Transcranial color-coded duplex ultrasonography of the circle of Willis
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Chapter 1

Introduction and Outline of the Thesis
Introduction

The circle of Willis has the ability to function as an anastomosis between the left and right carotid territories via the anterior communicating artery (AcoA) and between the basilar and carotid circulation via the posterior communicating artery (PcoA). Thomas Willis was the first to understand the functional importance of this arterial anastomosis at the base of the brain, named after him. His ideas about collateral flow through the circle to ensure adequate irrigation of both cerebral hemispheres in case of occluded carotid arteries, and in this way to protect patients from brain infarction, were shrewed. Willis theories were endorsed by autopsy studies performed 300 years later which showed that circles of Willis in infarcted brains had a higher number of hypoplastic vessel segments (Figure 1) than brains without such infarctions.

Figure 1. Autopsy specimen of the circle of Willis of a patient who died from an ischemic stroke, showing 'threadlike' hypoplastic posterior communicating arteries (PcoA), hampering collateral flow from the basilar artery to the carotid arteries. AcoA, anterior communicating artery; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery. Dissection performed by A.W.J. Hoksbergen and B. Fülesdi at the department of pathology of the Debrecen University Medical School in Hungary.

For many years brain infarction was attributed to reduced blood flow to the brain caused by obstruction of extracranial and intracranial large and small arteries. This belief in hypoperfusion and hemodynamic-related causes of cerebral ischemia promoted therapies aimed at augmenting brain blood flow especially to underperfused ischemic brain regions. Examples of such therapies are endarterectomy of stenosed carotid arteries and extracranial-intracranial bypass surgery for occluded carotid arteries. However, during the past two decades the emphasis on ischemic stroke pathogenesis has largely switched from hemodynamic-related explanations to thromboembolism as the predominant mechanism. Nevertheless, the close relation between
severity of extracranial arterial stenosis and brain infarction\textsuperscript{12}, the correlation between impaired functional blood flow reserve and subsequent brain infarction\textsuperscript{13,14}, and the correlation of reduced collateral blood flow with a poor prognosis\textsuperscript{15-18} indicates that ischemic stroke pathogenesis is a multifactorial process. This has led to a reappraisal of hemodynamic factors in stroke pathogenesis.\textsuperscript{19-20} Impaired clearance or washout of emboli, has been proposed as an important link between hypoperfusion, embolism and ischemic stroke.\textsuperscript{21} This indicates that in patients with severe carotid artery occlusive disease an effective collateral function of the circle of Willis might not only protect the brain from ischemia caused by a critical reduction in cerebral perfusion pressure\textsuperscript{14,15,22}, but also from the harmful effects of thromboembolism.\textsuperscript{21,23}

In the era of Thomas Willis, hypotheses on the role of the circulation in stroke pathogenesis could only be formulated by postmortem examination of patients. Today, as a result of the explosive increase in technical knowledge, it has become possible to visualize the blood circulation in vivo. This has opened the way to further study the role of pathological flow conditions in patients with cerebrovascular disease. The traditional way of visualizing the circulation is by intra-arterial angiography. However, in a continuous effort to develop noninvasive diagnostic tools, more recent techniques like ultrasound (Figure 2), computed tomography and magnetic resonance (MR) imaging have evolved.

![Image of ultrasound system](image)

\textbf{Figure 2.} Ultrasound system.
Although the skull represents a tough barrier for ultrasound waves, it has become possible to examine the blood flow in the major cerebral arteries of the circle of Willis with special low-frequency transducers, initially with 'blind' Doppler investigation. Transcranial color-coded duplex ultrasonography (TCCD) is a recently developed technique, enabling visualization and simultaneous measurement of the blood flow velocity and direction in the major cerebral arteries of the circle of Willis. With TCCD the actual presence or absence of collateral flow in the circle of Willis can be determined. Furthermore, with the help of carotid artery compression tests, the collateral ability of the circle of Willis can be assessed. When compared with conventional angiography, TCCD has shown a sensitivity and specificity for the identification of collateral flow via the AcoA of 98% and 100%, and for the PcoA of 84% and 94%, respectively. Although many anatomic and radiological studies involving the configuration of the circle of Willis, with special emphasis on the integrity of the collateral vessels, have been published, data on the hemodynamic potential of the circle of Willis are largely lacking.

Outline of the Thesis
The main objectives of this thesis are:

I To determine the possibilities of TCCD to examine the hemodynamics in the circle of Willis in a target group of atherosclerotic patients and to provide reference data of the cerebral circulation

II To investigate the collateral function of the circle of Willis in atherosclerotic patients with TCCD, in order to determine:
- the range of functional collateral variations in the circle of Willis
- the influence of nonfunctional collaterals on hemispherical perfusion during carotid occlusion
- the arterial threshold diameter allowing for cross-flow through the collaterals of the circle of Willis

III To determine if MR angiography is able to identify functional collaterals in the circle of Willis

IV To determine if nonfunctional anterior and posterior collateral pathways in the circle of Willis are a risk factor for ischemic stroke.
These objectives were achieved by studying three cohorts of subjects:

1. Patients with peripheral arterial occlusive disease who did not have symptoms of cerebrovascular disease. These patients were recruited from the vascular surgical ward or the vascular outpatient clinic of the Academic Medical Center in Amsterdam.
2. Patients with clinical signs of ischemic stroke admitted to the Stroke Unit of the Department of Neurology of the Debreceen University Medical School in Hungary.
3. Healthy persons, recruited via a local Dutch newspaper.

**Chapter 2**

In this chapter a short overview is presented of the potential role of transcranial ultrasound in patients with carotid artery disease. The TCCD technique of scanning the circle of Willis and the assessment of its collateral function with carotid compression tests is thoroughly discussed.

**Chapter 3**

As clinically important cerebrovascular disease is mainly found in elderly atherosclerotic patients, TCCD may well have the highest potential diagnostic benefits in such patients. An important limitation of transcranial ultrasonography is its heavy dependence on the acoustic property of the temporal bone, which worsens with ageing, notably in women. In this chapter, the success rate of TCCD regarding visualization of the basal cerebral arteries of the circle of Willis in atherosclerotic vascular patients older than 60 years without symptoms of cerebrovascular disease is described. Additionally, reference data are provided, and any possible male/female differences are compared.

**Chapter 4**

In the literature, data on the collateral configuration of the circle of Willis in subjects without cerebrovascular disease has been gathered by means of postmortem examinations or, more recently, by MR angiography studies. However, assessment of the true collateral potential of the circle of Willis requires the use of carotid artery compression tests to simulate carotid occlusion. In this chapter, the range of collateral variations in the circle of Willis as determined by TCCD and carotid compression tests in atherosclerotic subjects without cerebrovascular symptoms is reported.

**Chapter 5**

Deviations of the 'normal' Willisian polygon, interfering with adequate collateral function, are frequently found. Various authors have shown through anatomical studies of normal
brains that a typical polygon configuration occurs in only 20% to 50% of individuals. In this chapter, the influence of a functionally incomplete circle of Willis on hemispherical perfusion during carotid occlusion is described. The study population consisted of atherosclerotic vascular patients without hemodynamically significant extracranial arterial occlusive disease. Carotid occlusion is simulated by means of carotid artery compression. Simultaneous with carotid compression the flow velocity change in the middle cerebral artery is recorded. To assess the influence of nonfunctional anterior and/or posterior collateral pathways on hemispherical perfusion during carotid occlusion, the velocity decrease in the middle cerebral artery resulting from carotid compression is compared between functionally complete and incomplete circles of Willis in a group of atherosclerotic vascular patients without symptoms of cerebrovascular disease.

Chapter 6
Up to now, a threshold of 1.0 mm to define hypoplasia or inadequacy of intracranial collateral vessels has been widely used in anatomic studies. In a minority of studies was a threshold of 0.5 mm used to define hypoplasia of collateral arteries. However, the arbitrary diameters of 0.5 or 1.0 mm have never been discussed in terms of functional significance. In this chapter the results of a study are described, which was performed to assess the collateral artery threshold diameter for supplying collateral flow through the circle of Willis. This study is part of a larger study performed to assess the collateral function of the circle of Willis in acute stroke patients. Patients in this larger study who died, were dissected. The diameters of the arteries making up the circle of Willis were measured and this data was compared with the premortem TCCD data.

Chapter 7
MR angiography is an attractive, noninvasive technique to assess the anatomy of the circle of Willis. However, it is not clear whether opacification of intracranial collaterals on conventional angiograms or MR angiograms proves that they can act as functional collaterals when carotid arteries become stenotic or occluded. The aim of the study described in this chapter is to assess whether MR angiography is able to identify functional intracranial collaterals. MR angiography of the circle of Willis in healthy subjects is performed and the results are compared with TCCD combined with carotid compression tests, which is considered the standard of reference for the assessment of the collateral function of the circle of Willis.
Chapter 8
Data on the actual collateral function of the circle of Willis in ischemic stroke patients are largely lacking. The distribution of functionally complete and incomplete circles of Willis in a population of patients with ischemic stroke is unknown. In this chapter, the collateral function of the circle of Willis in patients with an acute ischemic stroke, with and without severe occlusive disease of the internal carotid arteries, is described. The relation between deficient collateral flow via the circle of Willis and ischemic stroke in case of severe carotid artery occlusive disease, defined as >70% stenosis or occlusion, is investigated. This is achieved by performing a case-control study, in which the collateral function of the circle of Willis in patients with acute ischemic stroke (the Debrecen cohort) is compared with the collateral function of the circle of Willis in atherosclerotic vascular patients without ischemic stroke (the Amsterdam cohort).

References
Chapter 1


