (VMR-CO_2) was used. All transcranial Doppler data were stored on hard disc for off-line analysis. The mean of the right and left hemodynamic parameter was used for analyses if both middle cerebral arteries could be insonated adequately. The one-sided hemodynamic parameter was used if a window failure appeared on one side.

Measurements of Other Covariates

The following variables were considered as possible confounding variables: age, gender, education, cognitive function as measured by the Mini Mental State Examination (MMSE), stroke and peripheral arterial disease. Education was measured on an ordinal scale and later dichotomized at the median of the baseline sample into low and high education. A history of stroke was obtained from all subjects through direct questioning and computerized linkage with general practitioner medical records. It was considered positive when confirmed by a physician. The ankle-to-brachial-index was used as an indicator of peripheral atherosclerosis. We assessed ankle-to-brachial index by taking the ratio of the systolic blood pressure measured at the tibial artery to the systolic blood pressure measured at the right arm. Subjects with an ankle-to-brachial index less than 0.9 were considered to suffer from peripheral arterial disease.[21]

Statistical Analysis

The associations between hemodynamic parameters and depressive disorders were addressed in three ways. First, analysis of covariance (ANCOVA) was used to calculate means of the screen positive subjects and the reference group, adjusted for age and gender. This analysis was also performed making a distinction between subjects with depressive disorders and subjects with subclinical depressive symptom. In addition, we controlled this analysis for education, stroke, cognitive function, and history of major depression before age 60. Second, logistic regression analysis was used to calculate odds ratios (OR) for the association between hemodynamic parameters and the presence of depressive disorders. We assessed tertiles of hemodynamic parameters to allow for a non-linear relationship. In this model we included only the variables associated with hemodynamic indices to avoid an unstable model. Third, we studied possible effect modification by stratifying for peripheral arterial disease and history of depression.

RESULTS

Table 1 compares the demographic characteristics and confounding variables of the 116 participants who were screen positive and the 1977 participants who were screen negative for depression.

Older age, female gender, education, a history of major depression before age 60,

Table 1
Characteristics from participants with and without depressive symptoms.*

	Non-depressed (n=1977)	CES-D-score ≥ 16 (n=116)
Age, years	71.1 (6.5)	72.8 (6.6)
Male, %	54.1	41.4
Primary education only, %	58	42
Previous stroke, %	2.3	6.0
MMSE score	27.9 (1.8)	27.1 (2.6)
Peripheral arterial disease, %	16.2	24.6
Major depression before age 60, %	3.5	6.9

*Values are unadjusted means (SD) or percentages

Table 2
Association between cerebral hemodynamic parameters and depressive symptoms*

	Non-depressed (n=1977)	CES-D score ≥ 16 (n=116)	
	mean	mean	adjusted difference (95% CI)
Blood flow velocity (cm/s)			
– end diastolic	32.5	29.6	-2.2 (-3,7; -0.6)
– mean	50.5	47.8	-2.7 (-4.9; -0.6)
– peak systolic	86.5	82.5	-3.9 (-7.4; -0.3)
Vasomotor reactivity (%/kPa)	3.9	3.1	-0.6 (-1.1;-0.1)

*Analysis of covariance adjusted for age, gender, education, cognitive function and history of stroke
Values represent crude means and adjusted differences (95% CI), pairwise comparison with non-depressed reference group

previous stroke and cognitive function were all associated with current depressive symptoms.

Subsequent psychiatric work up revealed that 42 subjects in the screen positive group had a depressive disorder as defined by DSM-IV. These were classified as major depression (n=15), dysthymia (n=9) or minor depression (n=18). The remaining subjects were either classified as anxiety disorders and other psychiatric disease (n=8) or did not meet criteria for an Axis I psychiatric disorder (n=61, subclinical depressive symptoms).

We found significant differences in cerebral hemodynamic parameters between subjects with and without depressive symptoms. Subjects with depressive symptomatology as determined by the CES-D had lower mean cerebral blood flow velocity (age and gender adjusted mean difference: -2.9 cm/s; 95% CI: (-5.0;-0.8); p=0.007) and reduced

Table 3
Association between cerebral hemodynamic parameters and depression.*

	Non-depressed (n=1977)	Subclinical depressive symptoms (n=61)		Depressive disorders (n=42)	
	mean	mean	adjusted difference†	mean	adjusted difference†
Blood flow velocity (cm/s)					
– end diastolic	32.5	30.5	-1.0 (-2,9; 0.9)	27.8	-4.0 (-6.6; -1.4)
– mean	50.5	48.5	-1.3 (-3.9; 1.2)	44.9	-5.1 (-8.5; -1.6)
– peak systolic	86.5	84.4	-2.0 (-6.3; 2.4)	79.2	-7.1 (-12.9;-1.3)
Vasomotor reactivity (%/kPa)	3.9	2.7	-0.9 (-1.5;-0.2)	3.3	-0.3 (-1.1; 0.5)

*Analysis of covariance adjusted for age, gender, education, cognitive function and history of stroke
† Values represent crude means and adjusted differences (95% CI), pairwise comparison with non-depressed reference group, same covariates

Table 4
The relation between tertiles of cerebral hemodynamic parameters and depression expressed as odds ratios

	Number of subjects	Odds ratios* (95% CI)		
		CES-D score ≥16 (n=116)	Subclinical depressive symptoms‡ (n=61)	Depression† (n=42)
Mean blood flow velocity				
1st	692	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd	697	1.2 (0.7;2.0)	1.2 (0.7;2.2)	1.2 (0.5;2.9)
3rd	703	1.9 (1.2;3.1)	1.4 (0.8;2.6)	2.6 (1.2;5.8)
Enddiastolic blood flow velocity				
1st	694	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd	692	1.0 (0.6;1.7)	0.9 (0.5;1.6)	1.2 (0.5;2.8)
3rd	705	1.8 (1.1;2.9)	1.3 (0.7;2.3)	2.6 (1.2;5.7)
Peaksystolic blood flow velocity				
1st	695	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd	692	1.3 (0.8;2.1)	1.3 (0.7;2.4)	1.3 (0.6;2.9)
3rd	706	1.7 (1.0;2.7)	1.4 (0.8;2.6)	1.9 (0.9;4.2)
Vasomotor reactivity				
1st	669	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd	674	2.2 (1.3;3.8)	2.7 (1.3;5.7)	1.5 (0.7;3.2)
3rd	671	2.0 (1.2;3.5)	2.7 (1.3;5.6)	1.2 (0.5;2.6)

Note: the numbers of cases with subclinical depressive symptoms and depression do not add up to 116 because 5 subjects had no psychiatric work-up and 8 screen positive subjects had other psychiatric diseases.
*Logistic regression adjusted for age, gender, cognitive function
‡Subjects with depression excluded from analysis
† Subjects with subclinical depressive symptoms excluded from analysis

vasomotor reactivity (age and gender adjusted mean difference: -0.7 %/kPa; 95% CI: (-1.2;-0.2); p=0.008). Table 2 shows the relation between cerebral hemodynamic parameters and depressive symptoms additionally adjusted for education, history of stroke and cognitive function.

In a further analysis, screen positive subjects were classified according to the severity of the depressive symptoms (Table 3). Subjects with subclinical depressive symptoms and subjects with depressive syndromes were included as distinct groups, whereas subjects with other Axis 1 disorders were excluded. The results showed a consistent pattern for end diastolic, mean and peak systolic blood flow velocity. Blood flow velocity of subjects with depressive syndromes was significantly lower compared to the reference group. The mean values of subjects with subclinical depressive symptoms lay in between. A different pattern was observed for vasomotor reactivity. Subjects with subclinical depressive symptoms had a lower vasomotor reactivity than non-depressed reference subjects, whereas there was no clear difference between subjects with depressive syndromes and the reference group.

Table 4 shows odds ratios for depressive symptoms per tertile of hemodynamic parameter adjusted for age, sex and cognitive function. The particular contributions of subjects with subclinical depressive symptoms and subjects with depressive syndromes are also presented in this table. It can be seen that significantly more subjects with depression were found in the lowest tertile of blood flow velocity. As concerns vasomotor reactivity, the middle and the lower tertile were associated with an increased risk for subclinical depressive symptoms.

The observed relationships between depressive status and cerebral hemodynamic parameters were not altered after we controlled for history of major depression before age 60 and peripheral arterial disease. There were more subjects with peripheral arterial disease in both the group with subclinical depressive symptoms (28.8%) and the group with depressive syndromes (25.0%) as compared to the reference group (16.5%), but the relationship between blood flow velocity or vasomotor reactivity and depression was neither explained nor modified by peripheral arterial disease (data not shown).

DISCUSSION

This large population-based study showed that depressive symptoms are accompanied by hemodynamic changes as assessed by transcranial Doppler. Both cerebral blood flow velocity and vasomotor reactivity were found to be lower in depressed subjects after the effects of age, sex, education, history of stroke and cognitive function were controlled for. To our knowledge this study is the first to report results of transcranial Doppler ultrasound measurements and depression in a population based sample. It therefore extends the existing research on vascular depression and supports the notion that cerebrovascular impairment may be a cause of depressive symptoms in the elderly.

Some limitations of this study must be discussed. It can be argued that selection bias may have influenced the outcome of this study at two points. Firstly, TCD measure-

ments were not performed in all subjects participating in the third survey of the Rotterdam study. Secondly, TCD measurements were unsuccessful in nearly one third of subjects. It is more likely that the latter might have introduced bias because the first selection was completely at random. Participants in which TCD measurements were unsuccessful were on average older and more likely to be female. The differences in age and gender reflect the increase in temporal bone acoustic thickness with age and in postmenopausal women.[22] This can adversely affect the transmission of the ultrasound and as a consequence often prevents TCD measurements. Hyperostosis, which is predominantly found in women, is also thought to preclude TCD measurements.[23] Since old age and female gender are positively associated with depressive symptoms, persons with mood disorders were underrepresented in this study. This could impede the detection of modest associations and consequently a relation between depressive syndromes and vasomotor reactivity may not have been detected. On the other hand, we do not consider this very likely because we did observe a relation between blood flow velocities and depressive syndromes in the study population.

The strength of the present large, population-based study is the psychiatric work-up in subjects who were screen positive on the CES-D. A previous study in an elderly Dutch population reported a sensitivity of 100% using the same cut off point and misclassification of disease is therefore unlikely to have influenced our results.[19] Furthermore, we were able to determine in which group depressive symptoms were due to depressive syndromes and perform analysis along the worsening spectrum of affective illness. Our finding that less than half of screen positive subjects suffered from depressive syndromes is in accordance with low positive predictive value for the CES-D screening procedure. However, careful interpretation of our findings concerning subclinical depressive symptoms is necessary, because the concept is related to the screening instrument used.[24]

The term "vascular depression" was introduced five years ago to describe the hypothesis postulated earlier by Alexopoulos et al. who suggested that geriatric depression encompasses a high percentage of patients with neurologic brain disorders.[1] While few clinical differences exist between early- and late-onset depression,[7] their position has been supported by studies showing that late-onset depression have more neuroradiological abnormalities compared to contemporaries.[25] Others have investigated the vascular depression hypothesis in clinical samples or healthy subjects utilizing PET or SPECT. While some authors have reported no difference in cerebral blood flow most have observed regional differences in frontal or temporal areas.[26-28] The few studies exclusively including elderly subjects reported a more widespread decrease in radiotracer uptake.[29,30] Whether this indeed reflects cerebrovascular disease and structural deficits remains unclear.

Different mechanisms for altered cerebral blood flow velocity as measured by TCD have been postulated.[31] Reduced blood flow may reflect altered cerebral metabolism, an intrinsic property of the vascular smooth muscle, or a neuronal dysfunction of sympathetic nerve fibers. Several studies support the view that metabolic autoregulation is

of key importance for cerebral blood flow velocity.[32] This mechanism explains increased flow velocity during cognitive activity best.[33] As reduced cognitive activity is a well recognized symptom of depressive disorder, a reduction of blood flow velocity can be interpreted as an epiphenomenon of depression. The decreased blood flow velocity in our study might mainly reflect the diminished demand in depressive states and does not necessarily support the vascular hypothesis.

Vasomotor reactivity on the other hand, probably is a good indicator of microangiopathy. A reduction means that the cerebral arterioles are unable to compensate decreased perfusion by vasodilatation.[34] In clinical studies of patients with stroke or transient ischemic attacks reduced vasomotor reactivity has repeatedly been reported.[11,35] However, we did not observe a significant reduction in vasomotor reactivity in subjects with depressive syndromes. Reduced vasomotor reactivity was accounted for by subjects with subclinical depressive symptoms. This suggests that cerebrovascular pathology may be less important in the more severely diseased. It is conceivable that especially the subjects with comorbidity related to cerebrovascular disease suffer from subclinical depressive symptoms. Admittedly, this interpretation and its possible clinical implications remain speculative because the non-depressed CES-D screen positive group most certainly is a heterogeneous group. It demonstrates that subjects with depressive symptoms may fall in distinct categories and future research on the vascular depression should not rely on questionnaire assessment only.

In summary, we were able to demonstrate that depressive symptoms are associated with changes both in blood flow velocity and vasomotor reactivity. Our finding of reduced vasomotor reactivity suggests that vascular pathology may be a causal factor in subjects with subclinical depressive symptoms. Furthermore, our data show that reduced cerebral blood flow velocity might be a consequence of reduced demand in depressed subjects and does not necessarily reflect microangiopathy.

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Chapter 6

CEREBRAL HEMODYNAMIC INDICES IN ACUTE HEMISPHERIC ISCHEMIC STROKE

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Abstract

Objectives: To study cerebral hemodynamic indices in patients with acute hemispheric ischemic stroke in relation to stroke type, stroke severity and clinical outcome.

Methods: Twenty-two patients with a clinical diagnosis of acute hemispheric ischemic stroke were studied within 72 hours after stroke onset and after 6 months. Cerebral hemodynamic indices were measured by means of transcranial Doppler. Stroke severity was scored retrospectively by means of the NIH Stroke Scale and clinical outcome by means of the modified Rankin scale.

Results: Within 72 hours from stroke onset, peak systolic flow velocity and cerebrovascular CO_2 reactivity were lower in the symptomatic than in the asymptomatic hemisphere with respective differences of -12.6 cm/sec [95% CI: -25.1; -0.1] and -0.4 %/kPa [95% CI: -0.6; -0.01]. At 6 months, mean flow velocity on the asymptomatic side was 8.3 cm/sec lower [95% CI: 0.5-16.1] than in the same hemisphere measured within 72 hours. Cerebrovascular CO_2 reactivity in the symptomatic hemisphere, measured within 72 hours of stroke onset, was -1.5 %/kPa [95% CI: -2.8; -0.2] lower in patients with atrial fibrillation (AF) than in patients with other causes. In patients with AF, peak systolic and end diastolic flow velocity were lower in the asymptomatic hemisphere than in patients without AF (mean differences: -27.6 cm/sec [95% CI: -54.3; -0.9] and -17.6 cm/sec [95% CI: -33.6; -1.6], respectively). The difference in end diastolic flow velocity between asymptomatic and symptomatic hemisphere was higher in patients with lacunar infarctions than in those with other stroke subtypes, both in the acute phase and at 6 months. Furthermore, the difference in CVR-CO_2 between asymptomatic and symptomatic hemisphere was lower in patients with lacunar infarctions at 6 months (-0.2 *versus* 0.5). Patients with NIH Stroke Scale < 4 had higher mean flow velocity on the symptomatic side and higher end diastolic flow velocity and lower pulsatility index on the asymptomatic side. No relationship was found between the cerebral hemodynamic indices and clinical outcome.

Conclusions: Cerebral hemodynamic indices are influenced by acute hemispheric ischemic stroke in the symptomatic as well as the asymptomatic hemisphere. A "steal" phenomenon may play a role in hemispheric ischemia, particularly in atrial fibrillation. Differences between the symptomatic and the asymptomatic hemisphere appear to be largest in patients with lacunar infarctions. Cerebral hemodynamic indices are related to stroke severity, but not to clinical outcome.

INTRODUCTION

Following its introduction in 1982 by Aaslid and co-workers,[1] transcranial Doppler (TCD) has become an established technique to examine and monitor cerebral blood flow velocity and the arterial pulsatility index in the basal cerebral arteries and to quantify cerebrovascular CO2 reactivity, which reflects the compensatory dilatory mechanism of the intracerebral arterioles[2] and is thought to be a more sensitive hemodynamic index than the level of resting blood flow velocity.[3]

Stroke-related changes in cerebral hemodynamics have already been described by Meyer et al. in 1973.[4,5] Since then, changes in cerebral blood flow, blood flow velocity and cerebral vasomotor reactivity have been described in ischemic cerebrovascular disease,[6-17] as well as in experimental cerebral infarction.[18,19] Some studies have reported changes in cerebral hemodynamics due to acute hemispheric ischemia on both sides,[8,9,19,20] but it remains unclear whether alterations in hemodynamic indices are limited to the affected hemisphere or that cerebral ischemia influences arterial blood flow in both hemispheres. Whether changes in cerebral hemodynamic indices occur only during the period of ischemia or persist is also unknown. Although recent studies have supported the observation that cerebrovascular CO_2 reactivity may be reduced in lacunar disease,[9,10,14] as well as in low-flow infarctions,[6,8,16] and cortical infarcts,[8,9] it still has to be determined which of the cerebral hemodynamic indices are associated with stroke subtype and clinical outcome.

We studied the association between cerebral hemodynamic indices, assessed by means of TCD within 72 hours after stroke onset and at 6 months, and stroke subtype and clinical outcome in 22 consecutive patients with a clinical diagnosis of acute hemispheric ischemic stroke.

STUDY POPULATION AND METHODS

Study Population

All patients with a clinical diagnosis of acute hemispheric ischemic stroke and admitted to the Department of Neurology of the University Hospital Rotterdam-Dijkzigt were studied. If no informed consent could be obtained or temporal bone window failure occurred on both sides, patients were excluded from the study. Patients with ischemia in the posterior circulation were also excluded. The current analysis is based on 22 patients, examined from February-September 1997. We prospectively studied these patients within a period of 72 hours of stroke onset, representing the (sub)acute phase and at 6 months after onset.

Stroke Type

Etiological stroke types were scored according to the TOAST classification.[21] This classification distinguishes 5 subtypes of ischemic stroke: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. We also made a simple distinction between lacunar

and non-lacunar infarction.[22] Lacunar infarction was diagnosed if the patient presented with a pure motor stroke, a pure sensory stroke, ataxic hemiparesis, or a sensorimotor stroke in the absence of a visual field defect and evidence of higher cerebral dysfunction and with a hypodense lesion ≤ 15 mm in diameter on CT or no visible infarct.[23]

Stroke Severity and Clinical Outcome

Stroke severity was scored retrospectively by means of the NIH Stroke Scale (NIHSS) on admission.[24] Clinical outcome was assessed by means of the modified Rankin scale on admission and at 6 months after onset of symptoms. Clinical improvement was defined as an improvement of 1 or more points on the modified Rankin scale.

Transcranial Doppler Assessment

Transcranial Doppler ultrasonography monitoring was performed (Multi-Dop X-4, DWL, Sipplingen, Germany) within a period of 72 hours after stroke onset and after 6 months at follow-up. Cerebral blood flow velocity (cm/s) was measured in the middle cerebral artery (MCA) on both sides if possible. End diastolic flow velocity (EDV), peak systolic flow velocity (PSV) and mean flow velocity (MCV) were recorded automatically. The mean flow velocity was calculated automatically as (PSV+(EDVx2)/3). The pulsatility index (PI) was defined as (PSV-EDV/MCV). It was measured automatically with fast Fourier transformation. The PI values were determined in both middle cerebral arteries, over five cardiac cycles and their mean was used for the analyses. Cerebrovascular CO_2 reactivity (CVR-CO_2) measurements were done as follows: the cerebral blood flow velocity in the MCA was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Participants then inhaled a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes. CVR-CO_2 was defined as percentage increase in MCV during inspiration of 5% CO_2 divided by the absolute increase in end-tidal CO_2 during the same time-period (%/kPa). End-tidal CO_2 pressure (%/kPa) was recorded continuously with a CO_2 analyzer (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2.[2] TCD-8 DWL special software (VMR-CO_2) was used.

Data analysis

We computed the difference in cerebral hemodynamic indices with 95% CI between the symptomatic and asymptomatic MCA, and between early and late measurements of the same MCA, using the (paired) t statistics, i.e. assuming equal variance in the two samples. The difference in cerebral hemodynamic indices in patients with and without clinical improvement was analyzed by means of independent-samples t test. We used a score of 4 on the NIH Stroke Scale as cut off point in our analyses, as this was the median value.

Table 1
Baseline characteristics from patients with acute hemispheric ischemic stroke (N=22).

	Baseline
Age (yrs)	61.8 (15.8)
Women, N (%)	9 (41)
Stroke type	
Large-artery atherosclerosis, N (%)	5 (23)
Cardioembolism, N (%)	4 (18)
Small-vessel occlusion, N (%)	4 (18)
Stroke of other determined etiology, N (%)	5 (23)
Stroke of undetermined etiology, N (%)	4 (18)
NIHSS, median	4
P25	1.75
P75	7.75
Lacunar infarction, N (%)	10 (45)

Values represent means (%)
Lacunar infarction was diagnosed if the patient presented with a pure motor stroke, a pure sensory stroke, ataxic hemiparesis, or a sensorimotor stroke in the absence of a visual field defect and evidence of higher cerebral dysfunction and with a hypodense lesion ≤ 15 mm in diameter on CT or no visible infarct

RESULTS

Baseline characteristics from the patients with TCD examinations are shown in Table 1. All patients with a cardioembolic stroke had atrial fibrillation. Mean time between stroke onset and the first TCD examination was 38 hours (SD 18.3). Comparison of cerebral hemodynamic indices between both hemispheres, measured within 72 hours of stroke onset, was possible in 17 patients, as 5 had unilateral window failure. Seven patients were lost to follow up: 4 refused a second transcranial Doppler examination, 2 died and 1 could not be reached at her home address. Consequently, we were able to obtaine adequate TCD data at 6 months in 15 patients. Nine patients had improved 1 or more points on the modified Rankin scale at final follow-up.

The influence of acute ischemic hemispheric stroke on the cerebral hemodynamic parameters is shown in Table 2. Measured within 72 hours of stroke onset, PSV and CVR-CO_2 were lower in the symptomatic hemisphere than in the asymptomatic hemisphere and their mean differences were -12.6 cm/sec [95% CI: -25.1; -0.1] and -0.4 %/kPa [95% CI: -0.6; -0.01], respectively. No statistically significant differences between the symptomatic and the asymptomatic hemisphere were observed at 6 months.

MCV on the asymptomatic side was 8.3 cm/sec lower [95% CI: 0.5-16.1] at 6 months compared with that within 72 hours of stroke onset, in the 13 patients in whom it was possible to compare both values.

There were no differences in cerebral hemodynamic indices between patients with or without symptomatic high-grade internal carotid artery stenosis. Table 3 shows the dif-

Table 2
Cerebral hemodynamic indices within 72 hours of acute hemispheric ischemic stroke onset and at 6 months follow-up (N=17).

	< 72 hours			6 months		
Cerebral hemodynamic indices*	**Symptomatic**	**Asymptomatic**	**Mean difference†**	**Symptomatic**	**Asymptomatic**	**Mean difference†**
EDV (cm/s)	34.5	39.7	−5.2 [−11.7;1.2]	34.0	37.4	−3.4 [− 9.6;2.9]
MCV (cm/s)	59.1	61.9	−2.8 [−11.4;5.7]	54.2	60.5	−6.3 [−15.8;3.2]
PSV (cm/s)	84.3	96.9	−12.6 [−25.1; −0.1]	84.3	92.2	−7.9 [−21.7;5.9]
Pulsatility index	0.98	1.01	−0.03 [−0.1;0.07]	0.95	0.97	−0.02 [−0.1;0.09]
CVR-CO_2 (%/kPa)	2.0	2.4	−0.4 [−0.6;−0.01]	1.7	1.9	−0.2 [−0.6;0.2]

*Values represent means
EDV = end diastolic cerebral blood flow velocity
MCV = mean cerebral blood flow velocity
PSV = peak systolic cerebral blood flow velocity
CVR-CO_2 = cerebrovascular CO_2 reactivity
†Mean differences [95% CI] between symptomatic and asymptomatic indices and were calculated by means of paired-samples t test

Table 3
Differences in cerebral hemodynamic indices, measured within 72 hours of stroke onset, between patients with NIHSS < 4 and NISSS ≥ 5, with and without atrial fibrillation and with and without lacunar infarctions.

	Symptomatic hemisphere			Asymptomatic hemisphere		
Cerebral hemodynamic indices	**NIHSS < 4 *vs.* ≥ 5**	**AF + *vs.* –**	**Lacunar + *vs.* –**	**NIHSS < 4 *vs.* ≥ 5**	**AF + *vs.* –**	**Lacunar + *vs.* –**
EDV (cm/s)	6.9 [-3.1;17.0]	-9.1 [-21.4;3.1]	-3.6 [-14.1;7.0]	15.2 [2.6;27.8]	-17.6 [-33.6; -1.6]	7.9 [-6.2;22.0]
MCV (cm/s)	15.0 [4.0;26.0]	-13.3 [-28.3;1.7]	6.9 [-6.0;19.9]	16.5 [-1.3;34.2]	-18.4 [-40.9;4.1]	11.0 [-7.7;29.7]
PSV (cm/s)	4.7 [-14.0;23.5]	-8.3 [-31.0;14.4]	-1.4 [-20.2;17.5]	10.2 [-13.4;33.8]	-27.6 [-54.3; -0.9]	9.0 [-14.7;32.7]
Pulsatility index	-0.1 [-0.3;0.1]	0.2 [-0.1;0.4]	0.1 [-0.1;0.3]	-0.2 [-0.4; -0.02]	0.2 [-0.1;0.5]	-0.1 [-0.3;0.2]
CVR-CO_2 (%/kPa)	0.4 [-0.8;1.7]	-1.5 [-2.8;-0.2]	1.0 [-0.1;2.1]	0.6 [-0.5;1.7]	-0.8 [-2.2;0.5]	0.8 [-0.2;1.9]

Values represent mean differences [95% CI] and were calculated by means of independent-samples t test
EDV = end diastolic cerebral blood flow velocity
MCV = mean cerebral blood flow velocity
PSV = peak systolic cerebral blood flow velocity
CVR-CO_2 = cerebrovascular CO_2 reactivity
NIHSS = NIH Stroke Scale
AF = atrial fibrillation

Table 4
Differences in cerebral hemodynamic indices between symptomatic and asymptomatic hemisphere, by modifying variables.

Cerebral hemodynamic indices	<72 hours			6 months		
Atrial fibrillation	**Present**	**Absent**	**Mean difference***	**Present**	**Absent**	**Mean difference***
EDV (cm/s)	-1.5	7.3	-8.8 [-23.8;6.2]	-8.0	4.5	-12.5 [-33.7;8.7]
MCV (cm/s)	0.9	3.4	-2.5 [-23.4;18.3]	-2.5	7.2	-9.7 [-44.2;24.8]
PSV (cm/s)	0.0	16.5	-16.5 [-45.7;12.8]	-12.0	9.9	-21.9 [-70.4;26.6]
Pulsatility index	0.1	0.01	0.1 [-0.2;0.3]	0.1	0.01	0.1 [-0.3;0.5]
CVR-CO_2 (%/kPa)	0.8	0.2	0.6 [-0.1;1.3]	0.1	0.2	-0.1 [-1.0;1.4]
Non-lacunar stroke						
EDV (cm/s)	11.8	-0.6	12.4 [0.7;23.9]	10.0	-2.2	12.2 [2.4;21.9]
MCV (cm/s)	6.6	-0.6	7.2 [-10.1;24.6]	12.9	0.8	12.1 [-6.1;30.3]
PSV (cm/s)	22.0	4.2	17.8 [-6.3;41.9]	19.0	-1.3	20.3 [-5.0;45.6]
Pulsatility index	-0.03	0.1	-0.1 [-0.3;0.1]	-0.1	0.1	-0.2 [-0.4;0.1]
CVR-CO_2 (%/kPa)	0.1	0.5	-0.4 [-1.0;0.3]	-0.2	0.5	-0.7 [-1.4;-0.04]
Severe stroke						
EDV (cm/s)	0.1	9.8	-9.7 [-22.0;2.7]	0.2	7.2	-7.0 [-19.3;5.3]
MCV (cm/s)	-1.3	6.5	-7.8 [-25.1;9.4]	1.4	12.3	-10.9 [-29.5;7.8]
PSV (cm/s)	3.6	20.6	-17.0 [-41.2;7.3]	2.8	14.0	-11.2 [-39.5;17.2]
Pulsatility index	0.1	-0.02	0.1 [-0.1;0.3]	0.1	-0.1	0.2 [-0.03;0.4]
CVR-CO_2 (%/kPa)	0.2	0.5	-0.3 [-0.9;0.3]	0.1	0.3	-0.2 [-1.0;0.7]

*Values represent mean differences [95% CI] and were calculated by means of independent-samples t test
EDV = end diastolic cerebral blood flow velocity
MCV = mean cerebral blood flow velocity
PSV = peak systolic cerebral blood flow velocity
CVR-CO_2 = cerebrovascular CO_2 reactivity
Severe stroke was defined as NIHSS $\geq$ 5

ferences in cerebral hemodynamic indices, measured within 72 hours of stroke onset, between patients with NIHSS < 4 or NISSS ≥ 5, with or without atrial fibrillation, and with or without lacunar infarctions. CVR-CO_2 in the symptomatic hemisphere, measured within 72 hours of stroke onset, was -1.5 %/kPa [95% CI: -2.8; -0.2] lower in patients with atrial fibrillation than in patients with other causes of stroke. In patients with atrial fibrillation, PSV and EDV were lower in the asymptomatic hemisphere than in patients with other stroke subtypes and their mean differences were -27.6 cm/sec [95% CI: -54.3; -0.9] and -17.6 cm/sec [95% CI: -33.6; -1.6], respectively. The differences between patients with or without atrial fibrillation had disappeared at 6 months after stroke onset.

Patients with NIH Stroke Scale < 4 had higher MCV on the symptomatic side and higher EDV and lower PI on the asymptomatic side and their mean differences were 15.0 cm/sec [95% CI: 4.0;26.0], 15.2 cm/sec [95% CI: 2.6;27.8] and -0.2 [95% CI: -0.4;-0.02], respectively (Table 3). Although the cerebral blood flow velocities in the symptomatic hemisphere were higher in patients with clinical improvement than in those without, these differences did not reach statistical significance.

Table 4 shows the differences in cerebral hemodynamic indices, measured within 72 hours of acute hemispheric ischemic stroke onset and at 6 months, between symptomatic and asymptomatic hemisphere, in patients with NIH Stroke Scale < 4, atrial fibrillation and lacunar infarctions. The difference in EDV, measured within 72 hours of stroke onset, between asymptomatic and symptomatic hemisphere in patients with lacunar infarctions was higher than in patients with other infarct types (11.8 versus -0.6 cm/sec). At 6 months, the difference in EDV between asymptomatic and symptomatic hemisphere was still higher in patients with lacunar infarctions (10.0 versus -2.2 cm/sec). Furthermore, the difference in CVR-CO_2 at 6 months between asymptomatic and symptomatic hemisphere was lower in patients with lacunar infarctions (-0.2 versus 0.5).

DISCUSSION

This study shows that acute hemispheric ischemic stroke affects cerebral hemodynamic indices in both hemispheres, up to 72 hours. In accordance with earlier studies, we found that CVR-CO_2 was lower in the symptomatic hemisphere than in the contralateral side. The results suggest that hemispheric ischemic stroke is accompanied by a rise in MCV in the asymptomatic hemisphere in the (sub)acute phase. In patients with a cardioembolic stroke, CVR-CO_2 in the symptomatic hemisphere and PSV and EDV in the asymptomatic hemisphere, measured within 72 hours of stroke onset, were significantly lower than in patients with other stroke subtypes. We found no relationship between cerebral hemodynamic indices and clinical outcome.

Before these findings can be accepted, some methodological issues must be considered. First, all patients (all women; mean age 82 years) with bilateral window failure were excluded from the study, which may have caused some bias. Second, in order to

make a meaningful comparison between the hemodynamic indices in both hemispheres, we assumed that there are no large differences in patients without stroke. This is supported by a return to normal after 6 months in the present study, and by population-based data on cereral hemodynamics, assessed by means of TCD.[25] Finally, because of the small sample size of our study, confidence intervals were wide and small differences may have been overlooked.

Cerebral blood flow and flow velocity alterations and changes in cerebral vasomotor reactivity have been described in ischemic cerebrovascular disease,[6-17] as well as in experimental cerebral infarction.[18,19] Altered blood flow in cerebral ischemia has been observed in both the symptomatic hemisphere and the contralateral side.[8,9,19,20] One explanation for changes in hemodynamics in the asymptomatic hemisphere has been the assumption of an intracerebral "steal" phenomenon.[26-28] Others have postulated the existence of interhemispheric and intrahemispheric diaschisis in different distant sites following a hemispheric infarction.[11] Studies on changes of the cerebrovascular CO_2 reactivity in the acute phase of ischemic stroke have yielded different results. Some authors have reported a decreased vasomotor reactivity on the symptomatic side,[8,9,17] whereas others have found a significant increase in the ischemic area.[11] These different observations may be explained by the difference in study designs and diversity of included patients and measurement methods.

Several explanations for changes in cerebral hemodynamic indices due to cerebral ischemia have already been postulated. During focal cerebral ischemia, alterations of endothelial cell reactivity, coagulation system activation, and oxygen free radical generation are some of the documented events affecting microvascular integrity.[29] Granulocyte-endothelial cell activation, changes in endothelial permeability, and coagulation system and platelet activation appear to be triggered during ischemia, which amongst other things may lead to alterations in microvascular flow and vasoparalysis.[17,29,30] Whether these changes in cerebral hemodynamics are associated with clinical improvement is unknown.

Reduction of the cerebrovascular CO_2 reactivity has been described in lacunar and microangiopathic disease,[9,10,14] as well as in low-flow or watershed infarctions,[6,8,16] and in territorial or cortical infarcts.[8,9] It has been suggested that the observed decrease in cerebral CO_2 reactivity in lacunar and microangiopathic disease may be attributed to diffuse arteriolosclerosis.[10,14] A remarkable observation in our study was the lower cerebrovascular CO_2 reactivity in the symptomatic hemisphere in the acute phase in patients with a cardioembolic stroke, all of whom had atrial fibrillation. This observation could not be explained by differences in flow velocity between patients with minor and severe strokes alone. When we assume that lower cerebrovascular CO_2 reactivity in patients with atrial fibrillation represents maximal dilation of the intracerebral arterioles, we would expect higher flow velocity in the middle cerebral artery on the ipsilateral side. Two possible explanations may be put forward for the absence of this finding. Patients with atrial fibrillation have either occlusions of major branches ipsilateral to the infarction or a "steal" phenomenon may be present in the contralateral hemisphere.

No previous studies have addressed differences in cerebral hemodynamic indices between the symptomatic and asymptomatic hemisphere and between different ischemic stroke subtypes are not available. Our observations show that patients with lacunar infarcts more often had large differences in cerebral hemodynamic indices between the symptomatic and the asymptomatic hemisphere.

Data on the relationship between cerebral hemodynamics and stroke severity and clinical outcome are equally scarce. We found that patients with NIH Stroke Scale < 4 had higher MCV on the symptomatic side and higher EDV and lower PI on the asymptomatic side. No statistically significant associations were observed between cerebral hemodynamic indices and clinical outcome. Cerebral blood flow asymmetry in the acute stage (within 8 hours) of a hemispheric stroke is considered to be of value in predicting clinical outcome.[31] It has also been suggested that cerebral vasomotor reactivity may have a potential value in the prediction of hemorrhagic transformation of ischemic regions.[32] It has been postulated that changes in cerebral hemodynamics in the acute phase of cerebral ischemia may have important implications with regard to post-stroke prognosis and management of blood pressure in the acute post-ictal period.[12]

In conclusion, our study suggests that cerebral hemodynamic indices are influenced by acute hemispheric ischemic stroke in the symptomatic as well as the asymptomatic hemisphere and that a "steal" phenomenon may play a role, particularly in atrial fibrillation. Largest differences between the symptomatic and the asympomatic hemisphere were found in patients with lacunar infarcts. Cerebral hemodynamic indices are related to stroke severity, but not to clinical outcome. Future studies should elucidate the clinical and pathophysiological relevance of cerebral hemodynamic parameters, measured by means of transcranial Doppler, in patients with acute hemispheric ischemic stroke.

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CEREBRAL HEMODYNAMICS AND CLINICAL PERFORMANCE IN NORMAL PRESSURE HYDROCEPHALUS BEFORE AND AFTER SHUNT SURGERY

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Abstract

Objectives: To study prospectively the relationship between cerebral hemodynamics and clinical performance in normal pressure hydrocephalus (NPH) before and after ventriculoperitoneal shunt surgery.

Methods: Between June 1998 and November 1999, 10 consecutive patients with NPH were studied prospectively before and 3 months after shunt surgery. Cerebral blood flow velocities in the middle cerebral artery, pulsatility index and cerebrovascular CO_2 reactivity were measured by means of transcranial Doppler. Clinical performance was scored by means of a NPH scale, comprising a gait and dementia scale and the modified Rankin scale. Both transcranial Doppler and clinical ratings were performed by independent examiners. Clinical improvement was defined a priori as an improvement on the modified Rankin scale of more than one point and a reduction of at least 15% on the NPH scale.

Results: Peak systolic cerebral blood flow velocity was lower and cerebrovascular CO_2 reactivity was higher after shunt surgery compared with preoperative values (mean difference 10.7 cm/s (95%CI 2.3-19.1) and 1.4 %/kPa (95%CI 0.1-2.7), respectively). Pre and postoperative enddiastolic cerebral blood flow velocity was higher in patients with clinical improvement (mean difference 10.4 cm/s (95%CI 0.8-20.2) and 10.9 cm/s (95%CI 0.4-21.3), respectively). Postoperative mean and peak systolic cerebral blood flow velocity were also higher in patients with clinical improvement (mean difference 21.7 cm/s (95%CI 7.7-35.8) and 16.0 cm/s (95%CI 2.2-29.9), respectively). The difference in change of mean cerebral blood flow velocity between patients who did or did not improve was statistically significant and amounted to 7.4 cm/s (95%CI 0.6-14.2).

Conclusions: Our data suggest that shunt surgery improves cerebrovascular CO_2 reactivity in patients with NPH. Higher mean cerebral blood flow velocity before surgery in patients with NPH is associated with clinical improvement after shunt surgery, and clinical improvement is accompanied by a rise in mean cerebral blood flow velocity.

INTRODUCTION

The trias of gait disturbance, memory deficit, and urine incontinence is suggestive for normal pressure hydrocephalus (NPH) syndrome, although there are no absolute criteria for a definite diagnosis as yet. Cerebrospinal fluid shunt surgery may improve the clinical symptoms, but this treatment fails in certain patients without recognizable shunt problems.

Introduced in 1982 by Aaslid and co-workers, transcranial Doppler (TCD) has become an established technique for the non-invasive examination of cerebral hemodynamics. Cerebrovascular CO_2 reactivity, which reflects the compensatory dilatory mechanism of the intracerebral arterioles[1] is thought to be a more sensitive hemodynamic index than the level of resting blood flow,[2] and can be quantified by means of TCD. TCD monitoring has already been advocated as screening procedure in patients with NPH,[3,4] although its true value is still debated.

Cerebral blood flow alterations after surgery in low-pressure hydrocephalus have already been described in 1969.[5] Cerebral hemodynamic data in normal pressure hydrocephalus are scarce and information on changes in cerebral hemodynamics induced by shunt surgery, are conflicting. Some authors have found no changes in one or more cerebral hemodynamic parameters after shunt surgery,[6-8] whereas others did find significant improvement in cerebral blood flow,[9-11] cerebrovascular reactivity,[6,10-12] and a concomitant decrease in pulsatility index.[13] Whether these changes in cerebral hemodynamics are associated with clinical improvement is unknown.

The association between changes in cerebral hemodynamics after shunt surgery and clinical performance in patients with NPH has not been examined prospectively. We investigated this before and after shunt surgery in 10 consecutive patients with the typical NPH syndrome.

STUDY POPULATION AND METHODS

Study Population

All patients with a clinical diagnosis of NPH, supported by computer tomography of the brain and who were admitted to the departments of Neurology and Neurosurgery of the University Hospital Rotterdam-Dijkzigt were studied. The current analysis is based on the first 12 patients, examined from June 1998 until November 1999. We prospectively studied these patients before and 3 months after shunt surgery.

Clinical Performance

Clinical performance was scored by an independent examiner by means of an NPH-scale and the modified Rankin scale,[14] before and three months after shunt surgery. The NPH-scale comprised a gait scale (range 2-40) and a dementia scale (range 4-40).[15] The modified Rankin scale was used to score functional disability. Clinical improvement was defined a priori as an improvement on the modified Rankin scale of at least 2 points and a reduction of at least 15% on the NPH-scale.

Transcranial Doppler Assessment

Transcranial Doppler ultrasonography monitoring was performed by an independent examiner (Multi-Dop X-4, DWL, Sipplingen, Germany) before and three months after shunt surgery. Cerebral blood flow velocity (cm/s) was measured in the middle cerebral artery on both sides if possible. Enddiastolic, peak systolic and mean cerebral blood flow velocity were recorded automatically. The pulsatility index was defined as (peak systolic cerebral blood flow velocity - enddiastolic cerebral blood flow velocity) / mean cerebral blood flow velocity and was measured automatically with fast Fourier transformation. The pulsatility index values were determined in both middle cerebral arteries, over five cardiac cycles and their mean was used for the analyses. Cerebrovascular CO_2 reactivity measurements were done as follows: the cerebral blood flow velocity was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Participants then inhaled a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes. Cerebrovascular CO_2 reactivity was defined as percentage increase in mean cerebral blood flow velocity during inspiration of 5% CO_2 / the absolute increase in end-tidal CO_2 in the same time period (%/kPa). End-tidal CO_2 pressure (kPa) was recorded continuously with a CO_2 analyser (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2.[1] TCD-8 DWL special software (VMR-CO_2) was used.

Shunting procedure

All patients in the study received a ventriculoperitoneal shunt (PS Medical, low or medium pressure valve) The valve type depended on the estimated a priori risk of developing subdural effusions as judged by the neurosurgeon. The ventricular catheter was inserted in the right occipital horn and the peritoneal catheter was placed in the abdominal cavity via a small transverse incision in the left upper quadrant of the abdominal wall. Adequacy of the shunt system was always tested postoperatively by means of X-rays of the skull and abdomen and CT scan three months postoperatively.

Data analysis

Except for the enddiastolic cerebral blood flow velocity, all right and left hemodynamic parameters were significantly correlated (r=0.79, p=0.04 for the mean cerebral blood flow velocity; r=0.96, p<0.001 for the peak systolic cerebral blood flow velocity; r=0.99, p<0.0001 for the pulsatility index; r=0.99, p<0.0001 for the cerebrovascular CO_2 reactivity) and therefore their mean was used for the analyses if both middle cerebral arteries could be insonated adequately. Although not significant, right and left enddiastolic cerebral blood flow velocities were highly correlated (r=0.68, p=0.09) and therefore their mean was also used in the analyses. In case of one-sided window-failure, the contralateral cerebral hemodynamic parameter was used in the analyses. The relationship between the cerebral hemodynamic parameters and shunt surgery was analysed by paired-samples T test. The association between clinical performance and the cerebral hemodynamic parameters was analysed by means of independent-samples t test.

RESULTS

Combined clinical and transcranial Doppler data were obtained in 10 of 12 patients. One male patient refused shunt surgery and one female patient had window failure on both sides and both were therefore excluded from the present analyses. All remaining patients were men and their mean age was 70 years (range 47-84).

The preoperative modified Rankin scale grade ranged from 2 to 5 and the postoperative from 0 to 5. Nine patients improved on the modified Rankin scale after surgery, whereas only three improved more than one point. Preoperative NPH score ranged from 10 to 79, whereas the postoperative NPH score ranged from 10 to 69. Seven patients had a reduction of at least 15% on the NPH-scale after surgery. All 3 patients with an improvement of more than one point on the modified Rankin scale (range two-four) improved more than 15% on the NPH scale (range 28.8-58.9%). No patients showed improvement on the dementia scale and three patients showed improvement on the gait scale. Repositioning of the peritoneal catheter after the initial shunting procedure was indicated in one patient. Bilateral subdural effusions that required burr-hole evacuation were observed in two patients and in one of them a low pressure valve was replaced by a medium pressure valve.

The influence of shunt surgery on the cerebral hemodynamic parameters is shown in table 1. Postoperative cerebral blood flow velocities and pulsatility index were lower and cerebrovascular CO_2 reactivity was higher compared with their preoperative values in the whole group. Statistical significance was reached for the peak systolic cerebral blood flow velocity and cerebrovascular CO_2 reactivity (mean difference 10.7 cm/s [95%CI 2.3-19.1] and 1.4 %/kPa [95%CI 0.1-2.7], respectively).

Table 2 shows the cerebral hemodynamic parameters before and after shunt surgery in patients with and without clinical improvement, defined as an improvement on the modified Rankin scale of at least 2 points and a reduction of at least 15% on the NPH-scale. Pre- and postoperative enddiastolic cerebral blood flow velocity was higher in patients with clinical improvement (mean difference 10.4 cm/s [95%CI 0.8-20.2] and 10.9 cm/s [95%CI 0.4-21.3], respectively). Postoperative mean and peak systolic cer-

Table 1
Cerebral hemodynamic parameters before and after shunt surgery in NPH patients.

Cerebral hemodynamic parameters	Preoperative	Postoperative	Mean difference (95% CI)
Enddiastolic cerebral blood flow velocity (cm/s)	24.0	22.4	1.6 (-1.5-4.7)
Mean cerebral blood flow velocity (cm/s)	38.0	35.5	2.5 (-1.4-6.3)
Peak systolic cerebral blood flow velocity (cm/s)	71.8	61.1	10.7 (2.3-19.1)
Pulsatility index	1.26	1.12	0.14 (-0.1-0.4)
Cerebrovascular CO_2 reactivity (%/kPa)	2.2	3.6	1.4 (0.1-2.7)

Values represent means
p Value was calculated by means of paired-samples T test.

Table 2
Cerebral hemodynamic parameters before and after shunt surgery in NPH patients with and without clinical improvement.

	Preoperative			Postoperative		
	Improvement	No improvement	Mean difference (95% CI)	Improvement	No improvement	Mean difference (95% CI)
Enddiastolic cerebral BFV (cm/s)	31.3	20.9	10.4 (0.8-20.2)	30.0	19.1	10.9 (0.4-21.3)
Mean cerebral BFV (cm/s)	48.0	33.7	14.3 (-0.2-28.8)	50.7	29.0	21.7 (7.7-35.8)
Peak systolic cerebral BFV (cm/s)	88.7	64.6	24.1 (-1.6-49.8)	72.3	56.3	16.0 (2.2-29.9)
Pulsatility index	1.09	1.34	0.25 (-0.6-1.1)	0.93	1.20	0.27 (-0.3-0.8)
Cerebrovascular CO_2 reactivity (%/kPa)	1.9	2.3	0.4 (-1.4-2.3)	3.0	3.9	0.9 (-2.0-3.7)

Values represent means
BFV = blood flow velocity
p Value was calculated by means of independent-samples t test.

ebral blood flow velocity were also higher in patients with clinical improvement (mean difference 21.7 cm/s [95%CI 7.7-35.8] and 16.0 cm/s [95%CI 2.2-29.9], respectively). Mean cerebral blood flow velocity increased on average by 2.7 cm/s in the 3 patients who improved after surgery and decreased 4.7 cm/s in patients without clinical improvement. The difference in change of mean cerebral blood flow velocity between patients who did or did not improve was statistically significant and amounted to 7.4 cm/s [95%CI 0.6-14.2]. Preoperative peak systolic and mean cerebral blood flow velocity and cerebrovascular CO_2 reactivity were higher and pulsatility index was lower in patients with clinical improvement compared with those without, but these differences did not reach statistical significance.

No statistically significant associations were found between cerebral hemodynamic parameters in patients with improvement on the gait scale alone compared to patients without. Preoperative cerebrovascular CO_2 reactivity showed a trend towards higher values in patients with improvement on the gait scale compared with those without (3.1 %/kPa and 1.8 %/kPa, respectively).

DISCUSSION

This is the first prospective study which shows an association between higher cerebral blood flow velocity before shunt surgery in patients with the NPH syndrome and postoperative clinical improvement. The results suggest that postoperative clinical improvement is accompanied by a rise in mean cerebral blood flow velocity. Shunt surgery improves cerebrovascular CO_2 reactivity, although in this study no relationship was found with clinical outcome.

A global cerebral blood flow reduction, more severe in the frontal lobes, has been observed in patients with normal pressure hydrocephalus.[9,16] Most authors believe that this reduction in cerebral blood flow in patients with NPH is a result of increased intraparenchymal pressure in the brain with compression of small-calibre vessels.[17,18] Others believe that the fall in cerebral blood flow is a secondary phenomenon resulting from a decrease in cerebral metabolism caused by the decrease in volume of brain tissue in normal pressure hydrocephalus.[19-21] Some authors have found no alterations in cerebral hemodynamics after shunt therapy,[6-8] whereas others found significant improvement in cerebral blood flow[9-11] and cerebrovascular reactivity,[6,10-12] and a concomitant reduction in pulsatility index.[13] In accordance with earlier studies, we found that mean cerebral blood flow velocity increased in patients with clinical improvement.[22] A remarkable observation was the decrease in blood flow velocities in patients without clinical improvement after shunt surgery.

Whether changes in cerebral hemodynamics eventually lead to clinical improvement is unclear. The pathophysiologic mechanism underlying clinical improvement after shunt surgery in NPH is still unknown, and may include restoration of regional cerebral blood flow[6,9-11,16] and metabolic improvement.[17] Fritz et al. suggested that patients with coexistent cerebrovascular disease, identified by means of a carbogen reactivity below

25%, may have an unfavorable surgical prognosis.[23] Others have found, however, that patients with NPH could not be characterised by distinct patterns of global cerebral blood flow and that shunt surgery did not invariably improve global cerebral blood flow in patients with clinical improvement.[8]

It is unclear whether and how coexistent vascular disease may influence the cerebral hemodynamic parameters and eventually clinical outcome. Some authors have suggested that associated cerebrovascular disease contributes to unfavourable results.[24] One explanation for unfavorable outcome after shunt surgery in patients with cerebrovascular disease may be the presence of atherosclerosis related factors and their negative influence on restoration of regional and global cerebral hemodynamics.[17,25]

In conclusion, our study suggests that shunt surgery in patients with normal pressure hydrocephalus improves cerebrovascular CO_2 reactivity. Higher mean cerebral blood flow velocity before surgery in these patients is associated with clinical improvement after shunt surgery, and clinical improvement is accompanied by a rise in mean cerebral blood flow velocity. Future studies should elucidate the clinical and pathogenetic relevance of cerebral hemodynamic parameters, assessed by means of transcranial Doppler, in patients with normal pressure hydrocephalus.

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GENERAL DISCUSSION

THIS THESIS DESCRIBES observational studies on the cerebral hemodynamic indices, assessed by means of transcranial Doppler, in the general elderly population and in patients with neurological diseases. Population-based data were obtained in the Rotterdam Study, a prospective cohort study among 7,983 participants aged 55 years and over, conducted in a suburb of Rotterdam. The second part of this dissertation describes the influence of two neurological diseases on the cerebral hemodynamic indices. These data were obtained from patients with acute ischemic hemispheric stroke and normal pressure hydrocephalus who were admitted to the Neurological and Neurosurgical wards of the University Hospital Rotterdam-Dijkzigt.

In this chapter, the main findings will be summarized and compared with the results from other studies. I shall end up with recommendations for future research.

MAIN FINDINGS

Our data from the population-based Rotterdam Study confirm the high percentage of window failure (up to 36.5%) in the non-hospitalized elderly. This is in agreement with others who reported a window failure of 40%.1 This inadequacy for the ultrasonic beam to penetrate the thin bone of the temporal region of the skull in our population-based studies increased with advancing age, especially in women, which has also been noticed by others.[2,3]

Cerebral blood flow velocity and cerebrovascular CO_2 reactivity declined with increasing age, which was accompanied by a concomitant rise in pulsatility index. This age dependency of cerebral hemodynamics continued up to the 10th decade of normal life. Data from hospital-based studies support these findings.[4,5] Sex dependency of cerebral blood flow velocity was unequivocal as no differences were found in cerebrovascular CO_2 reactivity between men and women. We have found that the contribution of peripheral arterial disease to age dependency of cerebral hemodynamic indices was limited, altough other studies support the arteriolosclerotic pathogenesis of these associations.[6,7]

The contribution of cholesterol and its subfractions to changes in cerebral hemodynamics still remains to be clearified. We found a significant increase in cerebrovascular CO_2 reactivity with increasing levels of HDL-cholesterol and a decrease with an increasing total cholesterol/HDL ratio. The inverse relationship between lipoprotein accumulation and cerebrovascular reactivity has been supported in earlier research,[8] whereas other studies could not confirm this association.[9,10]

The Rotterdam Scan Study was used to study the relationship between cerebrovascular CO_2 reactivity and white matter lesions on MRI. Cerebrovascular CO_2 reactivity was inversely associated with deep subcortical and total periventricular white matter lesions, supporting the hypothesis that some white matter lesions may be associated with hemodynamic ischemic injury to the brain. This inverse association between decreased cerebrovascular CO_2 reactivity and the severity of white matter lesions was already observed by others.[11,12]

Cerebral blood flow velocity was found to be significantly lower in individuals with dementia and cognitive decline and, in addition, a decreased cerebrovascular CO_2 reactivity was observed in persons who declined in cognitive performance most rapidly in the preceding years.

In subjects with depressive symptoms, reduced cerebral blood flow velocities and lower cerebrovascular CO_2 reactivity were found compared with individuals without.

Our hospital-based studies were limited to patients with acute hemispheric ischemic stroke in whom the transcranial Doppler examinations were performed within 72 hours of stroke onset and at 6 months and into patients with a clinical diagnosis of normal pressure hydrocephalus in whom TCD was performed before and after cerebrospinal fluid shunt surgery.

We found that in patients with acute hemispheric ischemic stroke, especially in patients with a cardioembolic stroke, cerebrovascular CO_2 reactivity was significantly lower in the symptomatic hemisphere compared with the contralateral side. This reduction of cerebrovascular CO_2 reactivity in territorial or cortical infarcts has already been reported by others.[13,14] We also observed an increase in mean cerebral blood flow velocity in the asymptomatic hemisphere in the subacute phase. This phenomenon may be explained as inverse "steal" phenomenon.[15,16]

In patients with a clinical diagnosis of normal pressure hydrocephalus, we observed improvement of the cerebrovascular CO_2 reactivity after cerebrospinal fluid shunt surgery. This confirms an earlier report.[17] We found an association between the cerebral hemodynamic indices and clinical outcome. In patients with clinical improvement, higher mean cerebral blood flow velocity before surgery was related to postoperative clinical improvement. Furthermore, clinical improvement after surgery was accompanied by a rise in mean cerebral blood flow velocity.

CEREBROVASCULAR (VASOMOTOR) REACTIVITY

Cerebral vasomotor reactivity, or cerebrovascular reserve capacity, reflects the compensatory dilatory mechanism to a vasodilatory stimulus of the intracerebral arterioles,[18] and is considered to provide a more sensitive hemodynamic index than the level of resting blood flow.[19] Vasomotor agents alter the resistance of the cerebral vessels that occur at the level of cerebral arteries 400μm in diameter or less. As the large basal cerebral arteries remain relatively constant in diameter, transcranial Doppler can provide a measure of relative flow changes in response to small changes in diameter in the distal arterial bed. The cerebrovascular reactivity can be assessed by measuring changes in blood flow velocities in response to acetazolamide injection, CO_2 inhalation, or hyperventilation and is reproducible over time.[20] There is a high and statistically significant correlation between CO_2-induced and acetazolamide-induced vasomotor reactivity ($r=0.79$), indicating a strong similarity of the vasodilatative effects of CO_2 and acetazolamide on the cerebral arteries and both techniques are considered valid to measure reduction in

perfusion reserve.[21] This correlation between CO_2-induced and acetazolamide-induced vasomotor reactivity is present in the absence of occlusive major cerebral artery disease, since a reduced acetazolamide-induced vasomotor reactivity has been described in patients with a preserved CO_2-induced vasomotor reactivity.[22] The CO_2 method of testing is preferred as it is safer, its effect is stronger and offers greater certainty regarding which arterial segments are affected.[23] Carbon dioxide is a potent cerebral vasomotor agent and plays a significant role in the dynamic regulation of blood flow in accordance with changes in regional metabolic demands that occur with variations in neuronal activity. It has been suggested that a central neurogenic mechanism with a cholinergic link,[24] and a nitric oxide-related endothelial function[25] may be responsible, at least in part, for the cerebrovascular effect of CO_2.

The cerebral vasomotor response to changes in the arterial CO_2 pressure usually reflects the cerebral perfusion capacity under physiological conditions. Several pathological circumstances can affect this mechanism. Cerebral vasomotor reactivity may be influenced by posture anesthesia, drugs (e.g. non-steroid anti-inflammatory drugs) and neurological diseases, such as carotid stenosis, obstructive sleep apnoea syndrome, Shy-Drager syndrome, diabetes mellitus, brain injury, subarachnoid hemorrhage and ischemic stroke. Even an inverse relation between cerebral vasomotor reactivity and platelet activation in asymptomatic cerebral thrombosis,[26] and hyperhomocysteinemia[27] has been described.

Regarding cerebrovascular reactivity, it is generally believed that information on systemic blood pressure is essential, as vasomotor reactivity may be greater at high blood pressure.[28] However, the exact influence of systemic blood pressure on cerebral vasomotor reactivity is not known. It is essential to measure cerebrovascular reactivity in supine position as it alters in seated position.[20]

The clinical applications of cerebral vasomotor reactivity are limited at the present time. Based on class III evidence, transcranial Doppler is given a type C recommendation for the evaluation of cerebral vasomotor reactivity by the American Society of Neuroimaging and the Neurosonology Research Group of the World Federation of Neurology (see appendix).[23]

CEREBRAL HEMODYNAMIC INDICES AND ATHEROSCLEROSIS

Changes in cerebral hemodynamics due to atherosclerotic carotid artery disease have been described in great detail. Little is known about the relationship between intracranial arteriolosclerosis and the cerebral hemodynamic indices, measured by means of transcranial Doppler. Recent observations suggest that cerebral microangiopathy may play an important role in changes in cerebral blood flow velocity and cerebrovascular CO_2 reactivity and that the reduction of cerebrovascular CO_2 reactivity might even indicate the severity of microangiopathy.[29,30]

Diabetes mellitus

Cerebral hemodynamic changes related to diabetes mellitus have been described.[31-36] These studies showed a lower cerebrovascular CO_2 reactivity and higher pulsatility index in patients with diabetes, both type 1 and type 2. It is unclear whether disease duration plays a role in changes in cerebral hemodynamics. Some authors could not find a relationship between cerebral blood flow velocity and cerebrovascular reactivity on the one hand and disease duration on the other.[35] Others found that impaired vascular reactivity in the brachial artery in insulin-dependent diabetes mellitus was related to disease duration.[37]

Changes in cerebral hemodynamic indices in patients with diabetes have been attributed to microangiopathic changes of the cerebral vessels.[31,33] An argument supporting this hypothesis is the association between impairment of cerebrovascular reactivity and the presence and severity of retino- and nephropathy.[34] Transitory alterations in pulsatility index and cerebrovascular reactivity have also been observed in children with diabetic ketoacidosis.[36] It has been suggested that diabetics may have an increased risk of cerebrovascular disease because of the diminished cerebrovascular reactivity.[32]

Hypertension

Even with intact autoregulation, hypertension shows both short-term and long-term effects on cerebral hemodynamics. In patients with a long duration (more than 5 years) of hypertension, lower flow velocities and higher pulsatility index has been observed and the mean velocity was inversely related to the duration of hypertension.[38] Women with pre-eclampsia and normal blood pressure before their pregnancies were found to have similar abnormalities in cerebral hemodynamics as women with chronic hypertension by demonstrating an increase in estimated cerebral perfusion pressure by means of TCD.[39] Cerebrovascular reactivity has been observed to be impaired in hypertensive patients,[40] even without neurological deficits or computed tomography abnormalities.[41] However, others could find no difference in vasomotor reactivity between hypertensive and normotensive patients.[42] It has been suggested that microvascular reactivity is affected by hypertension before the development of cerebrovascular accidents,[43] and that enlargement of the left atrium seems to correlate well with the severity of the impairment in vasomotor reactivity.[41] In patients with disturbed autoregulation, e.g. after subarachnoid hemorrhage, induced hypertension may alter cerebral blood flow velocities. Antihypertensive medication may improve flow velocity and cerebrovascular reactivity.[40]

Smoking

The effect of cigarette smoking on cerebral circulation depends on the pharmacological properties of the absorbed nicotine, including different sensitivity of each subject to nicotine.[44] Information on the effect of nicotine on cerebral hemodynamics is scarce. An increase in cerebral blood flow velocity has been observed as an acute effect of nicotine,[44-46] and lower cerebrovascular reactivity has been found in smokers compared with non-smokers.[45]

CEREBRAL HEMODYNAMIC INDICES AND RADIOLOGICAL ABNORMALITIES

Comparitive studies between TCD parameters and radiological abnormalities on computed tomography (CT), magnetic resonance imaging (MRI) and others such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) are scarce.

Computed tomography

In patients with symptomatic middle cerebral artery (MCA) stenosis, abnormal TCD is highly suggestive of MCA stenosis, although a false negative TCD, compared with CT angiography, can be found in 40% of the patients and occurs especially in more distal (M1 or M2) stenoses.[47] Associations between cerebral hemodynamic indices and patterns of infarctions on CT have also been described. It has been concluded that low-flow infarctions are associated with significantly reduced cerebrovascular reactivity in patients with high grade stenoses and occlusions of the internal carotid artery.[48,49] Finally, the amount of blood clots on the initial CT after subarachnoid hemorrhage has been found to be significantly correlated with cerebral blood flow velocity measurements.[50]

Magnetic resonance imaging

In patients with carotid disease, determined by means of MRI, cerebral hemodynamics in relation to patterns of collateral flow, measured by means of TCD, has been examined. It has been concluded that collateral flow via the anterior communicating artery was a sign of well-preserved hemodynamic status, whereas no collateral flow via the circle of Willis or flow via only the posterior communicating artery was a sign of deteriorated cereral perfusion.[51] In patients with acute stroke, low flow velocities on TCD correlated well with hyperintense vessels signs on MRI.[52] And patients with microangiopathy, demonstrated on MRI, were found to have lower cerebrovascular reactivity.[29] White matter lesions on MRI in relation to TCD parameters have scarcely been described. Although decreased cerebral blood flow and cerebrovascular reactivity have been observed in patients with leukoaraiosis in SPECT studies, no associations were found in TCD examinations.[53]

A close linear relation between language-related flow velocity changes in the middle cerebral artery and regional blood flow, measured by means of functional MRI in adults, have also been described.[54] It has been postulated that abnormal TCD and MRI examinations are often discordant in patients with sickle cell disease and that these two examinations may therefore reveal different aspects of the pathophysiology of central nervous system injury in these patients.[55]

Others

TCD and SPECT comparison studies have been described in several neurological diseases as migraine, meningitis, carotid disease and stroke. Comparison of TCD assessed flow velocity and cerebral blood flow has been studied both in vitro and in vivo. In

experimental cerebral ischemia, decreased flow velocity in the MCA appeared to reflect the reduction in flow in the affected hemisphere.[56] In patients with cerebral ischemia, a linear relationship has been found between flow velocity and blood flow, assessed by means of SPECT.[57] It has therefore been suggested that cerebral blood flow velocity can be used as a quantitative parameter for tissue perfusion in cerebral ischemia.

Cerebral hemodynamic indices do not correlate with hemispheric measurements of oxygen metabolism by PET and consequently, TCD is not useful in assessing impairments of cerebral metabolism.[58]

RECOMMENDATIONS FOR FUTURE RESEARCH

Since its introduction almost two decades ago, TCD has shed more light on cerebral hemodynamics. Nonetheless, TCD is still considered a research tool in the majority of diagnoses in general neurological and neurosurgical practice and its clinical use and prognostic value still have not been determined. A type A recommendation (strong positive recommendation, based on class I evidence or overwhelming class II evidence when circumstances prelude randomized clinical trials) for TCD has only been given for sickle cell disease.[23] The application of the same criteria in different laboratories may facilitate the standardization of TCD examinations and support the reproducibility of clinical reports based on TCD parameters.

Future clinical research concerning transcranial Doppler should focus on the identification of patients with a high risk of recurrence of cerebral ischemia. The accuracy of TCD in detecting potential sources of cardiac embolism should be studied. Furthermore, it should be investigated whether TCD improves the accuracy of the clinical diagnosis of small vessel disease, in combination with other neuro-radiological examinations, such as magnetic resonance imaging.

Finally, the population-based Rotterdam (Scan) Study lends itself well to study the association between cerebral hemodynamic indices on the one hand and indicators of atherosclerosis, clotting disorders and radiological abnormalities on the other.

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SUMMARY

IN THIS THESIS, explorative studies on cerebral hemodynamic parameters, assessed by means of transcranial Doppler, in the elderly and in clinical neurological diagnoses are described.

The first 5 chapters deal with the changes in cerebral hemodynamics in the elderly who participated in the Rotterdam Study. The Rotterdam Study is a prospective population-based cohort study on frequency and determinants of disease among elderly persons. At baseline (1990-1993), 7,983 inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, participated. Follow-up examinations were done in 1993-1994 and 1997-1999. From the third survey on (1997-1999), cerebral blood flow velocity in the middle cerebral artery, pulsatility index and cerebrovascular CO_2 reactivity measurements by means of transcranial Doppler ultrasonography were incorporated in the study protocol.

In **chapter 1**, we studied the relationship between age and sex and the cerebral hemodynamic indices. We found that end diastolic, mean cerebral blood flow velocity and cerebrovascular CO_2 reactivity declined with increasing age in both men and women, whereas peak systolic cerebral blood flow velocity declined with increasing age in women only. The pulsatility index increased with increasing age in both sexes. End diastolic, mean and peak systolic cerebral blood flow velocities were lower in men compared with women. Pulsatility index was higher in men compared with women. The relation between sex and the cerebral hemodynamic indices remained equivocal, as there was no sex difference in cerebrovascular CO_2 reactivity by the different age categories. Adjustment for presence of peripheral arterial disease did not change the magnitude of these associations. **Chapter 2** shows the associations between blood lipids (total cholesterol, HDL-cholesterol and their ratio) and cerebrovascular CO_2 reactivity. Cerebrovascular CO_2 reactivity increased with increasing levels of HDL cholesterol and participants with higher levels of HDL cholesterol had a higher cerebrovascular CO2 reactivity. In addition, we found that cerebrovascular CO_2 reactivity decreased with an increasing total cholesterol/HDL ratio and participants with a lower total cholesterol/HDL ratio had a higher cerebrovascular CO_2 reactivity. There was no linear relationship between total cholesterol and cerebrovascular CO_2 reactivity. Additional adjustment for confounding vascular risk factors did not alter the magnitude of these associations.

In chapter 3 we determined the association between cerebrovascular CO_2 reactivity and white matter lesions on MRI in 73 consecutive individuals from the Rotterdam Scan Study who also participated in the Rotterdam Study. Cerebral CO_2 reactivity was inversely associated with severe deep subcortical and total periventricular white matter lesions. Individuals with higher cerebral CO_2 reactivity had a significantly lower mean score of total periventricular white matter lesions. Individuals with higher cerebral CO_2 reactivity had also a significantly lower mean score of total deep subcortical white matter lesions volume. Individuals in the lowest tertile of cerebral CO_2 reactivity were found to have the highest mean score of white matter lesions in all three periventricular regions, whereas individuals in the highest tertile of cerebral CO_2 reactivity had the lowest mean score. The inverse association between cerebral CO_2 reactivity and white

matter lesions seemed strongest with periventricular white matter lesions adjacent to the lateral ventricular wall. Better cerebral CO_2 reactivity was associated with less deep subcortical lesions, irrespective of the size of the lesions.

In **chapter 4** we examined the association between the cerebral hemodynamic indices and dementia and cognitive performance. All cerebral hemodynamic parameters were lower in demented compared with non-demented persons. Among non-demented subjects, those who had declined in cognitive performance in the period before TCD assessment had the lowest cerebral blood flow velocities and cerebrovascular CO_2 reactivity. Persons with low cognitive performance had a lower cerebrovascular CO_2 reactivity as well. **Chapter 5** reveals the relationship between depressive disorders and cerebral hemodynamic indices. Subjects with depressive symptoms had reduced cerebral blood flow velocities. Cerebral blood flow velocity was increasingly reduced along the worsening spectrum of the affective illness. The overall reduction in cerebrovascular CO_2 reactivity, however, was accounted for by subjects with subclinical depressive symptoms.

In the second part of this dissertation, we describe 2 hospital-based studies on cerebral hemodynamic indices, assessed by means of TCD. In the last 2 chapters, we reveal the influence of two neurological diseases on cerebral hemodynamics. These data were obtained from patients that were admitted on the Neurological and Neurosurgical wards of the University Hospital Rotterdam-Dijkzigt.

In **chapter 6**, we examined changes in cerebral hemodynamic indices in patients with acute hemispheric ischemic stroke. TCD examinations were done within 72 hours of stroke onset and at 6 months follow-up. All flow velocities, pulsatility index and cerebrovascular CO_2 reactivity were higher on the asymptomatic side both in the acute phase as well at 6 months. Measured within 72 hours of stroke onset, peak systolic cerebral blood flow velocity and cerebrovascular CO_2 reactivity were lower in the symptomatic hemisphere compared with the asymptomatic hemisphere. Mean cerebral blood flow velocity on the asymptomatic side was lower at 6 months follow-up compared with the value, measured within 72 hours of stroke onset. Cerebrovascular CO_2 reactivity in the symptomatic hemisphere, measured within 72 hours of stroke onset, was lower in patients with a cardioembolic stroke compared with patients with other stroke subtypes. In patients with a cardioembolic stroke, peak systolic and end diastolic cerebral blood flow velocity were lower in the asymptomatic hemisphere compared with patients with other stroke subtypes. No statistical significant associations were observed between cerebral hemodynamic indices and clinical outcome. In **chapter 7**, we studied patients with a clinical diagnosis of normal pressure hydrocephalus before and after cerebrospinal fluid shunt surgery. Postoperative peak systolic cerebral blood flow velocity was lower and cerebrovascular CO_2 reactivity was higher compared with their preoperative values. Pre- and postoperative enddiastolic cerebral blood flow velocity was higher in patients with clinical improvement, defined a priori as an improvement on the modified Rankin scale of more than one point and a reduction of at least 15% on the NPH scale. Postoperative mean and peak systolic cerebral blood flow velocities were also higher in patients with clinical improvement. Preoperative cerebrovascular CO_2 reactivity showed a trend

towards higher values in patients with improvement on the gait scale compared with those without.

TCD sheds more light on cerebral hemodynamics, but in general neurological and neurosurgical practice, it is still considered a research tool. Future clinical research should focus on whether TCD improves the accuracy of the clinical diagnosis of small vessel disease, in combination with other neuro-radiological examinations, such as magnetic resonance imaging. Furthermore, the population-based Rotterdam (Scan) Study lends itself well to study the association between cerebral hemodynamic indices and indicators of atherosclerosis.

SAMENVATTING

IN DIT PROEFSCHRIFT worden observationele bevindingen beschreven over de cerebrale hemodynamische parameters, verkregen met behulp van de transcraniële Doppler. Dit onderzoek werd onder andere verricht als onderdeel van het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek (*the Rotterdam Study*), een prospectief bevolkingsonderzoek naar de frequentie en oorzaken van chronische ziekten bij ouderen. Het ERGO onderzoek begon in 1990-1993 met 7983 inwoners van 55 jaar en ouder, woonachtig in Ommoord, een wijk van Rotterdam. In 1993-1994 en in 1997-1999 werd iedereen opnieuw onderzocht. Vanaf het derde vervolgonderzoek (1997-1999) werden de cerebrale bloedstroomsnelheid in de middelste hersenslagader, de pulsatiliteitsindex en de cerebrovasculaire CO_2-reactiviteit, gemeten door middel van het transcraniële Doppler ultrageluid, in het studieprotocol opgenomen.

In **hoofdstuk 1** hebben we de relatie tussen leeftijd en geslacht en de cerebrale hemodynamische indices bestudeerd. Hieruit bleek dat de einddiastolische cerebrale bloedstroomsnelheid, de gemiddelde cerebrale bloedstroomsnelheid en de cerebrovasculaire CO_2-reactiviteit afnamen met het toenemen van de leeftijd bij vrouwen en mannen. De piek systolische cerebrale bloedstroomsnelheid nam alleen af bij vrouwen. De pulsatiliteitsindex nam af met het toenemen van de leeftijd bij beide sexen. De einddiastolische, gemiddelde en piek systolische cerebrale bloedstroomsnelheid waren lager bij mannen vergeleken met vrouwen. De pulsatiliteitsindex was hoger bij mannen vergeleken met vrouwen. De relatie tussen geslacht en de cerebrale hemodynamische indices blijft enigszins dubbelzinnig, omdat er geen verschil in geslacht werd gevonden in de cerebrovasculaire CO_2-reactiviteit in de verschillende leeftijdscategorieën. Correctie voor de aanwezigheid van perifeer arterieel vaatlijden liet de grootte van deze verbanden onveranderd. **Hoofdstuk 2** laat de associaties zien tussen bepaalde bloedvetten (totale cholesterol, HDL-cholesterol en hun ratio) en de cerebrovasculaire CO_2-reactiviteit. De cerebrovasculaire CO_2-reactiviteit nam toe met toenemende spiegels van het HDL cholesterol en deelnemers met hogere spiegels van het HDL cholesterol hadden een hogere cerebrovasculaire CO_2-reactiviteit. Daarnaast vonden we dat cerebrovasculaire CO_2-reactiviteit afnam met toenemende spiegels van de totale cholesterol/HDL ratio en deelnemers met een lagere totale cholesterol/HDL ratio hadden een hogere cerebrovasculaire CO_2-reactiviteit. Er was geen lineair verband tussen het totale cholesterol en de cerebrovasculaire CO_2-reactiviteit. Aanvullende correctie voor vasculaire risicofactoren die deze relatie mogelijk zouden kunnen beïnvloeden, liet de grootte van deze verbanden onveranderd.

In **hoofdstuk 3** hebben we de relatie tussen de cerebrovasculaire CO_2-reactiviteit en witte-stofafwijkingen op MRI vastgesteld in 73 opeenvolgende deelnemers aan de Rotterdam Scan Studie die tevens deelnamen aan het ERGO onderzoek. De cerebrovasculaire CO_2-reactiviteit was omgekeerd geassocieerd met ernstige diepe subcorticale en de totale hoeveelheid periventriculaire witte-stofafwijkingen. Individuen met een hogere cerebrovasculaire CO_2-reactiviteit hadden een significant lagere gemiddelde score van totale periventriculaire witte-stofafwijkingen. Individuen met een hogere cerebrovasculaire CO_2-reactiviteit hadden ook een significant lagere gemiddelde score van het totale

volume van diepe subcorticale witte-stofafwijkingen. Individuen in de laagste tertiel van cerebrovasculaire CO_2-reactiviteit hadden de hoogste gemiddelde score van witte-stofafwijkingen in alle drie de periventriculaire regio's, terwijl individuen in de hoogste tertiel van de cerebrovasculaire CO_2-reactiviteit de laagste gemiddelde score hadden. De omgekeerde relatie tussen de cerebrovasculaire CO_2-reactiviteit en witte-stofafwijkingen leek het sterkst met de periventriculaire witte-stofafwijkingen gelegen net naast de laterale ventrikel. Een betere cerebrovasculaire CO_2-reactiviteit was geassocieerd met minder diepe subcorticale laesies, ongeacht de grootte van de afwijkingen.

In **hoofdstuk 4** hebben we het verband bestudeerd tussen de cerebrale hemodynamische indices en dementie en cognitieve prestatie. Hieruit bleek dat alle cerebrale hemodynamische parameters in demente personen lager waren vergeleken met niet-demente personen. **Hoofdstuk 5** beschrijft het onderzoek naar de relatie tussen depressieve stoornissen en de cerebrale hemodynamische indices. Personen met depressieve symptomen hadden verlaagde cerebrale bloedstroomsnelheid. De cerebrale bloedstroomsnelheid was toenemend verminderd gedurende het verslechterende spectrum van de ziekte.

Naast het bovenbeschreven bevolkingsonderzoek hebben wij TCD onderzoeken verricht bij patiënten die opgenomen zijn geweest op de afdelingen neurologie en neurochirurgie van het Academisch Ziekenhuis Rotterdam-Dijkzigt. In de laatste twee hoofdstukken belichten wij de invloed van twee neurologische ziekten op de cerebrale hemodynamiek.

In **hoofdstuk 6** beschrijven wij de veranderingen in de cerebrale hemodynamische indices bij patiënten met een acuut hemisferaal herseninfarct. De TCD onderzoeken in deze studie vonden plaats binnen 72 uur van het begin van de klachten en bij 6 maanden. De bloedstroomsnelheden, de pulsatiliteitsindex en de cerebrovasculaire CO_2-reactiviteit waren alle hoger aan de asymptomatische kant in de acute fase en bij 6 maanden. De piek systolische bloedstroomsnelheid en de cerebrovasculaire CO_2-reactiviteit, gemeten binnen 72 uur, waren in de symptomatische hemisfeer lager ten opzichte van de asymptomatische zijde. De gemiddelde cerebrale bloedstroomsnelheid in de asymptomatische hemisfeer, gemeten bij 6 maanden, was lager ten opzichte van de waarde in de acute fase. De cerebrovasculaire CO_2-reactiviteit in de symptomatische hemisfeer, gemeten binnen 72 uur na het starten van de klachten, was lager in patiënten met een cardioembolisch herseninfarct vergeleken met patiënten met een ander type herseninfarct. In patiënten met een cardioembolisch herseninfarct waren de piek systolische en einddiastolische cerebrale bloedstroomsnelheid lager in de asymptomatische hemisfeer vergeleken met patiënten met een ander type herseninfarct. Er werden geen statistisch significante verbanden gevonden tussen de cerebrale hemodynamische indices en de klinische gevolgen. In **hoofdstuk 7** hebben we patiënten met een normale druk hydrocefalus voor en na een ventriculoperitoneale drainoperatie onderzocht. De postoperatieve piek systolische cerebrale bloedstroomsnelheid was lager en de cerebrovasculaire CO_2-reactiviteit was hoger vergeleken met de pre-operatieve waardes. De pre- en postoperatieve einddiastolische cerebrale bloedstroomsnelheid was hoger in patiënten met klinische verbetering, die van tevoren was gedefinieerd als een verbete-

ring van meer dan 1 punt op de gemodificeerde Rankin schaal en een reductie van minstens 15% op de NPH schaal. De postoperatieve gemiddelde en piek systolische cerebrale bloedstroomsnelheid waren eveneens hoger in patiënten met klinische verbetering. De pre-operative cerebrovasculaire CO_2-reactiviteit vertoonde een trend naar hogere waardes bij patiënten met klinische verbetering op de loopscore vergeleken met patiënten zonder verbetering.

Transcraniële Doppler kan een deel van de cerebrale hemodynamiek in kaart brengen, hoewel het nog steeds als onderzoeksinstrument wordt beschouwd. Door toekomstig klinisch TCD onderzoek zal moeten blijken of de nauwkeurigheid van de klinische diagnose "small vessel disease" verbeterd kan worden. Dit dient veelal te gebeuren in combinatie met andere neuro-radiologische onderzoeksmethoden, zoals MRI. Daarnaast is het ERGO onderzoek geschikt om de relatie tussen de cerebrale hemodynamische indices en indicatoren van atherosclerose te bestuderen.

List of abbreviations

ANCOVA	=	analysis of covariance
ERGO	=	Erasmus Rotterdam gezondheid en ouderen
CBF	=	cerebral blood flow
CBFV	=	cerebral blood flow velocity
CES-D	=	center for epidemiologic studies-depression symptom scale
CI	=	confidence interval (betrouwbaarheidsinterval)
CO_2	=	carbon dioxide
CT	=	computed tomography
CVR-CO_2	=	cerebrovascular CO_2 reactivity
DSM IV	=	diagnostic and statistical manual of mental disorders (IV)
HDL	=	high-density lipoprotein cholesterol
kPa	=	kiloPascal
MCA	=	middle cerebral artery
MHz	=	mega Hertz
mmHg	=	millimeter kwik
MMSE	=	mini mental state examination
MRI	=	magnetic resonance imaging
NIHSS	=	national institute of health stroke scale
NPH	=	normal pressure hydrocephalus
OR	=	odds ratio
PD	=	proton density
PET	=	positron emission tomography
pi	=	pulsatility index
PSE	=	present state examination
$r^{(2)}$	=	correlatie coëfficient
SPECT	=	single photon emission computed tomography
T	=	tesla
TCD	=	transcranial Doppler
TOAST	=	trial of Org 10172 in acute stroke treatment
VMR	=	(cerebral) vasomotor reactivity = cerebrovascular reactivity
WML	=	white matter lesions

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1982-1989	M.D., Medical School, University of Amsterdam, The Netherlands.
1990-1992	Resident in Neurology (AGNIO), Dept. of Neurology St. Elisabeth Hospitaal, Curaçao, Dutch Antilles.
1992-1994	Resident in Neurosurgery (AGNIO), Dept. of Neurosurgery University Hospital Rotterdam, The Netherlands.
1994-2000	Resident in Neurology (AGIO), Dept. of Neurology University Hospital Rotterdam, The Netherlands.
2000	Neurologist, Department of Neurology University Hospital Rotterdam, The Netherlands.

Research projects:

Changes in volume and geometry after acute myocardial infarct of the left ventricle
Department of Pathology
Academic Medical Centre, Amsterdam
September-November 1986

Endomyocardial biopsy in unknown cardiac disease
Department of Cardiology
Academic Medical Centre, Amsterdam
October 1988 - March 1989

The central cord syndrome
Department of Neurology
St. Elisabeth Hospitaal, Curaçao, Dutch Antilles
November 1990 -December 1991

Cerebral hemodynamic indices measured by means of transcranial Doppler
Department of Neurology, University Hospital Rotterdam
Department of Epidemiology & Biostatistics, Erasmus University Rotterdam
July 1996 -

LIST OF PUBLICATIONS

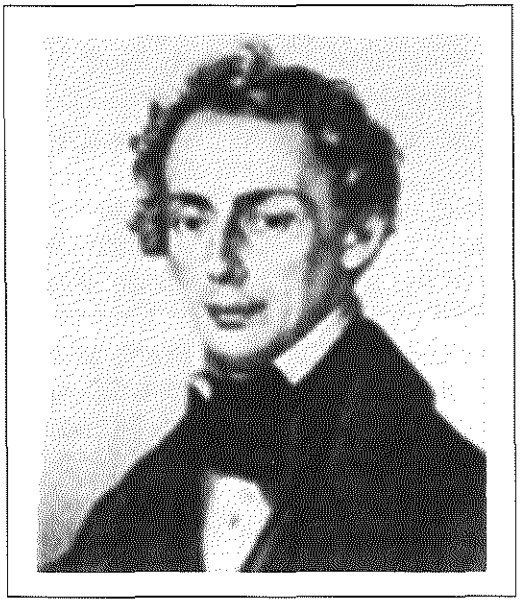
This thesis:

1. SLM Bakker, F-E de Leeuw, JC de Groot, PJ Koudstaal, A Hofman, MMB Breteler. Cerebral vasomotor reactivity and white matter lesions in the elderly. Neurology 1999;52:578-583.
2. SLM Bakker, F-E de Leeuw, PJ Koudstaal, A Hofman, MMB Breteler. Cerebral vasomotor reactivity, cholesterol and HDl-cholesterol in the elderly. Neurology 2000;54: 987-989.
3. SLM Bakker, F-E de Leeuw, T den Heijer, PJ Koudstaal, A Hofman, MMB Breteler. Cerebral hemodynamics in the elderly. A population based study. Submitted.
4. A Ruitenberg, SLM Bakker, PJ Koudstaal, A Hofman, MMB Breteler. Cerebral hemodynamics and cognitive decline and dementia in the Rotterdam Study. Submitted.
5. H. Tiemeier, SLM Bakker, PJ Koudstaal, A Hofman, MMB Breteler. Cerebral hemodynamics and depressive disorders in the elderly. The Rotterdam Study. Submitted.
6. SLM Bakker, AD Wijnhoud, DWJ Dippel, PJ Koudstaal. Cerebral hemodynamic indices in acute hemispheric ischemic stroke. Submitted.
7. SLM Bakker, AJW Boon, AD Wijnhoud, DWJ Dippel, PJ Koudstaal. Cerebral hemodynamics in normal pressure hydrocephalus before and after shunt surgery. Submitted.

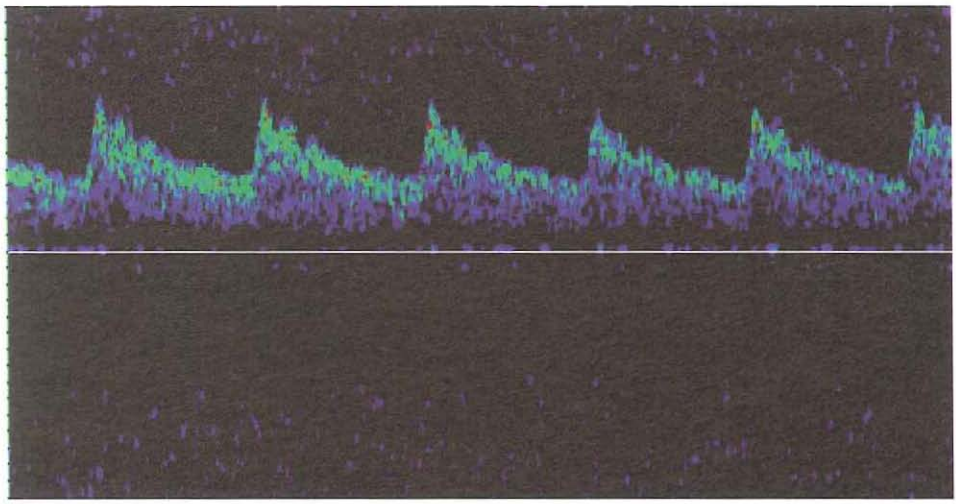
Other publications:

1. SLM Bakker, DJ Kamphuis, RE Rico. Het centrale-ruggemergsyndroom. Nederlands Tijdschrift voor Genees-kunde 1993;137(12):587-591.
2. SLM Bakker, J Kluytmans, J den Hollander, S-T Lie. Subdural empyema caused by Escherichia coli; Hematogenous dissemination to a preexisting chronic subdural hematoma, a case report. Clinical Infectious Diseases 1995;21:458-459.
3. DWJ Dippel, F van Kooten, SLM Bakker, PJ Koudstaal. Interobserver agreement for 10% categories of angiographic carotid stenosis. Stroke 1997;28-2483-2485.
4. AM Lievense, SLM Bakker, DWJ Dippel, MA Taams, PJ Koudstaal PJ, AJJC Bogers. Intracranial high-intensity transient signals after homograft or mechanical aortic valve replacement. The Journal of Cardiovascular Surgery 1998;39:613-617.
5. DWJ Dippel, A de Kinkelder, SLM Bakker, F van Kooten, H van Overhagen, PJ Koudstaal. The diagnostic value of colour duplex ultrasound for symtpomatic carotid stenosis in clinical practice. Neuroradiology 1999;41:1-8.
6. SLM Bakker, D Hasan, HWC Bijvoet. Compression of visual pathway by anterior cerebral artery aneurysm. Acta Neurologica Scandinavica 1999;99:204-207.
7. M Kros, H van den Berge, HLJ Tanghe, SLM Bakker. Right temporal lobe glioblastoma presenting in the left orbit. J Neurosurg 2000;92:702-705.
8. Kros JM, Cella F, Bakker SLM, Paz Y Geuze D, Maarten Egeler R. Papillary meningioma with pleural metastasis. Case report and literature review. Acta Neurol Scand. 2000;102:200-202

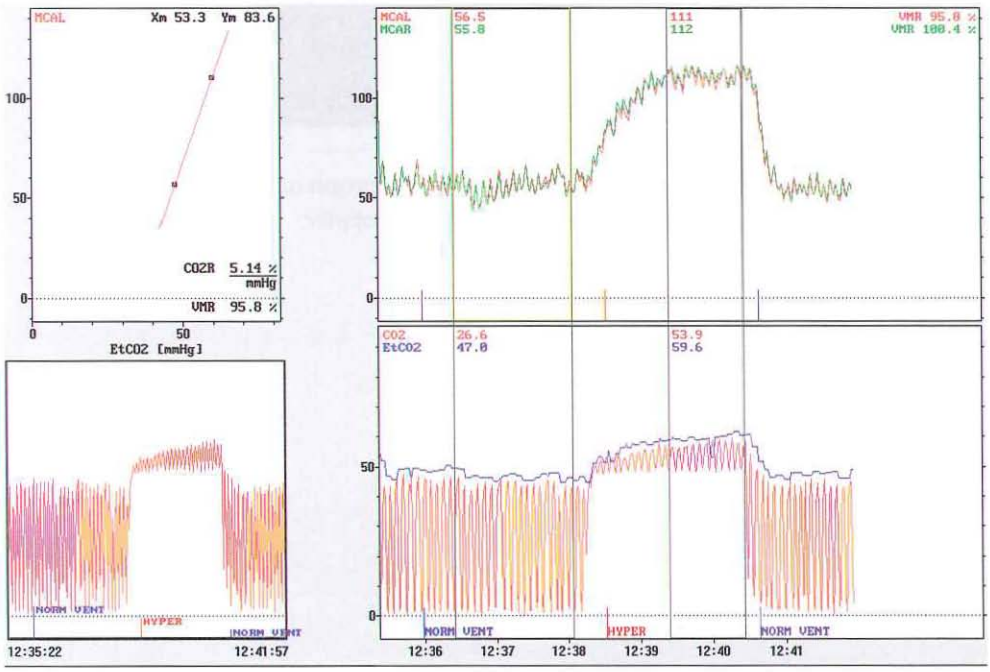
APPENDIX



The only known photograph of Christian Andreas Doppler, taken in 1845.



Normal waveform of the middle cerebral artery.



Normal cerebrovascular CO_2 reactivity in a healthy 27 year old female.

Neurosonology societies and research groups

1. American Society of Neuroimaging
2. The Neurosonology Research Group of the World Federation of Neurology
3. The European Society of Neurosonoolgy and Cerebral Hemodynamics

Summary of the effectiveness of transcranial Doppler for specific disorders

Application	Rating	Quality of evidence	Strength of recommendation
Ischemic cerebrovascular disease	Established	Class II	Type B
Subarachnoid hemorrhage	Established	Class II	Type B
Arteriovenous malformations	Established	Class III	Type C
Perioperative monitoring	Promising	Class III	Type C
Periprocedural monitoring	Investigational	Class III	Type D
Cerebral circulatory arrest	Established	Class II	Type B
Migraine	Investigational	Class III	Type D
Sickle cell disease	Effective	Class I	Type A
Meningeal infection	Promising	Class III	Type C
Cerebral vein thrombosis	Investigational	Class III	Type D

Adopted from Babikian et al. J Neuroimaging 2000;10:101-115.

Strength of TCD Recommendation Rating from the Neurosonology societies and research groups

Type A. Strong positive recommendation, based on class I evidence or overwhelming class II evidence when circumstances prelude randomized clinical trials.

Type B. Positive recommendation, based on class II evidence.

Type C. Positive recommendation, based on strong consensus of class III evidence.

Type D. Negative recommendation, based on inconclusive or conflicting class II evidence.

Type E. Negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on class II or class I evidence.

Adopted from Babikian et al. J Neuroimaging 2000;10:101-115.