Diagnostic Impact of Cerebral Transit Time in the Identification of Microangiopathy in Dementia
A Transcranial Ultrasound Study

Imke Puls, MD; Kurt Hauck, MD; Klaus Demuth, MD; Anja Horowski, MD; Mira Schließer; Petra Dörfler, MD; Peter Scheel, MD; Klaus V. Toyka, MD; Karlheinz Reiners, MD; Martin Schöning, MD; Georg Becker, MD

Background and Purpose—The diagnosis and quantification of microangiopathy in dementia is difficult. The assessment of small-vessel disease requires expensive and sophisticated nuclear medicine techniques. This study was performed to identify microangiopathy related to the integrity of cerebral microcirculation by sonographic measurements (arteriovenous cerebral transit time [cTT]).

Methods—We performed transcranial color-coded duplex sonography in 40 patients with vascular dementia, 20 patients with Alzheimer’s disease or Lewy body disease, and 25 age-matched controls. The clinical diagnosis was established by history of dementia and neuroimaging findings. Cognitive impairment was assessed by the Mini-Mental State Examination and Alzheimer’s Disease Assessment Scale. cTT is defined as the time required by an ultrasound contrast agent to pass from a cerebral artery to a vein. This was measured by recording the power-Doppler intensity curves in the P2 segment of the posterior cerebral artery and the vein of Galen. Previous studies have shown a prolongation of cTT in patients with cerebral microangiopathy.

Results—cTT was substantially prolonged in patients with vascular dementia (5.8 seconds; 25th percentile 4.5; 75th percentile 7.5; U test, P<0.001) compared with controls (3.1 seconds; 2.3; 3.4) but not in patients with degenerative dementia (3.7 seconds; 3.7; 4.2). In patients with vascular dementia, cTT was significantly correlated with cognitive impairment.

Conclusions—cTT may be useful tool to disclose small-vessel disease in demented patients. Examination is noninvasive and quickly performed. It may be also useful in follow-up examinations in patients undergoing therapy. (Stroke. 1999;30:2291-2295.)

Key Words: Alzheimer’s disease ■ cerebrovascular circulation ■ ultrasonography, Doppler, transcranial ■ ultrasonography, Doppler, duplex ■ vascular dementia

The clinical differentiation between senile dementia of the Alzheimer type and vascular dementia is difficult, and the correlation between clinical and pathological changes is poor.1,2 The identification of vascular pathology is important because early management of risk factors may delay onset or reduce the severity of vasculopathy. At present, the diagnosis of cerebral microangiopathy is based on clinical findings and CT and MRI findings. These techniques display the structural consequences of an advanced cerebral microangiopathy. For identification of early stages of small-vessel disease, sophisticated neuroimaging techniques such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) are required. These methods are expensive, time consuming, and not easily available.3-5

Recently, we introduced a new sonographic application, the arteriovenous cerebral transit time (cTT), for the evaluation of cerebral microcirculation: cTT is measured by transcranial color-coded duplex sonography (TCCS) with use of ultrasound contrast agents. The method is based on the assumption that the time required by an ultrasound contrast agent to pass from the cerebral arteries to the veins should be prolonged in patients with small-vessel disorders. A pilot study showed that patients with evidence of cerebral microangiopathy indeed had a prolonged cTT compared with healthy subjects.6

The present study was performed to assess whether cTT is altered in patients with vascular dementia and whether this method could help to differentiate vascular dementia from other types of dementia.

Subjects and Methods
We examined 40 patients (median age 71 years [range 46 to 92 years]; 27 men and 13 women) with clinical and radiological...
evidence of vascular dementia according to the DSM-IV classification.7–9 Inclusion criteria were the diagnosis of dementia, a history of focal neurological deficits with at least 1 lacunar stroke, multiple lacunes and leukaraiosis identified by CT and MRI, and vascular risk factors including arterial hypertension (repeated systolic values of >160 mm Hg).

In the group of degenerative dementia, 20 patients (median age: 67.5 years [range 40 to 83 years], 7 male, 13 female) were included. Twelve patients fulfilled the DSM-IV criteria for probable Alzheimer’s disease,10 and eight patients had dementia with Lewy bodies (DLB) according to the clinical guidelines reported by McKeith et al.11 None of these patients had a history of focal neurological deficits, hypertension, diabetes, increased serum fats or lacunes and leukaraiosis on CT.

All patients had a full neurological and psychiatric examination. Focal neurological and psychiatric deficits, blood pressure, heart rate and the walking-time for a distance of 18 m were recorded. Cognitive deficits were quantified using the Mini-Mental State Examination12 (MMSE) and Alzheimer’s Disease Assessment Scale13 (ADAS). Laboratory examinations included hematocrit and fibrinogen. All patients had a cranial CT scan. To complete hemodynamic assessment, all patients and controls were submitted to a transthoracic echocardiographic examination (Sonoline CF, Siemens AG) to determine the cardiac ejection fraction.14,15 In addition, they underwent sonographic examination with TCCS (Elegra, Siemens AG) of the major extracranial and intracranial arteries.

For comparison, we enrolled 25 control subjects (median age 65 years [range 59 to 77 years]; 17 men and 8 women) with neuromuscular diseases or healthy volunteers. None of the control subjects had a history of stroke-related deficits or vascular risk factors. All subjects underwent neurological and psychiatric examination to exclude dementia. The MMSE score was >28 in these probands.

Exclusion criteria for patients and controls included sonographic evidence of a stenosis of major extracranial or intracranial arteries or evidence of territorial infarcts, heart failure, arrhythmia, or coronary heart disease. All subjects gave informed consent according to the Declaration of Helsinki. The study was approved by the local ethics committee.

For extracranial sonography we used a 5.0-MHz linear-array probe. Transcranial examinations were performed with a 2.5-MHz phased-array probe through a transtemporal bone window.16 All patients and controls had an adequate acoustic bone window for transcranial sonography. With color-duplex mode, peak systolic and end-diastolic as well as mean blood flow velocities were recorded bilaterally from the proximal segments of the middle, anterior, and posterior cerebral arteries. CT scan was performed with continuous non-overlapping slices (slice thickness 5 mm) from the skull base up to the sellar region and 10 mm from the sella to the vertex (CT 9800, CT-MAX, General Electric).

cTT Assessment

For baseline examination, the diencephalon displaying the thalamus, the pineal gland, the supracerebellar cistern, and postpontine portions of the ambient cistern covering the P2 segment of the posterior cerebral artery and the vein of Galen were depicted in 1 axial scanning plane at the level of the third ventricle.6 Doppler signals of the P2 segment of the posterior cerebral artery and the vein of Galen were identified. The vein of Galen was detected dorsally to the pineal gland, and the P2 segment of the posterior cerebral artery was depicted lateral to the pineal gland. Sonographic identification of these vessels was verified by pulsed-wave Doppler examinations that showed typical arterial and venous flow signals.17 If the vein of Galen or the posterior cerebral artery were not detected by native TCCS, Doppler sonographic verification was always performed at the end of cTT measurement after ultrasound contrast agent was given intravenously.

A bolus of contrast agent (5 mL Levovist [Schering], 400 mg/mL) was injected into the cubital vein at a constant injection speed (1 mL/s). This ultrasound contrast agent consists of transpulmonary stable microbubbles formed in a galactose suspension, which significantly increases the ultrasound signal intensity by approximately 25 dB.17 The examination was done in power mode. It was stored on hard disc at 5 images per second. Subsequently, the analysis of power-Doppler signal intensity changes in comparison with baseline intensity was performed offline over the total examination period, including approximately 300 images (Echo Tech System). The time-intensity curves were recorded from 2 defined regions of interest (ROI) superimposed on the postpontine P2 segment of the posterior cerebral artery and the vein of Galen (Figure 1). The following parameters were assessed: wash-in time (ie, the time from contrast agent injection to the beginning of the signal intensity increase in the posterior cerebral artery) and cTT (ie, the latency of signal intensity increase between the P2 segment of the posterior cerebral artery and the vein of Galen). Two measurements were performed in each patient to assess the intraindividual variability. The average cTT was calculated from these 2 measurements. In 20 control subjects we repeated cTT measurements after 6 months to prove reproducibility of measurements.

Statistical Analysis

Descriptive statistics of patient and control characteristics and sonographic measurements are given as median values with 25th and 75th percentiles. For comparison and correlations of cTT and wash-in time with clinical data, we used nonparametric statistical tests (Spearman rank correlation, Mann Whitney U test; Statistica). The level of significance for all statistical tests was set at P<0.05.

Results

The contrast agent (Leovist) was tolerated in all subjects without notable side effects. Age, sex, blood pressure, heart rate, walking time, cardiac ejection fraction, and blood tests (hematocrit and fibrinogen), as well as results of neuropsychological tests for each patient group and controls, are given in Table 1. No significant differences in these criteria were identified between the 3 groups except for the MMSE and ADAS, because these values indicated more severe cognitive
deficits in patients with degenerative dementia compared with vascular dementia (Table 1).

The results of transcranial Doppler recordings with angle-corrected peak systolic flow velocities of the basal cerebral arteries, cTT, and wash-in time are given in Table 2. In 10 subjects (11%) time-intensity curves were not assessable because no exact onset of signal intensity increase was unequivocally identifiable. In patients with vascular dementia, cTT (median 5.8 seconds; 25th percentile 4.5; 75th percentile 7.5) was significantly prolonged compared with tia, cTT (median 5.8 seconds; 25th percentile 4.5; 75th percentile 6.7 seconds; 2.8; 4.2) and control subjects (median 3.1 seconds; 2.3; 3.4) (Mann-Whitney U test, *P<0.05, †P<0.01). Differences between cTT of patients with degenerative dementia and controls were not significant (U test, *P=0.16). The wash-in time showed neither significant differences between these 3 groups (Mann Whitney U test, *P>0.22; Table 2) nor a correlation with cTT (Spearman rank correlation, r=0.2, P=0.07). In addition, cTT showed a significant correlation with the resistance index of the posterior cerebral artery (Spearman rank correlation, P<0.01).

Reproducibility of cTT Measurement
Correlation of repeated cTT measurements showed a high consistency of results in the 75 subjects in whom 2 time-intensity curves were assessable (first cTT: median 3.2 seconds, 3.6, 5.1; second cTT: median 3.7 seconds, 3.2, 5.6; Spearman rank correlation, r=0.76). cTT measurements repeated after 6 months in 20 control subjects also indicated the robustness of this sonographic parameter (Spearman rank correlation, r=0.73).

Correlation of cTT and Wash-in Time With the Severity of Dementia
In patients with vascular dementia, an inverse correlation was found between cTT and cognitive impairment as measured by MMSE (Spearman rank correlation, r=−0.49, P<0.001; Figure 3). In patients with degenerative dementia, cTT did not correlate with these tests (Spearman rank correlation, r<0.24, P>0.09), although cognitive impairment was more severe in this group (Table 1).

Correlation of cTT With Patient Characteristics and Blood Values
cTT and wash-in time was similar in men and women (U test, P=0.42 and P=0.14). Age did not influence cTT in control

### Table 1. Group Data for General Measures and Functional Tests

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=25)</th>
<th>Degenerative Dementia (n=20)</th>
<th>Vascular Dementia (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 (60; 72)</td>
<td>65 (60; 76)</td>
<td>71 (62; 78)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>(17/8)</td>
<td>(7/13)</td>
<td>(27/13)</td>
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<tr>
<td>Blood pressure, mm Hg</td>
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<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>132 (120; 140)</td>
<td>140 (130; 150)</td>
<td>140 (130; 160)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 (75; 85)</td>
<td>85 (70; 90)</td>
<td>85 (80; 90)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>76 (68; 76)</td>
<td>80 (76; 88)</td>
<td>76 (68; 84)</td>
</tr>
<tr>
<td>Walking time, s</td>
<td>14 (13; 18)</td>
<td>21 (15; 35)*</td>
<td>20 (15; 33)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>74 (72; 79)</td>
<td>75 (70; 79)</td>
<td>71 (65; 73)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41 (37; 41)</td>
<td>39 (37; 41)</td>
<td>41 (40; 43)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>2.7 (2.4; 3.0)</td>
<td>3.2 (2.9; 4.4)</td>
<td>4.1 (3.2; 4.9)*</td>
</tr>
<tr>
<td>MMSE</td>
<td>30 (30; 30)</td>
<td>22 (18; 27)†</td>
<td>25 (23; 28)†</td>
</tr>
<tr>
<td>ADAS, cognitive</td>
<td>...</td>
<td>26.0 (15.5; 37.0)</td>
<td>19.0 (15.0; 30.0)</td>
</tr>
<tr>
<td>ADAS, noncognitive</td>
<td>...</td>
<td>7.0 (3.5; 11.0)</td>
<td>6.0 (3.5; 11.5)</td>
</tr>
</tbody>
</table>

Values given are median values (25th percentile; 75th percentile). Significant differences of 1 of these items in patients with dementia compared with controls by Mann Whitney U test: *P<0.05, †P<0.01.

### Table 2. Angle-Corrected Doppler Measurements of the Basal Cerebral Arteries (Angle-Corrected Peak Systolic Flow), cTT, and Wash-in Time in Patients With Vascular and Degenerative Dementia and in Control Subjects

<table>
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<tr>
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<td>41 (37; 41)</td>
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<tr>
<td>Fibrinogen, mg/dL</td>
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<td>3.2 (2.9; 4.4)</td>
<td>4.1 (3.2; 4.9)*</td>
</tr>
<tr>
<td>MMSE</td>
<td>30 (30; 30)</td>
<td>22 (18; 27)†</td>
<td>25 (23; 28)†</td>
</tr>
<tr>
<td>ADAS, cognitive</td>
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Values given are centimeters per second, unless otherwise noted, with median values in parentheses (25th percentile; 75th percentile). MCA indicates middle cerebral artery; ACA, anterior cerebral artery; and PCA, posterior cerebral artery. Significant differences of 1 of these items in patients with dementia compared with controls by Mann Whitney U test: *P<0.05, †P<0.01.
subjects (Spearman rank correlation, $r=0.21$, $P=0.29$) but did in patients with degenerative (Spearman rank correlation, $r=0.48$, $P=0.02$) and vascular types of dementia (Spearman rank correlation, $r=0.37$, $P=0.01$). In none of the groups was a correlation between cTT and walking speed, hematocrit, and fibrinogen determined (Spearman rank correlation, $r<0.3$, $P>0.05$).

**Correlation of cTT and Wash-in Time With Hemodynamic Parameters**

In patients and control subjects, a weak negative correlation was seen between heart rate and cTT (Spearman rank correlation, $r=-0.24$, $P=0.04$) but no correlation between cTT and blood pressure or cardiac ejection fraction as measured by echocardiography was found (Spearman rank correlation, $r<0.2$, $P>0.09$). None of these hemodynamic parameters had a major effect on the wash-in time (Spearman rank correlation, $r<0.12$, $P>0.09$).

**Discussion**

Our findings show that cTT is prolonged in patients with small-vessel disorders of the central nervous system. Because cTT measures the time required by an ultrasound contrast agent to pass from the cerebral arteries to the veins, we propose that cTT assessed the functional consequences of the microvascular network pathology. Prolongation of cTT likely reflects a microvascular rarefaction or increased small-vessel resistance. Correlation of cTT and the severity of cognitive impairment in patients with vascular dementia but not in patients with degenerative types of dementia further supports the notion that cTT is related to the severity of microangiopathy.

Although cTT differed substantially between patients with vascular dementia and those with degenerative types of dementia or control subjects, a broad overlap of cTT values of all 3 groups was noticed (Figure 2). This is not surprising, because some degree of vascular pathology is often recognized in patients diagnosed as Alzheimer’s disease, while Alzheimer’s disease pathology is frequently found in patients with a clinical diagnosis of vascular dementia. Therefore, we suggest that cTT may help to disclose the severity of microcirculatory impairment in different types of dementia.

As with all ultrasound techniques, results from the examinations are highly dependent on the skills and experience of the examiner. In terms of an insufficient bone window, it may be difficult or impossible to identify the posterior cerebral artery or the vein of Galen. An acceptable variability of cTT measurements can be achieved only if time-intensity curves are recorded from the same arterial and venous segments. Third, discontinuous pulsatile wash-in of contrast agent impedes the exact start of the time-intensity curve ascent. It is conceivable that a circumscribed small-vessel disease affecting only the anterior circulation (eg, as in cerebral vasculitis) may be missed with this measurement. Nevertheless, the low variability of serial cTT measurements and the limited influ-

**Figure 2.** Median cTT in patients with vascular dementia, patients with degenerative dementia (Alzheimer’s disease and Lewy body disease), and control subjects. cTT differences between patients with vascular dementia and controls were significant ($U$ test, $P<0.001$). Differences between degenerative dementia and controls were small and not significant ($U$ test, $P=0.16$).

**Figure 3.** Correlation between cTT and cognitive impairment as measured by the MMSE in patients with vascular dementia (Spearman rank correlation: $r=-0.49$, $P<0.001$). Dotted lines indicate 95% CIs.
ence of hemodynamic factors in the present study indicate that cTT is a robust and reproducible method for the assessment of cerebral microcirculation. However, the influence of extracranial and intracranial stenoses as well as cardiac failure and dysrhythmias must assessed by further studies.

The identification of small-vessel disease in patients with dementia may be important for the choice of therapy. Serial cTT measurements could be helpful in determining the progression of microangiopathy and the efficacy of treatment. Further studies are in progress to examine whether brain perfusion quantified by PET correlates with cTT and whether cTT measured in the posterior circulation differs from cTT recorded in anterior parts of the brain.

Acknowledgments

The study was supported by the Schering Deutschland GmbH and Siemens AG, Germany. The authors wish to thank Dr. I. Fauth for acquiring patients with degenerative dementia.

References


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Stroke. 1999;30:2291-2295
doi: 10.1161/01.STR.30.11.2291

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