Symptomatic internal carotid artery occlusion: The implications of haemodynamic compromise

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Symptomatic internal carotid artery occlusion: The implications of haemodynamic compromise

Symptomatische occlusie van de arteria carotis interna:
De rol van gestoorde hemodynamiek
(met een samenvatting in het Nederlands)

Proefschrift

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door

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te Hardenberg

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General introduction

General introduction

An occlusion of the internal carotid artery (ICA) is found in approximately 9% of patients who present with transient ischaemic attack (TIA) or ischaemic stroke.[1-2] Patients with a symptomatic ICA occlusion have an annual risk of recurrent stroke of about 5-6%, based on a meta-analysis of studies between 1966 and 1999.[3] In theory, emboli from the heart or from atherosclerotic lesions in proximal arteries cannot reach the brain via the ICA when this artery is occluded. However, emboli might arise from the distal or proximal stump of the occluded ICA,[4] or from plaques in the contralateral ICA or ipsilateral external carotid artery (ECA)[5-6] and travel via collateral pathways to the hemisphere distal to the ICA occlusion. Another potential cause of recurrent ischaemia in patients with ICA occlusion is impaired cerebral perfusion. This so-called 'haemodynamic' cause can be supported by the clinical observation that patients with ICA occlusion more often present with symptoms that are associated with precipitating factors, such as rising or exercise, that may lead to a temporary decrease in cerebral perfusion pressure.[7-8] Patients with ICA occlusion may also present with limb-shaking TIAs, which is supposed to be associated with an impaired flow state of the brain.[9] Patients with ICA occlusion and a demonstrated compromised flow state of the brain have a relatively high risk of recurrent ischaemic stroke of about 12% per year.[10-11]

There are several diagnostic tests available that could provide information on whether it is likely that haemodynamic compromise play a role. For example, the pattern of infarcts on MRI may provide additional information, as the presence of borderzone infarcts, in particular in the internal borderzone area, is associated with haemodynamic compromise.[12] Internal borderzone infarcts are located between the deep and superficial arterial system of the middle cerebral artery (MCA), or between the supply territories of the anterior cerebral artery (ACA) and MCA in the white matter along or above the lateral ventricle in a so-called 'rosary-like' pattern.[8] Another investigation that may be considered is an angiography to study the presence of additional stenoses in cerebropetal arteries and the type of collateral pathways. It has been suggested that the presence of leptomeningeal collaterals from the posterior cerebral artery to the vascular territory of the ACA or MCA is indicative of a poor haemodynamic state of the brain.[13-15] In addition, there are various techniques to measure the cerebral autoregulatory capacity,[16] including trancranial Doppler, stable xenon or ^{133}Xe CT, N-isopropyl-p-[^{123}I]-iodoamphetamine single photon emission computed tomography,[17] positron emission tomography (PET),[10, 18-19] often with vasodilatory challenges, or more recently, CT and MRI perfusion techniques.[20-21]

However, it is unknown which method should be preferred for measuring haemodynamic compromise.[22]

On the basis of PET measurements patients can be classified in different haemodynamic stages.[23] If the cerebral perfusion pressure (CPP) decreases, lowering of cerebral blood flow (CBF) will be prevented by a compensatory increase of cerebral blood volume (CBV) by means of vasodilatation. This is the phase of cerebral autoregulation that is called haemodynamic stage 1. If the CPP decreases further and CBV can no longer compensate, CBF will decrease. As the brain cells need oxygen, the amount of oxygen extracted from the blood (OEF) will increase. Patients with an increased OEF are classified as haemodynamic stage 2, the phase of failure of cerebral autoregulation, indicative of a state of misery perfusion of the brain. PET is the only method that can directly measure OEF and thereby identifying patients with stage 2 haemodynamic failure.[23-24] An increased OEF has been found to be associated with an increased risk of recurrent stroke.[10, 18] However, PET is time-consuming and complicated, needing specific technical facilities and expertise, and therefore transcranial Doppler (TCD) with measurement of the CO_2-reactivity may be considered as an alternative method to measure the flow state of the brain.

Treatment of patients with symptomatic ICA occlusion is focused on secondary prevention with optimal antithrombotic medication, a statin, control of hypertension and diabetes, and lifestyle-recommendations.[25-27] In patients on blood pressure lowering medication who have recurrent TIAs of presumably haemodynamic origin, this medication may be tapered for a short period. Good results of tapering antihypertensive medication have been reported by case studies,[28-30] but there is no evidence for this strategy from controlled studies.
Another treatment option may be an extracranial-intracranial (EC/IC) bypass operation, which is a bypass from the superficial temporal artery to the middle cerebral artery.[31] The recent Carotid Occlusion Surgery Study (COSS) investigated the effect of the EC/IC bypass operation in selected patients with an increased OEF as measured by oxygen-15 PET. The results showed that the two-year risk of ipsilateral ischaemic stroke was between 20% and 25% in both the surgical and non-surgical group (p=0.78) despite an improvement in OEF ratio.[11] Other types of revascularization, such as carotid endarterectomy (CEA) of the contralateral ICA or of the ipsilateral ECA, or surgery or stenting of the vertebral artery, in patients with symptomatic ICA occlusion may be considered as well, but evidence that these treatments reduce the risk of stroke is lacking.[8, 32-36]

Aim of the thesis

The subject of this thesis is the study of haemodynamic aspects of symptoms, treatment and outcome in patients who present with TIA or minor disabling ischaemic stroke associated with an ICA occlusion. Aims were (1) to improve the identification of the patient at increased risk of recurrent ischaemic stroke based on clinical characteristics and haemodynamic measurements with transcranial Doppler with CO_2-reactivity or oxygen-15 PET studies; and (2) to study the haemodynamic effect of a therapeutic strategy consisting of surgery or stenting of stenosed cerebropetal arteries or tapering of antihypertensive medication.

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Symptomatic internal carotid artery occlusion: a long-term follow-up study

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Abstract

Background

Information on outcome of patients with occlusion of the internal carotid artery (ICA) is limited by the short duration of follow-up and lack of haemodynamic studies on the brain.

Methods

We prospectively investigated 117 consecutive patients with transient or moderately disabling cerebral or retinal ischaemia associated with ICA occlusion between September 1995 and July 1998, and followed them until June 2008. We determined the risk of recurrent ischaemic stroke and other vascular events and prognostic factors, including collateral pathways and transcranial Doppler CO_2-reactivity.

Results

Patients (mean age 61 ± 9 years; 80% male) were followed for a median time of 10.2 years; 22 patients underwent endarterectomy for contralateral ICA stenosis and 16 extracranial/intracranial bypass surgery. Recurrent ischaemic stroke occurred in 23 patients, resulting in an annual rate of 2.4% (95% CI 1.5 – 3.6). Risk factors for recurrent ischaemic stroke were age (HR 1.07, 1.02 – 1.13), cerebral rather than retinal symptoms (HR 8.0, 1.1 – 60), recurrent symptoms after documented occlusion (HR 4.5, 1.6 – 12), limb-shaking TIAs at presentation (HR 7.7, 2.6 – 22), history of stroke (HR 2.9, 1.2 – 6.7) and leptomeningeal collaterals (HR 5.1, 1.5 – 17), but not CO_2-reactivity (HR 1.01, 0.99 – 1.02). The composite event of any vascular event occurred in 57 patients, resulting in an annual rate of 6.4% (95% CI 4.9 – 8.2).

Conclusion

The prognosis of patients with TIA or minor stroke and ICA occlusion depends on age, several clinical factors and the presence of leptomeningeal collaterals. The long-term risk of recurrent ischaemic stroke is much lower than that of other vascular events.

Introduction

Patients with transient ischaemic attack (TIA) or ischaemic stroke associated with an occlusion of the internal carotid artery (ICA) have a risk of recurrent stroke of approximately 5–6% per year.[1] In the subgroup of patients with symptomatic ICA occlusion in whom a compromised haemodynamic state of the brain has been demonstrated, this risk is around 12% per year.[2,3] The information on long-term outcome in patients with symptomatic ICA occlusion is limited by short duration of follow-up[2-4] or by a lack of information on the flow state of the brain.[5-10] Since the large extracranial/intracranial (EC/IC) bypass trial did not show any benefit of bypass surgery in preventing recurrent stroke in patients with symptomatic ICA occlusion in general,[10] the current standard treatment involves antithrombotic medication and management of vascular risk factors. Whether an EC/IC bypass operation or carotid endarterectomy (CEA) of a contralateral ICA stenosis can prevent stroke in a subgroup of patients with symptomatic ICA occlusion is uncertain.[3, 11-14] We previously reported the short-term outcome of a prospectively collected cohort of patients with symptomatic ICA occlusion.[15] The aim of the current follow-up study was to investigate the long-term outcome of this cohort and to study risk factors including haemodynamic characteristics for recurrent ischaemic stroke.

Patients and methods

Patients

We prospectively included 117 consecutive patients with symptoms of transient or at most moderately disabling (modified Rankin scale, mRS ≤3[16]) cerebral or retinal ischaemia associated with an ipsilateral ICA occlusion, who were referred to the Department of Neurology at the University Medical Centre Utrecht, The Netherlands between September 1995 and July 1998. All patients had had symptoms within six months prior to inclusion in the study. The presence of the ICA occlusion was confirmed by digital subtraction angiography showing absence of filling of the extracranial ICA or common carotid artery (CCA). Patients were excluded if the ICA occlusion was caused by dissection or radiation therapy. All patients were interviewed about clinical characteristics and risk factors as listed in *Table 1*, with special attention for clinical characteristics suggesting a haemodynamic cause of symptoms such as limb-shaking,[17] precipitation of symptoms by rising from a sitting or lying position, exercise, transfer from a cold to a warm environment, a decrease of blood pressure, or retinal claudication.[18] Furthermore, we documented whether

patients had had any ongoing symptoms after occlusion of the carotid artery had been demonstrated (but before inclusion in the study).

All patients underwent magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain. Cerebral infarcts were considered symptomatic if their location corresponded with the patients' symptoms and were classified as territorial, watershed, lacunar (diameter ≤15 mm) or large subcortical.[19] The degree of stenosis of the contralateral ICA was measured on the angiograms according to the NASCET criteria.[20] The presence of collateral pathways was assessed by the combined information from the angiogram and transcranial Doppler (TCD). Collateral pathways via either the anterior communicating artery or the posterior communicating artery were considered present if either of these showed at least filling of the middle cerebral artery (MCA) branches on the angiogram or if TCD showed reverse flow in the first part of the anterior cerebral artery ipsilateral to the symptomatic ICA occlusion. Reversal of flow in the ipsilateral ophthalmic artery on TCD was considered a sign of collateral circulation via the external carotid artery (ECA). Leptomeningeal collaterals were considered present if pial branches from the posterior cerebral artery extending as far as the vascular territory of the MCA or anterior cerebral artery (beyond the usual posterior cerebral artery territory) were visualized on the angiogram after selective catheterization of one of the vertebral arteries beyond normal variability.[21] Patients underwent TCD with measurement of the CO_2-reactivity to investigate cerebrovascular reserve capacity. The CO_2-reactivity after carbogene inhalation was measured as the relative change in blood-flow velocity in the MCA and expressed as a percentage as described previously.[15]

Treatment consisted of antithrombotic medication and management of vascular risk factors. Patients with a 70–99% stenosis of the contralateral ICA were offered CEA. Patients with symptoms of cerebral ischaemia that continued after documentation of the ICA occlusion and evidence of presumably haemodynamic origin (i.e. the presence of specific symptoms associated with a haemodynamic cause, a watershed infarct or low CO_2-reactivity) were offered treatment with the high-flow EC/IC bypass.[22]

The study was approved by the institutional review board of the University Medical Centre Utrecht and written informed consent was obtained from all patients.

Follow-up and outcome

Patients were followed at regular intervals in the outpatient clinic until November 1999. Final follow-up information was obtained by structured telephone interviews of the patients in June 2008. If the patient had died, we obtained information of their relatives or their general practitioner. In case of a possible outcome event, we determined the mRS by a standardized questionnaire[23] and retrieved medical records and CT or MRI scans of the brain in case of recurrent stroke. The primary outcome was any first recurrent ischaemic stroke defined as the acute onset of new focal neurological deficit of cerebral origin persisting for more than 24 hours without haemorrhage on CT or MRI scan of the brain. The secondary outcome event was defined as the composite event of a non-fatal ischaemic or haemorrhagic stroke, non-fatal myocardial infarction (MI) or death due to vascular causes, whichever happened first.[15] Vascular death was defined as death from fatal stroke, fatal MI, sudden death, terminal heart failure, systemic bleeding, pulmonary embolism or complications after vascular surgery. Fatal stroke was defined as death within 30 days after stroke or death after major stroke (mRS≥4), in the absence of other clear causes.[24] Any death that was not clearly non-vascular, or if no information was available about the cause of death, was classified as 'other vascular.'[25]

Data analysis

We determined annual rates of recurrent ischaemic stroke and of the combined outcome of vascular events with the Kaplan-Meier method. The survival analysis started from the time of inclusion in the study. We used a Cox proportional hazards model for univariable analysis of predefined risk factors for the primary and secondary outcome events, resulting in hazard ratios (HRs) with 95% confidence intervals (CIs). The primary outcome recurrent ischaemic stroke was subdivided into any recurrent ischaemic stroke and only ipsilateral ischaemic stroke. Variables with a p-value of <0.15 in the univariable analysis were included in a multivariable model. To exclude the influence of surgical treatment on the effect of predefined risk factors on the occurrence of the primary outcome event, we also performed the Cox proportional hazards analysis with censoring of patients at the time of CEA of a contralateral ICA stenosis or at the time of an EC/IC bypass.

Results

In total, we included 117 patients (mean age 61 years, range 35–79, 80% male). Ninety-three (80%) patients had presented with cerebral ischaemic

Table 1. Analysis of risk factors for recurrent ischaemic stroke in patients with symptomatic internal carotid artery occlusion (n=117)

	Ischaemic stroke		Univariable analysis	Age and sex adjusted analysis	Censored age and sex adjusted analysis*
	Yes n = 23	*No n = 94*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Age† (years), mean ± SD	65 ± 7	60 ± 9	1.07 (1.02 – 1.12)	1.07 (1.02 – 1.13)	1.07 (1.00 – 1.13)
Male	18 (78)	76 (81)	0.8 (0.3 – 2.3)		0.7 (0.2 – 2.5)
Cerebral symptoms at presentation	22 (96)	71 (76)	6.0 (0.8 – 45)	8.0 (1.1 – 60)	4.3 (0.6 – 34)
- Transient ischaemic attack	7 (30)	16 (17)			
- Ischaemic stroke	15 (65)	55 (59)			
Retinal symptoms only at presentation	1 (4)	23 (25)			
Haemodynamic characteristics	5 (22)	11 (12)	2.1 (0.8 – 5.7)	2.4 (0.9 – 6.6)	0.6 (0.1 – 4.8)
- Limb-shaking	5 (22)	4 (4)	5.8 (2.1 – 16)	7.7 (2.6 – 22)	2.4 (0.3 – 19)
Recurrent symptoms after documented occlusion	18 (78)	38 (40)	4.7 (1.7 – 13)	4.5 (1.6 – 12)	3.7 (1.2 – 11)
Current cigarette smoking	16 (70)	70 (75)	0.8 (0.3 – 2.0)		0.9 (0.3 – 3.1)
Hypertension	11 (48)	51 (54)	0.8 (0.3 – 1.7)		0.8 (0.3 – 2.2)
Diabetes Mellitus	3 (13)	18 (19)	0.7 (0.2 – 2.4)		1.1 (0.2 – 5.1)
Hyperlipidaemia‡	19 (83)	80 (85)	0.9 (0.3 – 2.5)		1.2 (0.3 – 5.4)
History of stroke	9 (39)	18 (19)	2.6 (1.1 – 6.1)	2.9 (1.2 – 6.7)	3.0 (0.96 – 9.3)
History of ischaemic heart disease	8 (35)	25 (27)	1.7 (0.7 – 3.9)		0.5 (0.1 – 2.3)
History of peripheral vascular disease	9 (39)	27 (29)	1.7 (0.7 – 3.9)		1.4 (0.4 – 4.4)
History of vascular disease in first-degree relative	18 (78)	65 (69)	1.6 (0.6 – 4.3)		2.0 (0.6 – 7.4)
Contralateral carotid occlusion	1 (4)	23 (25)	0.2 (0.02 – 1.2)	0.2 (0.02 – 1.3)	0.2 (0.02 – 1.3)
Contralateral carotid stenosis ≥70%	5 (22)	24 (26)	0.8 (0.3 – 2.1)		1.3 (0.3 – 6.5)
Collateral circulation via anterior or posterior communicating artery§	20/20 (100)	70/73 (96)	NE		NE
Reverse flow in ophthalmic artery¶	15/18 (83)	67/75 (89)	0.5 (0.1 – 1.7)		1.3 (0.1 – 11)
Leptomeningeal collaterals**	7/15 (47)	14/61 (23)	2.5 (0.9 – 6.9)	5.1 (1.5 – 17)	2.0 (0.3 – 11)
CO_2-reactivity†† (%), mean ± SD	21 ± 33	15 ± 19	1.01 (0.99 – 1.02)		1.0 (0.99 – 1.03)
Watershed infarction‡‡	7/16 (44)	25/62 (40)	1.1 (0.4 – 2.9)		0.6 (0.1 – 2.8)

* Analysis with censoring at the time of the first revascularization procedure. † HR for age is expressed as the increase in hazard for every incremental year. ‡ Defined as patients with either a history of hyperlipidaemia, patients on drugs because of hyperlipidaemia or patients with levels of cholesterol, triglycerides, or high-density lipoprotein cholesterol beyond the normal ranges. § In 24 patients, the presence of collateral circulation via either the anterior communicating artery or posterior communicating artery could not be determined. ¶ In 24 patients, the flow direction in the ophthalmic artery could not be determined. ** In 41 patients, the angiography was insufficient to define the presence of leptomeningeal collaterals. †† CO_2-reactivity ipsilateral to the symptomatic ICA occlusion could be measured in 21 of 23 patients with and in 88 of 94 patients without a recurrent ischaemic stroke. HR is expressed as the increase in hazard for every per cent increase in CO_2-reactivity. ‡‡ In 32 of 78 patients with a symptomatic ischaemic lesion on CT or MRI, we classified the infarct as watershed. NE, not estimable.

symptoms, whereas 24 (20%) patients had had only retinal ischaemic symptoms (retinal infarction in three, transient monocular blindness in 19 and chronic ocular ischaemic syndrome in five patients; three patients had two of these symptoms). Symptoms with haemodynamic characteristics were present in 16 patients; limb-shaking in nine, retinal claudication in three, symptoms after rising in five, after exercise in three and after low blood pressure in two patients. Seventy-eight (66%) patients had a symptomatic infarct on their CT or MRI, which we classified as territorial in 31 patients, watershed in 32, lacunar in 11 and large subcortical in four patients. Of 117 patients, 40 (34%) patients underwent a surgical revascularization procedure after a median of 46 days after inclusion (range 3–623 days). Twenty-two patients underwent CEA of a 70–99% contralateral ICA stenosis. One of them also had angioplasty for severe stenosis of the proximal part of the CCA on the side of the occlusion 14 days after the CEA because of recurrent TIAs. One patient underwent stenting of the contralateral ICA 20 months after inclusion in the study because of recurrent TIAs due to a contralateral ICA stenosis that had progressed from moderate to severe (>70%). Another patient underwent endarterectomy of a 90% stenosis of the ECA. Sixteen patients underwent EC/IC bypass surgery. Six patients with a 70–99% stenosis of the contralateral ICA chose not to be operated on and in another patient CEA was not possible because the stenosis extended to the carotid siphon.

Risk of recurrent ischaemic stroke

The median follow-up time until recurrent ischaemic stroke or death was 10.2 years (range 7 days to 12.8 years). None of the patients was lost to follow-up. Of the 117 patients, 52 (44%) died during follow-up. Any recurrent ischaemic stroke occurred in 23 (20%) patients, resulting in an annual rate of 2.4% (95% CI 1.5 – 3.6). The risk of any recurrent ischaemic stroke was highest in the first 1.5 years after presentation (*Figure 1*) (annual rate 8.0%, 95% CI 4.4 – 13.0). As shown in *Table 2*, 15 of the 23 patients had an ipsilateral ischaemic stroke, whereas eight ischaemic strokes occurred in another vascular territory. Nine of the 23 recurrent ischaemic strokes were major, resulting in an mRS≥4 (of which six were fatal) and 13 were at most moderately disabling strokes (mRS≤3). In one patient, we could not reliably determine the mRS because of co-morbidities. In three patients the (minor) ischaemic stroke occurred during the time they were waiting for the planned operation. Recurrent ischaemic stroke after the intervention occurred in six patients after an EC/IC bypass operation (four within 30 days, one after eight months and one almost 12 years after the operation), in two patients after CEA of the contralateral ICA (three and four years after surgery) and in one patient immediately after angioplasty of the CCA. Eleven of

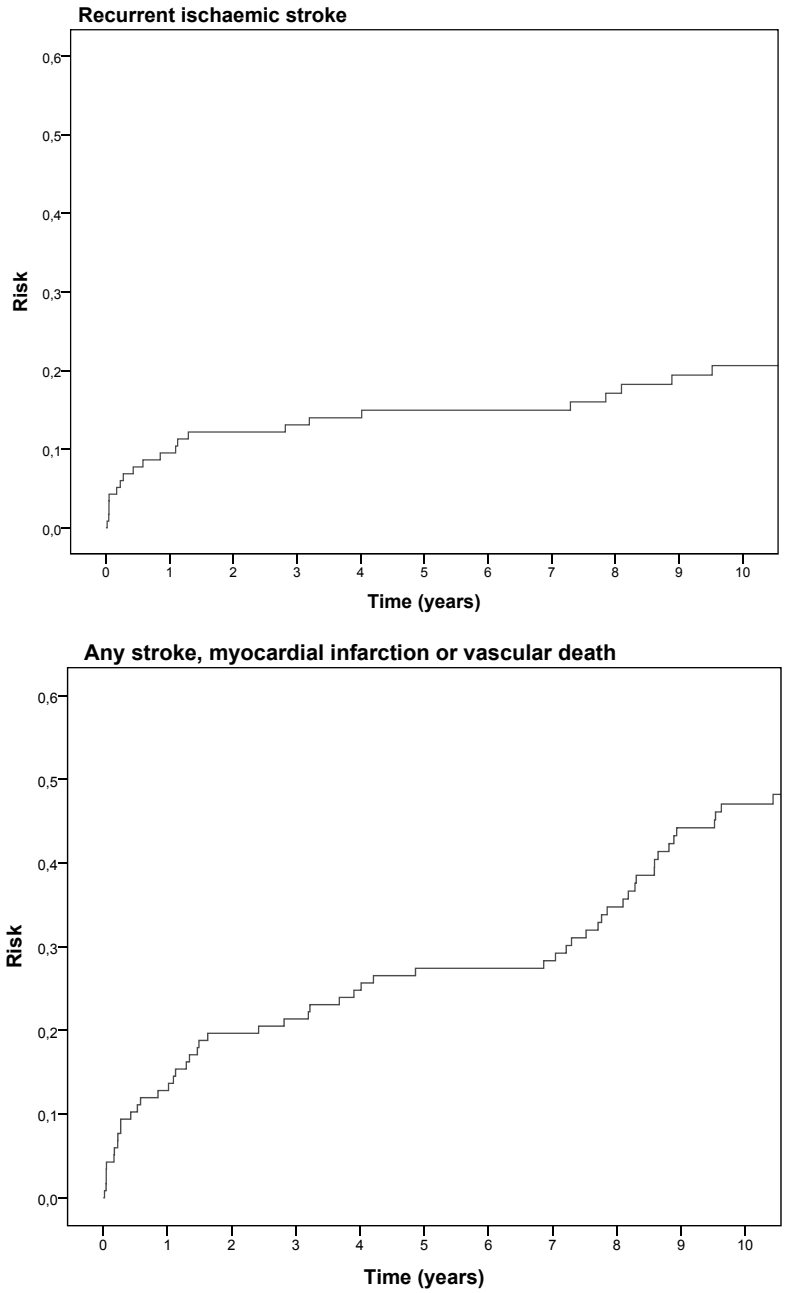

Figure 1. Time-to-event curves for recurrent ischaemic stroke (upper part) and for any stroke, myocardial infarction or vascular death (lower part) in patients with symptomatic ICA occlusion (n=117).

Table 2. Overview of the primary and secondary outcome events

	All patients n=117	Medical treatment n=77	Intervention n=40		
			Carotid endarterectomy contralateral ICA n=22	*Extracranial/ intracranial bypass n=16*	*Other surgery* n=2*
Primary outcome					
Recurrent ischaemic stroke	23	11	3†	9 (3 before surgery)	0
Ipsilateral stroke	15	5	3	7	
Modified Rankin Scale ≤3	13	6	2	5	
Fatal stroke	6	4	1	1	
Secondary outcome					
Non-fatal ischaemic stroke	17	7	2	8	
Non-fatal MI	11	6	2	3	
Non-fatal cerebral haemorrhage	1	1	0	0	
Vascular death	28	21	6	1	

* One patient underwent stenting of the contralateral ICA, another patient underwent carotid endarterectomy (CEA) of the ipsilateral external carotid artery. † One patient had the recurrent ischaemic stroke after angioplasty of the ipsilateral common carotid artery 14 days after CEA of the contralateral ICA.

the 77 (14%) patients who did not undergo a revascularization procedure had a recurrent ischaemic stroke. Two of them were known to have a contralateral ICA stenosis. The annual rate of recurrent ischaemic stroke in patients who did not undergo a revascularization operation was 2.1% (95% CI 1.2 – 3.6).

Risk factors for recurrent ischaemic stroke

Table 1 shows the relationship between baseline characteristics and the recurrence of ischaemic stroke. Patients with cerebral symptoms had an eightfold (age- and sex-adjusted HR 8.0, 95% CI 1.1 – 60) higher risk of recurrent ischaemic stroke than patients with retinal symptoms only. Continuation of symptoms after documented occlusion was associated with a fourfold (HR 4.5, 95% CI 1.6 – 12) higher risk of recurrent ischaemic stroke. Other risk factors were older age (HR 1.07, 95% CI 1.02 – 1.13), the presence of limb-shaking (HR 7.7, 95% CI 2.6 – 22), history of stroke (HR 2.9, 95% CI 1.2 – 6.7) and the presence of leptomeningeal collaterals on angiography (HR 5.1, 95% CI 1.5 – 17). TCD CO_2-reactivity was not predictive for the risk of recurrent ischaemic stroke (HR 1.01, 95% CI 0.99 – 1.02). Bilateral ICA occlusion tended to be associated with a lower risk of recurrent ischaemic stroke (HR 0.2, 95% CI 0.02 – 1.3). Because of the relatively small number of recurrent ischaemic strokes, we refrained from further multivariable analysis. When we restricted the analysis to ipsilateral recurrent ischaemic stroke, age- and sex-adjusted risk factors were continuation of symptoms after documented carotid occlusion (HR 7.3, 95% CI 1.7 – 33), limb-shaking (HR 7.8, 95% CI 2.4 – 26) and leptomeningeal collaterals (HR 5.3, 95% CI 1.2 – 23). The analysis with censoring at the time of the first revascularization procedure showed that the age- and sex-adjusted factors continuation of symptoms after documented carotid occlusion (HR 3.7, 95% CI 1.2 – 11) and older age (HR 1.07, 95% CI 1.00 – 1.13) remained significantly associated with recurrent ischaemic stroke.

Risk of the composite outcome of any vascular event

Vascular outcome events occurred in 57 (49%) patients. This included 28 vascular deaths (including six fatal ischaemic strokes, one fatal intracerebral haemorrhage, one fatal MI, six terminal heart failures, 11 sudden deaths, three other vascular causes), 17 non-fatal ischaemic strokes, one non-fatal intracerebral haemorrhage in the basal ganglia and 11 non-fatal MIs. Overall, of the 52 patients who died during follow-up the causes of death were vascular in 40 patients (in 28 vascular death as first event, in 12 vascular death after non-fatal stroke or MI as first event), and non-vascular in 12 patients (malignant disease in seven, infectious disease in three, renal disease in one, and an undiagnosed gradually progressive disease in one patient). The annual rate of the composite

Table 3. Analysis of risk factors for any stroke, myocardial infarction or vascular death in patients with symptomatic ICA occlusion (n=117)

	Any stroke, myocardial infarction or vascular death		Univariable analysis	Multivariable analysis
	Yes n = 57	*No n = 60*	*HR (95% CI)*	*HR (95% CI)*
Age (years), mean ± SD	64 ± 9	58 ± 9	1.06 (1.03 – 1.09)	1.06 (1.02 – 1.1)
Male	47 (83)	47 (78)	1.1 (0.6 – 2.2)	
Current cigarette smoking	42 (74)	44 (73)	1.1 (0.6 – 1.9)	
Hypertension	32 (56)	30 (50)	1.2 (0.7 – 1.9)	
Diabetes Mellitus	9 (16)	12 (20)	0.9 (0.4 – 1.8)	
Hyperlipidaemia	48 (84)	51 (85)	1.0 (0.5 – 2.0)	
History of stroke	17 (30)	10 (17)	1.9 (1.1 – 3.3)	2.0 (1.1 – 3.5)
History of ischaemic heart disease	23 (40)	10 (17)	2.3 (1.3 – 3.9)	1.8 (1.1 – 3.2)
History of peripheral vascular disease	19 (33)	17 (28)	1.4 (0.8 – 2.4)	
History of vascular disease in first-degree relative	43 (75)	40 (67)	1.3 (0.7 – 2.4)	

vascular endpoint was 6.4% (95% CI, 4.9 – 8.2; *Figure 1*). Multivariable analysis showed that age (HR 1.06, 95% CI 1.02 – 1.09; *Table 3*), a history of stroke (HR 1.9, 95% CI 1.1 – 3.5) and a history of ischaemic heart disease (HR 1.8, 95% CI 1.1 – 3.2) were independent risk factors for the occurrence of any vascular event.

Discussion

This 10-year follow-up study shows that patients with TIA or minor ischaemic stroke and ICA occlusion, treated with EC/IC bypass in case of recurrent symptoms of presumably haemodynamic origin or treated with CEA in case of contralateral ICA stenosis, have an annual risk of recurrent ischaemic stroke of 2.4%, with the highest risk in the first 1.5 years after presentation. Elderly patients, those who present with cerebral instead of retinal ischaemic symptoms, patients with limb-shaking, recurrent symptoms after documented occlusion, a history of stroke, and those who have leptomeningeal collaterals on their angiogram have an increased risk of recurrent ischaemic stroke. CO_2-reactivity as measured with TCD did not predict recurrence of ischaemic stroke. We were able to obtain a complete and very long duration of follow-up of a large cohort of well-documented prospectively studied patients. The largest study on outcome in patients with symptomatic ICA occlusion to date is the EC/IC bypass trial,[10] in which 423 patients who received best medical treatment were

followed for 4.5 years. This study reported an annual rate of ischaemic stroke of 6.3%, but measurements of the haemodynamic state of the brain were not performed. Other prospective follow-up series of patients with symptomatic ICA occlusion had a mean duration of follow-up of at most 4 years and found annual rates of ischaemic stroke between 5% and 10%,[3-4, 6, 26-27] except for one study that found an annual rate of 2%.[9] Some of these studies also included patients who presented with major stroke.[4, 6] The comparatively low recurrent stroke rate that we found can be explained in three ways. First, we showed that patients who present with symptomatic ICA occlusion have the highest risk of recurrent ischaemic stroke in the first 1.5 years, and the risk of stroke is relatively low thereafter. Second, a considerable proportion of the patients in our study had presented with retinal ischaemic symptoms only. Patients with retinal symptoms only have a lower risk of ischaemic stroke than patients who present with cerebral ischaemic symptoms.[3, 28] Third, in previous decades, medical secondary prevention has improved with the introduction of statins,[29] dipyridamole in combination with aspirin[30] and more rigorous control of blood pressure.[31]

In contrast to other studies,[26, 32] TCD CO_2-reactivity in this study was not predictive of recurrent ischaemic stroke. In previous studies, the results may have been confounded by including patients without symptoms as well as patients with symptoms. Asymptomatic patients have a relatively low stroke risk[33] and a relatively high cerebrovascular reactivity.[26] Similar to our findings after 2 years follow-up,[15] we found that the presence of leptomeningeal collaterals on the angiogram was predictive of recurrent ischaemic stroke. Although the role of these collaterals in the flow state of the brain needs further investigation,[34-35] it is suggested that the finding of leptomeningeal collaterals is indicative of haemodynamic compromise.[36-38] The risk of the composite endpoint of any vascular event of 6.4% per year is relatively high when compared to the risk of 4% per year in patients with TIA or minor stroke not selected because of carotid disease,[30] probably indicating that patients with a symptomatic ICA occlusion have relatively severe generalized vascular disease.

This study was a single-centre study. Patients with a symptomatic ICA occlusion were referred from all over the Netherlands to a tertiary university hospital and referral bias may have played a role. However, patients with frequent and ongoing symptoms are probably more likely to be referred than those with only one event and no further symptoms. Therefore, the risk of recurrent ischaemic stroke that we report would rather be over- than underestimated. Another limitation of our study is that it does not reflect true natural history,

as we advised CEA in patients with a >70% stenosis of the contralateral ICA and EC/IC bypass operation in selected patients with recurrent symptoms of cerebral ischaemia of presumed haemodynamic origin. Recently, another observational study showed that CEA of the contralateral ICA in 39 patients with symptomatic or asymptomatic ICA occlusion resulted in improvement of the vasomotor reactivity compared with 32 control patients who did not undergo CEA. However, they did not find any beneficial effect of CEA on the rate of recurrent stroke or death in the long-term.[14] Although there is no evidence from randomized controlled trials that CEA of a contralateral ICA stenosis or EC/IC bypass operation can prevent stroke, we advised these operations because we estimated the risk of recurrent stroke to be high if patients were treated with best medical treatment only. Whether this treatment strategy may have prevented ischaemic stroke in some patients remains unclear. In fact, five operated patients suffered a stroke within 30 days of the operation and four of the 35 patients who were operated on without any complications suffered a recurrent stroke after 5 years on average. Because of the selection bias with regard to treatment, we could not statistically compare outcome in medically and surgically treated patients. A third limitation is that the follow-up of our patients did not include serial duplex scanning or CT-angiography to reconfirm the occlusion after several years. Although infrequently, it has been found that spontaneous recanalization of an occluded ICA can occur, and a remaining high-grade stenosis would expose a patient at increased risk of an embolic event.[39]

Despite complete occlusion of the ICA, patients who have not suffered a major stroke at the time of occlusion have a relatively low risk of recurrent stroke, in particular once no stroke has occurred in the first 18 months. While this information is reassuring to the patients, it should be noted that their risk of other vascular events is significant and meticulous control of vascular risk factors is of key importance. Patients who continue to have symptoms after documentation of the ICA occlusion have a relatively high risk of recurrent ischaemic stroke. Although our study was not designed to evaluate the effectiveness of several treatment strategies, we suggest that, particularly in patients with ongoing symptoms after documented occlusion and a contralateral ICA stenosis, a CEA may be considered. EC/IC bypass surgery is associated with a considerable risk of postoperative stroke, in particular in unstable patients with repeated TIAs.[22] Whether or not EC/IC bypass surgery can prevent stroke in patients with demonstrated haemodynamic compromise will be answered by the ongoing Carotid Occlusion Surgery Study.[40]

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3

Bilateral carotid artery occlusion with transient or moderately disabling ischaemic stroke: clinical features and long-term outcome

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Abstract

Background
Information on the prognosis of patients with transient ischaemic attack or moderately disabling ischaemic stroke associated with bilateral internal carotid artery (ICA) occlusion is scarce.

Methods
We prospectively studied 57 consecutive patients (46 men; mean age 60 ± 9 years) with bilateral ICA occlusion who had presented with unilateral transient or moderately disabling cerebral or retinal ischaemic symptoms. We determined the long-term risk of recurrent ischaemic stroke and the composite outcome of stroke, myocardial infarction or vascular death.

Results
Four patients had a recurrent ischaemic stroke during a mean follow-up of 5.9 years, resulting in an annual stroke rate of 1.2% (95% CI 0.3 – 3.1). Risk factors for recurrent ischaemic stroke could not be identified. Eighteen patients suffered a stroke, myocardial infarction or vascular death, resulting in an annual rate for major vascular events of 5.3% (95% CI 3.1 – 8.3). Age and a history of ischaemic heart disease were significant risk factors for future vascular events.

Conclusion
Patients with transient or moderately disabling symptoms of cerebral or retinal ischaemia associated with bilateral ICA occlusion have a relatively low risk of recurrent ischaemic stroke. Although this study was not designed to compare conservative treatment with surgical intervention, the favourable outcome suggests that a policy of medical therapy and control of risk factors may be justified in these patients.

Introduction

A transient ischaemic attack (TIA) or ischaemic stroke is associated with complete occlusion of one of the internal carotid arteries (ICA) in about 9% of patients in hospital based series.[1-2] In a single study of 2,228 patients with TIA or stroke only eight patients (0.4%) had bilateral ICA occlusion.[2] Information on the management and prognosis of patients with bilateral occlusion of the ICA is limited by the small numbers of patients studied and the short duration of follow-up in the majority of studies.[3-12] Some studies on outcome of patients with TIA or stroke associated with bilateral ICA occlusion have emphasized a high risk of recurrent ischaemic stroke[3, 5, 7] and therefore have recommended surgical revascularization by means of an extracranial-intracranial (EC/IC) bypass or endarterectomy of an external carotid artery (ECA). In contrast, a meta-analysis of the outcome of patients with transient or moderately disabling signs and symptoms associated with ICA occlusion suggested that patients with a bilateral ICA occlusion may fare as well or even better than patients with unilateral ICA occlusion.[13] When confronted with a patient with symptomatic bilateral ICA occlusion in clinical practice, information on the risk of new vascular events is essential to weigh the risks and benefits of treatment other than antithrombotic medication and control of vascular risk factors, such as revascularization procedures. We performed a longitudinal study of a large series of consecutive patients with bilateral ICA occlusion who had presented with transient or moderately disabling cerebral or retinal ischaemia to determine the long-term risk of recurrent ischaemic stroke and other major vascular outcome events and to describe haemodynamic characteristics in relation to the risk of recurrent stroke.

Patients and Methods

Patients

We prospectively included consecutive patients who were referred to the Department of Neurology of the University Medical Centre of Utrecht, The Netherlands, between January 1990 and February 2007 because of bilateral ICA occlusion that had caused transient (lasting <24 hours) or at most moderately disabling symptoms of ischaemia of the eye or brain (modified Rankin score ≤3[14]). Transient ischaemic attack (TIA) or stroke was defined as the acute onset of neurological deficit, without signs of haemorrhage on computed tomography (CT) scan or magnetic resonance imaging (MRI). Ischaemic symptoms of the eye included transient monocular blindness, retinal infarction or chronic ocular

ischaemia.[15] The bilateral ICA occlusion (100% obstruction, defined as absence of contrast filling of both ICAs) was preferentially documented by conventional digital subtraction angiography. If magnetic resonance angiography or duplex ultrasonography already had demonstrated the absence of flow in both ICAs, conventional angiography was performed only in patients in whom visualization of the collateral circulation was important in considering a surgical revascularization procedure. We excluded patients with dissection or ICA occlusion associated with radiation-induced vasculopathy. All patients were interviewed at baseline about their symptoms and about vascular risk factors as listed in *Table 1*. This included specific questions about symptoms suggestive of a haemodynamic origin of TIAs or stroke, e.g. limb-shaking, retinal claudication or occurrence of TIAs or stroke subsequent to rising from a sitting or lying position or to exercise, extensive blood loss, cardiac failure, postprandial hypotension or transition from a cold to warm environment.[16] We also documented whether patients continued to suffer from neurological symptoms after bilateral ICA occlusion had been diagnosed. The study was approved by the medical ethics committee of the University Medical Centre Utrecht.

Collateral pathways and transcranial Doppler CO_2-reactivity

The presence of stenosis in the subclavian arteries, common carotid arteries (CCAs), ECAs, vertebral arteries (VAs), basilar artery, and collateral blood flow pathways were assessed on the digital subtraction angiograms. The degree of stenosis was measured according to the NASCET criteria[17] and dichotomized as a stenosis of ≥50% or less than that. Collateral blood flow pathways were studied for the symptomatic hemisphere. Collateral blood flow via the ophthalmic artery (OphthA) was considered present if selective catheterization of the CCA showed filling of intracranial arteries distal from the carotid syphon via the ECA and OphthA. Collateral blood flow via the posterior communicating artery (PComA) was considered present if selective catheterization of one of the VAs showed filling of the anterior cerebral artery (ACA) or middle cerebral artery (MCA) branches via the PComA. Angiography of the posterior circulation was also used to study leptomeningeal collateral blood supply from the posterior cerebral artery (PCA) to the vascular territory of the ACA and MCA.

All patients underwent transcranial Doppler (TCD) with assessment of the CO_2-reactivity to investigate cerebrovascular reserve capacity.[16] The CO_2-reactivity after carbogene inhalation was measured as the relative change in blood flow velocity in the MCA and expressed as a percentage. A CO_2-reactivity of <20% was considered abnormal, since this value corresponds with the mean CO_2-reactivity minus two times the standard deviation (SD) in normal controls.[18]

Treatment and follow-up

All patients received antithrombotic medication and management of vascular risk factors. Long-term monitoring of medication compliance and risk factor control was left to the general practitioner. Patients with ≥70% stenosis of the ECA on the symptomatic side were offered carotid endarterectomy (CEA). Patients with frequently recurring cerebral symptoms and haemodynamic features as described above or low TCD CO_2-reactivity were offered extracranial-intracranial (EC/IC) bypass operation according to the method of Tulleken.[19-21] Follow-up was performed by telephone-interviews of patients, their relatives or their general practitioners. All possible events of recurrent ischaemic or haemorrhagic stroke were verified by revision of the medical records and CT scan or MRI of the brain. The primary outcome event was fatal or non-fatal ischaemic stroke, defined as a new neurological deficit that persisted for more than 24 hours, and that was not associated with signs of haemorrhage on CT scan or MRI of the brain. The secondary outcome event was the composite event of fatal or non-fatal ischaemic or haemorrhagic stroke, myocardial infarction or vascular death, whichever occurred first. Causes of vascular death included terminal heart failure, sudden death, systemic bleeding, pulmonary embolism or complications after vascular surgery.

Data analysis

The annual risks for the primary and secondary outcome event were calculated, with 95% confidence intervals (CIs). The baseline characteristics as listed in *Table 1* were compared between patients with and without subsequent ischaemic stroke. The association of vascular risk factors with the outcome events was assessed by a Cox proportional hazards model and expressed as hazard ratio (HR) with 95% CI. Risk factors that showed an association with the outcome event with a p-value <0.15 in the univariable analysis were included in a multivariable model.

Results

A total of 57 patients (mean age 60, range 42–79 years; 46 men) were included. Thirty-six (63%) patients had presented with moderately disabling ischaemic stroke, 12 (21%) with cerebral TIA and nine (16%) patients with retinal ischaemic symptoms only (*Table 1*). Retinal ischaemic symptoms included transient monocular blindness in five, retinal infarction in two and chronic ocular ischaemic syndrome in two patients. Of the 48 patients with cerebral ischaemic symptoms, four patients had had retinal ischaemic symptoms as well. In 36

Table 1. Baseline characteristics of 57 patients with bilateral ICA occlusion and mean differences in the presence of these characteristics in patients with (n=4) and without (n=53) a recurrent ischaemic stroke.

Baseline characteristics	All patients	Recurrent ischaemic stroke		Mean differences
	n=57	*Yes (n=4)*	*No (n=53)*	
	n (%)[a]	*n (%)[a]*	*n (%)[a]*	*(95% CI)*
Age in years (mean ± SD)	60 ± 9	62 ± 9	60 ± 10	2 (–7 to 12)
Male sex	46 (81)	4 (100%)	42 (79%)	21% (–21 to 62)
Cerebral ischaemic symptoms	48 (84)	4 (100%)	44 (83%)	17% (–21 to 55)
- cerebral TIA	12 (21)	2 (50%)	10 (19%)	
- cerebral ischaemic stroke	36 (63)	2 (50%)	34 (64%)	
Retinal ischaemic symptoms only	9 (16)	0 (0%)	9 (17%)	
Haemodynamic symptoms[b]	10 (18)	1 (25%)	9 (17%)	8% (–32 to 48)
- limb-shaking	5			
- subsequent to rising	0			
- subsequent to exercise	2			
- after transition cold to warm	1			
- retinal claudication	2			
- other	1			
Symptoms after documented bilateral occlusion	23 (40)	2 (50%)	21 (40%)	10% (–41 to 62)
Smoking	46 (81)	4 (100%)	42 (79%)	21% (–21 to 62)
Hyperlipidaemia	44 (77)	2 (50%)	42 (79%)	–29% (–73 to 14)
Hypertension	49 (86)	4 (100%)	45 (85%)	15% (–21 to 52)
Diabetes mellitus	13 (23)	1 (25%)	12 (23%)	2% (–42 to 47)
History of ischaemic heart disease	13 (23)	1 (25%)	12 (23%)	2% (–42 to 47)
History of vascular disease in first-degree relative	32 (56)	3 (75%)	29 (58%)	17% (–35 to 69)
History of peripheral vascular disease	16 (28)	1 (25%)	15 (28%)	–3% (–51 to 44)
CO_2-reactivity symptomatic side % (mean ± SD)[c]	13 ± 15	12 ± 21	14 ± 15	–2 (–18 to 14)
CO_2-reactivity asymptomatic side % (mean ± SD)[c]	17 ± 18	29 ± 33	15 ± 16	13 (–38 to 64)

Mean differences are differences in proportions with 95% CIs. [a] Unless otherwise specified. [b] One patient had two haemodynamic symptoms. Other haemodynamic symptoms included neurological deficits associated with hypotension in one patient. [c] CO_2-reactivity was measured on the symptomatic side in 42 and on the asymptomatic side in 43 patients.

(63%) of 57 patients the left hemisphere or eye had been symptomatic and in 21 (37%) the right hemisphere or eye. Ten (18%) patients had had clinical symptoms suggestive of a haemodynamic origin, such as limb-shaking or precipitation of symptoms after rising or exercise. In 23 (40%) of 57 patients neurological symptoms had continued after the bilateral carotid occlusion had been documented. TCD CO_2-reactivity on the symptomatic side was below 20% in 28 (67%) of 42 patients and on the asymptomatic side in 25 (58%)

of 43 patients. None of the patients had a stenosis ≥70% of the ECA on the symptomatic side. Two patients underwent an uncomplicated EC/IC bypass operation and were censored at the time of operation.

Collateral blood flow patterns

Cerebral angiography was performed in 43 (75%) patients. The presence of additional lesions in cerebropetal arteries and collateral blood flow patterns are shown in *Table 2*. The majority of patients had collateral flow via the posterior circulation (90%). Twenty-three (70%) patients had collateral blood flow towards the symptomatic hemisphere via the OphthA, but in none of these patients this was the only collateral blood flow pathway present. Three patients showed no collateral flow via the PComA; in one of these a connection was visualized between the vertebral artery and the distal ICA with filling of ACA and MCA branches. In the two other patients the perfusion of the symptomatic hemisphere was dependent on flow via the OphthA and leptomeningeal vessels. The angiogram of three patients showed collateral flow via the OphthA on the asymptomatic side through the anterior communicating artery (AComA), with filling of the ACA in the symptomatic hemisphere in one patient and of the ACA and MCA in the symptomatic hemisphere in two patients (*Figure 1*).

Table 2. Description of additional lesions of cerebropetal arteries on the angiograms (n=43), and of collateral blood flow patterns.

	All patients *n=43*			
Additional lesions cerebropetal arteries	*(n)*			
CCA stenosis	2 / 0[a]			
occlusion	4 / 4[a]			
ECA stenosis	2 / 7[a]			
occlusion	1 / 1[a]			
VA unilateral stenosis	16			
unilateral occlusion	2			
Collateral blood flow pathways[b]	*n (%)*	*Only ACA*	*Only MCA*	*ACA + MCA*
PComA	26 (90)	0	8	18
AComA (via contralateral OphthA)	3 (9)	1	0	2
OphthA	23 (70)	2	7	14
Leptomeningeal	14 (42)			

[a] On the symptomatic side / asymptomatic side. [b] Collateral blood flow towards the symptomatic hemisphere via the PComA could be assessed in 29 patients, via the AComA in 34 patients and via the OphthA and leptomeningeal vessels in 33 patients. Collateral blood flow is further specified for filling of only ACA, only MCA or both ACA and MCA branches.

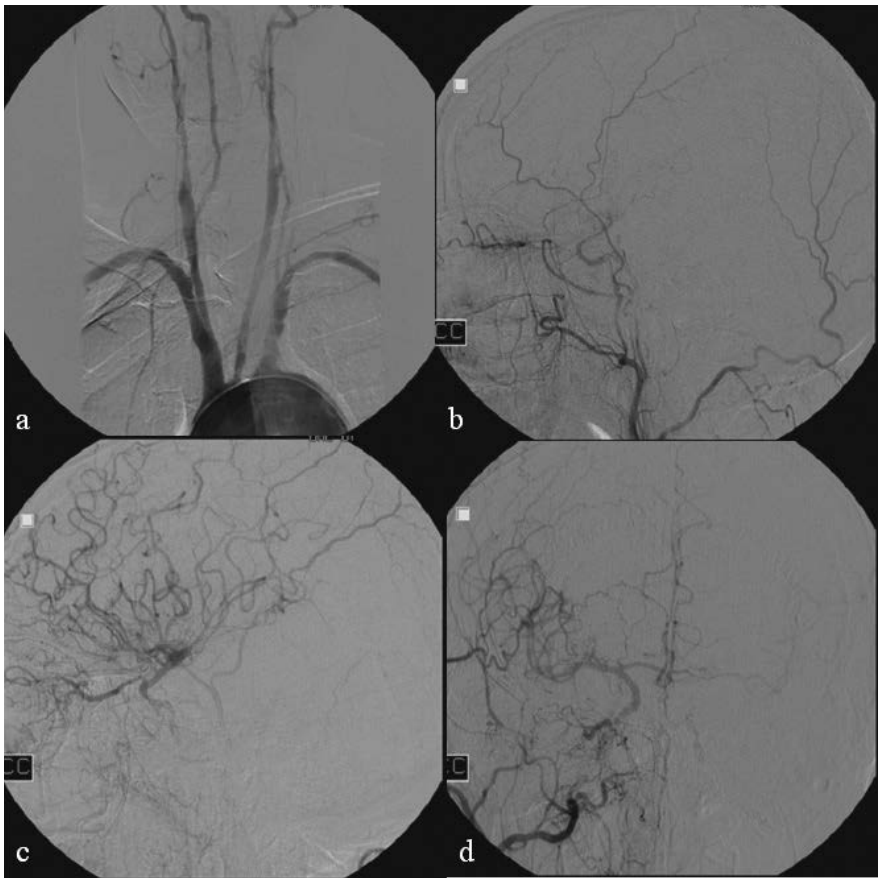

Figure 1: Angiogram of a 64-year-old man with bilateral ICA occlusion with collateral blood flow towards the left symptomatic hemisphere via the OphthA on the asymptomatic side, who did not suffer a recurrent ischaemic stroke during a follow-up period of 3.2 years; (a) bilateral ICA occlusion; (b) selective catheterization of the left CCA shows filling of only a few MCA branches via the OphthA; (c) selective catheterization of the right CCA shows extensive filling of ACA and MCA branches in the right hemisphere and (d) of the left hemisphere via the right OphthA and subsequently the AComA with filling of ACA and MCA branches.

Follow-up: primary outcome measure

Mean duration of follow-up was 5.9 years (range 2 months–16.5 years). Of the 57 patients, four (7%) men had a recurrent ischaemic stroke, which was fatal in two patients. The corresponding annual stroke rate was 1.2% (95% CI 0.3 – 3.1). *Table 1* summarizes the baseline characteristics of patients with and without a recurrent ischaemic stroke. Of the four patients with recurrent stroke, none had presented with only retinal ischaemic symptoms. One of the four patients had presented with symptoms suggestive of a haemodynamic origin. Two of the

patients with recurrent stroke had had ongoing neurological symptoms after the bilateral ICA occlusion had been documented. TCD CO_2-reactivity on the symptomatic or asymptomatic side did not differ between patients with and without recurrent stroke. *Table 3* shows the clinical characteristics and the type of collateral pathways utilized at baseline of the four patients with recurrent ischaemic stroke. Because of the small number of recurrent ischaemic strokes, Cox proportional hazards modelling of possible determinants of recurrent ischaemic stroke, including the type of collateral pathways and TCD CO_2-reactivity, could not be performed.

Table 3. Characteristics of the four patients with recurrent ischaemic stroke

	Patient 1	Patient 2	Patient 3	Patient 4
Subsequent infarction	Fatal ipsilateral	Non-fatal contralateral PCA territory	Non-fatal ipsilateral	Fatal contralateral
Time interval between inclusion and recurrent stroke (months)	18	23	30	115
Other comorbidities at the time of recurrent stroke	Gastric bleeding	–	Atrial fibrillation	–
Additional stenosis or occlusion on angiogram at baseline	VA occlusion	ECA 50%[a] VA 90%	CCA occlusion* VA 50%	CCA 50%[b]
Collateral flow via PComA	+	+	+	Not visualized
Collateral flow via OphthA	+	–	–	+
Leptomeningeal vessels	–	+	–	Not visualized
CO_2-reactivity symptomatic side %	0	–4	42	11
CO_2-reactivity asymptomatic side %	4	4	73	32

[a] On the asymptomatic side. [b] On the symptomatic side.

Follow-up: secondary outcome measure

Eighteen (32%) patients had an ischaemic or haemorrhagic stroke, myocardial infarction or died from a vascular cause, corresponding to an annual event rate of 5.3% (95% CI 3.1 – 8.3). In addition to four ischaemic strokes, four patients suffered from an intracerebral haemorrhage (fatal in three) and four patients had non-fatal myocardial infarction. Other vascular causes of death apart from stroke were cardiac failure in two patients, sudden death in three patients and complications after peripheral vascular surgery in one patient. The intracerebral haemorrhage was located in the basal ganglia with intraventricular extension in three patients and in the fourth patient the diagnosis was based on the symptoms of acute headache, vomiting and a hemiparesis followed by death. Age (HR 1.07, 95% CI 1.01 – 1.14) and a history of ischaemic heart disease (HR

3.6, 95% CI 1.3 – 10) were associated with the secondary outcome measure (*Table 4*). In a multivariable analysis including age, hypertension and a history of ischaemic heart disease, the HR for the composite endpoint associated with age was 1.06 (95% CI 0.99 – 1.12) and for a history of ischaemic heart disease 2.4 (95% CI 0.8 – 6.8).

Table 4. Univariable relation of patient characteristics to the composite outcome event of ischaemic or haemorrhagic stroke, myocardial infarction or vascular death, expressed in hazard ratios (HRs) with 95% CIs.

Patient characteristics	Stroke, myocardial infarction or vascular death during follow-up (n%)		HR (95% CI)
	Yes (n=18)	*No (n=39)*	
Age in years (mean ± SD)	62 ± 8	59 ± 10	1.07 (1.01 – 1.14)
Male sex	17 (94%)	29 (74%)	3.8 (0.5 – 29)
Smoking	13 (72%)	33 (85%)	0.5 (0.2 – 1.4)
Hyperlipidaemia	13 (72%)	31 (80%)	0.8 (0.3 – 2.3)
Hypertension	17 (94%)	32 (82%)	5.4 (0.7 – 43)
Diabetes	3 (17%)	10 (26%)	0.9 (0.3 – 3.3)
History of ischaemic heart disease	7 (39%)	6 (15%)	3.6 (1.3 – 10)
History of vascular disease in first-degree relative	11 (65%)	21 (57%)	1.3 (0.5 – 3.5)
History of peripheral vascular disease	5 (28%)	11 (28%)	1.1 (0.4 – 3.2)

Discussion

This largest longitudinal study to date of patients with bilateral carotid occlusion presenting with transient or moderately disabling symptoms of cerebral or retinal ischaemia shows a relatively low risk of recurrent ischaemic stroke. We could not identify determinants of the risk of recurrent stroke. Age and a history of ischaemic heart disease are risk factors for major vascular events in general (any stroke, myocardial infarction or vascular death).

The previously reported annual stroke rates in patients with bilateral ICA occlusion range between 0% and 13%.[3-11] The largest prospective follow-up study on bilateral ICA occlusion with non- or moderately disabling symptoms so far was published more than 20 years ago and consisted of 34 patients, of whom 11 patients suffered a stroke during a mean duration of follow-up of 3.5 years.[11] That the annual stroke rate in our study was comparatively low may be partly attributed to the relatively large proportion of patients with retinal ischaemic symptoms included in our study; it has been found before that patients with unilateral occlusion and only symptoms of retinal ischaemia have

a lower risk of recurrent stroke than those with cerebral ischaemic symptoms.[16, 22] Another explanation may be that medical treatment for secondary prevention of stroke and control of vascular risk factors is currently more effective than two or three decades earlier. Most other follow-up studies found annual stroke rates between 0% and 6%, which is more in agreement with our findings. However, these included only a small number of patients (between 8 and 21),[3, 8-10] or described only patients who underwent an EC/IC bypass operation[5] or various revascularization operations including EC/IC bypass.[7]

It has been suggested that in patients with bilateral ICA occlusion who survive without major stroke, the collateral blood flow pathways are particularly efficient and maintain cerebral perfusion.[10] We found extensive collateral blood flow patterns in the symptomatic hemisphere in the majority of patients, including the patients who later on had a recurrent stroke. Although the low event rate did not allow a formal analysis of collateral pathways as determinants of recurrent stroke, we found that subsequent infarction occurred not only in patients with additional collateral blood flow via the OphthA or leptomeningeal blood vessels, which are considered secondary pathways,[23] but also in patients with collateral blood flow via the PComA without collateral blood flow via secondary pathways. In addition, not all patients with only secondary collateral pathways suffered a recurrent ischaemic stroke. In line with our results, two previous studies of patients with bilateral ICA occlusion also failed to find an association between the type of collateral blood flow pathways and recurrent stroke.[11-12] We hypothesize that to survive bilateral ICA occlusion without major stroke, extensive collateral blood flow pathways must already have developed at the time of first presentation. This view may be supported by the results of a subgroup analysis of the Asymptomatic Carotid Atherosclerosis Study (ACAS), in which medically treated asymptomatic patients with a stenosis of the ICA of 60% or more and a contralateral ICA occlusion had a lower risk of death (during first 30 days) and stroke (cumulative 5-year rate 3.5%) than patients without contralateral ICA occlusion (cumulative 5-year rate 11.7%).[24]

Since the presence of bilateral ICA occlusion is a sign of very severe atherosclerotic disease, a high rate of other vascular events can be expected. In agreement with other studies,[8, 10] we found that indeed recurrent ischaemic stroke made up only a modest proportion of the vascular events that occurred during the time of follow-up. In previous follow-up studies the risk of stroke, myocardial infarction or vascular death in patients who were not selected because of carotid disease, amounted to 4% per year in patients who were followed for a mean of 10 years after TIA,[25] and a cumulative 5-year risk of 29% after first ischaemic stroke.[26]

Another study of 2,739 patients with TIA or moderately disabling stroke treated with aspirin or the combination of aspirin and dipyridamole during a mean follow-up time of 3.5 years found an annual risk of stroke, myocardial infarction or vascular death between 3% and 4%.[27] Against this background, symptomatic bilateral occlusion in our series is associated with a comparable event rate of 5.3%.

This study has some limitations. First, the study cohort consisted of patients from all over the Netherlands, who were referred to a single tertiary university hospital and therefore referral bias most probably plays a role. However, patients with frequent and ongoing symptoms will probably have been more readily referred than those with only one event and no further symptoms. In that case, the risk of recurrent stroke that we report would rather be overestimated than underestimated. Second, follow-up was performed by telephone interviews instead of regular hospital visits and events that had only a minor impact on the patient's abilities may have been missed. Third, all patients were advised about the control of vascular risk factors, but we did not obtain information on how well vascular risk factors were indeed controlled in individual patients. However, despite possible non-compliance with medication we found a relatively low risk of recurrent ischaemic stroke. Fourth, two patients were censored at the time of an EC/IC bypass operation that was advised because of ongoing TIAs. It is uncertain whether these patients might have had an ischaemic stroke if they had not been operated.

In conclusion, this study shows that patients with transient or moderately disabling cerebral or retinal ischaemic symptoms associated with bilateral ICA occlusion have a relatively low risk of recurrent ischaemic stroke and a risk of any major vascular event that is comparable to this risk in patients with TIA or stroke in general. Although this study was not designed to compare conservative treatment with surgical intervention, our observations suggest that a policy of medical therapy and control of risk factors may be justified in these patients.

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4

Limb-shaking transient ischaemic attacks in patients with internal carotid artery occlusion: a case-control study

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Abstract

Limb-shaking is a specific clinical feature of transient ischaemic attacks (TIAs) that has been associated with a high-grade stenosis or occlusion of the internal carotid artery (ICA). The aim of this study was to describe the clinical characteristics of limb-shaking in patients with ICA occlusion and to investigate whether patients with limb-shaking have a worse haemodynamic state of the brain than patients with ICA occlusion without limb-shaking. We included 34 patients (mean age 62 ± 7 years, 82% male) with limb-shaking associated with ICA occlusion and 68 sex- and age-matched controls with cerebral TIA or minor disabling ischaemic stroke associated with ICA occlusion, but without limb-shaking. We investigated clinical characteristics, collateral pathways on contrast angiograms and CO_2-reactivity measured by transcranial Doppler. The results showed that limb-shaking usually lasted less than 5 min and was often accompanied by paresis of the involved limb. Compared with controls, patients with limb-shaking more frequently had symptoms precipitated by rising or exercise (odds ratio [OR] 14.2, 95% CI 4.2 – 47.9), more frequently had recurrent ischaemic deficits after documented ICA occlusion (but before inclusion in the study) (OR 8.2, 95% CI 2.3 – 29.3), more often had leptomeningeal collaterals (OR 6.8, 95% CI 2.0 – 22.7), and tended to have a lower CO_2-reactivity (mean 5% ± 16 versus 12% ± 17; OR 0.97 per 1% increase in CO_2-reactivity, 95% CI 0.94 – 1.00). In conclusion, limb-shaking TIAs in patients with ICA occlusion can be recognized by their short duration, are often accompanied by paresis and precipitated by rising or exercise and are indicative of an impaired haemodynamic state of the brain.

Introduction

Several case reports have described limb-shaking as a rare clinical feature of transient ischaemic attacks (TIAs).[1-8] Limb-shaking has been characterized by brief, jerky, coarse, involuntary movements involving an arm or leg[9-10] and has been associated with high-grade stenosis or occlusion of the internal carotid artery (ICA). Small observational studies have shown impaired cerebral blood flow (CBF) or cerebrovascular reserve capacity in patients with limb-shaking and ICA stenosis or occlusion in comparison with normal controls.[1, 11-14] Whether patients with ICA stenosis or occlusion with limb-shaking have a worse flow state of the brain than patients with ICA stenosis or occlusion without limb-shaking is unknown. Since the large extracranial-intracranial (EC/IC) bypass trial showed no benefit of EC/IC bypass surgery for prevention of stroke in patients with an ICA occlusion,[15] several studies have suggested that EC/IC bypass surgery may be of benefit in a subgroup of patients with impaired cerebral perfusion.[16-17] In that perspective, it may be important to recognize limb-shaking on the basis of the history and to investigate whether this specific subtype of TIA is associated with haemodynamic impairment. The purpose of this study was to describe the clinical characteristics of limb-shaking in patients with TIA or moderately disabling stroke associated with an occlusion of the ICA and to investigate whether patients with limb-shaking have a worse haemodynamic state of the brain than patients with symptomatic ICA occlusion without limb-shaking.

Methods

Patients

Between 1995 and 2008 we collected data from 313 patients with TIA or minor ischaemic stroke with, at most, moderately disabling cerebral or retinal ischaemic symptoms (modified Rankin scale ≤ 3[18]) associated with ICA occlusion, who were referred to the Department of Neurology, University Medical Centre Utrecht, The Netherlands. All patients had been symptomatic in the six months prior to the time of referral. Data, including the presence of limb-shaking, had been collected prospectively by two vascular neurologists (L.J.K and C.J.M.K.). Limb-shaking was defined as brief, jerky, coarse, involuntary movements of an arm or leg or both.[10] All patients were specifically asked for these symptoms of limb-shaking, and if present they were interviewed in detail about the duration, frequency and location of the limb-shaking, the presence of weakness accompanying the limb-shaking, and for precipitating factors such as rising, exercise, coughing, a meal, hyperextension of the neck, transition from

a cold to warm environment or taking antihypertensive medication. In addition, we documented whether additional cerebral or retinal ischaemic symptoms (retinal infarction or transient monocular blindness) were present.

The protocol for the current study was prepared after collection of all data, but before the analysis was performed. For each patient with limb-shaking we randomly selected two controls, matched for sex and age, who had presented during the same period with cerebral TIA (lasting <24 h) or moderately disabling ischaemic stroke (modified Rankin scale ≤3) associated with ICA occlusion, but who had not reported limb-shaking. The ICA occlusion was demonstrated by the absence of filling of the ICA by contrast angiography, or in one patient by absence of flow in the ICA on magnetic resonance angiography (MRA). The degree of an additional stenosis in the contralateral ICA, ipsilateral external carotid artery (ECA) or vertebral artery (VA) was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[19] Patients with an ICA occlusion caused by a dissection or a radiation-vasculopathy were not included. In patients and controls, we investigated the presence of vascular risk factors as listed in *Table 2*. The mean arterial blood pressure was calculated by two times the diastolic pressure plus the systolic pressure divided by three, and expressed in mmHg. All patients underwent magnetic resonance imaging (MRI) or computed tomography (CT) of the brain to investigate the presence of a symptomatic infarct. Infarcts were considered symptomatic if the location corresponded with the patients' symptoms and were classified as territorial, watershed, large subcortical or lacunar (diameter <15 mm).[20]

Collateral blood flow

Patients had contrast angiography to confirm the ICA occlusion and to visualize the collateral blood flow patterns. Collateral blood flow pathways were studied for the symptomatic hemisphere. We considered collateral blood flow via the ophthalmic artery (OphthA) as present if selective catheterization of the common carotid artery (CCA) showed filling of intracranial arteries distal to the carotid siphon via the ECA. Collateral pathways via the anterior communicating artery (AComA) or the posterior communicating artery (PComA) were considered present if these collateral pathways showed filling of the anterior or middle cerebral artery (MCA) branches ipsilateral to the symptomatic ICA occlusion. Leptomeningeal collaterals were considered present if pial branches from the posterior cerebral artery (PCA) extending as far as the vascular territory of the MCA or anterior cerebral artery (ACA) (beyond the usual PCA territory) were visualized on the angiogram after selective catheterization of one of the vertebral arteries (*Figure 1*).[21]

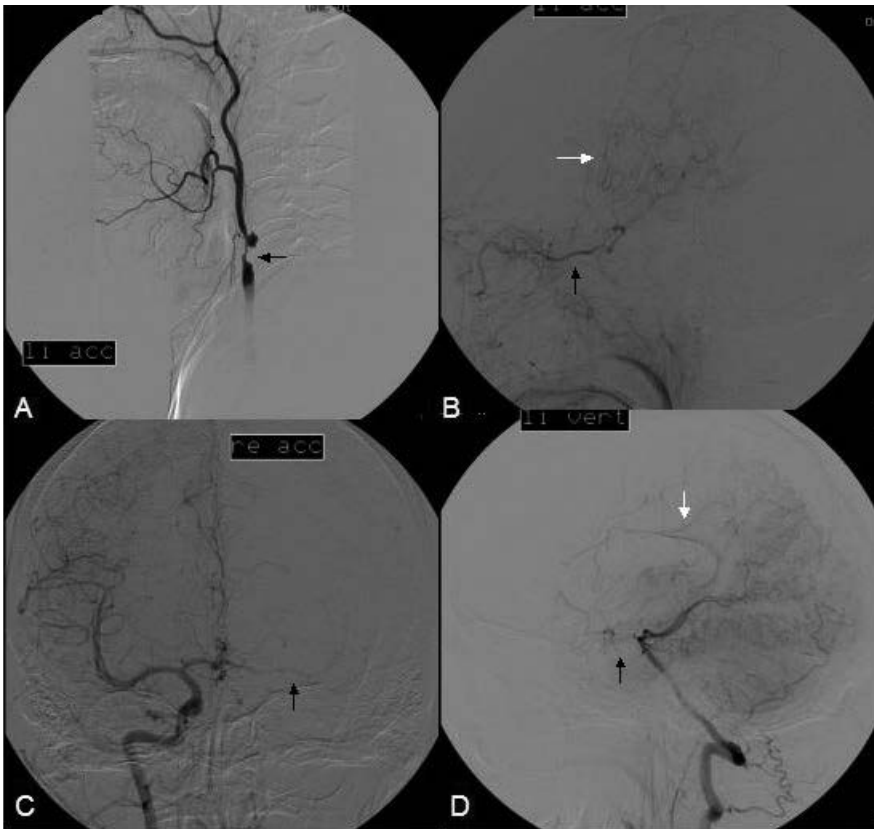

Figure 1. Angiogram of a 57 year-old patient with a left ICA occlusion and almost daily limb-shaking TIAs from the left hemisphere; (a) left ICA occlusion and severe stenosis of the ipsilateral common carotid artery (black arrow), (b) selective catheterization of the left common carotid artery shows filling of MCA branches (white arrow) via the ophthalmic artery (black arrow) in the left hemisphere; (c) selective catheterization of the right common carotid artery shows limited filling of MCA branches (black arrow) via the anterior communicating artery, (d) selective catheterization of the left vertebral artery shows filling of some MCA branches via the posterior communicating artery (black arrow) and filling of leptomeningeal collateral vessels (white arrow), originating from the posterior cerebral artery.

Transcranial Doppler (TCD) CO_2-reactivity

Transcranial Doppler (TCD) was performed with measurement of the CO_2-reactivity to investigate cerebrovascular reserve capacity. Details of this protocol have been described before.[22] The CO_2-reactivity after carbogene inhalation was the relative change in blood flow velocity in the MCA and expressed as a percentage. A CO_2-reactivity of <20% was considered abnormal, since this value corresponds with the mean CO_2-reactivity minus two times the standard deviation (SD) in normal controls.[23]

Data-analysis

We compared clinical characteristics, vascular risk factors, the presence and type of cerebral infarcts, the presence of a stenosis or occlusion in the contralateral ICA, ECA or vertebral arteries, collateral blood flow pathways, and CO_2-reactivity between patients with and without limb-shaking and expressed differences as odds ratios (ORs) with 95% confidence intervals (CIs). In a subgroup-analysis, patients with limb-shaking TIAs were compared with control patients with TIAs without limb-shaking (excluding control patients with ischaemic stroke). We used logistic regression analysis to study the effect of the time interval between the patient's last ischaemic symptoms and the CO_2-reactivity measurement on the association between limb-shaking TIAs and CO_2-reactivity and expressed this adjusted association as OR per 1% increase in CO_2-reactivity. Finally, we assessed the relationship between CO_2-reactivity and leptomeningeal collaterals by a multivariable regression model. The study was approved by the institutional review board of the University Medical Centre Utrecht.

Results

Of the 313 patients with symptomatic ICA occlusion, 34 (11%) reported limb-shaking. The characteristics of limb-shaking are shown in *Table 1*. The duration of limb-shaking was shorter than 5 min in the majority of patients. Most patients reported multiple episodes of limb-shaking. The arm was more frequently involved than the leg. In almost one-third of patients the arm and leg shook simultaneously. Most patients demonstrated shaking of their whole limb and not just the hand or foot. During or following limb-shaking, 28 (82%) of the 34 patients noticed a transient paresis of their arm or leg. In 14 (41%) patients limb-shaking occurred subsequent to precipitating factors such as rising, exercise or coughing (*Table 1*). *Table 2* shows the characteristics of the patients with limb-shaking and of controls. The presence of vascular risk factors was similar in patients with limb-shaking and controls, except for a history of hypertension that we found more often in patients with, than in those without, limb-shaking TIAs (OR 4.3, 95% CI 1.5 – 12.5). All patients with limb-shaking also reported symptoms other than limb-shaking; 27 (79%) patients had additional TIAs without limb-shaking (reported symptoms, isolated or combined, were paresis of a limb in 24, sensory symptoms in 12, dysphasia in six, and dysarthria in two patients), and seven (21%) patients had additional permanent deficit caused by a minor ischaemic stroke characterized by isolated or combined symptoms of paresis of a limb in six, sensory symptoms in one, and dysphasia in four patients. In the control-group, 22 (32%) patients had presented with

Table 1. Clinical characteristics of limb-shaking events among 34 patients with occlusion of the internal carotid artery

	Number of cases
Duration:	
<1 min	13
1–5 min	15
>5 min	3
unknown	3
Frequency of limb-shaking TIAs:	
1 episode	5
2–5 episodes in a month	18
>5 episodes in a month	11
Side of limb-shaking:	
right	21
left	13
Location:	
arm only	15
leg only	5
arm and leg together	9
sometimes arm only, sometimes leg only, sometimes together	5
Part of the arm:	
whole arm	25
lower arm and hand	2
hand only	2
Part of the leg:	
whole leg	19
only foot	0
Strength during or following limb-shaking:	
paresis	28
normal strength	2
unknown	4
Precipitating factors:[a]	*14*
rising	8
hyperextension neck	1
transition from cold to warm environment	1
exercise	5
meal	0
coughing	4
recent start of antihypertensive medication	1

[a] Precipitating factors were present in 14 patients. Four patients had two and one patient had three precipitating factors.

Table 2. Characteristics of patients with symptomatic ICA occlusion with (n=34) and without (n=68) limb-shaking, matched for age and sex

	Limb-shaking group *(n=34)*	Control group *(n=68)*
Mean age (years ± SD)	62 ± 7.6	62 ± 7.3
Male	28 (82%)	56 (82%)
Cigarette smoking in the last 5 years	29 (85%)	49 (72%)
Hypertension[a]	29 (85%)[b]	39 (57%)
Hyperlipidaemia[c]	30 (88%)	60 (88%)
Diabetes mellitus	6 (18%)	17 (25%)
History of ischaemic stroke (>6 months ago)	7 (21%)	11 (16%)
History of ischaemic heart disease	9 (27%)	19 (28%)
History of peripheral vascular disease	14 (41%)	23 (34%)
History of vascular disease in first-degree relative	26 (77%)	43 (63%)
Clinical features:		
Cerebral TIA without limb-shaking	27 (79%)[b]	22 (32%)
Ischaemic stroke	7 (21%)	46 (68%)
Additional retinal ischaemic symptoms	10 (29%)[b]	7 (10%)
Ischaemic symptoms after documented occlusion	31 (91%)[b]	38 (56%)
Precipitating factors[d]	16 (47%)[b]	4 (6%)
Mean arterial pressure (mmHg ± SD)	112 ± 15	116 ± 16
Infarcts:		
Symptomatic infarct[e]	16/33 (48%)[b]	54/68 (79%)
territorial	3 (19%)	19 (35%)
watershed, cortical	6 (38%)	19 (35%)
watershed, deep	0 (0%)	2 (4%)
large subcortical	3 (19%)	5 (9%)
lacunar	4 (25%)	9 (17%)
Cerebropetal arteries:		
Contralateral ICA occlusion	5/34 (15%)	12/68 (18%)
Contralateral ICA stenosis 50–99%	7/34 (21%)	27/68 (40%)
Stenosis ≥50% or occlusion of ipsilateral ECA	6/33 (18%)	8/67 (12%)
Stenosis ≥50% or occlusion of VA	15/27 (56%)[b]	15/63 (24%)

[a] Defined as a blood pressure >160/95 mmHg or the current use of antihypertensive medication. [b] Comparison of patients with and without limb-shaking, p <0.05. [c] Defined as patients with either a history of hyperlipidaemia, patients on drugs because of hyperlipidaemia or patients with levels of cholesterol, triglycerides, or high density lipoprotein cholesterol beyond the normal ranges. [d] In 14 patients the limb-shaking was precipitated by activities that may compromise cerebral perfusion, in two patients only additional TIAs without limb-shaking were precipitated by rising. In the control-group symptoms were precipitated by rising in two patients and by exercise in two patients. [e] 94 patients had an MRI scan of their brain, seven patients a CT-scan and in one patient a recent CT- or MRI scan could not be performed.

cerebral TIA and 46 (68%) patients with ischaemic stroke. Compared with controls, patients with limb-shaking more frequently presented with TIAs than with ischaemic stroke (OR 8.1, 95% CI 3.0 – 21.4), and more often had additional retinal ischaemic symptoms (OR 3.6, 95% CI 1.2 – 10.6). Precipitating factors

that may compromise cerebral perfusion, such as rising or exercise, were more often –but not always– present in patients with limb-shaking than in controls (OR 14.2, 95% CI 4.2 – 47.9). Patients with limb-shaking TIAs more frequently had recurrent ischaemic deficits after documented ICA occlusion (but before inclusion in the study) than control patients without limb-shaking (OR 8.2, 95% CI 2.3 – 29.3). Patients with limb-shaking less often had an infarct on their MRI or CT than controls (OR 0.2, 95% CI 0.1 – 0.6) and more often a stenosis or occlusion in one the vertebral arteries (OR 4.0, 95% CI 1.5 – 10.4). Patients with limb-shaking were seven times more often dependent on leptomeningeal collaterals than controls (OR 6.8, 95% CI 2.0 – 22.7, *Table 3*). We found a CO_2-reactivity <20% ipsilateral to the ICA occlusion in 24 (83%) patients with limb-shaking and in 43 (68%) patients without limb-shaking (OR 2.2, 95% CI 0.7 – 6.7). On average, CO_2-reactivity in patients with limb-shaking (mean 5% ± 16) tended to be lower than in those without limb-shaking (mean 12% ± 17; OR 0.97 per 1% increase in CO_2-reactivity, 95% CI 0.94 – 1.00). The median time interval between the most recent symptom and the CO_2-reactivity measurement was 18 (range 0–140) days in patients with limb-shaking and 57 (range 0–206) days in patients without limb-shaking. After adjustment of the OR for this time interval, the finding of a lower CO_2-reactivity in patients with limb-shaking TIAs lost significance in comparison with controls (adjusted OR 0.98 per 1% increase in CO_2-reactivity, 95% CI 0.95 – 1.01).

Table 3. Comparison of collateral blood flow pathways and TCD CO_2-reactivity between patients with ICA occlusion with (n=34) and without (n=68) limb-shaking

	Limb-shaking group *(n=34)*	Control group *(n=68)*	Odds ratio *(95% CI)*
Collateral flow via anterior communicating artery	18/28 (64%)	44/56 (79%)	0.5 (0.2 – 1.3)
Collateral flow via posterior communicating artery	21/24 (88%)	30/44 (68%)	3.3 (0.8 – 12.8)
Collateral flow via ophthalmic artery	20/30 (67%)	23/52 (44%)	2.5 (0.99 – 6.4)
Leptomeningeal vessels	21/25 (84%)	21/48 (44%)	6.8 (2.0 – 22.7)
CO_2-reactivity in %[a] (mean ± SD)	5 ± 16	12 ± 17	0.97 (0.94 – 1.00)[b]

[a] CO_2-reactivity on the symptomatic side could be measured in 29 patients with limb-shaking and in 63 patients without limb-shaking. In three patients TCD could not be performed and we had to exclude six patients because of an absent temporal bone window and one control patient with ischaemic stroke as an outlier with a CO_2-reactivity of 127%. [b] CO_2-reactivity is expressed as OR per 1% increase in CO_2-reactivity.

In the subgroup-analysis of patients with limb-shaking TIAs in comparison with control patients with TIAs without limb-shaking (excluding control patients with ischaemic stroke) leptomeningeal collaterals were more frequent in patients with limb-shaking (21 of 25, 84%) compared with patients without limb-shaking (6 of 16, 38%; OR 8.8, 95% CI 2.0 – 38.1). The mean CO_2-reactivity in patients with limb-shaking TIAs was significantly lower than the mean CO_2-reactivity in patients with TIAs without limb-shaking (5% ± 16 versus 17% ± 18; OR 0.96 per 1% increase in CO_2-reactivity, 95% CI 0.92 – 0.99). Also in this subgroup-analysis, the association between limb-shaking and a low CO_2-reactivity was dependent on the time interval (adjusted OR 0.96 per 1% increase in CO_2-reactivity, 95% CI 0.93 – 1.00). In a multivariable analysis including the factors leptomeningeal collaterals and CO_2-reactivity, the significant relationship between leptomeningeal collaterals and limb-shaking (OR 7.0, 95% CI 1.7 – 28.4) remained, as well as the trend for a lower CO_2-reactivity in patients with than in those without limb-shaking (OR 0.96 per 1% increase in CO_2-reactivity, 95% CI 0.92 – 1.00). This trend was no longer apparent after adjustment for the time interval between the last symptoms and TCD (adjusted OR 0.97 per 1% increase in CO_2-reactivity, 95% CI 0.92 – 1.01).

Discussion

This study shows that limb-shaking in patients with ICA occlusion usually lasts less than 5 min, is often accompanied by paresis of the involved limb and is often, but not necessarily precipitated by activities that may compromise cerebral perfusion such as rising, exercise or coughing. In comparison with patients with ICA occlusion without limb-shaking, patients with limb-shaking are about seven times more often dependent on leptomeningeal collaterals and tended to have a lower CO_2-reactivity. Compared with controls with TIAs without limb-shaking and no ischaemic stroke, the patients with limb-shaking TIAs had a significantly lower mean CO_2-reactivity. The time period between the last symptoms and the CO_2-reactivity measurement was shorter in patients with than in patients without limb-shaking, probably because patients with limb-shaking TIAs more frequently had recurrent ischaemic deficits after documentation of the ICA occlusion, which contributed to their relatively low CO_2-reactivity.

Compared with previous small case series of 5–12 patients,[10-11, 14] we were able to identify a relatively large group of patients with limb-shaking. We confirmed that limb-shaking TIAs occur in about 10% of patients with occlusion of the

ICA.[24] The underlying mechanism of limb-shaking is unclear, but most studies suggest that the shaking movements are caused by transient focal cerebral ischaemia.[1, 10-11, 13-14, 25] Limb-shaking TIAs may resemble epileptic seizures but can be distinguished by a normal level of consciousness, precipitation of symptoms by specific circumstances that may lower cerebral blood flow in patients with ICA occlusion, such as rising or exercise, the absence of tonic contractions or a march of symptoms, no involvement of the face or trunk, and no epileptic discharges on an EEG.[5, 11, 14] Various other hyperkinetic movements such as hemidystonia and hemichorea-hemiballism have also been described in relation to TIA or stroke,[25-28] but they are exceedingly rare with a prevalence of 1% in acute stroke.[26] In addition, those hyperkinetic movement disorders seem to be related to an ischaemic lesion in the basal ganglia or thalamic nuclei in the majority of patients[26, 28] whereas a specific location of cerebral ischaemia in patients with limb-shaking has not been found thus far.

Previous studies concluded that limb-shaking TIAs are likely to be caused by a low flow state of the brain and not by emboli, based on diminished vasomotor reactivity by TCD[3, 13-14] and cerebral blood flow by Xenon inhalation.[11, 13] However, of patients with ICA occlusion in general, 12% had an exhausted and 29% a diminished CO_2-reactivity when investigated by TCD.[29] Studies that included only symptomatic patients with an ICA occlusion found an impaired flow state of the brain in 48 to 79% of patients, irrespective of the presence of limb-shaking.[16, 30-31] In agreement with these studies, we found a diminished CO_2-reactivity in 68% of patients without limb-shaking. The patients with limb-shaking had a relatively lower CO_2-reactivity. When we restricted the analysis to patients with TIAs only, excluding patients who presented with ischaemic stroke, the lower CO_2-reactivity in patients with limb-shaking TIAs became even more prominent. This may be explained by the fact that in general, patients with ischaemic stroke associated with ICA occlusion more often have a low CO_2-reactivity than patients with TIAs.[31] Since most patients with limb-shaking TIAs had recurrent episodes of symptoms, their time interval between the last TIA and the TCD was shorter than for the patients without limb-shaking. In some patients CO_2-reactivity improves spontaneously over time,[29] and therefore we adjusted for the time interval between the last symptoms and TCD. This analysis showed that a short time period since the last TIA contributes to the relatively low CO_2-reactivity in patients with limb-shaking.

Another important finding was that patients with limb-shaking more often had leptomeningeal collaterals than patients with ICA occlusion without limb-shaking. Several previous studies have shown that leptomeningeal collaterals

were more often present in patients with a low cerebral blood flow[32] or impaired cerebrovascular reactivity[33-35] compared with patients without haemodynamic compromise, whereas one study of 17 patients with an increased oxygen extraction fraction (OEF) and 30 patients with a normal OEF found that the pattern of collaterals was not associated with an increased OEF.[36] However, in this study only two patients had pial leptomeningeal collaterals (retrograde filling of MCA branches to the level of the insula). Both of these two patients had an increased OEF. Another study showed that the presence of collateral flow by the ophthalmic artery or leptomeningeal vessels was significantly associated with an increased OEF, but that this relationship was confounded by the presence of cerebral infarcts.[37] Although the role of leptomeningeal collaterals in the flow state of the brain needs further investigation,[21, 38] we suggest that the finding of leptomeningeal collaterals in the majority of patients with limb-shaking supports the haemodynamic origin of limb-shaking TIAs. Because of the relationship between leptomeningeal collaterals and cerebrovascular reactivity,[33-35] we included both variables in a multivariable model and showed that the presence of leptomeningeal collaterals was independently associated with the presence of limb-shaking, and we still found a trend for a lower CO_2-reactivity in patients with limb-shaking.

Theoretically, patients with limb-shaking TIAs could benefit from treatment aimed at improving the cerebral perfusion. A few small case series described a decreased frequency or complete cessation of limb-shaking TIAs after EC/IC bypass or carotid endarterectomy.[10-11, 13-14] The preliminary results of the Japanese EC/IC Bypass Trial[39] showed a just significantly ($p = 0.046$) lower incidence of recurrent stroke in patients with symptomatic ICA or MCA stenosis or occlusion and haemodynamic compromise who underwent EC/IC bypass surgery in comparison with medically treated patients, but definite results have not yet been published in the English literature. The results of the Carotid Occlusion Surgery Study (COSS)[40] which investigates the beneficial effect of superficial temporal artery/MCA bypass surgery in patients with a symptomatic ICA occlusion and an increased OEF, are expected in 2014.

This study has some limitations. First, we do not have clinical follow-up data of all patients with symptomatic ICA occlusion. As a result, we could not determine the predictive value of the presence of limb-shaking for the risk of recurrent ischaemic stroke. Since limb-shaking is an uncommon feature that may be difficult to diagnose, reliable information on the long-term outcome of patients with limb-shaking is difficult to obtain. Second, we measured the haemodynamic state of the brain indirectly by TCD CO_2-reactivity, and measurement of the

haemodynamic state of the brain, including OEF, by means of oxygen-15 PET studies would have provided valuable additional information.[41] Third, we may have underestimated the presence of deep watershed ischaemic lesions as seven patients did not have an MRI but a CT instead. In addition, we only classified the symptomatic infarcts, whereas patients with ICA occlusion often have asymptomatic ischaemic lesions in the deep watershed area. Fourth, the current study inevitably had some element of retrospective ascertainment of the data, as it was not yet designed at the beginning of the prospectively collected series of patients with a symptomatic ICA occlusion. Fifth, we did not perform an inter-observer study with respect to the clinical diagnosis of limb-shaking. This might have influenced the frequency of limb-shaking in our series, although we strictly defined the criteria for this diagnosis before inclusion of patients. Finally, we did not perform EEG in all patients to confirm the absence of epileptic discharges at the time of limb-shaking.

In conclusion, we have further characterized the clinical features of limb-shaking TIAs that may improve their recognition by clinicians. Our results indicate that patients with an ICA occlusion and limb-shaking have a particularly impaired flow state of the brain compared with patients with ICA occlusion but without limb-shaking. Whether the presence of a simple clinical feature such as limb-shaking can be used to identify the patient who might benefit from a revascularization procedure remains to be determined.

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5

Comparison of oxygen-15 PET and transcranial Doppler CO_2-reactivity measurements in identifying haemodynamic compromise in patients with symptomatic occlusion of the internal carotid artery

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Abstract

Background

Transcranial Doppler (TCD) CO_2-reactivity and oxygen-15 positron emission tomography (PET) have both been used to measure the cerebral haemodynamic state in patients who may have a compromised blood flow. Our purpose was to investigate whether PET and TCD identify the same patients with an impaired flow state of the brain in patients with internal carotid artery (ICA) occlusion.

Methods

Patients with recent transient ischaemic attack (TIA) or minor ischaemic stroke associated with ICA occlusion underwent TCD with measurement of CO_2-reactivity and oxygen-15 PET within a median time interval of 6 days.

Results

We included 24 patients (mean age 64 ± 10). Seventeen patients (71%) had impaired CO_2-reactivity (≤20%), of whom six had absent reactivity (0%) or steal (<0%) in the hemisphere ipsilateral to the ICA occlusion. PET of the perfusion state of the hemisphere ipsilateral to the ICA occlusion demonstrated stage 1 (decreased cerebral blood flow [CBF] or increased cerebral blood volume [CBV] without increased oxygen extraction fraction [OEF]) in 13 patients and stage 2 (increased OEF) in two patients. In 12 patients (50%), there was agreement between TCD and PET, indicating haemodynamic compromise in ten and a normal flow state of the brain in two patients. There was no significant correlation between CO_2-reactivity and CBF ipsilateral/contralateral hemispheric ratio (r = 0.168, p-value 0.432), OEF ratio (r = –0.242, p-value 0.255), or CBV/CBF ratio (r = –0.368, p-value 0.077).

Conclusion

In patients with symptomatic ICA occlusion, identification of an impaired flow state of the brain by PET and TCD CO_2-reactivity shows concordance in only half of the patients.

Background

The risk of recurrent ischaemic stroke in patients who present with transient ischaemic attack (TIA) or ischaemic stroke, associated with an internal carotid artery (ICA) occlusion, may be as high as 12% per year in case of a demonstrated compromised flow to the brain.[1-3] Because of this increased risk, revascularization surgery has been considered in these patients. The Carotid Occlusion Surgery Study (COSS) used PET to select patients with symptomatic ICA occlusion and high oxygen extraction fraction (OEF) for inclusion in their study that aimed to investigate whether extracranial-intracranial (EC/IC) bypass surgery prevents recurrent stroke.[4] The results showed that the two-year risk of ipsilateral stroke did not differ between the surgical and non-surgical group (p=0.78) despite an improvement in OEF ratio and a bypass patency of 96% at the last follow up.[5] Other types of revascularization, such as carotid endarterectomy (CEA) of the contralateral ICA or of the ipsilateral external carotid artery, or surgery or stenting of the vertebral artery, for patients with symptomatic ICA occlusion may be considered as well, although firm evidence that these treatments reduce the risk of stroke is lacking.[1, 6-8]

The haemodynamic state of the brain can be subdivided into stage 0, the normal flow state of the brain; stage 1, the phase of vasodilatation to compensate for a decrease in blood flow towards the brain through cerebral autoregulation; and stage 2, the phase of autoregulation failure, with a compensatory rise in OEF.[9] Haemodynamic compromise stage 2 can only be demonstrated by positron emission tomography (PET) using oxygen-15-labelled tracers.[10] Previous oxygen-15 PET studies of patients with symptomatic ICA occlusion have shown a two-year risk between 25% and 75% of recurrent ischaemic stroke in those with an increased OEF in comparison with a risk between 5% and 10% in patients without an increased OEF.[2-3] A disadvantage of PET scans with O-15 tracers is that this technique is not widely available and has a failure rate between 20% and 40% for obtaining complete quantitative data, mostly due to technical difficulties.[2, 9, 11-12] A widely available and cheap alternative for identification of patients with haemodynamic compromise is transcranial Doppler (TCD) with measurement of cerebrovascular reactivity.[13-14] Although cerebrovascular reactivity cannot identify patients with haemodynamic stage 2, it allows distinction between normal and a compromised haemodynamic state. Little is known about the agreement between oxygen-15 PET and TCD CO_2-reactivity. If these two methods would identify the same patients as being at risk of future stroke, clinical trials may not need to be restricted to centres with PET facilities. The purpose of this study was to investigate whether, in

patients with recent TIA or stroke associated with ICA occlusion, oxygen-15 PET parameters and TCD CO_2-reactivity identify the same patients as having an impaired flow state of the brain.

Methods

Patients

We prospectively included 24 patients referred to the Department of Neurology, University Medical Centre Utrecht, the Netherlands, between December 2004 and September 2009. Patients were included if they had transient or, at most, moderately disabling (modified Rankin scale [mRS] ≤3[15]) neurological deficits associated with an ICA occlusion in the previous three months and complete oxygen-15 H_2O, O_2 and CO PET and TCD CO_2-reactivity studies. Contrast angiography was performed to confirm occlusion of the ICA and to study collateral pathways.[16] Patients were excluded if there was evidence of arterial dissection or radiation vasculopathy as cause of the occlusion of the ICA. Magnetic resonance imaging (MRI) of the brain was performed to investigate the presence of ischaemic lesions, and included a three dimensional (3D) T1 image needed for PET image analysis. Six patients were excluded because of incomplete PET data due to either failure to insert the arterial cannula (n=3) or technical difficulties (n=3). Two other patients were excluded because TCD measurement failed due to an absent temporal bone window. The institutional medical review board of the University Medical Centre Utrecht approved the study protocol. All patients provided written informed consent.

TCD CO_2-reactivity

CO_2-reactivity was measured by TCD using a Multi-Dop X device (DWL, Sipplingen, Germany) with two 2-MHz pulsed Doppler probes for insonation of cerebral vessels and a 4-MHz probe for the ophthalmic artery (OphthA), as described previously.[17] After a standard TCD to locate the cerebral vessels, CO_2-reactivity was measured simultaneously in both middle cerebral arteries (MCAs). Hypercapnia was induced by inhalation of a gas mixture containing 5% CO_2 and 95% O_2 (carbogene) through a mouthpiece connected to a respiratory balloon. A nose-clip ensured proper inhalation of carbogene. A spectral TCD recording of 5 s duration was acquired after breathing room air for 1 min and inhaling carbogene for 1.5 min. Readings of end-tidal CO_2 and blood pressure were taken just before carbogene inhalation and after 1.5 min. The average change in end-tidal pCO_2 was 12 mmHg (standard deviation (SD), 6 mmHg). CO_2-reactivity after carbogene inhalation was calculated as the relative

(percentage) change in blood flow velocity (BFV) in the MCA from the mean baseline BFV, expressed as a percentage. CO_2-reactivity ≤20% was considered as decreased as 20% corresponds with the mean CO_2-reactivity minus two SD in normal controls.[18] A CO_2-reactivity of 0% was defined as absent reactivity and <0% as steal of blood flow from the hemisphere ipsilateral to the ICA occlusion by other areas.

Positron emission tomography (PET) imaging

PET scans were acquired using an ECAT EXACT HR+ scanner (CTI/Siemens, Knoxville, Tennessee).[19] Each PET study consisted of three parts: (1) a dynamic emission scan (25 frames over 600 s) after intravenous administration of a bolus of 1,100 MBq [^{15}O]H_2O to measure CBF, (2) a dynamic emission scan (20 frames over 600 s) after a 30 s net inhalation of approximately 300 MBq [^{15}O] O_2 gas through a nasal cannula to derive oxygen consumption and calculate OEF, and (3) an emission scan (3 frames over 360 s) following a net inhalation of approximately 200 MBq [^{15}O]CO gas to measure cerebral blood volume (CBV). All emission scans were collected in 3D acquisition mode. To allow for radioactive decay, an additional five min period between scans was included, so that each administration was 15 min after the previous one. Finally, a ten min transmission scan was acquired for attenuation and scatter correction purposes of the emission scans. All scans were reconstructed using a standard FORE+2D filtered backprojection algorithm with a Hanning filter at Nyquist frequency. The arterial input function was measured continuously using an online blood sampling device.[20] In addition, at set times, manual samples were taken for calibration purposes and for assessment of plasma to whole blood ratios. Finally, the average arterial oxygen content was derived from blood gas analysis of three arterial samples. Further details of the scanning procedure can be found elsewhere.[12]

Image Analysis

Individual anatomical 3D T1 MR images were co-registered using summed [^{15}O]H_2O images. A standard template of flow territories of middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA)[21] was warped onto the co-registered MR image using Automated Image Registration software,[22] applying non-rigid 12 parameter perspective warping. Statistical Parametric Mapping (SPM02, London, UK, application in Matlab 7.0.4; MathWorks, Inc., Natick, MD, USA) was used for segmentation of grey and white matter. Areas of infarction were excluded manually. Parametric CBF, OEF and CBV images were generated using in-house developed software (written in IDL, 6.2, ITT, Boulder CO, USA).[23]

Data analysis

Normal CBF, OEF and CBV values were derived from 14 scans in seven healthy subjects (mean age 66 ± 7 years; five men), who underwent a PET scan on two separate occasions with a median time interval of seven days, as published previously.[12] Mean values of both scans for each healthy subject were used and the SD was calculated. CBF, OEF and CBV values in patients were considered to be abnormal if they were beyond mean values of normal controls ± 1.96 times the SD. Patients were divided into haemodynamic stages based on their values in grey matter of the MCA territory: patients with normal CBF (≥31.1 mL/min/100 mL), normal CBV (≤3.9 mL/100 mL), and normal OEF (≤55.7%) were classified as haemodynamic stage 0, patients with either decreased CBF or increased CBV (both signs of autoregulation), but normal OEF, as haemodynamic stage 1, and patients with increased OEF (>55.7%) as haemodynamic stage 2. In addition, CBV/CBF was calculated, as a measurement of mean transit time. Absolute CBF, OEF and CBV/CBF values in the MCA territory, together with their hemispheric ratios (ipsilateral/contralateral), were compared in patients with and without absent CO_2-reactivity or steal (CO_2-reactivity ≤0%) using the Student's t-test or, in case of non-parametric variables, the Mann-Whitney U-test. The same analysis was performed in patients with and without decreased CO_2-reactivity (CO_2-reactivity ≤20%). In addition, Pearson or, in case of non-parametric variables, Spearman correlation coefficients were calculated to assess relationships of CBF, OEF, and CBV/CBF with CO_2-reactivity.

Results

Clinical characteristics and angiogram findings of the 24 patients are shown in *Table 1*. The mean time between last symptoms and TCD was 33 ± 25 days. The median time between TCD and PET was six days (range 1–39). Seventeen patients had TCD before PET, and seven patients had TCD at most seven days after PET. Seventeen (71%) patients had impaired TCD CO_2-reactivity, of whom three had absent CO_2-reactivity and three showed a steal phenomenon. PET studies indicated that haemodynamic compromise was present in 15 (63%) patients, of whom 13 patients were classified as haemodynamic stage 1 (with decreased CBF in ten, increased CBV in three, and both decreased CBF and increased CBV in two patients) and two patients were classified as stage 2. As an example, *Figure 1* shows parametric images of a patient with stage 2 haemodynamic failure. In 12 (50%) of the 24 patients, TCD and PET showed

Table 1. Clinical characteristics of patients with a symptomatic ICA occlusion (n=24)

Characteristics	Number of patients (%)
Age (years, mean ± SD)	64 ± 10
Male	20 (83)
Clinical features at presentation:	
Cerebral TIA	17 (71)
Ischaemic stroke	7 (29)
Repeated symptoms after documented occlusion	22 (92)
Systolic blood pressure (mmHg, mean ± SD)	158 ± 28
Diastolic blood pressure (mmHg, mean ± SD)	86 ± 14
Vascular risk factors:	
Hypertension[a]	20 (83)
Hyperlipidaemia[b]	22 (92)
Diabetes mellitus	6 (25)
Cigarette smoking (current or in last 5 years)	13 (54)
History of stroke >3 months ago	7 (29)
History of ischaemic heart disease	8 (33)
MRI:	
Ischaemic lesions in MCA territory ipsilateral to ICA occlusion:	11 (45%)
endzone branche	3
large subcortical (>1.5 mm)	3
cortical borderzone	5
Angiogram:	
Bilateral ICA occlusion	1 (4)
Contralateral ICA stenosis ≥50%	9 (38)
Ipsilateral ECA stenosis ≥50%	6 (25)
Vertebral artery stenosis ≥50%	9 (38)
Collateral flow via anterior communicating artery	22 (92)
Collateral flow via ophthalmic artery	11 (46)
Collateral flow via posterior communicating artery[c]	20 (83)
Leptomeningeal collaterals[d]	17 (71)

[a] Hypertension was defined as blood pressure >160/95 mmHg or current use of antihypertensive medication. [b] Hyperlipidaemia was defined as either a history of hyperlipidaemia, current use on statins or levels of total cholesterol, triglycerids or high density lipoprotein cholesterol outside the normal ranges. [c] Presence of collateral flow via the posterior communicating artery could not be judged in one patient. [d] Presence of leptomeningeal collaterals could not be judged in one patient.

agreement in haemodynamic status. In ten of these 12 patients haemodynamic compromise was demonstrated by both TCD and PET. In two patients the flow state of the brain was normal on both TCD and PET. Of the 12 patients with different haemodynamic assessment on TCD and PET, seven patients with impaired CO_2-reactivity (–4%, 0%, 0%, 5%, 11%, 15%, and 19% respectively) had a normal haemodynamic state (stage 0) on PET. Of five patients with normal CO_2-reactivity, four were classified as stage 1 and one as stage 2 based

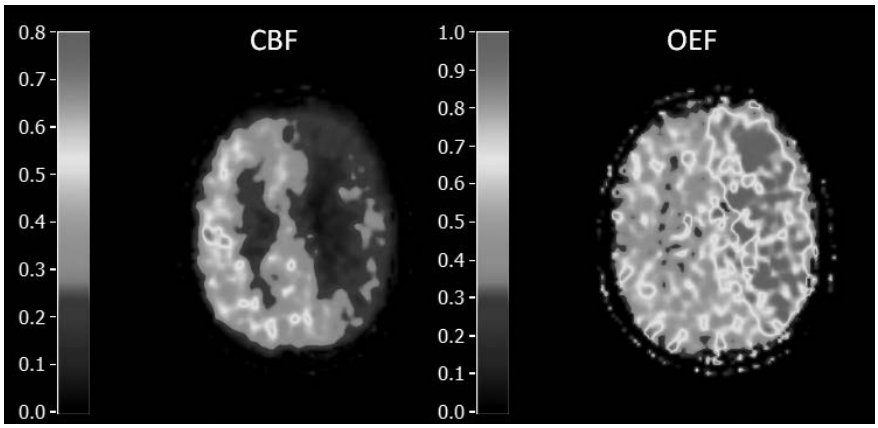

Figure 1. Parametric images of cerebral blood flow and oxygen extraction fraction.
Parametric images of cerebral blood flow (CBF) and oxygen extraction fraction (OEF) measured using PET in a 69-year-old man who presented with a minor ischaemic stroke in the left hemisphere with an occlusion of the left internal carotid artery. PET images show decreased CBF and increased OEF in the left hemisphere, indicating haemodynamic failure (stage 2). Using transcranial Doppler, CO_2-reactivity in the left middle cerebral artery was measured as –12%.

on PET findings. The other patient with stage 2 haemodynamic failure based on PET showed steal on CO_2-reactivity (–12%). In patients with agreement between PET and TCD, the median change in systolic blood pressure during TCD was 0 mmHg (interquartile range [IQR] 25), which did not differ from the median change in systolic blood pressure of 5 mmHg (IQR 10) in those without agreement (p=0.850). The median change in diastolic blood pressure in patients with agreement between PET and TCD (0 mmHg, IQR 5) did not differ from the median change in those without agreement (3.5 mmHg, IQR 10; p=0.257).

In *Table 2*, PET findings are compared between patients with and without impaired CO_2-reactivity, and between patients with and without absent reactivity or steal as measured by TCD. No significant differences were found in absolute CBF, OEF, and CBV/CBF values between patients with impaired and normal CO_2-reactivity, and between patients with and without absent CO_2-reactivity or steal. A prolonged mean transit time in the symptomatic hemisphere in relation to the asymptomatic hemisphere (CBV/CBF hemispheric ratio) was found to be associated with an impaired CVR (p= 0.035). *Figure 2* illustrates that on visual inspection ipsilateral/contralateral ratios of CBF, OEF, and CBV/CBF corresponded better with CO_2-reactivity than absolute ipsilateral values of CBF, OEF, and CBV/CBF. Nevertheless, there was no significant correlation between CO_2-reactivity and CBF hemispheric ratio (Pearson r = 0.168, p-value 0.432), OEF hemispheric ratio (Spearman r = –0.242, p-value 0.255), and CBV/

Table 2. Comparison of absolute ipsilateral PET values and hemispheric ratios with TCD CO_2-reactivity

	All patients	Impaired CVR (≤20%)	Normal CVR (>20%)	p-value	Absent CVR or steal (≤0%)	No absent CVR or steal (>0%)	p-value	Test
	n=24	*n=17*	*n=7*		*n=6*	*n=18*		
CO_2-reactivity (%), mean ± SD	15.5 ± 15.9	7.0 ± 8.7	36.0 ± 9.0		−2.7 ± 4.8	21.6 ± 13.5		
CBF (mL/min/100mL), mean ± SD	31.9 ± 5.6	32.3 ± 6.0	30.9 ± 4.8	0.572	30.8 ± 5.0	32.3 ± 5.9	0.598	t
CBF ratio, mean ± SD	0.88 ± 0.09	0.87 ± 0.08	0.90 ± 0.12	0.461	0.84 ± 0.09	0.89 ± 0.09	0.178	t
OEF (%), median (IQR)	45.1 (42.2 – 50.9)	45.0 (42.5 – 50.1)	47.8 (40.2 – 55.2)	0.634	47.6 (42.1 – 58.4)	45.0 (41.5 – 50.8)	0.424	U
OEF ratio, median (IQR)	1.06 (1.00 – 1.11)	1.06 (1.01 – 1.11)	1.08 (0.97 – 1.12)	0.949	1.09 (1.04 – 1.26)	1.05 (0.99 – 1.10)	0.116	U
CBV/CBF, mean ± SD	0.10 ± 0.03	0.10 ± 0.03	0.11 ± 0.03	0.563	0.09 ± 0.04	0.10 ± 0.02	0.266	t
CBV/CBF ratio, mean ± SD	1.27 ± 0.18	1.32 ± 0.15	1.15 ± 0.21	0.035	1.36 ± 0.15	1.24 ± 0.18	0.174	t

Comparison between patients with or without impaired TCD CO_2-reactivity and between patients with or without absent or steal CO_2-reactivity.
CBF, cerebral blood flow; CBV, cerebral blood volume; CVR, cerebrovascular reactivity; IQR, interquartile range; OEF, oxygen extraction fraction; t, Student's t test; U, Mann–Whitney test.

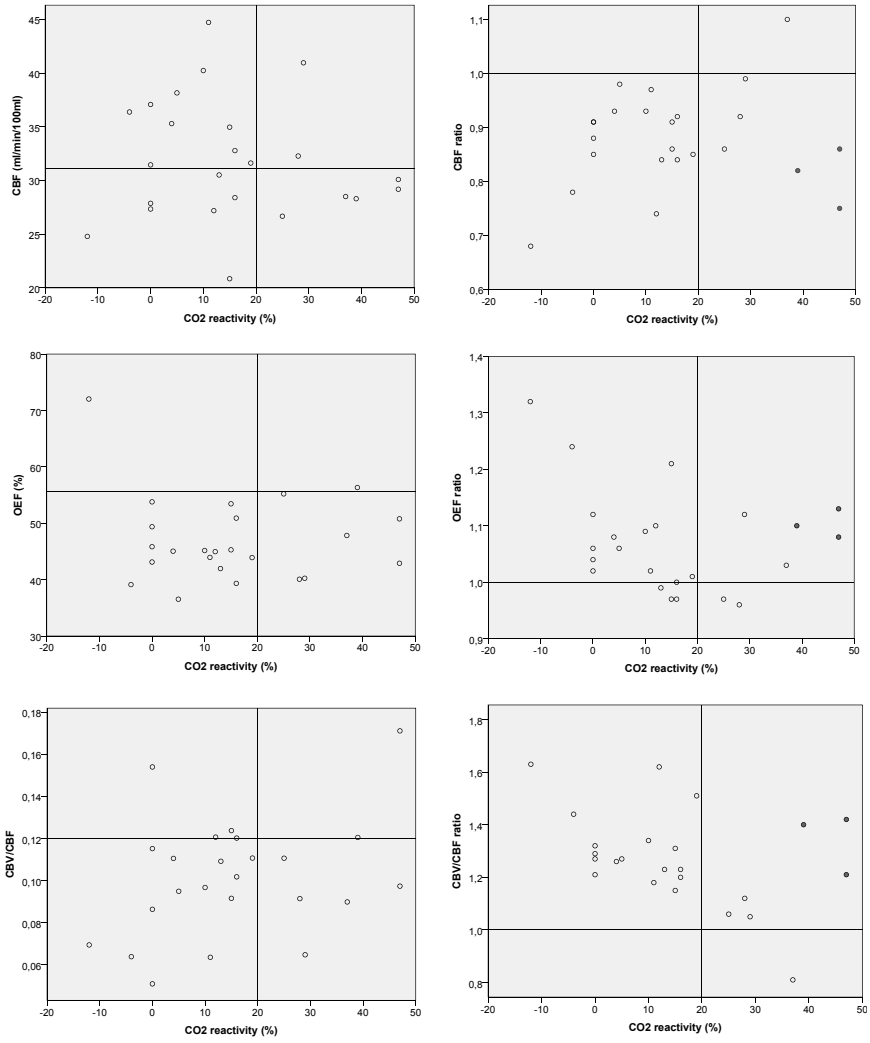

Figure 2. Relationship of CO_2-reactivity with PET values.
Scatter plots showing the relationships of CO_2-reactivity with cerebral blood flow (CBF) (upper panel), oxygen extraction fraction (OEF) (middle panel), and CBV/CBF (lower panel). Within each panel, absolute values are shown on the left and ipsilateral/contralateral ratios on the right. The grey dots in the panels on the right indicate the three outliers.

CBF hemispheric ratio (Pearson r = –0.368, p-value 0.077). Remarkably, three patients with high CO_2-reactivity (indicated with grey dots in *Figure 2*) were the main reason for the poor correlations. Two of them were males aged 45 and 73 years, and the female patient was 76 years old. The number of days between TCD and PET was at most seven days in these three patients. Only in one of

the three patients blood pressure during TCD increased with 50 mmHg systolic and 20 mmHg diastolic, in the other two the systolic blood pressure remained stable or decreased with 15 mmHg and the diastolic blood pressure remained stable. After excluding these three patients in a posthoc-analysis, significant correlations were obtained between CO_2-reactivity and CBF ratio (Pearson r = 0.563, p-value 0.008), OEF ratio (Spearman r = –0.542, p-value 0.011), and CBV/CBF ratio (Pearson r = –0.677, p-value 0.001).

Discussion

The main finding of this study is that, in patients with symptomatic ICA occlusion, identification of the presence or absence of haemodynamic compromise by oxygen-15 PET and TCD CO_2-reactivity corresponds in only half of patients. This is important as the presence of haemodynamic compromise has been shown to predict recurrent stroke[1-3] and may play a role in the decision whether or not to advise revascularization surgery. We did not find a difference in change in blood pressure during TCD between patients with and without agreement between PET and TCD. Therefore, it is unlikely that an increase in blood pressure during TCD resulting in an overestimated CO_2-response is responsible for the incongruent findings between PET and TCD. After excluding three patients with high CO_2-reactivity, a correlation with the various ipsilateral/contralateral PET ratios was found, albeit only at a moderate level. It is not clear why these three patients were outliers, as age or time between TCD and PET were not different from the other patients.

Previous studies investigating the relationship between cerebrovascular reactivity and CBF or OEF measured by PET included also patients with other types of vascular obstruction than ICA occlusion and reported conflicting results (*Table 3*). Only one previous study made the same comparison as we did between TCD CO_2-reactivity with oxygen-15 PET, but they selected 22 patients with hypertension and diabetes. In concordance with our findings, this study did not find an association between increased OEF and decreased TCD CO_2-reactivity.[24] Other studies have reported an association between impaired cerebrovascular reactivity to hypercapnia or acetazolamide measured with SPECT or stable-xenon CT studies and increased PET OEF.[25-29]

The results of the present study indicate that, in patients with recently symptomatic ICA occlusion, TCD measurements of the haemodynamic state of the brain cannot be replaced by oxygen-15 PET and vice versa for identification

Table 3. Overview of studies comparing cerebrovascular reactivity with CBF or OEF

Author	Method 1	Method 2	Sample (n)	ICA occl.	Sympt.	Agreement between methods
Fujimoto et al, 2002 [29]	IMP-SPECT + ACZ	^{15}O-PET	53	18	47	Haemodynamic compromise in 75% by method 1, 32% by method 2 (increased OEF, stage 2), and 64% by method 2 (stage 1) Correlation CVR (asymmetry index) with CBF/CBV r= 0.31 (p <0.05) Correlation CVR with OEF r= –0.64 (p <0.0001)
Herold et al, 1988 [25]	Xenon-SPECT + CO_2	^{15}O-PET	21	19	7	Haemodynamic compromise in 29% by method 1, 19% by method 2 (increased OEF) Correlation CVR with CBF/CBV r= 0.575 (p <0.01) Correlation CVR with oxygen extraction ratio r= –0.573 (p <0.01)
Imaizumi et al, 2002 [28]	IMP-SPECT + ACZ	^{15}O-PET	27	9	22	No data on number of patients with haemodynamic compromise Correlation CVR with CBV r= –0.31 (p< 0.01) Correlation CVR with OEF r= –0.55 (p< 0.0001)
Nariai et al, 1995 [26]	Xenon CT + ACZ	^{15}O-PET	11	4	10	No data on number of patients with haemodynamic compromise Correlation CVR with CBV r= –0.50 (p= 0.02) Correlation CVR with OEF r= –0.65 (p= 0.001)
Nemoto et al, 2004 [27]	Xenon CT + ACZ	^{15}O-PET	12	12	12	Haemodynamic compromise in 50% by method 1, 17% by method 2 (increased OEF) Correlation CVR with OEF r= –0.57 (p= 0.001)
Sugimori et al, 1995 [24]	TCD + CO_2	^{15}O-PET	22	2	7	Haemodynamic compromise in 52% by method 1, 9% by method 2 (increased OEF) Correlation CVR with CBF r= 0.47 (p < 0.05) Correlation CVR with OEF r= 0.20 (ns)

TCD, transcranial Doppler; CO_2, carbondioxide; ACZ, acetazolamide; CT, computed tomography; PET, positron emission tomography; CVR, cerebrovascular reactivity; CBF, cerebral blood flow; OEF, oxygen extraction fraction; CBV, cerebral blood volume.

of patients with haemodynamic compromise. This may be explained by important differences between TCD and oxygen-15 PET. First, TCD measures blood flow velocity in the MCA itself, whereas PET measures perfusion at the level of the brain tissue. The method of TCD relies on the assumption that changes in flow velocity are directly proportional to changes in CBF. For that to be true, the cross-sectional area of the insonated artery needs to remain constant.[30-31] In contrast, PET directly measures CBF, CBV and OEF, which are components of the autoregulation itself. In addition, TCD measures changes in flow velocity in response to hypercapnia, whereas PET, according to the scan protocol in this study, measures haemodynamic parameters at rest, i.e. without vasodilatory stimuli. Of the previous studies that compared the CBF response after a vasodilatory stimulus measured by SPECT or stable-xenon CT with TCD reactivity,[32-35] one study of 38 patients with ICA stenosis or occlusion found only a weak relation,[32] and others reported moderate to good correlations between CBF response after a challenge and TCD cerebrovascular reactivity.[33-35] It is possible that the agreement between TCD and PET in our study would have been better if a vasodilatory stimulus had also been included in the PET studies. An advantage of PET is that it does not only provide information on perfusion in the MCA territory but also on the flow state of the other vascular territories of the brain. TCD and PET do not only measure different physiologic parameters, but also use quite different techniques. As a gold standard for measuring the flow state of the brain is not yet available, the sensitivity and specificity of TCD and PET cannot be determined.[1, 10]

A strength of the present study in comparison with previous reports is that a more homogenous population of patients was included as all had recent symptoms of the hemisphere ipsilateral to an ICA occlusion. In addition, 92% of patients had ischaemic symptoms after documented occlusion, which is an important clinical risk factor for recurrent ischaemic stroke.[36] Furthermore, in contrast to some previous studies,[24-25] the majority of patients in our cohort showed haemodynamic compromise measured by TCD or PET. It is in this subcategory of patients that accurate identification of haemodynamic compromise has implications for prognosis and possible treatment decisions. This study has some limitations. First, the patients were not investigated by TCD and ^{15}O-PET on the same day. Compromised cerebral perfusion can improve over time.[37] Although the majority of patients (88%) had TCD and PET within two weeks, the time interval between TCD and PET may have contributed to the poor agreement. Second, the classification in haemodynamic stages may be a matter of debate. In the model of Derdeyn et al.[9] stage 1 was defined as a slight decrease of CBF and slight increase of OEF, with or without increase of CBV, but a cut-off value for a

slight difference was not provided. In another clinical PET study the patients were only divided into two groups with a normal or increased OEF.[3] We defined stage 1 as a decreased CBF or increased CBV, as both are signs of autoregulation. This study shows that both the comparison of haemodynamic stages by PET and TCD, as well as absolute values obtained by PET and TCD did not show agreement. Third, ten patients had an additional stenosis or occlusion in the contralateral ICA, which may have influenced the results in hemispheric ratios. Fourth, this study has a relatively small sample size. However, previous PET studies in relation to cerebrovascular reactivity were even smaller consisting of at most 19 patients with ICA occlusion.[25]

Conclusions

The present study shows that, in patients with symptomatic ICA occlusion, identification of presence or absence of haemodynamic compromise by oxygen-15 PET and TCD CO_2-reactivity corresponds in only half of patients. In future trials, PET and TCD CO_2-reactivity measurements cannot be used according to local preference to identify patients with haemodynamic compromise for study inclusion.

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6

Intervention versus standard medical treatment in patients with symptomatic occlusion of the internal carotid artery: a pilot study

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Submitted

Abstract

Background
Patients with symptomatic internal carotid artery (ICA) occlusion generally receive treatment by antithrombotic medication and control of vascular risk factors. Interventions like tapering antihypertensive medication or a revascularization procedure for stenosis of arteries that are important for collateral blood supply may be considered.

Objective
To investigate haemodynamic effects of interventional treatment consisting of either endarterectomy or endovascular treatment of stenosed cerebropetal arteries, or tapering of antihypertensive medication in comparison with standard medical treatment alone.

Methods
Twenty-three patients with symptomatic ICA occlusion underwent oxygen-15 positron emission tomography (PET) scanning at baseline and after three months. Twelve patients were randomized to intervention and 11 to standard medical treatment alone. Primary outcome was a change in cerebral blood flow (CBF), cerebral blood volume (CBV) and/or oxygen extraction fraction (OEF) after three months measured by PET. Normal values were derived from 14 scans of 7 healthy subjects.

Results
CBF in the middle cerebral artery territory ipsilateral to the ICA occlusion was lower in patients than in healthy controls (mean difference –5.2 mL/min/100mL, 95% CI –9.8 to –0.6). There were no differences in changes in CBF, CBV or OEF between the two groups. Only patients with compromised perfusion at presentation, showed a borderline significant increase in CBF of 2.8 mL/min/100mL (95% CI 0.0 to 5.7) after intervention (n=7).

Conclusion
This pilot study shows that in patients with symptomatic ICA occlusion, oxygen-15 PET did not detect differences in improvement of CBF, CBV or OEF between interventional and standard treatment.

Introduction

Patients with transient ischaemic attack (TIA) or ischaemic stroke associated with an occlusion of the internal carotid artery (ICA) have a risk of recurrent ischaemic stroke of around 12% per year when cerebral blood flow (CBF) is compromised.[1-3] Treatment consists of antithrombotic medication and control of vascular risk factors. Therapeutic strategies in patients with a symptomatic ICA occlusion aiming to improve cerebral perfusion could be endarterectomy or endovascular treatment of a significant stenosis in one of the cerebropetal arteries that may serve as a collateral pathway,[1,4-8] or tapering of antihypertensive medication.[9-10] Whether application of these therapeutic strategies improves flow to the brain as compared with standard medical treatment is unclear. Another type of treatment, extracranial/intracranial (EC/IC) bypass, has been studied recently by the Carotid Occlusion Surgery Study (COSS) in patients with symptomatic ICA occlusion and poor cerebral haemodynamics demonstrated by increased oxygen extraction fraction (OEF), measured by positron emission tomography (PET).[3, 11-12] This trial was stopped prematurely as the two-year risk of ipsilateral stroke was between 20 and 25% in both surgical and non-surgical groups (p= 0.78).[3] In the present study, oxygen-15 PET was used to investigate haemodynamic effects of endarterectomy or endovascular treatment of stenosed cerebropetal arteries, or tapering of antihypertensive medication in comparison with standard medical treatment alone in patients with a symptomatic ICA occlusion.

Materials and methods

Patients

Between December 2004 and September 2009, patients who had been referred to the University Medical Centre Utrecht with a symptomatic ICA occlusion were considered for participation in this randomized pilot study. Inclusion criteria were: (1) transient or at most moderately disabling (modified Rankin scale ≤ 3[13]) neurological deficits associated with ischaemia in the hemisphere ipsilateral to the ICA occlusion, (2) ICA occlusion proven by angiography, (3) symptoms present within the previous three months. Exclusion criteria were: (1) ICA occlusion caused by arterial dissection or radiation vasculopathy, (2) contra-indications for magnetic resonance imaging (MRI) (claustrophobia or metal objects in the body) or PET (pregnancy, blood donation in the previous three months or hemoglobin concentration <8.0 mmol/L), and (3) absence of any of the conditions that could be treated according to the therapeutic

strategy (see below). All patients were interviewed about their symptoms and risk factors as listed in *Table 1*, and underwent neurological examination, measurement of blood pressure and blood tests for glucose and lipids. Contrast angiography was performed in all patients to confirm occlusion of the ICA by absence of filling of the extracranial ICA, to assess collateral blood supply to the symptomatic hemisphere, and the presence of stenosis in the cerebropetal arteries.[14]

Patients were randomized between any intervention according to therapeutic

Table 1. Clinical characteristics and angiographic findings of patients with symptomatic occlusion of the internal carotid artery (n=23)

	Intervention *n=12*	Standard *n=11*
Age (years, mean ± SD)	68 ± 10	60 ± 12
Male	12	7
Clinical features at presentation:		
cerebral TIA	9	8
ischaemic stroke	3	3
Systolic blood pressure (mmHg, mean ± SD)	159 ± 25	167 ± 29
Diastolic blood pressure (mmHg, mean ± SD)	84 ± 15	91 ± 13
Vascular risk factors:		
Hypertension[a]	10	10
Hyperlipidaemia[b]	10	10
Diabetes Mellitus	2	3
Cigarette smoking (current or in last 5 years)	7	7
History of stroke >3 months ago	3	4
History of ischaemic heart disease	2	6
Angiogram:		
Contralateral ICA		
stenosis 50–69%	5	2
stenosis 70–99%	1	2
occlusion	0	1
Ipsilateral ECA stenosis ≥50%	4	1
Vertebral artery stenosis ≥50%	5	5
Collateral flow via anterior communicating artery	12	10
Collateral flow via ophthalmic artery	5	5
Collateral flow via posterior communicating artery	9[c]	11
Leptomeningeal collaterals	7[d]	9

[a] Blood pressure > 160/95 mmHg or the current use of antihypertensive medication. [b] Patients with either a history of hyperlipidaemia, patients on statins or patients with levels of total cholesterol, triglycerids or high density lipoprotein cholesterol outside normal ranges. [c] The presence of collateral flow via the posterior communicating artery could not be judged in one patient. [d] The presence of leptomeningeal collaterals could not be judged in two patients.

strategy or standard treatment. The therapeutic strategy could consist of, in order of preference, one of the following treatment options: (1) endarterectomy (CEA) of the contralateral ICA in case of a severe contralateral ICA stenosis in the presence of a functional anterior circle of Willis, (2) endarterectomy (CEA) of the external carotid artery (ECA) in case of a severe ipsilateral ECA stenosis in the presence of collateral blood supply via the ECA and ophthalmic artery, (3) endovascular treatment of the vertebral artery (VA) or subclavian artery in case of a severely stenosed VA or subclavian artery in the presence of collaterals via the vertebrobasilar system, and (4) tapering of antihypertensive medication for three months. In addition to the intervention, patients received standard medical treatment consisting of antithrombotic medication (aspirin and dipyridamole), a statin, treatment of hypertension to a targeted blood pressure of 140/90 mmHg (except for those randomized to tapering of antihypertensive drugs) and control of other vascular risk factors such as smoking and obesity. Patients who were assigned to standard treatment only, received the standard medical treatment mentioned above. To ensure equal distribution of patients with a low CBF in both groups,[15] randomization was carried out by minimization for CBF in three categories (CBF ≤33 mL/100g/min, CBF between 34–53 mL/100g/min or CBF ≥54 mL/100g/min), measured in the MCA-territory of the symptomatic hemisphere by arterial spin labelling (ASL)-MRI.[16] The ASL-MRI scan was made within one to 15 days of the baseline PET study, and included a 3D T1 image for PET image analysis. Patients were examined by oxygen-15 PET at the time of inclusion and three months thereafter. Randomization occurred as soon as the ASL-MRI scan was analyzed. After randomization, tapering of antihypertensive medication started immediately and endarterectomy or endovascular treatment was planned as soon as possible. Primary outcome was a change in CBF, CBV and/or OEF as measured by PET after three months. During those three months, we documented whether patients had recurrent TIA or stroke, defined as an acute onset of transient (<24 hours) or permanent new focal neurological deficits of cerebral origin without haemorrhage on CT or MRI. The institutional medical review board approved the study protocol, and all patients provided written informed consent.

PET data acquisition

Oxygen-15 PET scans were acquired using an ECAT EXACT HR+ scanner (CTI/Siemens, Knoxville, TN, USA).[17] Each PET study consisted of three parts: (1) a dynamic emission scan (25 frames over 600 s) after intravenous administration of a bolus of 1100 MBq [^{15}O]H_2O to measure CBF; (2) a dynamic emission scan (20 frames over 600 s) after a 30 s net inhalation of approximately 300 MBq [^{15}O]O_2 gas through a nasal cannula to derive oxygen consumption and calculate

OEF; (3) an emission scan (3 frames over 360 s) following a net inhalation of approximately 200 MBq [^{15}O]CO gas to measure CBV. All emission scans were collected in 3D acquisition mode. To allow for radioactive decay, an additional five min period between scans was included, so that each administration was 15 min after the previous one. Finally, a ten min transmission scan was acquired for attenuation and scatter correction purposes of the emission scans. All scans were reconstructed using a standard FORE+2D filtered backprojection algorithm with a Hanning filter at Nyquist frequency. The arterial input function was measured continuously using an online blood sampling device.[18] In addition, at set times, manual samples were taken for calibration purposes and for assessment of plasma to whole blood ratios. Finally, the average arterial oxygen content was derived from blood gas analysis of three arterial samples. Further details of the scanning procedure can be found elsewhere.[19]

Image Analysis

Individual anatomical 3D T1 MR images were co-registered with summed [^{15}O]H_2O images. A standard template of flow territories of middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA)[20] was warped onto the co-registered MR image using Automated Image Registration software,[21] applying non-rigid 12 parameter perspective warping. Statistical Parametric Mapping (SPM02, London, UK, application in Matlab 7.0.4; MathWorks, Inc., Natick, MD, USA) was used for segmentation of gray and white matter. Areas of infarction were excluded manually. Parametric CBF, CBV, and OEF images were generated using in-house developed software (written in IDL, 6.2, ITT, Boulder CO, USA).[22]

Data Analysis

Normal CBF, CBV, and OEF values were derived from 14 scans in seven healthy subjects (mean age 66 ± 7 years; five men), who underwent a PET scan on two separate occasions with a median time interval of seven days, as published previously.[19] Mean values of both scans for each healthy subject were used and the standard deviation (SD) was calculated. The test-retest variability of oxygen-15 PET was found to be good.[19] CBF, CBV, and OEF values in patients were considered to be abnormal if they were beyond mean values of normal controls ± 1.96 times the SD. Patients were divided into haemodynamic stages based on their values in grey matter of the affected MCA territory: patients with normal CBF (≥31.1 mL/min/100mL), normal CBV (≤3.9 mL/100mL) and normal OEF (≤55.7%) were classified in haemodynamic stage 0, patients with either decreased CBF (<31.1 mL/min/100mL) or increased CBV (>3.9 mL/100 mL), but normal OEF in haemodynamic stage 1, and patients with increased

OEF (>55.7%) in haemodynamic stage 2. Mean CBF in the MCA territory of patients was compared with data in healthy subjects, acquired using the same scanning procedure,[19] and expressed as a mean difference with 95% confidence intervals (CI). In the patients, differences between mean baseline grey matter CBF, CBV, and OEF values in ACA and MCA territories of patients at baseline and after three months were assessed by paired *t*-tests with 95% CI. Mean absolute change, adjusted for age and sex, in CBF, CBV, and OEF was compared between patients assigned to intervention and those who received standard treatment using linear regression analysis, and results were expressed as adjusted mean differences in change. Finally, pre-specified subgroup-analyses were performed in patients with haemodynamic stage 1 or 2 at presentation and between patients who were randomized to treatment with surgery or stenting of a stenosis in a collateral artery (excluding those who had tapering of antihypertensive medication) and those who received standard medical treatment.

Results

Complete PET data sets were obtained for 23 patients (mean age 64 ± 11 years; 19 men). Of 41 eligible patients, 14 failed to complete the initial PET study and were excluded and four others did not complete the PET study after three months. Reasons for PET failures are shown in *Figure 1*. Baseline characteristics of included and excluded patients did not differ. Twelve patients were assigned to intervention (eight stenting or surgery and four tapering of antihypertensive medication) and 11 to standard treatment. Clinical characteristics and presence of stenosis in cerebropetal arteries and collateral pathways are shown in *Table 1*. Twenty-two patients had recurrent ischaemic symptoms from the ipsilateral hemisphere after the ICA occlusion had been demonstrated, but before inclusion in the study. The time between last symptoms and first PET scan was on average 38 ± 23 days in both treatment groups. At baseline, ten patients were characterized as haemodynamic stage 0, 11 as stage 1 and two as stage 2. *Figure 2* shows parametric images of a typical patient with stage 2 haemodynamic failure. Patients with a symptomatic ICA occlusion had a mean CBF in the ipsilateral MCA territory of 32.2 ± 5.6, which was significantly lower (mean difference –5.2 mL/min/100mL, 95% CI –9.8 to –0.6) than that in healthy subjects (mean CBF MCA territory of 37.4 ± 3.2).[19] The mean time between PET scans at baseline and follow-up was 98 ± 10 (range 77–119) days. All patients were treated according to their randomization. Randomization occurred on average 5 ± 9 days after the baseline PET scan. Of the 12 patients assigned to

intervention (*Figure 1*), eight patients underwent stenting or surgery after a mean time of 15 ± 10 (range 1–29) days following the baseline PET scan. In four patients antihypertensive medication was tapered, which resulted in a mean increase in systolic blood pressure of 38 ± 9 mmHg. Intervention was complicated by a non-fatal myocardial infarction in one patient who underwent CEA of a contralateral ICA stenosis.

Table 2 shows that mean values of CBF, CBV, and OEF were similar at baseline and after three months, both in patients treated with intervention and in

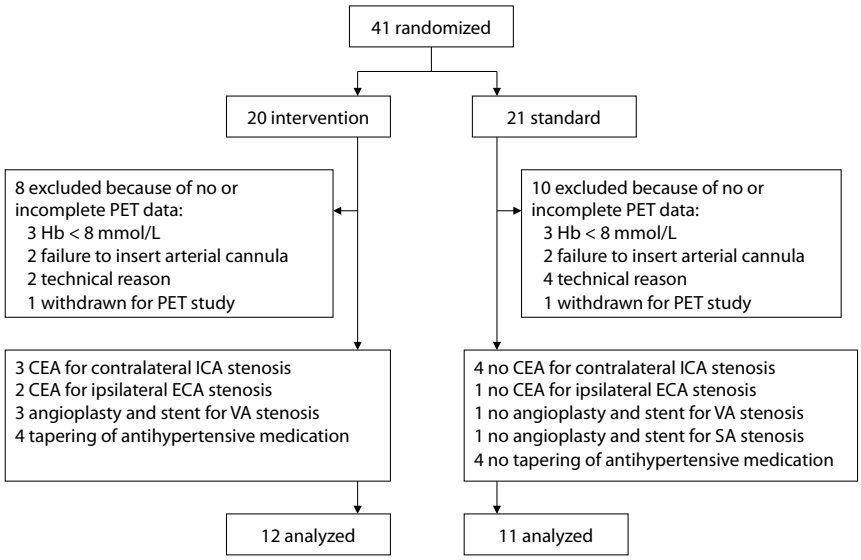

Figure 1. Trial profile. CEA, carotid endarterectomy; ICA, internal carotid artery; ECA, external carotid artery; VA, vertebral artery; SA, subclavian artery.

those assigned to standard treatment. However, CBF (*Figure 3*) changes were highly variable in individual patients. No differences in absolute CBF, CBV, and OEF changes after three months were observed between patients assigned to intervention and those assigned to standard treatment (*Table 2*). When adjusting mean differences in CBF, CBV and OEF between treatment groups for potential confounding effects of systolic and diastolic blood pressure, history of ischaemic heart disease, severity of contralateral ICA stenosis and ipsilateral ECA stenosis >50%, results remained essentially the same.

Table 3 shows a pre-defined subgroup analysis that compared the effect of treatment in the 13 patients with a compromised cerebral perfusion

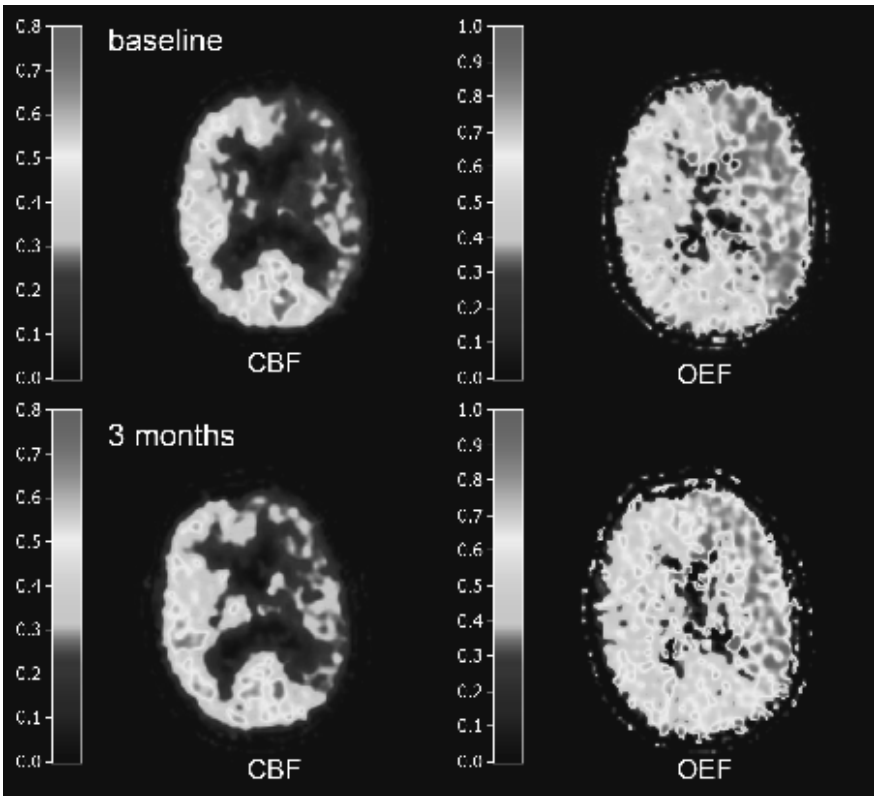

Figure 2. Parametric images of a patient with stage 2 haemodynamic failure. This 69-year-old man presented with a minor ischaemic stroke (without infarction on his MRI) and recurrent TIAs from the left hemisphere associated with a left ICA occlusion. The baseline PET study showed decreased cerebral blood flow (CBF) and increased oxygen extraction fraction (OEF) in the territories of both anterior and middle cerebral artery of the left hemisphere. This patient was randomized for tapering of antihypertensive medication. The PET study after three months showed a slight improvement in CBF and OEF. However, he still had recurrent TIAs in the presence of stage 2 haemodynamic failure.

(haemodynamic stage 1 and 2 combined) and in those classified in haemodynamic stage 0. Of the patients with normal CBF, CBV and OEF at baseline, five had undergone interventional treatment (CEA of the contralateral ICA in one, CEA of the ipsilateral ECA in one, stenting of the VA in one, and tapering of antihypertensive medication in two patients), which did not result in a further increase in CBF in the MCA territory (mean difference –3.1, 95% CI –13.1 to 6.9). Of the 13 patients with haemodynamic compromise, five underwent stenting or surgery (CEA of the contralateral ICA in two, CEA of the ipsilateral ECA in one, and stenting of the VA in two patients), in two the antihypertensive medication was tapered and six received standard treatment. The seven patients assigned to intervention had a mean CBF in the MCA territory of 27.2 ± 3.4 mL/min/100mL

Table 2. Comparison of haemodynamic state of the brain at baseline and after three months between patients assigned to intervention and those to standard treatment (n=23).

		Intervention n=12	Standard n=11	Unadjusted difference in change (95% CI)	Adjusted difference in change* (95% CI)
		mean ± SD	*mean ± SD*		
CBF MCA	baseline	31.3 ± 5.9	33.1 ± 5.4		
(mL/min/100mL)	3-months	31.6 ± 4.9	33.5 ± 4.7		
	change	0.34 ± 6.2	0.42 ± 4.1	–0.1 (–4.7 to 4.5)	–1.0 (–7.4 to 5.4)
CBF ACA	baseline	32.6 ± 5.8	35.2 ± 5.5		
(mL/min/100mL)	3-months	32.0 ± 4.2	35.0 ± 5.7		
	change	-0.56 ± 6.2	-0.28 ± 4.9	–0.3 (–5.2 to 4.6)	–1.6 (–8.4 to 5.2)
CBV MCA	baseline	3.0 ± 0.6	3.3 ± 0.9		
(mL/100mL)	3-months	3.5 ± 1.4	3.2 ± 0.6		
	change	0.60 ± 1.7	-0.09 ± 1.2	0.7 (–0.6 to 2.0)	0.09 (–1.7 to 1.9)
CBV ACA	baseline	3.0 ± 0.6	3.4 ± 1.0		
(mL/100mL)	3-months	3.5 ± 1.3	3.1 ± 0.7		
	change	0.49 ± 1.6	-0.23 ± 1.3	0.7 (–0.6 to 2.0)	0.08 (–1.6 to 1.8)
OEF MCA	baseline	46.4 ± 9.7	47.5 ± 5.5		
(%)	3-months	46.3 ± 7.9	48.4 ± 5.8		
	change	-0.08 ± 6.1	0.85 ± 6.8	–0.9 (–6.5 to 4.7)	3.1 (–4.1 to 10.3)
OEF ACA	baseline	44.4 ± 11.2	46.1 ± 6.2		
(%)	3-months	44.2 ± 7.3	47.2 ± 5.2		
	change	-0.17 ± 7.4	1.1 ± 6.3	–1.3 (–7.3 to 4.7)	3.1 (–4.6 to 10.8)

*Adjusted for age and sex. Measurements were performed ipsilateral to the side of the ICA occlusion. CBF, cerebral blood flow; CBV, cerebral blood volume; OEF, oxygen extraction fraction; MCA, middle cerebral artery; ACA, anterior cerebral artery.

at baseline, which increased to 30.0 ± 3.9 mL/min/100mL after three months (mean difference 2.8 mL/min/100mL, 95% CI 0.0 to 5.7). The mean increase in CBF in the MCA territory in patients treated by intervention was, however, not significantly different from the increase in CBF of 1.3 mL/min/100mL (95% CI –2.1 to 4.6) in patients who received standard treatment (adjusted mean difference of change –1.1 mL/min/100mL, 95% CI –7.8 to 5.7). The mean CBV in the MCA territory in patients with haemodynamic compromise treated with an intervention showed a small non-significant increase (mean difference 1.1 mL/100mL, 95% CI –0.7 to 2.9), and did not differ from the change in CBV in patients who received standard treatment (adjusted mean difference of change 1.4 mL/100 mL, 95% CI –2.4 to 5.1). Because only two patients were found to have an increased OEF at baseline, the effect of intervention on mean OEF after

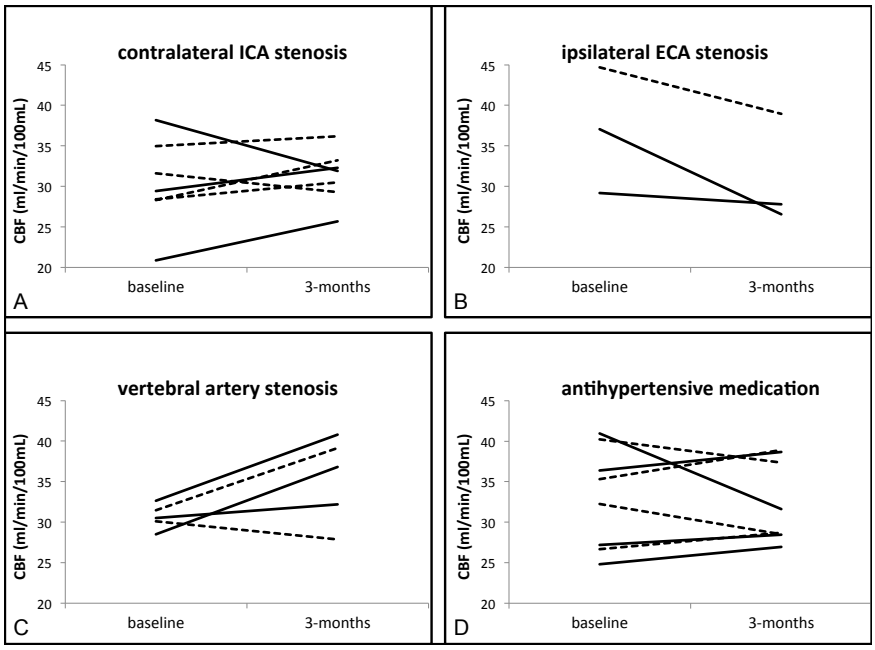

Figure 3. CBF changes over time in the MCA territory for individual patients randomized to (A) CEA of a contralateral ICA stenosis, (B) CEA of an ipsilateral ECA stenosis, (C) angioplasty and stent placement of a VA stenosis, and (D) tapering of antihypertensive medication. Patients randomized to intervention are indicated by continuous lines and patients randomized to standard treatment by dashed lines.

three months could not be formally compared. One of the two patients was assigned to standard treatment and after three months OEF was unchanged. In the other patient antihypertensive medication was tapered and OEF decreased from 72% to 66% after three months. The eight patients treated with surgery or stenting of a stenosis in a collateral artery had a mean CBF of 30.8 ± 5.4 mL/min/100mL at baseline and 31.8 ± 5.2 mL/min/100mL after three months (mean difference 0.97, 95% CI –4.6 to 6.6). In the 11 patients who received standard medical treatment alone, mean CBF was 33.1 ± 5.4 mL/min/100mL at baseline and 33.5 ± 4.7 mL/min/100mL after three months (mean difference 0.42, 95% CI –2.4 to 3.2). The change in CBF did not differ between these two groups of patients (adjusted mean difference of change –0.02 mL/min/100mL, 95% CI –7.2 to 7.1).

Clinical outcome

During the period between PET scans at baseline and after three months, ten (43%) of 23 patients had one or more recurrent TIAs. After the trial period, clinical follow-up continued with an overall median duration of 2.9 (range 0.5

Table 3. Mean CBF and CBV for patients with symptomatic ICA occlusion, classified in haemodynamic stage 0 (n=10) and haemodynamic stage 1 or 2 (n=13)

		Intervention	Standard	Unadjusted difference in change	Adjusted difference in change*
		mean ± SD	*mean ± SD*	*(95% CI)*	*(95% CI)*
Haemodynamic stage 0		n=5	n=5		
CBF MCA	baseline	37.0 ± 3.0	35.0 ± 5.6		
(mL/min/100mL)	3-months	33.9 ± 5.8	34.4 ± 5.2		
	change	–3.1 ± 8.1	–0.6 ± 5.3	–2.5 (–12.5 to 7.4)	–1.7 (–16.6 to 12.2)
CBV MCA	baseline	3.1 ± 0.6	2.8 ± 0.7		
(mL/100mL)	3-months	3.0 ± 0.7	3.5 ± 0.4		
	change	–0.2 ± 1.1	0.6 ± 1.0	–0.8 (–2.3 to 0.7)	–1.1 (–3.2 to 1.1)
Haemodynamic stage 1 or 2		n=7	n=6		
CBF MCA	baseline	27.2 ± 3.4	31.5 ± 5.2		
(mL/min/100mL)	3-months	30.0 ± 3.9	32.8 ± 4.6		
	change	2.8 ± 3.1	1.3 ± 3.2	1.6 (–2.2 to 5.4)	–1.1 (–7.8 to 5.7)
CBV MCA	baseline	2.9 ± 0.6	3.7 ± 0.8		
(mL/100mL)	3-months	4.0 ± 1.7	3.0 ± 0.6		
	change	1.1 ± 1.9	–0.7 ± 1.1	1.8 (–0.2 to 3.8)	1.4 (–2.4 to 5.1)

*Adjusted for age and sex. CBF, cerebral blood flow; CBV, cerebral blood volume; MCA, middle cerebral artery.

to 4.4) years. Three (13%) of the 23 patients had a recurrent ischaemic stroke during follow-up, and all three had also had TIAs during the period between PET scans at baseline and three months. Overall, two (25%) of the eight patients who had surgery or stenting, three (75%) of the four who had tapering of antihypertensive medication and five (45%) of the 11 who received standard medical treatment had one or more recurrent TIAs during the period between PET scans at baseline and after three months. At baseline, two of the ten patients with recurrent TIAs during the period between PET scans at baseline and three months were in haemodynamic stage 2. One had been treated by tapering of antihypertensive medication and the other received standard treatment. After three months, they were still in stage 2 haemodynamic failure. Three of the ten patients were in haemodynamic stage 1 at baseline. In one patient antihypertensive medication was tapered and he remained in stage 1 after three months, the second received standard treatment and the flow state improved to stage 0, and the third had CEA of the contralateral ICA but he experienced a minor ischaemic stroke (modified Rankin scale 2) in the hemisphere ipsilateral to the ICA occlusion 47 days thereafter. In this patient,

CBF was 29.4 mL/min/100mL at baseline, and 32.3 mL/min/100mL after three months. Because of ongoing TIAs he underwent an EC/IC bypass six days after the PET scan at three months. Unfortunately this procedure was complicated by a major ischaemic stroke in the hemisphere contralateral to the ICA occlusion one day postoperatively. He died two months later. Five of the ten patients were in haemodynamic stage 0 at baseline. One had been treated by CEA of the ipsilateral ECA, in another antihypertensive medication was tapered and three patients received standard treatment. Three of these patients (1 CEA, 2 standard treatment) with initially normal perfusion of the brain showed deterioration to stage 1 after three months. Two of these patients had a recurrent ischaemic stroke during clinical follow-up, including the one who was randomized for CEA of the ipsilateral ECA. In this patient, CBF was 37.1 mL/min/100mL at baseline, which deteriorated to 26.6 mL/min/100mL after three months. Because of ongoing TIAs he underwent CEA of the contralateral ICA five months after the 3-months PET scan. Nine months after CEA he had a major ischaemic stroke in the hemisphere ipsilateral to the ICA occlusion and he died three days later. The other patient with recurrent ischaemic stroke was randomized for standard treatment (not tapering antihypertensive medication). In this patient, CBF was 32.3 mL/min/100mL at baseline, which deteriorated to 28.5 mL/min/100mL after three months. He also had TIAs during the period between the two PET scans. Six months after the 3-months PET scan he still had recurrent TIAs and underwent an EC/IC bypass operation. Three months thereafter he had a major ischaemic stroke in the hemisphere contralateral to the ICA occlusion and he died one month later.

Discussion

This study shows that patients with recent symptoms of cerebral ischaemia associated with occlusion of the ICA on average have a lower CBF in the hemisphere ipsilateral to the occlusion than healthy subjects. Oxygen-15 PET showed that interventions aimed at improving cerebral perfusion caused a borderline significant increase in CBF in patients who had an impaired haemodynamic state of the brain at presentation. Improvement in CBF was, however, not different between interventional and standard treatment.

Current knowledge of cerebral haemodynamic and metabolic changes over time in medically treated patients with an ICA occlusion is based on small patient series and both improvement and deterioration over time has been described. In one study, ten medically treated patients with symptomatic

ICA occlusion and increased OEF underwent a second PET scan after 12 to 59 months.[23] Over time, patients showed on average an increase in CBF hemispheric (ipsilateral/contralateral) ratio and a decrease in OEF hemispheric ratio, but without changes in absolute values of CBF and OEF.[23] Another study of seven patients with symptomatic ICA occlusion and normal CBF and OEF at baseline found a significant decrease in CBF and increase in OEF after 24 to 64 months, implicating haemodynamic deterioration over time.[24] Other studies reported a bilateral increase in cerebrovascular reactivity measured by Transcranial Doppler (TCD) after CEA of a contralateral carotid stenosis in the presence of a symptomatic or asymptomatic ICA occlusion.[6-7, 25] In contrast to these studies, we did not find a significant effect of treatment aimed at improving the flow state of the brain when compared to control patients in a randomized design. A possible explanation could be that the cerebral haemodynamic state also improved without intervention. Patients with haemodynamic compromise at baseline who received standard treatment showed a small non-significant increase in CBF. It has been shown before that patients with ICA occlusion and a compromised flow state of the brain may improve spontaneously over time.[26] In addition, in patients with a normal haemodynamic state of the brain at baseline, a further increase in CBF would not be expected.

Hypertension is the most important vascular risk factor that can be treated. Therefore, tapering of antihypertensive medication as a treatment for recurrent signs and symptoms of presumed haemodynamic origin may be controversial, in particular since an association between high blood pressure and increased stroke risk has been shown in patients with an intracranial arterial stenosis.[27] In contrast, in patients with severe bilateral carotid stenosis, low blood pressure was found to be related to an increased stroke risk, and in patients with contralateral asymptomatic ICA occlusion no association between blood pressure and stroke risk was found.[10] In patients with TIA or stroke associated with ICA occlusion the effect of permissive hypertension has not been studied.

A limitation of our randomized pilot study may be that we did not select patients on the basis of demonstrated cerebral haemodynamic compromise. The design of the study was aimed at including patients at high risk of recurrent stroke by selection on clinical criteria: ischaemic symptoms of the brain after documented occlusion, excluding patients with eye symptoms alone and those with symptoms only before the ICA occlusion was documented without ongoing symptoms thereafter.[28] We had expected that these clinical criteria would have resulted in a much larger proportion of patients with haemodynamic stage 1 and 2. Another limitation might be heterogeneity in treating patients assigned

to intervention. Effects of tapering of antihypertensive medication on the haemodynamic state of the brain may well be different from those of surgery or stenting of stenosed arteries that may be important for collateral blood supply. Subgroup analysis of the present data comparing surgery or stenting of a stenosis in the contralateral ICA, ipsilateral ECA or VA with standard medical treatment alone did not show significant differences in CBF, but the number of patients may have been too small. Likewise, effects of surgery or stenting of the contralateral ICA on cerebral perfusion may be different than those of surgery or stenting of the ipsilateral ECA or VA. The third limitation is that a relatively high number of patients had to be excluded because they did not have two successfully performed PET studies. Our failure rate was similar to the rate of 22% for quantitative studies in the St Louis Study,[2, 12] and lower than in another PET study that reported a failure rate of 41%.[29] Fourth, this study focused on effects of treatment on the haemodynamic state of the brain of patients with symptomatic ICA occlusion, but the ultimate goal of treatment is to prevent recurrent ischaemic stroke. The COSS study could not demonstrate clinical benefits of an EC/IC bypass, although an improvement in mean OEF, measured by PET, was found.[3] This suggests that other factors may also be important in determining the risk of recurrent stroke. One such factor could be the time between last symptoms and the intervention. In the COSS study, the number of days between the patients' last symptoms and intervention was, on average, 75 days. New collateral pathways may have developed during that period resulting in spontaneous improvement in the haemodynamic state of the brain in both intervention and control groups. Fifth, patients were not systematically investigated for presence of cardiac failure, which might have affected cerebral haemodynamics. Finally, the sample size in our study was probably too small to detect differences between the two treatment strategies.

Although the results of this pilot study are not conclusive, some important lessons can be learned. Patients with TIA or ischaemic stroke in the hemisphere ipsilateral to the ICA occlusion are at risk of subsequent cerebral ischaemia. In these patients with symptomatic ICA occlusion, the clinical benefit of CEA or endovascular treatment of an additional stenosis in the cerebropetal arteries or tapering of antihypertensive medication has not been shown by a randomized trial. The recently published results of the Carotid Occlusion Surgery Study randomized trial[3] that showed no benefit of STA-MCA bypass surgery over medical treatment despite improvement of cerebral haemodynamics in the surgical group reinforce the need for other therapies to improve outcome in patients with ICA occlusion at high risk of recurrent stroke. Oxygen-15 PET is useful to identify a subgroup of patients with haemodynamic compromise,

but we could not demonstrate that stenting or surgery of stenosed cerebropetal arteries or tapering of antihypertensive medication improved the haemodynamic state of the brain to a large extent in comparison with standard treatment. Whether revascularization of collaterals or tapering of antihypertensive medication can reduce the risk of recurrent stroke can only be determined in a large randomized trial of patients with a symptomatic ICA occlusion at high risk of stroke.

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7

Internal borderzone infarction is associated with haemodynamic compromise in patients with internal carotid artery occlusion but not with recurrent stroke

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Submitted

Abstract

Purpose

In patients with occlusion of the internal carotid artery (ICA), the presence of internal borderzone (IBZ) infarcts has been associated with impaired perfusion to the brain. The aim of this study was to compare the vasomotor reactivity and collateral flow patterns in patients presenting with symptomatic ICA occlusion with and without IBZ infarcts and to assess whether the presence of IBZ infarcts predicts recurrent stroke.

Materials and Methods

Thirty-six patients with a recent TIA or minor ischaemic stroke associated with ICA occlusion underwent magnetic resonance imaging (MRI), digital subtraction angiography and transcranial Doppler (TCD) CO_2-reactivity examination. We compared collateral blood flow pathways on angiograms and CO_2-reactivity between patients with and without IBZ infarcts on MRI. All patients were followed-up at three and six months and yearly thereafter. We determined the predictive value of presence of IBZ infarcts with Cox proportional hazards analysis.

Results

Fifteen patients (42%) had IBZ infarcts on their MRI. No differences in collateral blood flow pathways were found between patients with and without IBZ infarcts. Mean CO_2-reactivity was lower in patients with IBZ infarcts (6%, SD 9%) than in patients without IBZ infarcts (20%, SD 14%; mean difference 14%, 95% CI 5 – 23). During a mean duration of follow-up of 2.4 years (SD 1.3), 3 (20%) patients with IBZ infarcts had a recurrent stroke versus 4 (19%) patients without IBZ infarcts (hazard ratio: 1.0 (95% CI 0.2 – 4.6).

Conclusion

In patients with symptomatic ICA occlusion, IBZ infarcts are associated with haemodynamic compromise but do not predict recurrent stroke.

Introduction

About 10% of patients presenting with an acute TIA or ischaemic stroke have ischaemic lesions on brain imaging in the borderzone between the supply territories of the main intracranial arteries.[1-3] This proportion increases to up to one-third of patients with a severe stenosis or occlusion of the internal carotid artery (ICA).[4-5] Cortical borderzone infarcts are localized in the borderzones between the supply territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA). Internal borderzone (IBZ) infarcts are localized in the watershed area between the deep and superficial systems of the MCA, or between the superficial arteries of the ACA and MCA in the semioval centre.[3, 6] Several studies have shown that the presence of borderzone infarcts in general is associated with haemodynamic impairment.[3, 5, 7-10] Studies that made a distinction between cortical and internal borderzone infarcts, found that in particular IBZ infarcts are associated with haemodynamic compromise.[11-13] It is unclear whether the presence of IBZ infarcts can be used to identify those patients who are at increased risk of recurrent ischaemic stroke. The aim of this study was to compare collateral flow patterns and cerebrovascular reactivity in patients with TIA or ischaemic stroke associated with ICA occlusion with and without IBZ infarcts and to investigate whether the presence of IBZ infarcts is associated with an increased risk of recurrent ischaemic stroke.

Patients and Methods

The study was approved by the institutional review board of the University Medical Centre Utrecht, The Netherlands, and written informed consent was obtained from all patients.

Patients

Between December 2004 and September 2009, patients who presented at the Department of Neurology of the University Medical Centre Utrecht, The Netherlands, with transient or at most moderately disabling symptoms (modified Rankin scale ≤ 3[14]) of cerebral ischaemia associated with an ipsilateral ICA occlusion were considered for study participation. This study was part of a prospective randomized pilot study on the haemodynamic effect of interventional treatment. All patients had symptoms within the last three months and after ICA occlusion was documented. Patients were excluded if the occlusion was caused by an arterial dissection or radiation vasculopathy

or if there were contra-indications to undergo an MRI (such as claustrophobia or metal objects in the body). All patients were interviewed about clinical characteristics and risk factors as listed in *Table 1*, with special attention for clinical characteristics suggesting a haemodynamic cause of symptoms such as limb shaking,[15] or precipitation of symptoms by rising from a sitting or lying position, exercise, transfer from a cold to a warm environment, or a decrease of blood pressure.

Collateral blood flow pathways

All patients had digital subtraction angiography to confirm the presence of the ICA occlusion. The stenosis grade of the contralateral ICA was assessed according to the NASCET criteria.[16] We considered collateral blood flow via the ophthalmic artery as present if selective catheterization of the common carotid artery showed filling of intracranial arteries distal to the carotid siphon via the external carotid artery (ECA) branches via the ophthalmic artery. Collateral pathways via the anterior communicating artery or the posterior communicating artery were considered present if these collateral pathways showed filling of the anterior or middle cerebral artery (ACA or MCA) branches ipsilateral to the symptomatic ICA occlusion. Leptomeningeal collaterals were considered present if pial branches from the posterior cerebral artery (PCA) extending as far as the vascular territory of the MCA or ACA (beyond the usual PCA territory) were visualized on the angiogram after selective catheterization of one of the vertebral arteries.[17]

Magnetic resonance imaging

The presence of ischaemic lesions was scored systematically by two investigators (S.P. and C.J.M.K.) using the MRI T1 and FLAIR sequences. Each ischaemic lesion in the hemisphere ipsilateral to the ICA occlusion was classified as territorial,[18] large subcortical, lacunar (< 15 mm), cortical borderzone or internal borderzone. IBZ infarcts were considered present if lesions were located in the corona radiata, between the territories of supply of the deep and superficial perforators of the MCA, or in the semioval centre between the superficial perforators of the ACA and MCA (*Figure 1*).[3,6] A cortical borderzone infarct was defined as a lesion in the cortical borderzone between the supply territory of the ACA and MCA, visible as fronto-parasagittal wedge, as a linear strip on the superior convexity, or as a lesion in the cortical borderzone between the supply territory of the MCA and PCA.[3]

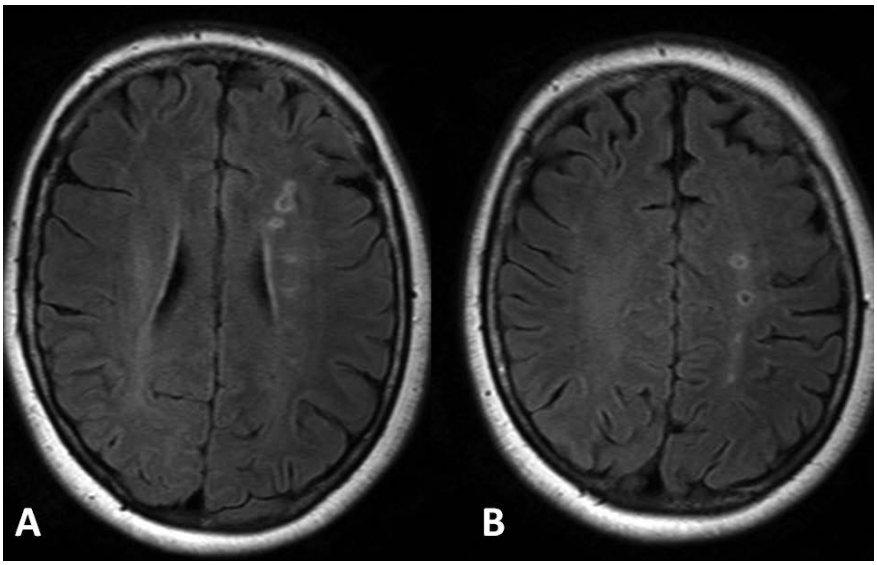

Figure 1. MR image of the brain of a 58-year-old woman presenting with recurrent TIAs from the left hemisphere associated with an occlusion of the left ICA. The FLAIR-sequence shows ischaemic lesions in the internal borderzone area in the corona radiata between the territories of supply of the deep and superficial perforators of the MCA (A), and in the semioval centre between the superficial perforators of the ACA and MCA (B).

TCD CO_2-reactivity

TCD with a Multi-Dop X device (DWL, Sipplingen, Germany) was applied to measure CO_2-reactivity with two 2-MHz pulsed Doppler probes for insonation of cerebral vessels and a 4-MHz probe for the ophthalmic artery (OphthA), as described previously.[19] After a standard TCD to locate the cerebral vessels, the CO_2-reactivity was measured simultaneously in both MCA's. Hypercapnia was induced by inhalation of a gas mixture containing 5% CO_2 and 95% O_2 (carbogene) through a mouthpiece connected to a respiratory balloon. A noseclip ensured proper inhalation of carbogene. A spectral TCD recording of 5 s duration was made after 1 min of breathing room air and after 1.5 min of carbogene inhalation. The CO_2-reactivity after carbogene inhalation was measured as the relative change in blood flow velocity (BFV) in the MCA from the mean baseline BFV and expressed as a percentage. A CO_2-reactivity ≤20% was considered as decreased since this value corresponds with the mean CO_2-reactivity minus two times the standard deviation (SD) in normal controls.[20]

Treatment and outcome

As this study was part of a randomized study on the effect of interventional treatment, patients were assigned between any intervention according to therapeutic strategy or standard treatment. The therapeutic strategy could consist of, in order of preference, one of the following treatment options: (1) endarterectomy of the contralateral ICA in case of a severe contralateral ICA stenosis in the presence of a functional anterior circle of Willis, (2) endarterectomy of the ECA in case of a severe ipsilateral ECA stenosis in the presence of collateral blood supply via the ECA and ophthalmic artery, (3) endovascular treatment of the vertebral artery (VA) or subclavian artery in case of a severely stenosed VA or subclavian artery in the presence of collaterals via the vertebrobasilar system, (4) tapering of antihypertensive medication for three months. In addition to intervention, patients received the standard medical treatment consisting of antithrombotic medication (aspirin and dipyridamole), a statin, treatment of hypertension to a target blood pressure of 140/90 mmHg (except for those randomized to tapering of antihypertensive drugs) and control of other vascular risk factors such as smoking and obesity. The patients who were assigned to standard treatment received standard medical treatment alone, including treatment of hypertension to a target blood pressure of 140/90 mmHg.

The haemodynamic effect of the treatment according to randomization was evaluated after three months, and thereafter treatment decisions were made by the team on the basis of whether a patient had recurrent ischaemic symptoms or not. Patients with symptoms of cerebral ischaemia that continued after three months and evidence of presumably haemodynamic origin (i.e. the presence of specific symptoms associated with a haemodynamic cause, a borderzone infarct or low CO_2-reactivity) were considered for treatment with the high flow extracranial/intracranial (EC/IC) bypass. All patients were followed-up in the outpatient clinic at three and six months and yearly thereafter to assess the occurrence of a recurrent TIA or ischaemic stroke, which was defined as the acute onset of new focal neurological deficit of cerebral origin persisting for less than 24 hours (TIA) or more than 24 hours (ischaemic stroke) without haemorrhage on CT or MRI scan of the brain.

Data-analysis

Patients were divided into two groups on the basis of the presence or absence of IBZ infarcts. The relationship between clinical characteristics and the presence of IBZ infarcts was analyzed by the Chi-square test with the significance-level at $p < 0.05$. The association between haemodynamic variables and the presence of IBZ infarcts was assessed by calculating Odds Ratio's (OR) for dichotomous variables, and for continuous variables mean differences, with a 95% confidence

interval (CI). To determine the potential influence of the elapsed time since symptom, the association between CO_2-reactivity measurement and the presence of IBZ infarcts was adjusted for the time between the most recent symptom and CO_2-reactivity measurement and expressed in OR with 95% CI. Finally, Cox regression analysis was used to determine the influence of the presence of IBZ infarcts on the risk of recurrent ischaemic stroke and on the combined endpoint of recurrent TIA or ischaemic stroke, resulting in a hazard ratio (HR) with 95% CI.

Results

Thirty-six patients were included. At baseline 15 patients (42%) had IBZ infarcts in the hemisphere ipsilateral to their ICA occlusion. One patient could not undergo contrast angiography because of an elevated creatinine level, and had MR-angiography to confirm the ICA occlusion. *Table 1* shows the clinical characteristics of the patients with and without IBZ infarcts. Patients with IBZ infarcts less often had a history of ischaemic heart disease than those without IBZ infarcts (OR 0.15, 95% CI 0.03 – 0.72) and less often had an additional territorial infarct present on their MRI (OR 0.17, 95% CI 0.03 – 0.94). All other baseline characteristics did not differ between patients with and without IBZ infarcts.

The haemodynamic measurements in relation to the presence of IBZ infarcts are summarized in *Table 2*. No differences in collateral blood flow pathways were found between patients with and without IBZ infarcts. Leptomeningeal collaterals were found in 85% of patients with IBZ infarcts, compared with 67% of patients without IBZ infarcts, but this difference did not reach statistical significance. TCD CO_2-reactivity could be measured in 30 patients. The mean CO_2-reactivity was lower in patients with (6%, SD 9%) than in patients without IBZ infarcts (20%, SD 14%; mean difference 14%, 95% CI 5 – 23; OR 0.90 per 1% increase in CO_2-reactivity, 95% CI 0.83 – 0.98). The median time interval between the most recent symptom and the CO_2-reactivity measurement was 23 (range 0 – 37) days in patients with IBZ infarcts and 37 (range 0 – 127) days in patients without IBZ infarcts. After adjustment of the OR for this time interval, the finding of a lower CO_2-reactivity in patients with IBZ infarcts than in those without IBZ infarcts remained significant (adjusted OR 0.91 per 1% increase in CO_2-reactivity, 95% CI 0.83 – 0.99). The mean duration of follow-up was 2.4 years (SD 1.3). The type of treatment for the patients with and without IBZ infarcts during follow-up is shown in *Table 1*. Seven patients (19%) had a recurrent

Table 1. Clinical characteristics in 36 patients with and without IBZ ipsilateral to their symptomatic ICA occlusion

	IBZ present *(n=15)*	IBZ absent *(n=21)*
Mean age (years ± SD)	65 ± 10	65 ± 10
Male	11 (73%)	17 (81%)
Cigarette smoking in the last 5 years	8 (53%)	10 (48%)
Hypertension[a]	12 (80%)	19 (91%)
Hyperlipidaemia[b]	13 (87%)	18 (86%)
Diabetes mellitus	4 (27%)	6 (29%)
History of ischaemic heart disease*	3 (20%)	13 (62%)
History of ischaemic stroke (> 3 months ago)	3 (20%)	6 (29%)
Clinical features:		
Ischaemic stroke at presentation	6 (40%)	5 (24%)
Precipitating factors	3 (20%)	4 (19%)
Limb-shaking TIAs	4 (27%)	7 (33%)
Mean arterial pressure (mmHg ± SD)	103 ± 13	106 ± 17
Additional ischaemic lesions ipsilateral to ICA occlusion:		
territorial*	2 (13%)	10 (48%)
cortical borderzone	4 (27%)	7 (33%)
large subcortical	1 (7%)	2 (10%)
lacunar	1 (7%)	4 (19%)
Cerebropetal arteries:		
Contralateral ICA occlusion	1 (7%)	2 (10%)
Contralateral ICA stenosis 50-99%	6 (40%)	8 (38%)
Ipsilateral ECA stenosis 50-99%	2 (13%)	3 (14%)
VA stenosis 50-99%	7 (47%)	8 (38%)
Treatment during follow-up:		
Interventional treatment:[c]	12 (80%)	11 (52%)
CEA contralateral ICA	3	1
CEA ipsilateral ECA	1	1
Angioplasty and stent vertebral or subclavian artery	4	3
EC/IC bypass	0	1
Tapering of antihypertensive medication	4	5
Standard medical treatment alone	3 (20%)	10 (48%)

* Variables with p-value <0.05 (Chi-square test). [a] Blood pressure >160/95 mmHg or the current use of antihypertensive medication. [b] Patients with either a history of hyperlipidaemia, patients on statins or patients with levels of total cholesterol, triglycerids or high density lipoprotein cholesterol outside normal ranges. [c] Four patients underwent more than one interventional treatment; three had a CEA of the contralateral ICA, one of them additionally underwent a bypass of the proximal ICA to the VA, and one had a bypass of the subclavian artery to the common carotid artery. IBZ, internal borderzone infarct; CEA, carotid endarterectomy; ICA, internal carotid artery; ECA, external carotid artery; EC/IC bypass, extracranial/intracranial bypass.

ischaemic stroke; three (20%) of 15 patients with IBZ infarcts and four (19%) of 21 patients without IBZ infarcts. Six of the seven recurrent infarcts occurred in the hemisphere ipsilateral to the previous symptomatic ICA occlusion. The recurrent infarct in the contralateral hemisphere occurred in a patient without an IBZ infarct at baseline. In two patients the recurrent ischaemic stroke was

Table 2. Collateral blood flow pattern and CO_2-reactivity in 36 patients with and without IBZ ipsilateral to their symptomatic ICA occlusion

	IBZ present *(n=15)*	IBZ absent *(n=21)*	Odds Ratio[a]
Collateral flow via AComA	11/14 (79%)[b]	17/20 (85%)	0.6 (0.1 – 3.8)
Collateral flow via PComA	10/13 (77%)	17/20 (85%)	0.6 (0.1 – 3.5)
Collateral flow via OphthA	6/14 (43%)	9/20 (45%)	0.9 (0.2 – 3.6)
Leptomeningeal vessels	11/13 (85%)	12/18 (67%)	2.8 (0.5 – 16.6)
CO_2-reactivity[c] in % (mean ± SD)	6 ± 9 (n=13)	20 ± 14 (n=17)	14 (5 – 23)[d]

[a] Unless otherwise specified. [b] Indicates the number of patients with the type of collateral flow present in relation to the number of patients in whom that type of collateral flow could be scored. [c] In five patients the CO_2-reactivity could not be obtained due to an absent temporal bone window. One patient was excluded because the TCD was done after interventional treatment. [d] Expressed in mean difference with 95% CI. IBZ, internal borderzone; AComA, anterior communicating artery; PComA, posterior communicating artery; OphthA, ophthalmic artery.

fatal. The annual rate for recurrent ischaemic stroke was 8.1% (95% CI 3.3 – 16.1). There was no association between the presence of IBZ infarcts and the risk of recurrent ischaemic stroke (HR 1.0 (95% CI 0.2 – 4.6). Twelve (80%) of the 15 patients with IBZ infarcts had a recurrent TIA or ischaemic stroke, whereas 11 (52%) of the 21 patients without IBZ infarcts had a recurrent TIA or infarct (HR 1.5, 95% CI 0.6 – 3.5).

Discussion

This study shows that in patients with a recent TIA or minor disabling ischaemic stroke and an ICA occlusion the presence of IBZ infarcts is associated with low CO_2-reactivity. No association was found between IBZ infarcts and the presence of a specific type of collateral pathways. Our study did not show a relationship between the presence of IBZ infarcts and the risk of future ischaemic stroke. All patients included in this study had ischaemic symptoms from the ipsilateral hemisphere after documentation of the ICA occlusion, which is known to be associated with an increased risk of recurrent stroke.[21] Even in this selected group, in which we expect haemodynamic compromise in the majority of patients, the presence of IBZ infarcts was clearly associated with a lower CO_2-reactivity. This finding supports the idea that IBZ infarcts are primarily caused by haemodynamic compromise. However, we could not demonstrate that the presence of IBZ infarcts was a predictor of recurrent ischaemic stroke. The annual rate of recurrent ischaemic stroke of 8.1% in the present study was comparable with some previous studies,[22-26] but those studies were performed before the era of rigid control of vascular risk factors. The annual stroke rate we found was higher compared with the 2.4% found in our previous ten-years follow-

up study on outcome of patients with a symptomatic ICA occlusion, who were not selected for ischaemic symptoms after documentation of ICA occlusion,[21] and also higher compared with the two-year risk of ischaemic stroke of 9.2% recently found in patients with ICA occlusion without misery perfusion.[27] This indicates that our patient population was a selected 'high-risk' group.

The association between IBZ infarcts and haemodynamic compromise is in line with previous studies.[11-13, 28-32] In these studies of at most 23 patients with IBZ infarcts the haemodynamic state of the brain was measured by TCD,[11, 28, 30-31, 33] single photon computed emission tomography (SPECT),[13, 29, 31] or positron emission tomography (PET).[12, 32] Three of these made a distinction between IBZ and cortical borderzone infarcts, and showed that in particular IBZ infarcts were associated with haemodynamic compromise.[11-13] Some studies included both symptomatic and asymptomatic patients,[13, 33] and some included patients with ICA stenosis as well.[13, 28, 31-32] A strength of our study in comparison with these previous studies[11-13, 28-32] is that we included a very homogeneous group of patients with very recent symptoms from the hemisphere ipsilateral to the ICA occlusion. A possible explanation that we did not find an association between the presence of IBZ infarcts and recurrent ischaemic stroke may be that also other factors than haemodynamic compromise contribute to the risk of future stroke. One such factor could be cardiac disease. A considerable proportion of patients, in particular patients without IBZ infarcts, had a history of ischaemic heart disease. Probably in some patients emboli from the heart may have passed through collateral routes and caused recurrent ischaemic stroke in the hemisphere ipsilateral to the ICA occlusion.[34-35]

This study also has some limitations. First, patients were part of a randomized study of two different treatment strategies. Patients with IBZ infarcts had been treated for stenosis in a blood vessel important as collateral pathway more frequently than patients without IBZ infarcts. Although the efficacy of surgical interventions of a stenosis in the contralateral ICA, ipsilateral ECA, or vertebral artery in patients with symptomatic ICA occlusion had not been proven, treatment may have influenced clinical outcome favourably and therefore might have introduced a bias in the analysis of the predictive value of IBZ infarcts on the risk of recurrent stroke. Second, the number of patients might have been too small to detect a significant association of IBZ infarcts with clinical outcome. In addition, due to relatively small numbers we were not able to adjust for other risk factors for recurrent stroke. Third, despite the association between the presence of IBZ infarcts and haemodynamic impairment, we found no relationship of IBZ infarcts with the presence of a particular type of

collateral pathway. This may be due to the fact that we could only judge whether a collateral pathway was present or not on contrast angiography. It would be of interest to study the importance of a collateral pathway to the territory ipsilateral of the ICA occlusion by quantifying the amount and diameters of collateral vessels to judge the total capacity of collateral pathways.

In conclusion, this study shows that in a selected group of patients who presented with TIA or minor disabling ischaemic stroke associated with an ICA occlusion the presence of IBZ infarcts is associated with a lower CO_2-reactivity compared with patients without IBZ infarct. Presence of an IBZ infarct cannot be utilized to estimate the risk of recurrent stroke in individual patients.

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8

General discussion

Patients who present with a transient ischaemic attack (TIA) or an at most moderately disabling ischaemic stroke associated with an occlusion of the internal carotid artery (ICA) have a relatively low risk of recurrent ischaemic stroke, in particular once no stroke has occurred in the first 18 months (Chapter 2). Even patients with a bilateral occlusion of the ICA have a low risk of recurrent ischaemic stroke (Chapter 2, 3). However, there is a subgroup of patients with ongoing symptoms after documentation of ICA occlusion or clinical signs of haemodynamic compromise that have a higher risk of recurrent ischaemic stroke (Chapter 2). In patients with a demonstrated haemodynamic compromised state of the brain the risk of recurrent ischaemic stroke may be increased up to 12% per year.[1-3] The studies in this thesis aimed to improve the identification of the patient at increased risk of recurrent ischaemic stroke based on clinical characteristics and haemodynamic measurements with transcranial Doppler (TCD) with CO_2-reactivity or oxygen-15 positron emission tomography (PET) studies. Another aim was to study the haemodynamic effect of a therapeutic strategy consisting of surgery or stenting of stenosed cerebropetal arteries or tapering of antihypertensive medication. In this chapter, I discuss the main findings of the studies in this thesis, including methodological shortcomings, their implications for clinical practice and challenges for further research.

Clinical symptoms and outcome

The risk of recurrent ischaemic stroke in patients who present with TIA or minor ischaemic stroke associated with an ICA occlusion was 5-6% per year based on a meta-analysis.[4] This meta-analysis included 44 studies published between 1961 and 1999, reporting on a total number of 3457 patients with a symptomatic ICA occlusion (n=2902) or intracranial stenosis or occlusion.[4] In our ten-year follow-up study of 117 patients with a symptomatic ICA occlusion, we found a two-times lower annual rate of recurrent ischaemic stroke of 2.4% (Chapter 2). One explanation for this relatively low rate of recurrent ischaemic stroke could be that treatment by antithrombotic medication and control of vascular risk factors has improved in the last decades. Optimal secondary prevention may have resulted in a lower rate of recurrent stroke.[5-7] Another explanation could be the long duration of follow-up in our study. An important finding of our study was that the risk of recurrent ischaemic stroke was highest in the first 1.5 years after presentation with an annual rate of 8%, and relatively low thereafter (Chapter 2). A third explanation could be that a considerable proportion of the patients in our study had presented with retinal ischaemic symptoms only. Patients with only retinal symptoms have a lower risk of ischaemic stroke

than patients who present with cerebral ischaemic symptoms.[2, 8-9] A fourth explanation could be that patients with a 70 to 99% stenosis of the contralateral ICA were offered carotid endarterectomy (CEA), and patients with symptoms of cerebral ischaemia that continued after documentation of the ICA occlusion and evidence of presumably haemodynamic origin were offered treatment with the high-flow EC/IC bypass. Probably this treatment strategy may have prevented the occurrence of recurrent ischaemic stroke in some patients. The presence of a bilateral ICA occlusion is a rare finding, and therefore little information was available about the outcome in these patients. The previously reported annual stroke rates in patients with bilateral ICA occlusion ranged between 0 and 13%,[10-18] but were based on small numbers. We showed in a cohort of 57 patients who did not suffer a major stroke that the risk of recurrent ischaemic stroke was low with 1.2% per year (Chapter 3). Patients with bilateral ICA occlusion and only minor or no neurological deficit probably have a very good collateral circulation, and therefore a low risk of recurrent stroke.

Several clinical features have been found to be associated with a relatively high risk of recurrent ischaemic stroke.[19] In our ten-year follow-up study we showed that the presence of recurrent symptoms of cerebral ischaemia after documentation of the ICA occlusion is associated with a five times higher risk of recurrent ischaemic stroke (Chapter 2). Another clinical feature associated with an increased risk of recurrent ischaemic stroke is limb-shaking (Chapter 2). Limb-shaking TIAs can be characterized by brief, jerky, coarse, involuntary movements of an arm or leg or both.[20] We have further characterized the signs of limb-shaking that may improve their recognition by clinicians (Chapter 4). Limb-shaking in patients with ICA occlusion usually lasts for less than 5 min, is often accompanied by paresis of the involved limb and is often, but not necessarily precipitated by activities that may compromise cerebral perfusion such as rising, exercise or coughing (Chapter 4). Limb-shaking TIAs may resemble epileptic seizures but can be distinguished by a normal level of consciousness, precipitation of symptoms by specific circumstances that may lower cerebral blood flow, the absence of tonic contractions or a march of symptoms, no involvement of the face or trunk, and no epileptic discharges on an electro-encephalography (EEG).[21-23] Patients with an ICA occlusion and limb-shaking have a particularly impaired flow state of the brain compared with patients with ICA occlusion but without limb-shaking (Chapter 4). Patients with ICA occlusion and only retinal ischaemic symptoms have a relatively low risk of cerebral infarction (Chapter 2). Sometimes patients complain about a gradual deterioration of vision of one eye, which may be caused by venous stasis retinopathy or chronic ocular ischaemia. About one third of patients with

ICA occlusion has signs of early chronic ocular ischaemia on ophthalmoscopy, and these signs are associated with an impaired flow state of the brain.[24]

Diagnostic investigations

The pattern of cerebral infarction on MR images provides indirect information on the flow state of the brain. A prevalence of borderzone infarcts on MRI of approximately 32% has been reported in patients with stenotic or occlusive carotid artery disease.[25-26] A distinction should be made between cortical borderzone infarcts, which are located between the territories of the ACA, MCA and PCA, and internal borderzone infarcts (IBZ), which are located between the deep and superficial arterial system of the middle cerebral artery (MCA), or between the supply territories of the anterior cerebral artery (ACA) and MCA in the white matter along or above the lateral ventricle in a so-called 'rosary-like' pattern.[19, 27-28] Within a group of patients with a symptomatic ICA occlusion, the patients with IBZ infarcts on their MRI were found to have a lower CO_2-reactivity than patients without IBZ infarcts (Chapter 7). This finding strongly supports the idea that the presence of IBZ infarcts is indicative of a poor haemodynamic state of the brain. We found no association between the presence of IBZ infarcts and the risk of recurrent stroke, but this needs further investigation in a larger study with longer duration of follow-up.

The perfusion of the brain in patients with ICA occlusion depends on the presence of sufficient collateral blood flow pathways. Additional stenosis in the contralateral ICA, ECA or vertebral arteries, or even more proximal vessels such as the subclavian arteries that may hamper collateral blood supply can often be demonstrated by CTA or MRA.[29] However, contrast angiography is of additional value to show the contribution of the various collateral pathways to the intracranial supply of the territory of the occluded ICA; the presence of leptomeningeal collateral vessels can only be seen by contrast angiography.[30] We showed that the presence of leptomeningeal collateral blood supply from the posterior cerebral artery to the supply territory of the occluded ICA was associated with a relatively high risk of recurrent ischaemic stroke (Chapter 2).

Transcranial Doppler (TCD) with measurement of the cerebrovascular reactivity is a widely available and cheap method for identification of patients with haemodynamic compromise. Previous studies have shown that an impaired cerebrovascular reactivity is associated with an increased risk of recurrent ischaemic stroke,[31-32] but the results of our long-term follow-up study could

not confirm the predictive value of TCD measurements (Chapter 2). Probably the results of the previous studies have been confounded by including both patients with and without symptoms. Asymptomatic patients have a relatively low stroke risk[33] and a relatively high cerebrovascular reactivity.[31-32]

Positron emission tomography (PET) using oxygen-15 labelled tracers is the most accurate method to measure the oxygen extraction fraction (OEF),[34, 35-36] which has been shown to be predictive of the risk of recurrent ischaemic stroke.[2,37] Our findings indicate that O-15 PET studies can be used to identify a subgroup of patients with haemodynamic compromise that may benefit from an interventional treatment aimed to increase cerebral perfusion (Chapter 6). A disadvantage of PET is that O-15 tracers are not widely available and consequently, in clinical practice, assessment of haemodynamic status using PET is limited. Our comparative study of PET and TCD in patients with symptomatic ICA occlusion showed that the identification of presence or absence of haemodynamic compromise by oxygen-15 PET and TCD CO_2-reactivity corresponds in only half of the patients (Chapter 5). This implicates that measurements of CBF, CBV and OEF using PET cannot be replaced by TCD CO_2-reactivity measurement and vice versa for selection of patients for EC/IC bypass surgery or another type of revascularization. In particular low TCD CO_2-reactivity values seemed to correspond best with PET measures. Possibly, TCD CO_2-reactivity can be used as a screening tool for haemodynamic compromise, in particular in patients with symptoms of the vascular territory of the MCA. If TCD shows impaired CO_2-reactivity and a revascularization procedure is considered, a PET study can provide additional information on the location and severity of haemodynamic compromise.

Management

The current standard treatment for patients with ICA occlusion is the same as for patients with TIA or ischaemic stroke in general, and consists of antithrombotic medication and strict control of vascular risk factors.[5-7] The importance of optimal secondary prevention is underlined by our finding that patients with ICA occlusion also have a significant risk of other vascular events, probably as an expression of severe generalized atherosclerotic disease (Chapter 2). A subgroup of patients with ICA occlusion, those with ongoing symptoms after documented ICA occlusion or those with a demonstrated compromised flow state of the brain, have a relatively high risk of recurrent ischaemic stroke.[19] In these patients interventional treatment with the aim to improve cerebral perfusion may be considered.

One such intervention could be tapering of antihypertensive medication as a treatment for recurrent signs and symptoms of presumed hemodynamic origin. Good results have been reported by some case studies.[11, 38-39] In patients with severe bilateral carotid stenosis, low blood pressure was found to be related to an increased stroke risk, and in patients with ICA stenosis and contralateral asymptomatic ICA occlusion no association between blood pressure and stroke risk was found.[40] In contrast, in patients with an intracranial arterial stenosis an association between high blood pressure and increased stroke risk has been shown.[41] In patients with TIA or stroke associated with ICA occlusion the effect of permissive hypertension has not been studied before. In our pilot study we could not demonstrate an increase in cerebral perfusion after tapering of antihypertensive medication (Chapter 6).

Another therapeutic strategy to improve cerebral perfusion may be endarterectomy or endovascular treatment of a significant stenosis in one of the cerebropetal arteries that can serve as collateral pathway.[19, 42-45] We used quantitative oxygen-15 PET to investigate the haemodynamic effect of these interventions in comparison with the standard medical therapy. Oxygen-15 PET showed that interventions aimed at improving cerebral perfusion (including tapering of antihypertensive medication) caused a borderline significant increase in CBF in patients who had an impaired haemodynamic state of the brain at presentation. Improvement in CBF was, however, not different between interventional and standard treatment (Chapter 6). Several previous case series have reported positive results after surgery or stenting of a stenosis in a collateral pathway in patients with ICA occlusion,[19, 42-45] but this strategy has not been studied before in a randomized design in comparison with standard medical therapy. A possible explanation for the lack of benefit in our study could be that the cerebral haemodynamic state also improved without intervention. Patients with haemodynamic compromise at baseline who received standard treatment showed a small non-significant increase in CBF. It has been shown before that patients with ICA occlusion and a compromised flow state of the brain may improve spontaneously over time.[46] In addition, some patients already had a normal hemodynamic state of the brain at baseline, and in these patients a further increase in CBF would not be expected.

Another interventional treatment, an EC/IC bypass, has been investigated recently by a randomized trial. The Carotid Occlusion Surgery Study (COSS) failed to show benefit of an EC/IC bypass over medical therapy in a selected group of patients with a symptomatic ICA occlusion and an increased OEF measured with PET.[3] There could be several reasons for the lack of benefit.[47] First, the two-

year risk of recurrent ischaemic stroke in the medical group was lower than originally hypothesized, 23% versus 40%.[3] An explanation for this difference could be the improvement in medical therapy over the last decade. Second, the COSS used a semi-quantitative, count-based hemispheric ratio technique to demonstrate haemodynamic compromise by PET.[48] Some have suggested that this count-based method identifies a different subset of patients compared to those identified by quantitative PET.[49] In addition, 18% of included patients had a contralateral ICA stenosis, which may have influenced hemispheric ratios. Third, there was a considerable rate of perioperative stroke (within 30 days after surgery) of 15%. Fourth, the mean time between the patients' most recent ischaemic symptoms and study enrolment was on average 75 days, suggesting that a large proportion of patients was clinically stable. In 75 days new collateral pathways may developed and result in spontaneous improvement in the haemodynamic state of the brain. The COSS demonstrated an increase in mean OEF after surgery, but patients on medical therapy did not have a follow-up PET. A positive result of the COSS study was a low rate of recurrent stroke after the first postoperative month. In my view, despite the lack of a beneficial effect of the EC/IC bypass, this procedure may still be considered in a very selected subgroup of clinically unstable patients, with ongoing symptoms despite optimal medical therapy. An EC/IC bypass operation should only be done in specialized centres with experience with this procedure and a sufficiently low perioperative morbidity.[47]

Methodological considerations

The studies in Chapter 2 and 3 are longitudinal cohort studies. The study cohort in both studies consisted of patients from all over the Netherlands, who were referred to a single tertiary university hospital and therefore referral bias most probably has played a role. However, patients with frequent and ongoing symptoms are probably more likely to be referred than those with only one event and no further symptoms. Therefore, the risk of recurrent ischaemic stroke that we report would rather be over- than underestimated. Another important limitation, in particular of the long-term follow-up study of patients with ICA occlusion, was that it does not reflect true natural history, as we advised CEA in patients with a >70% stenosis of the contralateral ICA and EC/IC bypass operation in selected patients with recurrent symptoms of cerebral ischaemia of presumed haemodynamic origin. Because of the selection bias with regard to treatment, we could not statistically compare outcome in medically and surgically treated patients. Furthermore, we have identified clinical risk factors

for the risk of recurrent ischaemic stroke but due to the relatively small number of outcome events we could not study these risk factors in a multivariable model. It remains unknown whether these factors have an independent or additional effect on the risk of recurrent ischaemic stroke. In other words, whether a patient with recurrent symptoms of cerebral ischaemia after documented ICA occlusion and limb-shaking TIAs and leptomeningeal collaterals on the angiogram has a higher risk of recurrent stroke compared with a patient with recurrent symptoms of cerebral ischaemia after documented ICA occlusion, but without limb-shaking and leptomeningeal collaterals, remains uncertain.

The study described in Chapter 6 had a randomized controlled design. The main study limitation was the small number of patients, caused by a slow inclusion rate and a relatively high number of patients that had to be excluded because they did not have two successfully performed PET studies. Reasons for incomplete PET data were anemia, failure to insert the arterial cannula necessary for blood sampling, technical problems or withdrawal of the patient for the PET study. Our failure rate was similar to the rate of 22% for quantitative studies in the St Louis Study,[2, 36] and lower than in another PET study that reported a failure rate of 41%.[50] A second limitation was that in the design of the study we aimed to include a 'high risk' group by selecting only patients with ischaemic symptoms of the brain after documented occlusion, and by excluding patients with eye symptoms only and those with symptoms only before the ICA occlusion was documented without ongoing symptoms thereafter. Thirteen of the 23 patients were in haemodynamic stage 1 and 2. We had expected that these clinical criteria would result in a much larger proportion of patients with haemodynamic compromise. Another problem with regard to patient selection was that it is likely that the "highest risk" patients, those with almost daily TIAs who were clinically unstable, were not included in the study, because the treating team did not feel comfortable in randomizing such a patient between interventional and standard medical treatment. This could also be an explanation for the low number of patients in haemodynamic stage 2 and the lack of a beneficial effect of interventional treatment. A third limitation was the heterogeneity in treatment in patients assigned to intervention. The effects of surgery or stenting and tapering of antihypertensive medication may be difficult to compare. We have chosen for this randomization scheme rather than designing separate studies for each of the treatment options, because all treatment options aim to improve cerebral perfusion, and because the number of eligible patients for each treatment would be too small.

Clinical implications

The risk of recurrent ischaemic stroke in patients with unilateral or bilateral ICA occlusion is relatively low. The risk of the occurrence of any other major vascular event is higher. This finding strengthens the importance of optimal secondary prevention. Therefore, in clinical practice, antithrombotic medication and strict control of vascular risk factors should be the cornerstone of treatment of patients with TIA or ischaemic stroke associated with ICA occlusion. There is no treatment of proven benefit for patients with a symptomatic ICA occlusion; however, an intervention may be considered in a subgroup of patients with signs of haemodynamic compromise. In this perspective, it is important to identify a subgroup of 'high risk' patients with ICA occlusion.

A proposal for the approach of patients with a symptomatic ICA occlusion is shown in the flow chart (*Figure 1*), which is based on the studies in this thesis, the current literature and our clinical experience with patients with ICA occlusion in the University Medical Centre Utrecht. We suggest that an additional work-up to investigate the haemodynamic state of the brain needs to be done only in patients at increased risk of recurrent ischaemic stroke based on the presence of recurrent ischaemic symptoms of cerebral origin after documented occlusion. Assessment of the flow state of the brain may start with MRI to visualize the presence and type of infarction, and TCD CO_2-reactivity. If a patient continues to have TIAs and interventional treatment is an option, it is important to perform contrast angiography to visualize the collateral blood flow pathways and intracranial supply of the territory of the occluded ICA. Oxygen-15 PET can help in identifying the patient with haemodynamic compromise who may benefit from interventional treatment. As long as there is no proven benefit of interventions such as surgery or stenting of collateral pathways or EC/IC bypass surgery, treatment policy should be discussed for each patient on an individualized basis in a multidisciplinary team consisting of at least a vascular neurologist, vascular surgeon, interventional neuro-radiologist, and vascular neurosurgeon. The final decision-making should be done by weighing the risks and benefits of interventional treatment together with the patient.

Approach of a patient who presents with TIA or ischaemic stroke associated with an ipsilateral carotid artery occlusion, demonstrated by ultrasound

History-taking, with special attention for:
- recurrence of ischaemic symptoms after documented occlusion
- cerebral or retinal origin of ischaemic symptoms
- limb-shaking
- precipitating circumstances such as rising from a supine position, exercise, transition from a cold to warm environment, having just consumed a meal, coughing, administration of antihypertensive drugs, or other drugs that might lower blood pressure (eg sildenafil), bleeding or anaemia
- monocular loss of vision after looking into bright light (retinal claudication)
- gradual deterioration of vision of one eye
- signs of cognitive impairment
- episodes of loss of consciousness

Examination:
- measure the blood pressure on both arms, and check for orthostatic hypotension

⇩

Diagnostic investigations:
- CTA or MRA to confirm occlusion of the ICA and to assess the presence of stenosis in one of the other cerebropetal arteries

⇩

Treat all patients with symptomatic ICA occlusion immediately with antithrombotic medication and strict regulation of vascular risk factors

Consulting the ophthalmologist is valuable to check for venous stasis retinopathy and chronic ocular ischaemic syndrome *

⇩

Did the patient have one or more recurrent ischaemic symptoms of cerebral origin after documented ICA occlusion?

⇩ YES → continue

⇩ NO → focus on optimal medical secondary prevention

- clinical observation on Stroke Unit and bedrest if patient has almost daily haemodynamic TIAs, precipitated by rising or exercise
- tapering of antihypertensive medication until symptoms have ceased, or until a maximum blood pressure of 200/120 mmHg, if patient receives blood pressure lowering medication and has almost daily haemodynamic TIAs

⇩

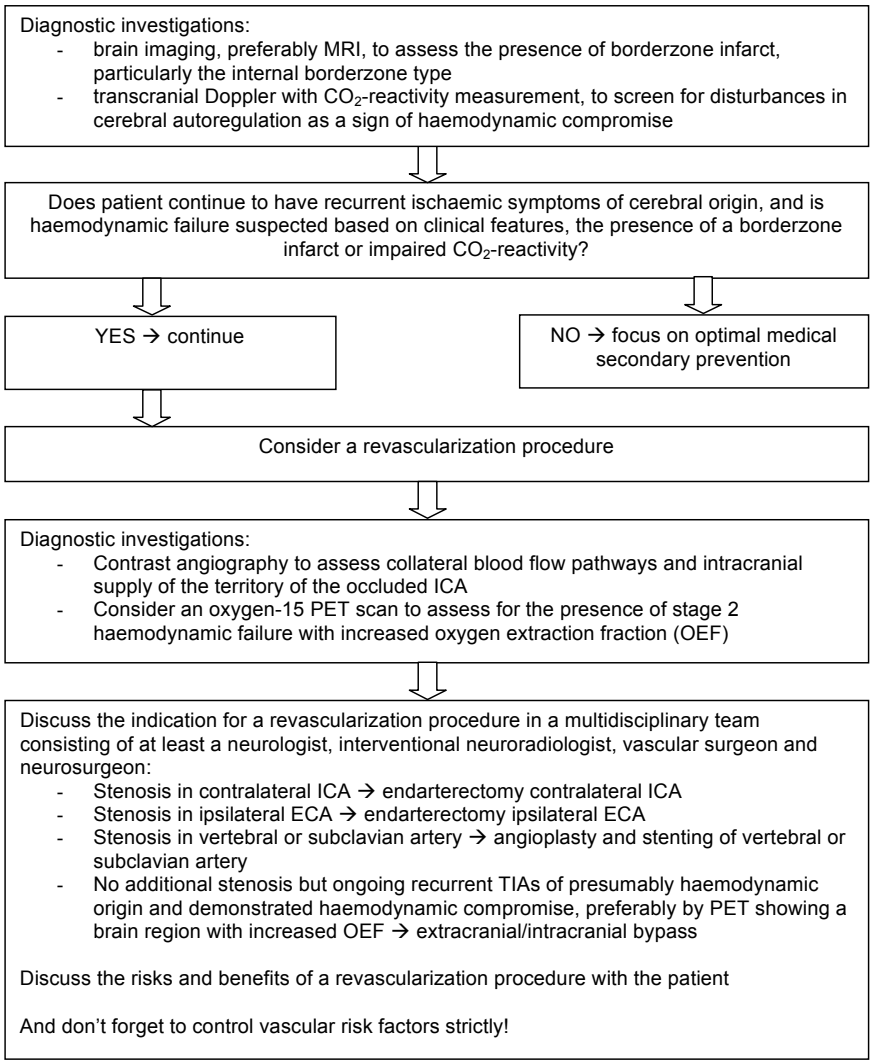

Figure 1. Flow chart for the approach of patients with a symptomatic ICA occlusion.

Future perspectives

Despite all previous studies in patients with ICA occlusion, many questions remain unanswered. Further systematic research aimed at the best treatment for patients with a symptomatic ICA occlusion should be performed. It is striking that many case studies report good results after a revascularization procedure, but well-designed prospective studies fail to show any beneficial effect. Patient selection most probably plays a role in the negative findings. A new trial to investigate the effect of surgery or stenting of a stenosis in one of the collateral blood flow pathways should include consecutive patients with symptoms of cerebral ischaemia after documentation of the ipsilateral ICA occlusion and a demonstrated impaired flow state of the brain. As in particular low TCD CO_2-reactivity values seem to correspond with PET measures, TCD may be used to measure haemodynamic compromise for patient selection. Incorporating TCD instead of PET in the study protocol has several advantages: TCD is cheap, less time-consuming, less effort for the patient and because it is widely available the trial can be multi-centered. A multi-centre design would be necessary to include sufficient patients to investigate the effect of surgery or stenting of a stenosis in one of the collateral blood flow pathways on recurrence of ischaemic stroke.

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Summary

Patients with TIA or ischaemic stroke associated with an internal carotid artery (ICA) occlusion have an annual risk of recurrent ischaemic stroke of approximately 5 to 6%, based on a meta-analysis of studies between 1966 and 1999. In patients with a demonstrated compromised flow state of the brain this risk may increase up to 12% per year. The identification of these 'high-risk' patients with haemodynamic compromise is challenging, because there is no gold standard in measuring the haemodynamic state of the brain. To date, there is no treatment of proven benefit in patients with a symptomatic ICA occlusion, other than optimal medical therapy and control of vascular risk factors. Interventional treatment may be considered in patients with haemodynamic compromise. The recent Carotid Occlusion Surgery Study (COSS) investigated the effect of the extracranial/intracranial (EC/IC) bypass operation in selected patients with an increased oxygen extraction fraction (OEF) as measured by oxygen-15 positron emission tomography (PET). The results showed that the two-year risk of ipsilateral stroke did not differ between the surgical and non-surgical group. An alternative therapeutic strategy to improve cerebral perfusion may be endarterectomy or endovascular treatment of a significant stenosis in one of the cerebropetal arteries that can serve as collateral pathway, or tapering of antihypertensive medication. The efficacy of these interventions in patients with a symptomatic ICA occlusion has never been studied in a randomized design. The aim of the studies described in this thesis is to provide more insight in the implications of haemodynamic compromise in relation to clinical features, prognosis and management in patients who present with TIA or minor disabling ischaemic stroke associated with an ICA occlusion. A general introduction to the subject is given in **Chapter 1**.

In **Chapter 2** we describe a prospective longitudinal cohort study of 117 patients with TIA or at most moderately disabling ischaemic stroke associated with an ICA occlusion. Patients were followed for a median time of 10.2 years; 22 patients underwent endarterectomy for contralateral ICA stenosis and 16 extracranial/intracranial bypass surgery. Recurrent ischaemic stroke occurred in 23 patients, resulting in an annual rate of 2.4% (95% confidence interval [CI], 1.5 – 3.6). The highest risk was in the first 1.5 years after presentation. Risk factors for recurrent ischaemic stroke were age (hazard ratio [HR] 1.07, 1.02 – 1.13), cerebral rather than retinal symptoms (HR 8.0, 1.1 – 60), recurrent symptoms after documented occlusion (HR 4.5, 1.6 – 12), limb-shaking TIAs at presentation (HR 7.7, 2.6 – 22), history of stroke (HR 2.9, 1.2 – 6.7) and leptomeningeal collaterals (HR 5.1, 1.5 – 17), but not CO_2-reactivity (HR 1.01, 0.99 – 1.02). The composite event of any vascular event occurred in 57 patients, resulting in an annual rate of 6.4% (95%CI, 4.9 – 8.2), which was much higher than the risk of recurrent ischaemic stroke alone.

The outcome in patients with TIA or at most moderately disabling ischaemic stroke and a bilateral ICA occlusion is described in **Chapter 3**. Fifty-seven patients were followed during a mean duration of 5.9 years. Four patients had a recurrent ischaemic stroke, resulting in an annual stroke rate of 1.2% (95% confidence interval (CI) 0.3 – 3.1). Risk factors for recurrent ischaemic stroke could not be identified. Eighteen patients suffered a stroke, myocardial infarction or vascular death, resulting in an annual rate for major vascular events of 5.3% (95% CI 3.1 – 8.3). Age and a history of ischaemic heart disease were risk factors for future vascular events.

More details on the clinical characteristics of limb-shaking in 34 patients with ICA occlusion are provided in **Chapter 4**. We found that limb-shaking in patients with ICA occlusion usually lasts less than five minutes, is often accompanied by paresis of the involved limb and is often, but not necessarily precipitated by activities that may compromise cerebral perfusion such as rising, exercise or coughing. In a case-control design, we studied whether patients with limb-shaking have a worse haemodynamic state of the brain than patients with ICA occlusion without limb-shaking. Compared with controls, patients with limb-shaking more frequently had symptoms precipitated by rising or exercise (Odds Ratio [OR] 14.2, 95% CI 4.2 – 47.9) and more frequently had recurrent ischaemic deficits after documented ICA occlusion (but before inclusion in the study) (OR 8.2, 95% CI 2.3 – 29.3). Patients with limb-shaking more often had leptomeningeal collaterals visualized on their angiogram compared with controls (OR 6.8, 95% CI 2.0 – 22.7), and tended to have a lower TCD CO_2-reactivity (mean 5% ± 16 versus 12% ± 17; OR 0.97 per 1% increase in CO_2-reactivity, 95% CI 0.94 – 1.00). These results indicate that patients with an ICA occlusion and limb-shaking probably have a more severe impaired flow state of the brain than patients with ICA occlusion but without limb-shaking.

Both 15-oxygen PET and TCD CO2-reactivity are used to evaluate cerebral perfusion, but it is not clear whether these methods identify the same patients with haemodynamic compromise. The study in **Chapter 5** describes the comparison of PET and TCD measurements in 24 patients with a symptomatic ICA occlusion. Seventeen (71%) patients had impaired CO_2-reactivity (≤20%), of whom six had absent reactivity (0%) or steal (<0%) in the hemisphere ipsilateral to the ICA occlusion. PET of the perfusion state of the hemisphere ipsilateral to the ICA occlusion demonstrated stage 1 (decreased CBF or increased CBV without increased OEF) in 13 patients and stage 2 (increased OEF) in two patients. In 12 patients (50%) there was agreement between TCD and PET, indicating haemodynamic compromise in ten and a normal flow state of the brain in two

patients. There was no significant correlation between CO_2-reactivity and CBF ipsilateral/contralateral hemispheric ratio (r = 0.168, p-value 0.432), OEF ratio (r = –0.242, p-value 0.255), or CBV/CBF ratio (r = –0.368, p-value 0.077). This study showed that in patients with symptomatic ICA occlusion, identification of an impaired flow state of the brain measured by PET and TCD CO_2-reactivity corresponds in only half of the patients. This implicates that measurement of CBF, OEF or CBF/CBV using PET cannot be replaced by TCD CO_2-reactivity measurement and vice versa for selection of patients for EC/IC bypass surgery or another type of revascularization.

In **Chapter 6** we investigated the haemodynamic effect of revascularization of collaterals or tapering of antihypertensive medication in comparison with standard medical therapy in patients with symptomatic ICA occlusion, measured by dynamic oxygen-15 PET. Twenty-three patients with recent symptoms associated with an ICA occlusion underwent PET scanning at baseline and after three months. Twelve patients were randomized to intervention (either endarterectomy or endovascular treatment of stenosed cerebropetal arteries, or tapering of antihypertensive medication) and 11 to best medical treatment alone. Normal values were derived from 14 scans of 7 healthy subjects. CBF in the middle cerebral artery territory ipsilateral to the ICA occlusion was significantly lower in patients than in healthy controls (mean difference –5.2 mL/min/100mL, 95% CI –9.8 to –0.6). There were no differences in changes in CBF, CBV or OEF between patients assigned to intervention and standard treatment. Only patients with compromised perfusion at presentation, showed a borderline significant increase in CBF of 2.8 mL/min/100mL (95% CI 0.0 to 5.7) after intervention (n=7). The results of this study were not conclusive, because the sample size was probably too small to detect differences between the two treatment strategies. In this pilot study, we could not demonstrate that stenting or surgery of stenosed cerebropetal arteries or tapering of antihypertensive medication improved the haemodynamic state of the brain to a large extent in comparison with standard treatment.

In **Chapter 7** we investigated whether the presence of ischaemic lesions in the region of the internal borderzone (IBZ) on MRI is indicative of haemodynamic compromise and whether it is associated with an increased risk of recurrent ischaemic stroke. Thirty-six patients with a symptomatic ICA occlusion were included in the study and all underwent magnetic resonance imaging (MRI), digital subtraction angiography and transcranial Doppler (TCD) CO_2-reactivity examination. An IBZ infarct on MRI was present in 15 of the 36 patients (42%). Mean CO_2-reactivity was lower in patients with IBZ infarcts (6%, SD 9%) than in

patients without IBZ infarcts (20%, SD 14%; mean difference 14%, 95% CI 5 – 23). This finding of a lower CO2-reactivity in patients with IBZ compared with patients without IBZ, within a selected group of patients with a symptomatic ICA occlusion, is suggestive of a haemodynamic origin of IBZ. During a mean duration of follow-up of 2.4 years (SD 1.3), 3 (20%) patients with IBZ infarcts had recurrent stroke versus 4 (19%) patients without IBZ infarcts (hazard ratio: 1.0, 95% CI 0.2 – 4.6). That we could not demonstrate an association between the presence of IBZ and the risk of recurrent ischaemic stroke might be related to the relatively small sample size. A larger study with longer duration of follow-up would be necessary to investigate the predictive value of the presence of IBZ on the risk of recurrent ischaemic stroke.

Finally, in **Chapter 8** the overall findings and implications for the future are discussed. Patients who present with TIA or at most moderately disabling ischaemic stroke associated with an occlusion of the internal carotid artery have a relatively low risk of recurrent ischaemic stroke, in particular if no stroke has occurred during the first 18 months after the first signs or symptoms. Even patients with a bilateral occlusion of the ICA have a relatively low risk of recurrent ischaemic stroke. However, there is a subgroup of patients with ongoing symptoms after documentation of ICA occlusion or clinical signs of haemodynamic compromise that have a higher risk of recurrent ischaemic stroke. Based on the studies in this thesis and previous studies, we suggest that only in these patients an additional work-up to investigate of the haemodynamic state of the brain needs to be done. MRI can be done to visualize the presence and type of infarction; the presence of internal borderzone infarction is indicative of haemodynamic compromise. TCD with CO_2-reactivity measurement may be used as a screening tool for haemodynamic compromise. If interventional treatment will be considered, contrast angiography can provide valuable information on collateral blood flow pathways and intracranial supply of the territory of the occluded ICA. Oxygen-15 PET can help in identifying patients with haemodynamic compromise who may benefit from interventional treatment and provide additional information on location and severity of haemodynamic compromise. As long as there is no proven benefit of interventions such as surgery or stenting of collateral pathways, treatment policy should be discussed for each patient on an individualized basis in a multidisciplinary team. A new trial to investigate the effect of surgery or stenting of a stenosis in one of the collateral blood flow pathways on recurrence of ischaemic stroke should be multi-centered and should include consecutive patients with symptoms of cerebral ischaemia after documentation of the ipsilateral ICA occlusion and a demonstrated impaired flow state of the brain.

Samenvatting

Patiënten met 'transient ischaemic attacks' (TIAs) of een ten hoogste matig ernstig invaliderend herseninfarct bij een ipsilaterale occlusie van de arteria carotis interna hebben een kans van ongeveer 5 tot 6% per jaar op een nieuw herseninfarct, gebaseerd op een meta-analyse van studies tussen 1966 en 1999. Bij patiënten met een carotis occlusie en tevens een aangetoonde gestoorde cerebrale doorbloeding, kan het jaarlijks risico op een nieuw herseninfarct oplopen tot 12%. De standaard behandeling van deze patiënten bestaat uit antitrombotische medicatie en het reguleren van vasculaire risicofactoren. Tot op heden is er geen bewijs voor een gunstig effect van andere interventies. In 1985 verschenen de resultaten van een grote internationale gerandomiseerde studie naar de effectiviteit van de extracraniële/intracraniële (EC/IC) bypass operatie. De conclusie was dat een EC/IC bypass operatie niet leidde tot een afname van de kans op een nieuw herseninfarct. Het belangrijkste commentaar op deze studie was dat er geen rekening gehouden was met de mate van cerebrale doorbloeding voorafgaande aan de operatie. Er werd gesuggereerd dat de bypass operatie mogelijk wel effectief zou kunnen zijn bij patiënten met een aangetoonde cerebrale doorbloedingsstoornis. In 2002 werd een nieuw gerandomiseerd onderzoek gestart, waarbij patiënten geselecteerd werden voor een bypass operatie op grond van een gestoorde cerebrale doorbloeding gemeten met positron emissie tomografie (PET) onderzoek. Echter, deze studie werd voortijdig gestaakt, omdat de resultaten geen verschillen lieten zien in het 2-jaars risico op een nieuw herseninfarct tussen de geopereerde en de niet-geopereerde groep (p= 0.78). Een andere behandelstrategie van patiënten met een symptomatische carotis occlusie, gericht op het verbeteren van de cerebrale doorbloeding, kan bestaan uit een endarteriëctomie of een endovasculaire behandeling van een significante stenose in één van de andere cerebropetale arteriën die als collaterale voorziening dienen, of het tijdelijk verminderen van de antihypertensieve medicatie. Het effect van deze interventies bij patiënten met een symptomatische carotis occlusie is niet eerder in een gerandomiseerde studie onderzocht.

Hoofdstuk 1 bevat een algemene inleiding, met een korte theoretische uiteenzetting en de daaruit voortkomende probleemstellingen. Omdat gesuggereerd wordt dat een deel van de patiënten, de subgroep met een aantoonbare cerebrale doorbloedingsstoornis, mogelijk wel baat zou kunnen hebben bij een interventie, wordt veel aandacht besteed aan de methoden om een cerebrale doorbloedingsstoornis aan te tonen. Een zuurstof (O)-15 PET scan is de enige directe methode om de zuurstof extractie fractie te bepalen, en dit is klinisch relevant omdat een verhoogde zuurstof extractie fractie voorspellend is gebleken op de kans op een nieuw herseninfarct. Een nadeel van PET is

dat O-15 tracers niet in elk ziekenhuis beschikbaar zijn, en om die reden is de toepassing van PET in de klinische praktijk beperkt. Een eenvoudig beschikbaar en goedkoper alternatief om patiënten met een doorbloedingsstoornis te identificeren is een transcranieel Doppler (TCD) onderzoek met meting van de CO_2-reactiviteit. Hoewel diverse methoden om de cerebrale doorbloeding te meten beschikbaar zijn, is er geen gouden standaard.
De twee belangrijkste doelstellingen van dit proefschrift zijn (1) het verbeteren van het herkennen van patiënten met een verhoogde kans op een nieuw herseninfarct op basis van klinische kenmerken en het meten van de cerebrale doorbloeding met TCD en PET, en (2) het verkrijgen van meer inzicht in het effect van een behandelstrategie bestaande uit een endarteriëctomie of een endovasculaire behandeling van een significante stenose in één van de andere cerebropetale arteriën, of het tijdelijk verminderen van de antihypertensieve medicatie.

Hoofdstuk 2 beschrijft een prospectief longitudinaal cohort onderzoek van 117 patiënten die zich presenteerden met een TIA of ten hoogste matig ernstig invaliderend herseninfarct bij een ipsilaterale carotis occlusie. Patiënten zijn gedurende een mediane tijd van 10.2 jaar gevolgd; 22 patiënten werden behandeld met een endarteriëctomie in verband met een contralaterale carotis stenose en 16 patiënten ondergingen een EC/IC bypass operatie. Drieëntwintig patiënten kregen een nieuw herseninfarct, resulterend in een jaarlijks risico van 2.4% (95% betrouwbaarheidsinterval [BI], 1.5 – 3.6). De eerste anderhalf jaar was de kans op een nieuw herseninfarct het grootst. Risicofactoren voor het krijgen van een nieuw herseninfarct waren leeftijd (hazard ratio [HR] 1.07, 1.02 – 1.13), cerebrale in plaats van alleen retinale symptomen (HR 8.0, 1.1 – 60), terugkerende symptomen na bewezen occlusie (HR 4.5, 1.6 – 12), limb-shaking TIAs bij presentatie (HR 7.7, 2.6 – 22), herseninfarct in de voorgeschiedenis (HR 2.9, 1.2 – 6.7) en leptomeningeale collateralen op het angiogram (HR 5.1, 1.5 – 17). TCD CO_2-reactiviteit was niet voorspellend voor de kans op het krijgen van een nieuw herseninfarct (HR 1.01, 0.99 – 1.02 per 1% toename in CO_2-reactiviteit). Het gecombineerde eindpunt van het optreden van een herseninfarct, hersenbloeding, myocardinfarct of vasculaire dood ontstond bij 57 patiënten, resulterend in een jaarlijks risico van 6.4% (95% CI, 4.9 – 8.2). De kans op een belangrijke vasculaire aandoening in het algemeen was dus duidelijk hoger dan de kans op een nieuw herseninfarct.

De klinische uitkomst bij patiënten met een TIA of ten hoogste matig ernstig invaliderend herseninfarct bij een bilaterale carotis occlusie werd bestudeerd in **Hoofdstuk 3**. Zevenenvijftig patiënten met een bilaterale carotis occlusie

zijn gevolgd gedurende gemiddeld 5.9 jaar. Vier van de 57 patiënten kregen een nieuw herseninfarct, resulterend in een risico van 1.2% per jaar (95% BI 0.3 – 3.1). Specifieke risicofactoren voor de kans op een nieuw herseninfarct konden niet worden onderscheiden. Achttien patiënten kregen gedurende de follow-up periode het gecombineerde eindpunt van herseninfarct, hersenbloeding, myocardinfarct of vasculaire dood. Het jaarlijks risico op dit gecombineerde eindpunt was 5.3% (95% BI 3.1 – 8.3), met leeftijd en een cardiale voorgeschiedenis als significante risicofactoren.

Meer details over de klinische kenmerken van limb-shaking in 34 patiënten met een carotis occlusie worden beschreven in **Hoofdstuk 4**. Het is gebleken dat limb-shaking bij patiënten met een carotis occlusie meestal korter dan vijf minuten duurt, vaak gepaard gaat met een parese van het betrokken ledemaat en vaak, maar niet altijd, voorafgegaan wordt door een activiteit waarbij de hersendoorbloeding tijdelijk kan verminderen, zoals opstaan, inspanning of hoesten. In een case-control design wilden we onderzoeken of patiënten met limb-shaking een slechtere doorbloeding van de hersenen hebben dan patiënten met een carotis occlusie die geen limb-shaking hebben. Vergeleken met controles hadden patiënten met limb-shaking vaker symptomen uitgelokt door opstaan of inspanning (Odds Ratio [OR] 14.2, 95% BI 4.2 – 47.9) en vaker terugkerende symptomen na bewezen occlusie (OR 8.2, 95% BI 2.3 – 29.3). Verder hadden patiënten met limb-shaking vaker leptomeningeale collateralen op het angiogram (OR 6.8, 95% BI 2.0 – 22.7), en was er een trend tot een lagere TCD CO_2-reactiviteit (gemiddelde CO_2-reactiviteit 5% ± 16 versus 12% ± 17; OR 0.97 per 1% toename in CO_2-reactiviteit, 95% BI 0.94 – 1.00). Deze resultaten tonen aan dat patiënten met een carotis occlusie en limb-shaking een meer gestoorde cerebrale doorbloeding hebben vergeleken met patiënten met carotis occlusie maar zonder limb-shaking.

Zowel 15-O PET als TCD CO_2-reactiviteit kunnen toegepast worden om de cerebrale perfusie te meten, maar het is niet bekend of de resultaten van deze twee methoden met elkaar overeenkomen. De studie in **Hoofdstuk 5** beschrijft de vergelijking van PET en TCD metingen bij 24 patiënten met een symptomatische carotis occlusie. Zeventien (71%) patiënten hadden een gestoorde CO_2-reactiviteit, waarvan zes patiënten een afwezige reactiviteit (0%) of een 'steal'(<0%) fenomeen hadden. Op basis van de PET metingen hadden 15 patiënten een doorbloedingsstoornis, waarvan 13 patiënten in fase 1 (met compensatie door cerebrale autoregulatie) en twee patiënten in fase 2 (met verhoogde OEF als gevolg van falende autoregulatie). Er waren vergelijkbare bevindingen tussen de PET en TCD bij 12 patiënten (50%). Er was geen

significante correlatie tussen CO_2-reactiviteit en CBF ipsilaterale/contralaterale hemisfeer ratio r = 0.168, p-waarde 0.432), OEF ratio (r = –0.242, p-waarde 0.255), of CBV/CBF ratio (r = –0.368, p-waarde 0.077). Deze studie toonde aan dat er bij de helft van de patiënten overeenstemming werd gezien tussen de resultaten van PET en TCD. Dit betekent dus dat metingen van CBF, OEF en CBF/CBV door PET niet zomaar vervangen kunnen worden door een TCD CO_2-reactiviteit meting, en andersom, bij de selectie van patiënten voor bijvoorbeeld een EC/IC bypass operatie of een andere vorm van revascularisatie.

In **Hoofdstuk 6** hebben wij in een gerandomiseerde pilot-studie onderzocht of bij patiënten met een symptomatische carotis occlusie revascularisatie van vernauwingen in bloedvaten belangrijk voor de collaterale bloedvoorziening of het afbouwen van antihypertensieve medicatie de cerebrale bloed doorstroming (flow) (CBF), het cerebrale bloed volume (CBV), en de zuurstof extractie fractie (OEF) gemeten met zuurstof (O)-15 PET kan verbeteren. Drieëntwintig patiënten met recente ischemische symptomen vanuit de hemisfeer ipsilateraal van de carotis occlusie ondergingen een PET scan bij aanvang van de studie en na drie maanden. Twaalf patiënten zijn geloot voor de behandelstrategie met interventie (endarteriëctomie of een endovasculaire behandeling van een significante stenose in een van de andere cerebropetale arteriën, of het tijdelijk verminderen van de antihypertensieve medicatie), en 11 patiënten kregen alleen optimale medicamenteuze behandeling. Normaalwaarden voor PET onderzoek zijn verkregen op basis van 14 scans van zeven gezonde personen. Het bleek dat de CBF in het gebied van de arteria cerebri media ipsilateraal van de carotis occlusie significant lager was bij patiënten dan bij gezonde personen (gemiddeld verschil –5.2 ml/min/100ml, 95% BI –9.8 tot –0.6). Er waren geen verschillen in de veranderingen van CBF, CBV en OEF na drie maanden tussen patiënten die behandeld waren met een interventie en patiënten die de standaard medicamenteuze behandeling kregen. Alleen in de subgroep van patiënten met een verminderde doorbloeding van de hersenen bij aanvang van de studie werd een trend tot stijging van de CBF van 2.8 ml/min/100ml (95% CI 0.0 tot 5.7) waargenomen na interventie (n=7). De resultaten van deze studie leidden niet tot een eenduidige conclusie. O-15 PET lijkt geschikt om een subgroep van patiënten met verminderde doorbloeding te onderscheiden die mogelijk wel baat kunnen hebben bij een interventie gericht op het verbeteren van de hersendoorbloeding. Echter, we hebben niet aan kunnen tonen dat behandeling met endarteriëctomie of een endovasculaire behandeling van een significante stenose in één van de andere cerebropetale arteriën, of het tijdelijk verminderen van de antihypertensieve medicatie, leidt tot een betere cerebrale doorbloeding dan optimale medicamenteuze behandeling.

In **Hoofdstuk 7** hebben wij onderzocht of de aanwezigheid van ischemische laesies in het diepe waterscheidingsgebied op een MRI duidt op een gestoorde cerebrale doorbloeding, en of dit geassocieerd is met een verhoogd risico op een nieuw herseninfarct. Zesendertig patiënten met een symptomatische carotis occlusie ondergingen een MRI hersenen, een angiografie, en een TCD CO_2-reactiviteitsmeting. Het beeld van een diep waterscheidingsinfarct was aanwezig in 15 van de 36 patiënten (42%). De gemiddelde CO_2-reactiviteit bedroeg 6% ± 9% in de patiënten met een diep waterscheidingsinfarct, en dat was significant lager dan de 20% ± 14% die werd gevonden bij patiënten zonder waterscheidingsinfarct (gemiddeld verschil 14%, 95% BI 5 – 23). Deze bevinding van een lagere CO_2-reactiviteit in patiënten met een diep waterscheidingsinfarct vergeleken met patiënten zonder diep waterscheidingsinfarct, binnen een geselecteerde groep van patiënten met een symptomatische carotis occlusie, is suggestief voor een hemodynamische oorzaak van dit type infarct. Gedurende een gemiddelde follow-up van 2.4 ± 1.2 jaar, hadden 3 (20%) patiënten met een diep waterscheidingsinfarct een nieuw herseninfarct vergeleken met 4 (19%) patiënten zonder diep waterscheidingsinfarct, resulterend in een hazard ratio (HR) 1.0 (95% BI 0.2 – 4.6) van diepe waterscheidingsinfarcten op het risico op een nieuw herseninfarct. Dat geen voorspellende waarde aangetoond kon worden is waarschijnlijk gerelateerd aan de relatief kleine onderzoekspopulatie in deze studie. Een studie met grotere patiëntenpopulatie zal nodig zijn om de voorspellende waarde van de aanwezigheid van ischemische laesies in het diepe waterscheidingsgebied op een MRI op een nieuw herseninfarct te onderzoeken.

Tot slot worden in **Hoofdstuk 8** de implicaties van de in Hoofdstuk 2 tot en met 7 beschreven studies voor de toekomst besproken. Patiënten die zich presenteren met een TIA of een ten hoogste matig ernstig invaliderend herseninfarct en een ipsilaterale carotis occlusie hebben een relatief laag risico op een nieuw herseninfarct, zeker als zich in de eerste 18 maanden geen herseninfarct heeft voorgedaan. Zelfs patiënten met een bilaterale carotis occlusie hebben een laag risico op een nieuw herseninfarct. Hoewel dit geruststellend lijkt voor de patiënten, moet opgemerkt worden dat het risico op andere belangrijke vasculaire aandoeningen aanzienlijk is. Ook hiervoor is optimale secundaire preventie en een strikte regulering van de vasculaire risicofactoren van groot belang. Gebaseerd op de studies in dit proefschrift en op eerdere publicaties suggereren wij dat alleen bij de patiënten met een verhoogde kans op een nieuw herseninfarct op basis van klinische symptomen aanvullende diagnostiek naar de hemodynamische toestand van de hersenen geïndiceerd is. MRI kan

worden verricht om de aanwezigheid en type van infarcering in beeld te brengen. De aanwezigheid van een diep waterscheidingsinfarct is indicatief voor een doorbloedingsstoornis. TCD met CO_2-reactiviteits meting kan worden overwogen als screening, maar is niet voorspellend gebleken op het risico op een nieuw herseninfarct. Bovendien is het van belang te realiseren dat, als een interventie wordt overwogen, TCD met CO_2-reactiviteit een PET meting niet kan vervangen voor de selectie van patiënten voor een EC/IC bypass operatie of een ander type van revascularisatie. O-15 PET kan helpen met het herkennen van een patiënt met een doorbloedingsstoornis die mogelijk een gunstig effect zou kunnen hebben van een interventie. Zo lang er geen bewijs is voor een gunstig effect van een interventie zoals operatie of stenten van een bloedvat belangrijk voor de collaterale bloedvoorziening of een EC/IC bypass operatie, zal het beleid voor iedere patiënt individueel bepaald moeten worden.

Samenvatting voor niet-medici

Een TIA of een herseninfarct worden gekenmerkt door plotseling optredende neurologische uitvalsverschijnselen, zoals een scheve mondhoek, verlamming van een arm of been of problemen met praten of zien. Als de klachten kortdurend aanwezig zijn wordt gesproken over een TIA, bij uitval gedurende meer dan 24 uur wordt gesproken over een herseninfarct. De oorzaak van zowel een TIA als een herseninfarct is een stoornis in de bloedtoevoer naar de hersenen. Vier slagaders zijn verantwoordelijk voor de bloedtoevoer naar de hersenen; twee aan de voorzijde in de hals (arteria carotis) en twee aan de achterzijde (arteria vertebralis). Bij ongeveer 9% van de patiënten die een TIA of herseninfarct doormaken, wordt een volledige afsluiting van de voorste halsslagader gevonden. Het risico op een nieuw herseninfarct nadat een afgesloten halsslagader is vastgesteld is ongeveer 5-6% per jaar op basis van eerdere studies. Bij patiënten met een verminderde doorbloeding van de hersenen kan dit risico oplopen tot 12% per jaar. Op dit moment bestaat de standaard behandeling uit bloedplaatjes-remmers en controle van vaatrisicofactoren, zoals suikerziekte en een verhoogd cholesterolgehalte. Als een halsslagader volledig is afgesloten, kan er geen operatie of stentplaatsing meer worden verricht aan die slagader zelf. Een operatie die wel overwogen kan worden is een ingreep waarbij er een omleiding (bypass) werd aangelegd. Eerder onderzoek liet geen voordeel zien van deze bypass-operatie, maar het is nog onduidelijk of deze operatie voor bepaalde patiënten wel zinvol zou kunnen zijn. Een operatie van een ernstige vernauwing in één van de andere slagaders naar de hersenen of uit het tijdelijk verminderen van medicatie tegen hoge bloeddruk zouden andere zinvolle vormen van behandeling kunnen zijn, maar hiervan is niet bekend of het beter is dan de standaard behandeling met medicijnen.

Hoofdstuk 1 bevat een algemene inleiding. Vanwege de gedachte dat een operatie van een ernstige vernauwing in een van de andere slagaders naar de hersenen, of een bypass-operatie, mogelijk wel zinvol kan zijn bij patiënten met een aantoonbare doorbloedingsstoornis van de hersenen, wordt veel aandacht besteed aan de methoden om de hersendoorbloeding te meten. Het meten van de hersendoorbloeding kan gedaan worden met positron emissie tomografie (PET) onderzoek. De fysiologische principes hiervan worden in **Hoofdstuk 1** uitgelegd. PET is de enige methode waarmee met behulp van radioactiviteit de zuurstofopname uit het bloed in de hersenen gemeten kan worden, en dit is belangrijk omdat een verhoogde zuurstofopname voorspellend is gebleken voor de kans op een nieuw herseninfarct. Een nadeel van de PET scan is dat deze methode maar beperkt beschikbaar is. Een eenvoudig beschikbaar en goedkoper alternatief om de hersendoorbloeding te meten is met een

ultrageluid-onderzoek (transcraniële Doppler, TCD) met meting van de CO_2 (koolzuur)-reactiviteit als maat voor de reserves die de hersenen kunnen aanspreken om de doorbloeding te verhogen. Het is niet bekend welke methode het beste is om de prognose van patiënten met een afsluiting van de voorste halsslagader te bepalen.
De twee belangrijkste doelstellingen van dit proefschrift zijn (1) het beter herkennen van patiënten met een verhoogde kans op een nieuw herseninfarct op basis van klinische kenmerken en het meten van de hersendoorbloeding met ultrageluid (TCD) en PET, en (2) het verkrijgen van meer inzicht in het effect van een behandelstrategie bestaande uit een operatie van een ernstige vernauwing in een van de andere slagaders naar de hersenen of uit het tijdelijk verminderen van medicatie tegen hoge bloeddruk.

Hoofdstuk 2 beschrijft een onderzoek van 117 patiënten met een TIA of ten hoogste matig ernstig invaliderend herseninfarct bij een afgesloten halsslagader. Patiënten zijn gedurende ruim 10 jaar gevolgd; 22 patiënten werden behandeld met een operatie van een ernstige vernauwing in één van de andere slagaders en 16 patiënten ondergingen een bypass-operatie. Drieëntwintig patiënten kregen een nieuw herseninfarct; dit betekent een risico van 2.4% per jaar. De eerste anderhalf jaar was de kans op een nieuw herseninfarct het grootst. Risicofactoren voor het krijgen van een nieuw herseninfarct waren: hogere leeftijd, klachten vanuit de hersenen in plaats van alleen vanuit het oog, terugkerende klachten na aangetoonde afgesloten halsslagader, uitvalsverschijnselen waarbij een arm of been ging schudden (limb-shaking TIAs), een eerder doorgemaakt herseninfarct en natuurlijke reservekanalen die zijn ontstaan op het oppervlak van de hersenen (leptomeningeale collateralen). TCD CO_2-reactiviteit was niet voorspellend voor de kans op het krijgen van een nieuw herseninfarct. Zevenenvijftig patiënten kregen een herseninfarct, hersenbloeding, hartinfarct of vasculaire dood. Dit betekent een risico van 6.4% per jaar. De kans op een belangrijke vaataandoening in het algemeen was dus duidelijk hoger dan de kans op een nieuw herseninfarct.

Bij sommige patiënten is de voorste halsslagader aan beide kanten afgesloten. De prognose van deze patiënten wordt besproken in **Hoofdstuk 3**. Zevenenvijftig patiënten met twee afgesloten voorste halsslagaders zijn gevolgd gedurende gemiddeld bijna 6 jaar. Vier van de 57 patiënten kregen een nieuw herseninfarct. Dit betekent een risico van 1.2% per jaar. Risicofactoren voor de kans op een nieuw herseninfarct konden niet worden onderscheiden. Achttien patiënten kregen een herseninfarct, hersenbloeding, hartinfarct of vasculaire dood. Het risico hierop was 5.3% per jaar. Hoge leeftijd en een hartaandoening in de

voorgeschiedenis waren de belangrijke risicofactoren.

Sommige patiënten beschrijven dat zij af en toe kortdurend last hebben van schudden van een arm of been of beiden. Dit kan passen bij limb-shaking TIAs. Meer details over de klinische kenmerken van limb-shaking TIAs van 34 patiënten met een afgesloten halsslagader worden beschreven in **Hoofdstuk 4**. Het is gebleken dat limb-shaking bij patiënten met een afgesloten halsslagader meestal korter dan vijf minuten duurt, vaak gepaard gaat met krachtsverlies van het betrokken ledemaat en vaak, maar niet altijd, voorafgegaan wordt door een activiteit waarbij de hersendoorbloeding tijdelijk kan verminderen, zoals opstaan, inspanning of hoesten.We hebben onderzocht of patiënten met limb-shaking een slechtere doorbloeding van de hersenen hebben dan patiënten met een afgesloten halsslagader die geen limb-shaking hebben. Patiënten met limb-shaking hadden vaker klachten die uitgelokt werden door bijvoorbeeld opstaan of inspanning en zij hadden vaker terugkerende klachten nadat de afgesloten halsslagader bewezen was. Verder was er een trend tot een lagere TCD CO_2-reactiviteit bij patiënten met limb-shaking TIAs. Patiënten met een afgesloten halsslagader en limb-shaking lijken dus een meer gestoorde hersendoorbloeding te hebben vergeleken met patiënten met een afgesloten halsslagader maar zonder limb-shaking. Of de aanwezigheid van een simpel kenmerk zoals limb-shaking gebruikt kan worden om patiënten te herkennen die mogelijk een voordeel zouden kunnen hebben van een operatie zal nog nader moeten worden uitgezocht.

Zowel PET als ultrageluid (TCD) onderzoek kunnen hiervoor gebruikt worden, maar het is niet bekend of de resultaten van deze twee methoden met elkaar overeenkomen. De studie in **Hoofdstuk 5** beschrijft de vergelijking van PET en ultrageluid metingen bij 24 patiënten met een afgesloten halsslagader. Zeventien (71%) patiënten hadden een gestoorde CO_2-reactiviteit gemeten met ultrageluid. Op basis van de PET metingen hadden 15 patiënten een doorbloedingsstoornis. Er was overeenkomst in resultaten tussen PET en ultrageluid bij 12 patiënten (50%). Er was geen significante correlatie tussen de absolute PET waarden en ultrageluid metingen. Deze studie toonde aan dat er bij de helft van de patiënten overeenstemming werd gezien tussen de resultaten van PET en ultrageluid. Dit betekent dus dat metingen met PET niet zomaar vervangen kunnen worden door een ultrageluid met CO_2-reactiviteit meting in de selectie van patiënten voor bijvoorbeeld een bypass-operatie of een andere interventie om de hersendoorbloeding te verbeteren.

In **Hoofdstuk 6** hebben wij onderzocht of bij patiënten met een afgesloten

halsslagader een operatie aan een vernauwing in een van de andere slagaders naar de hersenen of het afbouwen van bloeddruk-medicatie de hersendoorbloeding gemeten met een PET scan kan verbeteren. Drieëntwintig patiënten met een afgesloten halsslagader ondergingen een PET scan bij het begin van de studie en na drie maanden. Twaalf patiënten zijn geloot voor de behandeling met interventie (operatie van een ernstige vernauwing in een van de andere slagaders naar de hersenen of uit het tijdelijk verminderen van medicatie tegen hoge bloeddruk), en 11 patiënten kregen alleen de standaardbehandeling met medicatie. Normaalwaarden voor PET onderzoek zijn verkregen op basis van zeven gezonde personen. Het bleek dat, zoals verwacht, de patiënten een lagere bloeddoorstroming in de hersenhelft aan de kant van de afgesloten halsslagader hadden dan de gezonde personen. Er waren geen verschillen in de veranderingen van hersendoorbloeding na drie maanden tussen patiënten die behandeld waren met een interventie en patiënten die de standaard behandeling kregen. Alleen bij de patiënten met een verminderde doorbloeding van de hersenen aan het begin van de studie werd een stijgende trend van de hersendoorbloeding waargenomen na interventie (n=7). De resultaten van deze studie leidden niet tot een eenduidige conclusie. Met behulp van PET kon niet worden aangetoond dat behandeling met een interventie de doorbloeding van de hersenen meer verbeterde dan de standaard medicamenteuze behandeling. Wel lijkt PET onderzoek geschikt om een subgroep van patiënten met verminderde doorbloeding te onderscheiden die mogelijk wel baat kunnen hebben bij een interventie gericht op het verbeteren van de hersendoorbloeding.

Bij patiënten met een afgesloten halsslagader wordt vaak een MRI scan gemaakt om te kijken of er in de hersenen infarcten aanwezig zijn. Een specifiek type herseninfarct, namelijk het infarct in het diepe waterscheidingsgebied, wordt vaak gezien bij patiënten met een afgesloten halsslagader. De vraag of de aanwezigheid van een diep waterscheidingsinfarct wijst op een gestoorde hersendoorbloeding, en of dit een relatie heeft met een verhoogd risico op een nieuw herseninfarct, is het onderwerp van de studie beschreven in **Hoofdstuk 7**. Zesendertig patiënten met een afgesloten halsslagader werden onderzocht met een MRI scan van de hersenen. Een diep waterscheidingsinfarct was aanwezig in 15 van de 36 patiënten (42%). Patiënten met een diep waterscheidingsinfarct hadden een lagere CO_2-reactiviteit dan patiënten zonder diep gelegen waterscheidingsinfarct. Deze bevinding van een lagere CO_2-reactiviteit in patiënten met een diep waterscheidingsinfarct is suggestief voor een gestoorde hersendoorbloeding als oorzaak van dit type infarct. Deze patiënten zijn gemiddeld 2.4 jaar gevolgd. Drie (20%) patiënten met een diep

waterscheidingsinfarct kregen een nieuw herseninfarct vergeleken met 4 (19%) patiënten zonder diep waterscheidingsinfarct. Dit was niet verschillend. Dat geen voorspellende waarde aangetoond kon worden is waarschijnlijk gerelateerd aan het relatief kleine aantal patiënten in deze studie. Een studie met meer patiënten zal nodig zijn om de voorspellende waarde van de aanwezigheid van een diep waterscheidingsinfarct op een MRI op een nieuw herseninfarct te onderzoeken.

Tot slot worden in **Hoofdstuk 8** de implicaties van de in Hoofdstuk 2 tot en met 7 beschreven studies voor de toekomst besproken. Patiënten die zich presenteren met een TIA of een ten hoogste matig ernstig invaliderend herseninfarct en een afgesloten halsslagader hebben tegenwoordig waarschijnlijk een lager risico op een nieuw herseninfarct dan in het verleden werd aangenomen, zeker als zich in de eerste 18 maanden geen herseninfarct heeft voorgedaan. Zelfs patiënten met een dubbelzijdige afgesloten halsslagader hebben een laag risico op een nieuw herseninfarct. Hoewel dit geruststellend lijkt voor de patiënten, moet opgemerkt worden dat het risico op andere belangrijke vasculaire aandoeningen aanzienlijk is. Ook hiervoor is optimale secundaire preventie en een strikte regulering van de vasculaire risicofactoren van groot belang. Gebaseerd op de studies in dit proefschrift en op eerdere publicaties suggereren wij dat alleen bij de patiënten met een verhoogde kans op een nieuw herseninfarct op basis van klinische kenmerken aanvullend onderzoek naar de hersendoorbloeding nodig is. Een MRI scan kan worden verricht om de aanwezigheid en type van herseninfarct in beeld te brengen. De aanwezigheid van een diep waterscheidingsinfarct past bij een gestoorde hersendoorbloeding. Ultrageluidonderzoek met CO_2-reactiviteit meting kan worden overwogen als screening, maar is niet voorspellend gebleken op het risico op een nieuw herseninfarct. Bovendien is het van belang te realiseren dat, als een interventie wordt overwogen, ultrageluid een PET meting niet kan vervangen voor wat betreft de selectie van patiënten voor een bypass-operatie of een andere interventie om de hersendoorbloeding te verbeteren. PET onderzoek kan helpen met het herkennen van een patiënt met een doorbloedingsstoornis die mogelijk een gunstig effect zou kunnen hebben van een interventie. Zolang er geen bewijs is voor een gunstig effect van een interventie zoals operatie van een bloedvat belangrijk voor de bloedtoevoer naar de hersenen of een bypass-operatie, zal het beleid voor iedere patiënt individueel bepaald moeten worden.

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About the author

About the author

Suzanne Persoon werd geboren op 5 januari 1981 in Hardenberg, Overijssel. In 1998 behaalde zij haar VWO-diploma aan het Vechtdal College in Hardenberg. Vervolgens ging zij in Groningen Bewegingswetenschappen studeren. Tijdens deze studie kreeg zij steeds meer interesse voor het artsenvak. Nadat zij in 2002 afstudeerde in de Bewegingswetenschappen is zij gestart met de studie Geneeskunde aan de Rijksuniversiteit Groningen. Dit deed zij volgens het zij-instroom traject, zodat zij eind 2005 haar artsexamen behaalde. Aansluitend werkte zij een jaar als arts-assistent niet in opleiding op de afdeling neurologie van de Isala Klinieken in Zwolle. In 2007 kreeg zij een aanstelling als arts-assistent op de afdeling neurologie in het Universitair Medisch Centrum Utrecht. Een jaar later startte zij met wetenschappelijk onderzoek onder begeleiding van dr. C.J.M. Klijn en prof. dr. L.J. Kappelle. Daarnaast begon zij in 2008 met de opleiding tot neuroloog onder begeleiding van prof. dr. J.H.J. Wokke. In 2010 heeft zij drie maanden onderzoek gedaan naar de prognose van een post-anoxisch coma aan Stanford University in Palo Alto, Californië, VS, onder begeleiding van dr. C.A.C. Wijman. Vervolgens heeft zij het wetenschappelijk onderzoek dat resulteerde in dit proefschrift gecombineerd met de opleiding tot neuroloog. De opleiding tot neuroloog verwacht zij in 2015 af te ronden.

List of publications

List of publications

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