Progress Review

The Pathophysiology of Watershed Infarction in Internal Carotid Artery Disease

Review of Cerebral Perfusion Studies

Isabelle Momjian-Mayor, MD; Jean-Claude Baron, MD, FRCP, FMedSci

Background and Purpose—In carotid disease, infarcts can occur in the cortical as well as internal watershed (WS), or both. Better understanding the pathophysiology of WS infarcts would guide treatment. Two distinct hypotheses, namely low-flow and micro-embolism, are equally supported by neuropathological and physiological studies. Here we review the evidence regarding the mechanisms for WS stroke in carotid disease and whether they differ between cortical and internal WS infarcts.

Summary of Review—After a brief account of the anatomy of the WS and the cerebrovascular physiology in circumstances of low perfusion pressure, the literature concerning the mechanisms of WS infarction in carotid disease is reviewed and discussed with emphasis on imaging and ultrasound studies of the cerebral hemodynamics.

Conclusion—The evidence strongly favors a hemodynamic mechanism for internal WS infarction, especially regarding the so-called rosary-like pattern in the centrum semiovale. However, the relationships between cortical WS infarction and hemodynamic compromise appear more complicated. Thus, although severe hemodynamic compromise appears to underlie combined cortical and internal WS infarction, artery-to-artery embolism may play an important role in isolated cortical WS infarcts. Based on the high prevalence of microembolic signals documented by ultrasound in symptomatic carotid disease, a recent hypothesis postulates that embolism and hypoperfusion play a synergetic role, according to which small embolic material prone to lodge in distal field arterioles would be more likely to result in cortical micro-infarcts when chronic hypoperfusion prevails. Future studies combining imaging of brain perfusion, diffusion-weighted imaging, and ultrasound detection of microembolic signals should help resolve these issues. **(*Stroke*. 2005;36:567-577.)**

Key Words: carotid artery occlusion ■ cerebral blood flow ■ stroke ■ tomography emission, computed.

Watershed infarcts involve the junction of the distal fields of 2 nonanastomosing arterial systems. Classic neuropathologic studies[1] describe 2 distinct supratentorial WS areas: (1) between the cortical territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA); and (2) in the white matter along and slightly above the lateral ventricle, between the deep and the superficial arterial systems of the MCA, or between the superficial systems of the MCA and ACA. The former, superficial areas have been commonly referred to as the cortical watershed (CWS), and the latter have been referred to as the internal watershed (IWS).

In autopsy studies, CWS and IWS infarcts—also termed external and internal border-zone infarcts, respectively—together represent ≈10% of all brain infarcts.[2] However, because WS infarction is seldom fatal, this is probably an underestimate, and imaging studies in severe internal carotid artery (ICA) disease report an incidence ranging from 19% to 64%.[3–5]

Although the pathological[6,7] and imaging characteristics[3,8,9] of WS infarcts are well-described, their pathogenesis remains debated. Based on the well-established notion that severe systemic hypotension can cause bilateral WS infarction,[7,10] hemodynamic failure is classically thought to cause WS infarcts in ICA disease.[4,8,9,11] Susceptibility of the WS areas is thought to result from their situation of "distal field," where perfusion pressure is lowest,[12] and repeated episodes of hypotension in the presence of severe ICA disease is regarded as facilitating WS infarcts. However, the cortical distal field may not always correspond to the WS in situations in which a shift of the latter (as revealed angiographically by the pattern of leptomeningeal anastomoses) has occurred because of additional hypoplasia or stenosis of the proximal ACA, PCA, or MCA. The occasional occurrence of syncope at onset of WS stroke,[13,14] and the typical clinical presentation of episodic, fluctuating, or progressive weakness of the hand, occasionally associated with upper limb shaking, are consistent with, and classically considered as markers of, hemodynamic failure.[3,15,16] This interpretation is further supported by radiological studies showing that WS infarcts distal to ICA disease are more likely with a noncompetent circle of Willis.[17–19] In contrast, embolism from ICA disease

Received November 12, 2004; accepted November 22, 2004.
From the Department of Neurology and Stroke Unit, University of Cambridge, Cambridge, UK.
Current affiliation for I.M.-M. is the Department of Neurology, University Hospital, Geneva, Switzerland.
Correspondence to Dr J.-C. Baron, Department of Neurology, Addenbrooke's Hospital Box 83, Cambridge CB2 2QQ, UK. E-mail jcb54@cam.ac.uk

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000155727.82242.e1**

preferentially affects the stem and large branches of the MCA, producing cortical "wedge-shaped" and/or deep striato-capsular infarcts.[17,19]

In sharp contrast with this widely prevalent interpretation, several pathological reports emphasize the association of WS infarction with microemboli arising from unstable carotid plaques or from the stump of an occluded ICA. Jorgensen and Torvik[2] and Torvik and Skullerud[6] were the first to report that most of the occlusions observed in the leptomeningeal arteries over WS infarcts distal to ICA occlusion resulted from microemboli occluding the terminal vascular field, rather than being secondary to slowing of the cerebral blood flow (CBF). Beal et al[20] reported a patient in whom arm paresis developed after multiple transient ischemic attacks (TIAs) distal to ulcerative carotid plaque and who was found at autopsy to have multiple pial arteries occluded by cholesterol emboli in the border zone. Pollanen and Deck[21] reported 3 cases in which embolization of thrombotic material (from the heart in 2 cases and from the ICA in 1) caused the CWS infarct. Masuda et al[22] found atheromatous embolism to cause CWS infarcts by occlusion of the terminal cortical branches with small emboli (50 to 300 μm) mostly composed of cholesterol crystals, whereas territorial infarcts were related to larger fibrin emboli. Importantly, there is experimental evidence that small thrombi travel preferentially to WS areas because of their distinctly small size.[23] Interestingly, cerebral amyloid angiopathy has recently been proposed as a risk factor for microinfarcts in the CWS areas.[24]

Whereas these observations mainly applied to CWS infarction, a recent pathological study[25] of 12 patients with IWS infarcts suggested that ischemic lesions observed in the IWS area may also involve an embolic mechanism, either cardiac or artery-to-artery. In the majority of lesions, histology revealed a significant component of incompletely infarcted brain, which, according to the authors, would be consistent with transient embolic occlusion. However, occluding material was not directly observed.

Overall, therefore, there is considerable controversy regarding the pathophysiology of WS infarcts in critical ICA disease, with both the low-flow and the multi-embolic mechanism being considered based on substantial evidence for both. Interestingly, as is detailed, a synergetic association of these 2 mechanisms has been recently postulated.[26]

The purpose of this article is to review the evidence regarding the role of hypoperfusion versus emboli in the development of WS infarction in ICA disease, and to assess whether the mechanisms may differ between cortical and internal WS infarcts. Better understanding the underlying mechanisms of WS infarction would help identify those patients at high risk for, and provide an evidence-based rationale for preventing the occurrence and progression of, WS infarction. After a brief account of the anatomy of the WS and of the basic physiology of the cerebral circulation in circumstances of focally reduced perfusion pressure, the literature concerning the mechanisms of WS infarction in ICA disease is reviewed, with emphasis on the studies that assessed brain perfusion and hemodynamics with ultrasound techniques or physiological imaging. The overall significance of these findings is then briefly discussed.

WS Infarcts: Anatomy, Structural Imaging, and Angiography

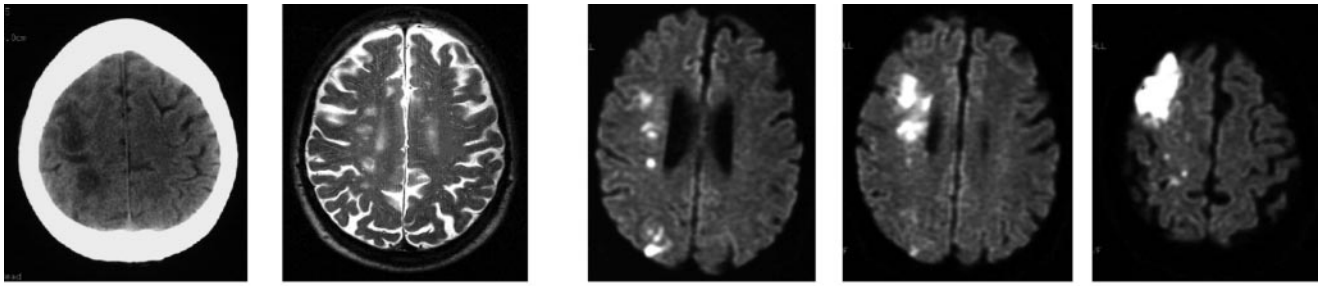
The CWS regions are boundary zones where functional anastomoses between the 2 arterial systems exist, ie, on the pial surface between the major cerebral arteries.[27] CWS infarcts represent the most familiar WS strokes. Anterior WS infarcts develop between the ACA and MCA territories, either or both as a thin fronto-parasagittal wedge extending from the anterior horn of the lateral ventricle to the frontal cortex, or superiorly as a linear strip on the superior convexity close to the interhemispheric fissure, whereas posterior WS infarcts develop between the ACA, MCA, and PCA territories and affect a parieto-temporo-occipital wedge extending from the occipital horn of the lateral ventricle to the parieto-occipital cortex.[1,28]

IWS infarcts can affect the corona radiata (CR), between the territories of supply of the deep and superficial (or medullary) perforators of the MCA, or the centrum semiovale (CSO), between the superficial perforators of the ACA and MCA.[1] However, in carotid disease, ie, the focus of this review, it is unlikely that hemodynamic insufficiency will affect equally the basal and the superficial MCA perforators, a situation that could, however, arise from eg, added MCA stem disease.

Structural Imaging

The impression that might be gained from the clinico-radiological literature is that the major WS areas occur at symmetrical, predictable sites in the hemisphere.[29] However, for both types of WS regions, there is substantial inter-individual and intra-individual variation. Using the minimum and maximum areas of MCA supply (as defined by van der Zwan et al)[30] to assess whether infarcts distal to a hemodynamically significant ICA disease would be regarded as territorial or border-zone, 64% were considered as WS infarcts when using the minimum area, but only 19% when using the maximum area of supply.[31] Identifying typical computed tomography (CT) or magnetic resonance (MR) patterns associated with border-zone infarction is therefore not always straightforward. In any individual patient, it may be on occasions difficult to decide on the basis of brain imaging whether an infarct has arisen from occlusion of a small cortical branch of the MCA or from hypoperfusion caused by established ICA disease.

On the basis of their radiological appearance, IWS infarcts have been divided into confluent and partial infarcts.[15] Confluent infarcts correspond to large cigar-shaped infarcts alongside the lateral ventricle, whereas partial IWS infarcts may appear either as a single lesion or in a chain-like (or "rosary-like") pattern in the CSO. However, partial IWS infarcts sometimes are difficult to distinguish from lacunar, medullary, or striatocapsular infarcts, as well as from leukoariosis. The latter, however, affects in a diffuse way the paraventricular WM bilaterally as it represents chronic diffuse white matter ischemia. Partial IWS infarct and leukoariosis may, however, coexist, particularly in the elderly. Regarding medullary infarcts, they correspond to small, immediately subcortical infarcts caused by occlusion of medullary arteries arising from the pial plexus.[32] They are generally smaller and more superficial than partial IWS infarcts,[33] but IWS and white matter medullary infarcts have



Illustrative examples of watershed infarcts in patients with ICA disease. A, Right-hemisphere anterior watershed infarct on CT, affecting a superior strip between the ACA and MCA cortical territories. B, Right-hemisphere internal watershed infarct in the centrum semi-ovale (rosary-like pattern) on T2-weighted magnetic resonance imaging. C, Three DWI cuts from a single patient showing a right-hemisphere acute infarct involving both the cortical watershed (mainly the anterior but also slightly the posterior watershed) and the internal watershed (rosary-like as well as confluent patterns).

been sometimes lumped together as so-called subcortical white matter infarcts because of the difficulty in distinguishing between them, further complicating classification.

Illustrative examples of WS infarcts are shown in the Figure.

Angiography: WS Infarct and the Circle of Willis

Although a noncompetent circle of Willis should be regarded as an additional predisposing condition in WS infarcts from ICA disease,[19] the role of supplency in the prevalence of WS infarcts is itself a matter of debate. The absence of collateral blood flow via the anterior communicating (ACoA) and the posterior communicating artery has been associated with WS infarcts (both CWS and IWS).[19,34] However, there are contradictory opinions on the protecting role of collateral flow. Accordingly, collateralization through the posterior communicating artery has been alternatively reported as protective[35,36] or without effect[37] on the prevalence of WS infarction. Moreover, supplency via the anterior communicating artery was associated with a significant reduction in the prevalence and volume of IWS infarcts only, thus of no consequence for CWS.[37]

Brain Perfusion and Hemodynamic Studies: Basic Physiology, Methods, and Study Design

The physiological response of the brain to reduced cerebral perfusion pressure (CPP) distal to ICA occlusion was established thanks to physiological imaging, initially positron emission tomography (PET),[38–40] and subsequently SPECT.[41] The initial response to a decline in the CPP is an autoregulatory vasodilatation of the resistive vessels (stage I of hemodynamic impairment).[42] This results in increased cerebral blood volume, longer mean transit time, and impaired response to vasodilatory challenge (hypercapnia or intravenously administered acetazolamide).[38–40] With further reduction in the CPP, the autoregulatory vasodilatation becomes inadequate and the CBF decreases. As neurons tend to maintain their oxidative metabolism, the oxygen tissue tension decreases and the oxygen extraction fraction (OEF) increases ("misery perfusion"[38] or stage II[42,43]). Below the CBF penumbra threshold, neuronal function is impaired and the affected tissue is at risk of infarction;[44] however, it is unknown if long-lasting reductions of CBF above the penumbra threshold may also result in infarction—complete or incomplete.

Materials and Methods

Regardless of the technique used, all the studies reviewed here aimed to detect reduced CPP in the affected ICA territory, in the form of either misery perfusion or impaired perfusion reserve, ie, reduced vasodilatory capacity, increased cerebral blood volume, or prolonged mean transit time.[43] In severe ICA disease, the CBF response may be abnormally reduced or even absent because of maximal vasodilation; a focal decrease in CBF may even occur ("steal phenomenon").[45] Techniques used have been either imaging-based, such as xenon CT, single-photon emission tomography (SPECT), PET, and MR-based perfusion (perfusion-weighted imaging [PWI]), or ultrasound-based, mainly transcranial Doppler sonography (TCD). One major difference between imaging techniques and TCD is that whereas the former allows one to assess perfusion directly in the brain region of interest (ROI), the latter assesses flow in the MCA trunk only, so it may lack sensitivity.

Design

Regarding design, studies reviewed here have either assessed the relationships between the presence of a WS infarct and the hemodynamic status of the carotid circulation, or directly measured perfusion in or near the WS infarct per se, for instance by drawing ROIs in the white matter of the affected CSO. Some studies, however, investigated patients without WS infarct and assessed the hemodynamic status in the WS areas. This diversity of designs occasionally complicates the comparison among studies.

Results

Even though the study of cortical WS infarction has been historically anterior and is still numerically superior to that of internal WS infarction, we review the latter first because, as will be seen, its pathophysiology appears less controversial than the former.

Since 1981, 33 perfusion studies addressing the issue of WS pathophysiology in ICA disease have been published in the English language. Tables 1 to 4 list these studies according to the investigative method used (PET in Table 1; SPECT, Xenon 133, and xenon CT in Table 2; TCD in Table 3; magnetic resonance imaging in Table 4). Note that 34 entries appear in the Tables as 1 study used 2 different techniques. Although some studies lumped together CWS and IWS infarcts as "low-flow infarcts," most did assess them separately or even directly compared them, which, as will be seen, turned out to be crucial. Within IWS infarcts, however, only a minority of studies made the important distinction between CR and CSO infarcts, another important issue. To facilitate reading, the findings regarding the pathophysiology of IWS and CWS infarcts are

TABLE 1. PET Studies

Authors and Year	Reference	Patient	ICA Disease	ROI	Infarct Location (N)	Findings
Baron et al 1981	38	1	Occlusion	MCAT AWS, PWS	None	Misery perfusion in PWS, reversed after EC–IC bypass
Samson et al 1985	61	12	Occlusion (11)	ACAT, MCAT, PCAT	MCAT(4), ACAT(1), lacunar (1),	Misery perfusion in AWS, PWS and MCAT, reversed in some
			MCAO (1)	AWS, PWS	CWS (5)	pts after EC–IC bypass
Leblanc et al 1987	63	7	Stenosis >80%	MCAT	IC (1)	Impaired hemodynamics in AWS
				AWS, PWS		
Leblanc et al 1989	64	15	Occlusion (8)	MCAT	IC (3)	Impaired hemodynamics in AWS
			Uni/bil stenosis (7)	AWS, PWS		
Carpenter et al 1990	65	32	Stenosis >50% or occlusion	MCAT AWS, PWS	None	No evidence of hemodynamic impairment
Yamauchi et al 1990	67	9	Occlusion	MCAT, ACAT, PCAT	CSO (8)	Greater hemodynamic compromise in PWS
				AWS, PWS		
Yamauchi et al 1990	57	7	Occlusion	PV WM, CSO	CSO	CSO lesions related to impaired hemodynamics
Yamauchi et al 1991	58	16	Occlusion (11)	ACAT, MCAT, PCAT	CSO/CR (5)	CSO lesions related to impaired
			Stenosis (5)	AWS, PWS	Subcortical (6)	hemodynamics
Levine et al 1991	68	18	Stenosis (8)	MCAT	None	Impaired hemodynamics in AWS
			Occlusion (5)	AWS, PWS		with ICAS >50%
			Nonstenotic plaque (5)			
Levine et al 1992	69	16	Stenosis (8)	MCAT	None	Impaired hemodynamics in AWS
			Occlusion (8)	AWS, PWS		
Yamauchi et al 1999	59	7	Occlusion	MCAT	CSO	Misery perfusion in the CSO
				AWS, PWS		
				CSO		
Derdeyn et al 2000	60	36	Occlusion	MCAT	MCAT/	No evidence of selective
				IWS	BG; normal WM	hemodynamic impairment in IWS
Derdeyn et al 2001	76	110	Occlusion uni/bil	MCAT	MCAT	Rosary-like pattern in IWS related
					CWS (9), IWS (17; rosary-like in 8)	to hemodynamic impairment; no hemodynamic impairment in CWS
Arakawa et al 2003	75	24	Occlusion (10) ICAS (6)	IWS, AWS, PWS MCAT	Lacunar or small cortical	Misery perfusion more frequently observed in IWS
			MCAS/MCAO (8)			No hemodynamic compromise observed in CWS

ACAT indicates anterior cerebral artery territory; AWS, anterior watershed; BG, basal ganglia; bil, bilateral; CR, corona radiata; CSO, centrum semiovale; CWS, cortical watershed; EC–IC, extracranial–intracranial; ICAO, internal carotid artery occlusion; ICAS, internal carotid artery stenosis; IWS, internal watershed; MCAO, middle cerebral artery occlusion; MCAS, middle cerebral artery stenosis; MCAT, middle cerebral artery territory; PCAT, posterior cerebral artery territory; pts, patients; PVWM, periventricular white matter; PWS, posterior watershed; ROI, region of interest; uni, unilateral; WM, white matter.

presented according to the following operational classification: (1) studies of "low-flow infarcts"; (2) studies that specifically assessed the pathophysiology of IWS infarcts; (3) studies that specifically assessed the pathophysiology of CWS infarcts; and (4) studies that directly compared the pathophysiology of IWS and CWS infarcts. The studies that prospectively assessed the impact of hemodynamic impairment on the risk of stroke in patients with symptomatic ICA disease are also briefly reported.

Studies of Low-Flow Infarcts

Six studies, some early but also a few recent, did not separately assess IWS and CWS areas,[46–51] implicitly assuming that their pathophysiology was similar. The number of patients enrolled ranged from 11 to 102; all were symptomatic ICA disease (stenosis or occlusion). Two studies used TCD,[46,47] 1 used Xenon-133,[48] and 3 used PWI.[49–51] All compared patients with low-flow infarcts to patients with territorial infarcts, and all found the former to be associated with a greater degree of hemodynamic compromise than the latter, in an area far exceeding the area of infarction.

Studies That Specifically Assessed the Pathophysiology of IWS Infarcts

Nine studies focused on the pathophysiology of IWS infarcts (note that in none did the authors explicitly state that associated CWS infarcts were excluded). Three used TCD,[52–54] 1 used SPECT,[55] 1 combined SPECT and TCD,[56] and 4 used PET.[57–60] They involved relatively small numbers

TABLE 2. SPECT and Xenon-CT Studies

Author and Year	Reference	Patient	ICA Disease (No.)	ROI	Infarct Location (No.)	Findings
Yonas et al 1985	62	1	Occlusion	ACAT, MCAT, PCAT, AWS, PWS	None	Greatest perfusion abnormality observed in PWS, reversed after EC–IC bypass
Waterston et al 1990	52	10	Occlusion (9) Stenosis (1)	Not stated	CSO (6) + CR (1) + CH + IC (3)	IWS infarcts related to hemodynamic compromise
Tatemichi et al 1990	66	1	Stenosis + ctr occlusion	Not stated	None	Selective vulnerability of AWS to hemodynamic compromise; reversed after EC-IC bypass
Weiller et al 1991	56	37	Occlusion (28) MCAO (1) None (8)	MCAT	IWS (17) MCAT (20)	IWS infarcts related to hemodynamic compromise
Chollet et al 1996	71	1	Occlusion + ctr stenosis	Not stated	AWS	Recurrence of AWS infarct due to hemodynamic compromise
Moriwaki et al 1997	74	29	Occlusion/stenosis (20) MCAO (9)	MCAT	CSO (12), CR (10) CWS and IWS (3) CWS alone (7)	IWS infarcts, but not CWS infarcts, related to hemodynamic compromise
Isaka et al 1997	55	23	Occlusion	WM	CSO	CSO lesions specific and sensitive for the presence and severity of hemodynamic compromise
Dettmers et al 1997	48	21	Occlusion/stenosis	Not stated	TI (14) + AWS (4) + IWS (3)	WS infarcts related to hemodynamic compromise

ACZ indicates acetazolamide; CH, caudate head; CR, corona radiata; ctr, contralateral; TI, territorial infarcts.

of symptomatic patients (range, 7 to 37). Seven of these studies considered patients with ICAO only,[52,54–60] whereas 2 enrolled patients with either severe ICA stenosis or ICA occlusion.[53,58] All studies except 1 (the PET study of Derdeyn et al 2000[60]) concluded that IWS infarcts are related to hemodynamic impairment.

In 2 of the 3 PET studies in which the IWS was directly assessed with ROIs, it was found to be affected by misery perfusion, indicating marked hemodynamic impairment.[57,59] In contrast, the third study, that of Derdeyn et al,[60] concluded that the IWS is not more susceptible than the cortical MCA areas to hemodynamic compromise, even though 9 patients

TABLE 3. TCD Studies

Author and Year	Reference	Patient	ICA Disease (No.)	Infarct Location (No.)	Findings
Ringelstein et al 1988	47	55	Occlusion uni (40)/bil (15)	LFI (20) TI (14)	WS infarcts related to hemodynamic impairment
Weiller et al 1991	56	37	Occlusion (28) MCAO (1) None (8)	IWS (17) MCAT (20)	IWS infarcts related to hemodynamic impairment
Provinciali et al 1993	46	30	Occlusion	IWS (12) CWS (2) MCAT (16)	WS infarcts related to hemodynamic impairment
Baumgartner et al 1994	70	112	Stenosis/occlusion	AWS (9) TI (26)	AWS infarct typically related to hemodynamic impairment
Ringelstein et al 1994	54	64	Occlusion	IWS (n=18) Territorial (n=28) No infarct (n=20)	Selective vulnerability of IWS to hemodynamic impairment
Krapf et al 1998	53	11	Occlusion uni (7)/bil (3) Bil siphon stenosis (1)	CSO (11) AWS (2)	Rosary-like CSO infarct typical for the presence of hemodynamic impairment
Bisschops et al 2003	37	70	ICAO		Significant association with hemodynamic impairment for IWS only

LFI indicates low-flow infarcts; TCD, transcranial Doppler.

showed increased OEF in the latter. Note, however, that patients with IWS infarcts were excluded from this study, while image analysis did not consider whether the OEF in the IWS was high, but rather whether it was higher than in the cortical MCA areas. These differences in study design may account for the apparent discrepancy with other reports.

Interestingly, 7 out of these 9 studies explicitly studied the CSO when addressing the issue of IWS infarcts,[53–55,57–60] most likely because, as stated, this is the IWS infarct expected to occur in ICA disease. So, the overall conclusion that IWS infarcts in ICA disease are related to hemodynamic impairment applies specifically to the CSO. More precisely, 5 of these studies[53,55,57–59] explicitly indicate the rosary-like pattern as typical for the presence of hemodynamic compromise. Furthermore, 1 study[55] directly compared the degree of hemodynamic impairment in CSO as compared with CR infarcts and concluded that CSO infarcts are specific and sensitive for the presence of hemodynamic impairment.

Studies That Specifically Assessed the Pathophysiology of CWS Infarcts

Fourteen investigations studied the CWS.[38,61–73] In 1 study only[70] did the authors explicitly state that associated IWS infarcts were excluded, which is, however, partly explained by the fact that interest in IWS infarcts is relatively recent. For instance, in 1 early PET study,[67] all symptomatic patients had IWS infarcts as well.

Of these 14 studies, 10 assessed patients with TIAs only and no CWS infarcts,[38, 62–69, 72] 2 assessed patients with CWS infarcts,[70,71] and 2 enrolled patients both with and without CWS infarcts.[61,73] There were 8 PET studies,[38, 61, 63–65, 67–69] 1 SPECT study,[71] 1 Xenon CT study,[62] 2 TCD studies,[66,70] and 2 perfusion MR studies.[72,73] All but 1 study[65] found a hemodynamic compromise in the CWS areas. This was true not only of the studies that assessed patients with TIAs only but also of those that investigated patients with CWS infarcts.

The observed hemodynamic abnormalities were reported to predominantly affect the anterior watershed (AWS)[63,64,66,68,69,72] more frequently than the posterior watershed (PWS).[38,67] Four studies assessed the CWS hemodynamics before and after successful revascularization, either extracranial–intracranial bypass[38,62] or carotid endarterectomy,[66,72] and each reported complete or partial resolution of the previously observed perfusion abnormalities.

Studies That Directly Compared the Pathophysiology of Both IWS and CWS Infarcts

Although 4 studies only belong to this category,[37,74–76] they are of particular significance because they directly compared the 2 WS areas. In 3 studies,[37,74,76] patients with isolated IWS or CWS infarcts were studied and their hemodynamic status compared, whereas in the fourth study[75] the comparison was made between CWS and IWS ROIs. Methods used were SPECT,[74] PET,[75,76] or TCD.[37] They involved 20, 110, 24, and 70 patients, respectively. All 4 studies reached the conclusion that there appears to exist a distinct mechanism underlying IWS and CWS infarction, ie, IWS infarcts are consistently associated with a hemodynamic compromise, while this is less significant for the CWS. Interestingly, within the IWS a comparison between the CSO and the CR was performed in 2 studies,[74,76] and both found that the CSO, and particularly the rosary-like pattern, was specifically related to hemodynamic impairment, in agreement with the already described findings of Isaka et al.[55] There are 2 additional important observations from this series of studies. Arakawa et al[75] found that although misery perfusion could affect both the IWS and the CWS, it never affected the CWS alone. Moriwaki et al[74] observed that tandem cortical and deep WS infarcts always involved the CSO and had greater hemodynamic compromise than present with isolated CWS infarcts. These findings therefore suggest that CWS infarcts may be underlain by hemodynamic compromise, but only when the deep WS, and more specifically the CSO, is also involved. This important observation may resolve the apparent discrepancy between the primary findings from these 4 studies and the aforementioned studies of CWS infarcts, because in the latter group of studies whether IWS infarcts were associated with CWS infarcts is not explicitly mentioned.

Relationships Between Hemodynamic Impairment and Risk of Stroke in Patients With ICA Occlusion

Itoh et al[77] reported a patient with TIAs and a tight intracranial right ICA stenosis, who on PET exhibited misery perfusion selectively in the ipsilateral AWS area and in whom cerebral infarction subsequently developed in the same area. Similarly, Yamauchi et al[78] reported a patient with right intracranial ICA stenosis who presented with mild left hemiparesis resulting from right AWS infarct. A PET study performed 2 months after the stroke revealed misery perfusion in the ipsilateral nonaffected PWS area. Three months later, the patient experienced a new infarct in the region of the PWS that specifically exhibited misery perfusion at the previous study.

Predictive Value of Hemodynamic Impairment on Subsequent Ipsilateral Stroke Risk in Patients With Symptomatic ICA Occlusion

Three PET studies[79–81] prospectively tested the hypothesis that increased OEF is an independent risk factor for subsequent ischemic stroke in patients with symptomatic ICA occlusion. The mean follow-up was 1 year, 31.5 months, and 5 years, respectively. All 3 studies found that patients with misery perfusion have a significantly higher risk for recurrent ipsilateral ischemic infarct at follow-up. An interesting information provided in Yamauchi et al[79] is that three-fourths infarcts involved the WS areas, and more specifically the area showing misery perfusion at baseline; similar information is not provided in the other studies.

These findings are in agreement with 3 prospective SPECT[82,83] or TCD[84] studies, and a number of retrospective studies not using PET.[85–91] Overall, these studies suggest that patients with reduced or exhausted vasodilatory capacity are at higher risk for subsequent stroke, although the risk appears substantially smaller than with misery perfusion, which reflects a more severe stage of hemodynamic impairment.

TABLE 4. MR Perfusion Studies

Author and Year	Reference	Patient	ICA Disease (No.)	ROI	Infarct Location	Findings
Detre et al 1998	49	11	Stenosis uni/bilat	ACAT, MCAT, PCAT	AWS + PWS	WS uniquely sensitive to hemodynamic compromise
			Occlusion	AWS, PWS	IWS	
Wiart et al 2000	72	13	Stenosis >80%	MCAT, AWS, PWS, CSO	None	Selective hemodynamic compromise in AWS
Chaves et al 2000	50	17	Stenosis (5) occlusion (2) ACAO (1) MCAS (1)	Visual assessment	CWS IWS MCAT ACAT	WS infarcts related to hemodynamic compromise in patients with high-grade ICAS; in patients without ICA disease, small WS infarcts possibly caused by micro-embolism; both mechanisms perhaps operative
Nasel et al 2001	73	34	Uni (24)	ACAT, MCAT,	CWS	CWS infarcts related to hemodynamic compromise
			Occlusion (10)	PCAT, AWS, PWS	BG	
Szabo et al 2001	51	102	Stenosis >50% (42) Occlusion (60)	Visual assessment	MCAT CSC CWS IWS	WS infarcts related to hemodynamic compromise in high-grade ICAS; in low-grade ICAS, no hemodynamic compromise (related to micro-embolism?)

CSC indicates cortico-subcortical.

Discussion

Despite using different methods for hemodynamic assessment, the literature on cerebral perfusion reviewed here provides evidence in favor of both the hemodynamic and the embolic mechanisms for WS infarction in ICA disease. Importantly, and despite some discrepancies, these studies further provide emerging evidence that different mechanisms may underlie CWS and IWS infarction (and more specifically CSO infarcts), ie, micro-embolic and hemodynamic, respectively. However, it is also clear from the literature that this dichotomy is likely too simplistic. For instance, there may be individual exceptions to general mechanisms depending, eg, on the collateral pattern distal to the occlusion. Also, the situation of tight stenosis—from where small thrombi or cholesterol emboli may arise—likely differs from that of an established occlusion, where hemodynamic problems are expected to be more frequent. The mere presence of hemodynamic impairment on tests does not necessarily mean it is the cause of WS infarcts. Finally, the conjunction of the embolic and hemodynamic mechanisms may be a key factor.[92] These and additional issues are briefly addressed.

IWS Infarcts

As reviewed, the rosary-like pattern of CSO infarcts appears to be specifically associated with hemodynamic impairment. The sensitivity of this area to hemodynamic failure may be explained by its anatomical situation between the territories of supply of the superficial perforators of the MCA and ACA. As such, it represents the most distal region perfused by the ICA. Given the length and diameter of the perforators and the low density of arterioles at this level,[93] perfusion pressure is likely to be lower in this terminal area than in the overlying cortex, making the CSO the area most vulnerable to hemodynamic impairment in ICA disease. However, factors responsible for the "chain-like" appearance of the infarcts are unclear. It has been suggested that in cases of severe ICA disease, the reduced CPP may not have the same influence on all superficial perforators, which do not anastomose to one another or with deep perforators, whose territories are not interdigitating and which therefore appear as functionally independent vascular units. Thus, in some terminal arteries, the perfusion may still be sufficient, whereas in others the blood flow may reach critical values even during physiological decreases in systemic blood pressure.[53] Small individual lesions arranged in a linear pattern would therefore result from such uneven perfusion.

However, a confluent pattern of lesions has also been observed in the CSO,[15] and this pattern has also been associated with hemodynamic impairment, although with weaker evidence.[19,53] Based on the anatomic study of Moody et al,[93] Krapf[53] proposed that in patients with impaired hemodynamics, the rosary-like pattern may result from brief declines in blood pressure, whereas the confluent pattern may be caused by longer-lasting impairments of the cerebral perfusion. According to this hypothesis, rosary-like infarcts may be considered precursors to a more profound event.

The association of IWS and CWS infarcts reported in some studies[19,74,76] indicates that in a situation of long-lasting and severe hypoperfusion, both WS areas may suffer damage. However, CSO infarcts clearly seem more sensitive to hemodynamic failure.[37,74–76] Thus, despite their small size, CSO infarcts represent the "tip of the iceberg" of decreased perfusion reserve, and as such may predict impending cortical stroke. Accordingly, misery perfusion was found to involve also the cerebral cortex of patients with CSO lesions,[75] and more generally, hemodynamic abnormalities are observed in an area far greater than the radiological lesions, regardless of the perfusion technique used.[19,52,53,55,56,58] Studies prospectively assessing the outcome of patients with CSO infarcts would be of interest to further our understanding of the significance of these lesions.

CWS Infarcts

The majority of studies also favor a hemodynamic mechanism for CWS infarcts. Although no study so far has directly compared the hemodynamics in the AWS and the PWS, the available data suggest that the AWS is the cortical border-zone area where the hemodynamic abnormalities are the most frequently documented.[63,64,66,68,69,72] In agreement with this observation, most CWS infarcts observed in combination with IWS infarcts involved the postulated AWS.[19,53] This in turn is consistent with a classic postmortem study of the border zones distal to ICA disease, where infarcts involved the CSO and the AWS.[28] This relative vulnerability of the AWS as compared with the PWS may be because the MCA and the ACA are both supplied only by the ICA, so critical stenosis or occlusion of the ICA will exert its maximum effect on the AWS. Any contralateral ICA disease and/or inefficient collateralization, particularly affecting the anterior portion of the circle of Willis, will add to this intrinsic vulnerability of the AWS. Conversely, stenosis or occlusion of the vertebro-basilar system, or a fetal-type PCA, may favor the involvement of the PWS, which probably accounts for individual observations of preferential involvement of the PWS.

At variance with the majority of the studies, however, 5 studies[37,65,74–76] (2 from the same team[65,76]) found no evidence of a hemodynamic impairment in CWS infarcts. One of these is an early PET study;[65] therefore, arguably methodological issues such as poor spatial resolution could have accounted for the findings. The other studies are those that directly compared the IWS to the CWS.[37,74–76] According to these studies, and consistent with some postmortem studies, isolated CWS infarcts in ICA disease would be caused by an embolic mechanism, whereas CWS infarcts coexistent with IWS infarcts would be associated with a major hemodynamic compromise.[74,76] It therefore appears crucial that any future study examining the pathogenesis of CWS infarction reports on the coexistence of IWS infarcts.

How do we account for the discrepancy between these 5 studies and the remaining literature on CWS infarcts? In 3 of these 5 studies,[37,74,76] the CWS area was not directly assessed, so the presence of hemodynamic impairment circumscribed to the CWS was not ruled out. In the study of Derdeyn et al,[76] there was a nearly significant trend for high OEF in patients with CWS infarcts, whereas in the study of Arakawa et al[75] high OEF was observed in the CWS in several patients but only in association with high OEF in the IWS as well. Thus, overall these studies do not rule out the presence of hemodynamic impairment associated with isolated CWS infarcts but show that IWS, and particularly CSO infarcts, are associated with much more significant and prevalent hemodynamic impairment than CWS infarcts. One possibility already mentioned is that some of the studies that reported CWS infarcts to be hemodynamically related in fact included many patients with associated IWS infarcts. Unfortunately, because interest in IWS infarction is relatively recent, no information is provided in these articles to allow one to retrospectively determine the occurrence of IWS infarcts. Additional possibilities to explain the discrepancy include: (1) patient selection, favoring inclusion of patients with presumed hemodynamic compromise; (2) retrospective design, based on the imaging data; (3) variability in the degree of ICA disease, which may have led to the predominance of a hemodynamic compromise, ie, including only ICA occlusion; and (4) too long delay from CWS stroke, whereby hemodynamic impairment may have spontaneously abated.[76]

Combined Hemodynamic and Embolic Mechanisms

There is currently growing interest in the view that hypoperfusion and artery-to-artery embolism coexist to explain WS stroke in patients with ICA disease.[26,92] As pointed out by Grubb et al,[81] the demonstration of hemodynamic failure at baseline does not necessarily prove that any subsequent stroke is purely hemodynamically mediated. Patients with impaired perfusion reserve may be more likely to have a stagnant flow that would increase the risk of artery-to-artery embolism,[94] whereas areas of marginal perfusion like in the WS areas may be more susceptible to the effect of emboli because of already exhausted vascular reserve or even partly exhausted OEF reserve.[26,95]

This hypothesis is further supported by the high prevalence of microembolic signals (MES) documented by TCD monitoring in recently symptomatic ICA stenosis. These signals are widely assumed to represent emboli passing through the insonated artery[96–101] and are thought to correspond to platelet or atheroma aggregates.[98,100] Their occurrence has been associated with high-grade ICA stenosis, and they have strong relationship with intraluminal thrombus and plaque ulceration.[102,103] They are also thought to be predictive of an increased risk of stroke in patients with either symptomatic or asymptomatic ICA stenosis.[104–108] Their observation therefore provides a possible link to the concept of embolism in predisposed hypoperfused cerebral regions.

Caplan and Hennerici[26] illustrated their hypothesis by reporting the case of a patient with severe ICAS in whom diffusion-weighted imaging (DWI) revealed a string of small rounded lesions in the immediately subcortical areas ipsilaterally, and TCD recorded MES in the ipsilateral MCA. The authors posited that decreased perfusion in WS areas reduces the clearance of microemboli that have entered these vulnerable regions. In turn, by blocking the vessels, small emboli would further exaggerate the local hypoperfusion.

The recent observation of multiple small round DWI lesions (undetectable on conventional imaging) encompassing the WS areas in patients with ICA or MCA stenosis provides general support to this hypothesis, because this type of DWI lesions is highly suggestive, although by no means pathognomonic, of mini-emboli.[92,109] Unfortunately, no study so far has combined DWI with an assessment of the WS areas by PWI MR and of MES by TCD. Using both DWI and PWI, Szabo et al[51] observed various patterns of brain infarction distal to ICA stenosis and, consistent with other studies,[110] attributed this heterogeneity to different stroke mechanisms linked with increasing ICA disease. In high-grade ICA stenosis, multiple random embolic lesions were a common feature, whereas increasing degrees of stenosis were associated with incremental hemodynamic compromise within the WS areas. The interpretation of these data was that some of the WS infarcts are likely caused by a combination of hemodynamic and embolic mechanisms. However, interpretation was constrained by the lack of TCD detection of microem-

boli together with the lack of characterization of the collateral blood supply.

Although a few studies have combined DWI and TCD detection of MES,[111–113] none has focused on the pathophysiology of WS infarction so far. However, the study of Wong et al[113] is of particular interest. This study addressed the mechanisms of *acute* cerebral infarction in patients with MCA stenosis and concluded, but did not prove, that the most common mechanisms of stroke in patients with MCA stenosis are an occlusion of a single penetrating artery to produce a small subcortical lacunar-like infarct and artery-to-artery embolism with impaired clearance of emboli producing small infarcts, especially in the deep WS. As expected with MCA stenosis, the IWS infarcts affected the white matter of the CR, between the territories of the deep perforators arising from the basal arteries and the superficial perforators of the MCA. According to these authors, therefore, in MCA disease, Caplan's hypothesis[26] would apply not only to the CWS but also to the IWS areas, which would be consistent with the recent pathological study of Lammie.[25]

Despite its overall appeal, however, Caplan's mixed hypoperfusion/emboli hypothesis remains unproven and could even be challenged on 3 grounds. First, small round DWI lesions in the CSO may not necessarily result from emboli but may just as well represent hemodynamic infarcts. Second, in Caplan and Hennerici's case report,[26] the appearance of the DWI lesions, namely immediately subcortical, may not clearly represent WS infarcts but could just as well represent multiple emboli in medullary arteries.[32] Finally, the association of MES with DWI lesions does not prove the embolic origin of the latter, but MES and hypoperfusion-based WS infarcts may be 2 independent rather than causally related events secondary to ICA disease.

Conclusions and Future Prospects

Despite numerous studies, the pathogenesis of WS infarction still remains debated, particularly concerning CWS infarcts. Regarding IWS infarction, the available evidence overall favors a hemodynamic mechanism, especially for the rosary-like pattern affecting the CSO. Nevertheless, some recent imaging and pathological studies raise the possibility that an embolic mechanism may occasionally contribute even to IWS infarcts. The relationship between CWS infarction and hemodynamic insufficiency appears weaker than for the IWS, except when both CWS and IWS infarcts are associated, although this remains not completely proven because of small samples so far. Although an embolic mechanism may be involved in isolated CWS infarcts, a recent hypothesis, only partially supported to date, posits that an underlying hemodynamic compromise facilitates the development of infarcts in the CWS when small emboli lodge in the "distal field." Further evidence in favor or against this hypothesis is awaited. The ability to identify micro-embolism in vivo using TCD should enhance our understanding of CWS and IWS infarct mechanisms. Moreover, additional information on the mechanism of WS infarction should gather from the increasing applications of DWI and PWI MR, which allow the detection of subtle acute ischemic lesions—whether emboli-based or hemodynamic-based. A better understanding of the mechanisms underlying WS infarcts should eventually impact the management of patients with ICA disease and result in improved outcome.

References

1. Zulch KJ. Uber die entstenhung und lokalisation der hirninfarkte. *Acta Neurol Chir*. 1961;7(Suppl):1–117.
2. Jorgensen L, Torvik A. Ischaemic cerebrovascular diseases in an autopsy series. 2. Prevalence, location, pathogenesis, and clinical course of cerebral infarcts. *J Neurol Sci*. 1969;9:285–320.
3. Bogousslavsky J, Regli F. Unilateral watershed cerebral infarcts. *Neurology*. 1986;36:373–377.
4. Ringelstein EB, Zeumer H, Angelou D. The pathogenesis of strokes from internal carotid artery occlusion. Diagnostic and therapeutical implications. *Stroke*. 1983;14:867–875.
5. Wodarz R. Watershed infarctions and computed tomography. A topographical study in cases with stenosis or occlusion of the carotid artery. *Neuroradiology*. 1980;19:245–248.
6. Torvik A, Skullerud K. Watershed infarcts in the brain caused by microemboli. *Clin Neuropathol*. 1982;1:99–105.
7. Adams JH, Brierley JB, Connor RC, Treip CS. The effects of systemic hypotension upon the human brain. Clinical and neuropathological observations in 11 cases. *Brain*. 1966;89:235–268.
8. Bogousslavsky J, Regli F. Borderzone infarctions distal to internal carotid artery occlusion: prognostic implications. *Ann Neurol*. 1986;20:346–350.
9. Bladin CF, Chambers BR. Frequency and pathogenesis of hemodynamic stroke. *Stroke*. 1994;25:2179–2182.
10. Brierley JB, Excell BJ. The effects of profound systemic hypotension upon the brain of m. Rhesus: Physiological and pathological observations. *Brain*. 1966;89:269–298.
11. Shuaib A, Hachinski VC. Mechanisms and management of stroke in the elderly. *CMAJ*. 1991;145:433–443.
12. Mohr JP. Distal field infarction. *Neurology*. 1969;19:279.
13. Howard R, Trend P, Russell RW. Clinical features of ischemia in cerebral arterial border zones after periods of reduced cerebral blood flow. *Arch Neurol*. 1987;44:934–940.
14. Yanagihara T, Sundt TM Jr, Piepgras DG. Weakness of the lower extremity in carotid occlusive disease. *Arch Neurol*. 1988;45:297–301.
15. Bladin CF, Chambers BR. Clinical features, pathogenesis, and computed tomographic characteristics of internal watershed infarction. *Stroke*. 1993;24:1925–1932.
16. Brown MM, Wade JP, Bishop CC, Russell RW. Reactivity of the cerebral circulation in patients with carotid occlusion. *J Neurol Neurosurg Psychiatry*. 1986;49:899–904.
17. Pessin MS, Hinton RC, Davis KR, Duncan GW, Roberson GH, Ackerman RH, Mohr JP. Mechanisms of acute carotid stroke. *Ann Neurol*. 1979;6:245–252.
18. Rodda RA. The arterial patterns associated with internal carotid disease and cerebral infarcts. *Stroke*. 1986;17:69–75.
19. Mull M, Schwarz M, Thron A. Cerebral hemispheric low-flow infarcts in arterial occlusive disease. Lesion patterns and angiomorphological conditions. *Stroke*. 1997;28:118–123.
20. Beal MF, Williams RS, Richardson EP, Jr., Fisher CM. Cholesterol embolism as a cause of transient ischemic attacks and cerebral infarction. *Neurology*. 1981;31:860–865.
21. Pollanen MS, Deck JH. Directed embolization is an alternate cause of cerebral watershed infarction. *Arch Pathol Lab Med*. 1989;113:1139–1141.
22. Masuda J, Yutani C, Ogata J, Kuriyama Y, Yamaguchi T. Atheromatous embolism in the brain: a clinicopathologic analysis of 15 autopsy cases. *Neurology*. 1994;44:1231–1237.
23. Pollanen MS, Deck JH. The mechanism of embolic watershed infarction: Experimental studies. *Can J Neurol Sci*. 1990;17:395–398.
24. Suter OC, Sunthorn T, Kraftsik R, Straubel J, Darekar P, Khalili K, Miklossy J. Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. *Stroke*. 2002;33:1986–1992.
25. Lammie GA, Wardlaw JM. Small centrum ovale infarcts–a pathological study. *Cerebrovasc Dis*. 1999;9:82–90.
26. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol*. 1998;55:1475–1482.
27. Adams RD, Van der Eecken HM. Vascular diseases of the brain. *Annu Rev Med*. 1953;4:213–252.

28. Romanul FC, Abramowicz A. Changes in brain and pial vessels in arterial border zones: a study of 13 cases. *Arch Neurol*. 1964;11:40–65.
29. Damasio H. A computed tomographic guide to the identification of cerebral vascular territories. *Arch Neurol*. 1983;40:138–142.
30. van der Zwan A, Hillen B, Tulleken CA, Dujovny M, Dragovic L. Variability of the territories of the major cerebral arteries. *J Neurosurg*. 1992;77:927–940.
31. Lang EW, Daffertshofer M, Daffertshofer A, Wirth SB, Chesnut RM, Hennerici M. Variability of vascular territory in stroke. Pitfalls and failure of stroke pattern interpretation. *Stroke*. 1995;26:942–945.
32. Bogousslavsky J, Regli F. Centrum ovale infarcts: Subcortical infarction in the superficial territory of the middle cerebral artery. *Neurology*. 1992;42:1992–1998.
33. Read SJ, Pettigrew L, Schimmel L, Levi CR, Bladin CF, Chambers BR, Donnan GA. White matter medullary infarcts: Acute subcortical infarction in the centrum ovale. *Cerebrovasc Dis*. 1998;8:289–295.
34. Miralles M, Dolz JL, Cotillas J, Aldoma J, Santiso MA, Gimenez A, Capdevila A, Cairols MA. The role of the circle of willis in carotid occlusion: assessment with phase contrast MR angiography and transcranial duplex. *Eur J Vasc Endovasc Surg*. 1995;10:424–430.
35. Hendrikse J, Hartkamp MJ, Hillen B, Mali WP, van der Grond J. Collateral ability of the Circle of Willis in patients with unilateral internal carotid artery occlusion: border zone infarcts and clinical symptoms. *Stroke*. 2001;32:2768–2773.
36. Schomer DF, Marks MP, Steinberg GK, Johnstone IM, Boothroyd DB, Ross MR, Pelc NJ, Enzmann DR. The anatomy of the posterior communicating artery as a risk factor for ischemic cerebral infarction. *N Engl J Med*. 1994;330:1565–1570.
37. Bisschops RH, Klijn CJ, Kappelle LJ, van Huffelen AC, van der Grond J. Association between impaired carbon dioxide reactivity and ischemic lesions in arterial border zone territories in patients with unilateral internal carotid artery occlusion. *Arch Neurol*. 2003;60:229–233.
38. Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with 15o positron emission tomography. *Stroke*. 1981;12:454–459.
39. Gibbs JM, Leenders KL, Wise RJ, Jones T. Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion. *Lancet*. 1984; 1:182–186.
40. Powers WJ, Raichle ME, Grubb RL, Jr. Positron emission tomography to assess cerebral perfusion. *Lancet*. 1985;1:102–103.
41. Vorstrup S, Boysen G, Brun B, Engell HC. Evaluation of the regional cerebral vasodilatory capacity before carotid endarterectomy by the acetazolamide test. *Neurol Res*. 1987;9:10–18.
42. Derdeyn CP, Grubb RL, Jr., Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. *Neurology*. 1999;53:251–259.
43. Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL, Powers WJ. Variability of cerebral blood volume and oxygen extraction: Stages of cerebral haemodynamic impairment revisited. *Brain*. 2002;125:595–607.
44. Baron JC. Mapping the ischaemic penumbra with pet: Implications for acute stroke treatment. *Cerebrovasc Dis*. 1999;9:193–201.
45. Vorstrup S. Tomographic cerebral blood flow measurements in patients with ischemic cerebrovascular disease and evaluation of the vasodilatory capacity by the acetazolamide test. *Acta Neurol Scand Suppl*. 1988; 114:1–48.
46. Provinciali L, Ceravolo M, Minciotti P. A transcranial doppler study of vasomotor reactivity in symptomatic carotid occlusion. *Cerebrovasc Dis*. 1993;3:27–32.
47. Ringelstein EB, Sievers C, Ecker S, Schneider PA, Otis SM. Noninvasive assessment of CO2-induced cerebral vasomotor response in normal individuals and patients with internal carotid artery occlusions. *Stroke*. 1988;19:963–969.
48. Dettmers C, Solymosi L, Hartmann A, Buermann J, Hagendorff A. Confirmation of CT criteria to distinguish pathophysiologic subtypes of cerebral infarction. *AJNR Am J Neuroradiol*. 1997;18:335–342.
49. Detre JA, Alsop DC, Vives LR, Maccotta L, Teener JW, Raps EC. Noninvasive MRI evaluation of cerebral blood flow in cerebrovascular disease. *Neurology*. 1998;50:633–641.
50. Chaves CJ, Silver B, Schlaug G, Dashe J, Caplan LR, Warach S. Diffusion- and perfusion-weighted MRI patterns in borderzone infarcts. *Stroke*. 2000;31:1090–1096.
51. Szabo K, Kern R, Gass A, Hirsch J, Hennerici M. Acute stroke patterns in patients with internal carotid artery disease: a diffusion-weighted magnetic resonance imaging study. *Stroke*. 2001;32:1323–1329.
52. Waterston JA, Brown MM, Butler P, Swash M. Small deep cerebral infarcts associated with occlusive internal carotid artery disease. A hemodynamic phenomenon? *Arch Neurol*. 1990;47:953–957.
53. Krapf H, Widder B, Skalej M. Small rosarylike infarctions in the centrum ovale suggest hemodynamic failure. *AJNR Am J Neuroradiol*. 1998;19:1479–1484.
54. Ringelstein EB, Weiller C, Weckesser M, Weckesser S. Cerebral vasomotor reactivity is significantly reduced in low-flow as compared to thromboembolic infarctions: the key role of the Circle of Willis. *J Neurol Sci*. 1994;121:103–109.
55. Isaka Y, Nagano K, Narita M, Ashida K, Imaizumi M. High signal intensity on T2-weighted magnetic resonance imaging and cerebral hemodynamic reserve in carotid occlusive disease. *Stroke*. 1997;28: 354–357.
56. Weiller C, Ringelstein EB, Reiche W, Buell U. Clinical and hemodynamic aspects of low-flow infarcts. *Stroke*. 1991;22:1117–1123.
57. Yamauchi H, Fukuyama H, Harada K, Yamaguchi S, Miyoshi T, Doi T, Kimura J, Iwasaki Y, Asato R, Yonekura Y. White matter hyperintensities may correspond to areas of increased blood volume: correlative MR and PET observations. *J Comput Assist Tomogr*. 1990;14:905–908.
58. Yamauchi H, Fukuyama H, Yamaguchi S, Miyoshi T, Kimura J, Konishi J. High-intensity area in the deep white matter indicating hemodynamic compromise in internal carotid artery occlusive disorders. *Arch Neurol*. 1991;48:1067–1071.
59. Yamauchi H, Fukuyama H, Nagahama Y, Katsumi Y, Hayashi T, Okazawa H, Yonekura Y. Selective cerebral hematocrit decrease in the centrum semiovale after carotid artery occlusion: A pet study. *J Cereb Blood Flow Metab*. 1999;19:109–114.
60. Derdeyn CP, Simmons NR, Videen TO, Yundt KD, Fritsch SM, Carpenter DL, Grubb RL, Jr., Powers WJ. Absence of selective deep white matter ischemia in chronic carotid disease: a positron emission tomographic study of regional oxygen extraction. *AJNR Am J Neuroradiol*. 2000;21:631–638.
61. Samson Y, Baron JC, Bousser MG, Rey A, Derlon JM, David P, Comoy J. Effects of extra-intracranial arterial bypass on cerebral blood flow and oxygen metabolism in humans. *Stroke*. 1985;16:609–616.
62. Yonas H, Gur D, Good BC, Latchaw RE, Wolfson SK, Jr., Good WF, Maitz GS, Colsher JG, Barnes JE, Colliander KG, et al. Stable xenon CT blood flow mapping for evaluation of patients with extracranial-intracranial bypass surgery. *J Neurosurg*. 1985;62:324–333.
63. Leblanc R, Yamamoto YL, Tyler JL, Diksic M, Hakim A. Borderzone ischemia. *Ann Neurol*. 1987;22:707–713.
64. Leblanc R, Yamamoto YL, Tyler JL, Hakim A. Hemodynamic and metabolic effects of extracranial carotid disease. *Can J Neurol Sci*. 1989;16:51–57.
65. Carpenter DA, Grubb RL, Jr., Powers WJ. Borderzone hemodynamics in cerebrovascular disease. *Neurology*. 1990;40:1587–1592.
66. Tatemichi TK, Young WL, Prohovnik I, Gitelman DR, Correll JW, Mohr JP. Perfusion insufficiency in limb-shaking transient ischemic attacks. *Stroke*. 1990;21:341–347.
67. Yamauchi H, Fukuyama H, Kimura J, Konishi J, Kameyama M. Hemodynamics in internal carotid artery occlusion examined by positron emission tomography. *Stroke*. 1990;21:1400–1406.
68. Levine RL, Dobkin JA, Rozental JM, Satter MR, Nickles RJ. Blood flow reactivity to hypercapnia in strictly unilateral carotid disease: Preliminary results. *J Neurol Neurosurg Psychiatry*. 1991;54:204–209.
69. Levine RL, Rozental JM, Nickles RJ. Blood flow asymmetry in carotid occlusive disease. *Angiology*. 1992;43:100–109.
70. Baumgartner RW, Regard M. Role of impaired co2 reactivity in the diagnosis of cerebral low flow infarcts. *J Neurol Neurosurg Psychiatry*. 1994;57:814–817.
71. Chollet F, Rolland Y, Albucher JF, Manelfe C, Marc-Vergnes JP, Guiraud-Chaumeil B. Recurrent right hemiplegia associated with progressive ipsilateral carotid artery stenosis. *Stroke*. 1996;27:753–755.
72. Wiart M, Berthezene Y, Adeleine P, Feugier P, Trouillas P, Froment JC, Nighoghossian N. Vasodilatory response of border zones to acetazolamide before and after endarterectomy: an echo planar imaging-dynamic susceptibility contrast-enhanced MRI study in patients with high-grade unilateral internal carotid artery stenosis. *Stroke*. 2000;31:1561–1565.
73. Nasel C, Azizi A, Wilfort A, Mallek R, Schindler E. Measurement of time-to-peak parameter by use of a new standardization method in

patients with stenotic or occlusive disease of the carotid artery. *AJNR Am J Neuroradiol*. 2001;22:1056–1061.
74. Moriwaki H, Matsumoto M, Hashikawa K, Oku N, Ishida M, Seike Y, Watanabe Y, Hougaku H, Handa N, Nishimura T. Hemodynamic aspect of cerebral watershed infarction: assessment of perfusion reserve using iodine-123-iodoamphetamine SPECT. *J Nucl Med*. 1997;38:1556–1562.
75. Arakawa S, Minematsu K, Hirano T, Tanaka Y, Hasegawa Y, Hayashida K, Yamaguchi T. Topographic distribution of misery perfusion in relation to internal and superficial borderzones. *AJNR Am J Neuroradiol*. 2003;24:427–435.
76. Derdeyn CP, Khosla A, Videen TO, Fritsch SM, Carpenter DL, Grubb RL, Jr., Powers WJ. Severe hemodynamic impairment and border zone–region infarction. *Radiology*. 2001;220:195–201.
77. Itoh M, Hatazawa J, Pozzilli C, Matsuzawa T, Abe Y, Fukuda H, Fujiwara T, Watanuki S, Ido T. Positron CT imaging of an impending stroke. *Neuroradiology*. 1988;30:276–279.
78. Yamauchi H, Fukuyama H, Fujimoto N, Nabatame H, Kimura J. Significance of low perfusion with increased oxygen extraction fraction in a case of internal carotid artery stenosis. *Stroke*. 1992;23:431–432.
79. Yamauchi H, Fukuyama H, Nagahama Y, Nabatame H, Nakamura K, Yamamoto Y, Yonekura Y, Konishi J, Kimura J. Evidence of misery perfusion and risk for recurrent stroke in major cerebral arterial occlusive diseases from PET. *J Neurol Neurosurg Psychiatry*. 1996;61:18–25.
80. Yamauchi H, Fukuyama H, Nagahama Y, Nabatame H, Ueno M, Nishizawa S, Konishi J, Shio H. Significance of increased oxygen extraction fraction in five-year prognosis of major cerebral arterial occlusive diseases. *J Nucl Med*. 1999;40:1992–1998.
81. Grubb RL, Jr., Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EL, Powers WJ. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA*. 1998;280:1055–1060.
82. Kuroda S, Houkin K, Kamiyama H, Mitsumori K, Iwasaki Y, Abe H. Long-term prognosis of medically treated patients with internal carotid or middle cerebral artery occlusion: can acetazolamide test predict it? *Stroke*. 2001;32:2110–2116.
83. Ogasawara K, Ogawa A, Yoshimoto T. Cerebrovascular reactivity to acetazolamide and outcome in patients with symptomatic internal carotid or middle cerebral artery occlusion: a xenon-133 single-photon emission computed tomography study. *Stroke*. 2002;33:1857–1862.
84. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain*. 2001;124:457–467.
85. Kleiser B, Widder B. Course of carotid artery occlusions with impaired cerebrovascular reactivity. *Stroke*. 1992;23:171–174.
86. Kuroda S, Kamiyama H, Abe H, Houkin K, Isobe M, Mitsumori K. Acetazolamide test in detecting reduced cerebral perfusion reserve and predicting long-term prognosis in patients with internal carotid artery occlusion. *Neurosurgery*. 1993;32:912–919.
87. Yonas H, Smith HA, Durham SR, Pentheny SL, Johnson DW. Increased stroke risk predicted by compromised cerebral blood flow reactivity. *J Neurosurg*. 1993;79:483–489.
88. Webster MW, Makaroun MS, Steed DL, Smith HA, Johnson DW, Yonas H. Compromised cerebral blood flow reactivity is a predictor of stroke in patients with symptomatic carotid artery occlusive disease. *J Vasc Surg*. 1995;21:338–344; discussion 344–335.
89. Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive factor of stroke in asymptomatic patients? *Stroke*. 1996;27:2188–2190.
90. Vernieri F, Pasqualetti P, Passarelli F, Rossini PM, Silvestrini M. Outcome of carotid artery occlusion is predicted by cerebrovascular reactivity. *Stroke*. 1999;30:593–598.
91. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, Caltagirone C. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283:2122–2127.
92. Schwartz A, Gass A, Hennerici MG. Is there a need to reclassify acute stroke patients? *Cerebrovasc Dis*. 1998;8(Suppl 1):9–16.
93. Moody DM, Bell MA, Challa VR. Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: An anatomic study. *AJNR Am J Neuroradiol*. 1990;11:431–439.
94. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol*. 1991;29:231–240.
95. Bozzao A, Floris R, Gaudiello F, Finocchi V, Fantozzi LM, Simonetti G. Hemodynamic modifications in patients with symptomatic unilateral stenosis of the internal carotid artery: evaluation with MR imaging perfusion sequences. *AJNR Am J Neuroradiol*. 2002;23:1342–1345.
96. Spencer MP, Thomas GI, Nicholls SC, Sauvage LR. Detection of middle cerebral artery emboli during carotid endarterectomy using transcranial Doppler ultrasonography. *Stroke*. 1990;21:415–423.
97. Siebler M, Sitzer M, Steinmetz H. Detection of intracranial emboli in patients with symptomatic extracranial carotid artery disease. *Stroke*. 1992;23:1652–1654.
98. Markus H. Transcranial doppler detection of circulating cerebral emboli. A review. *Stroke*. 1993;24:1246–1250.
99. Markus HS, Tegeler CH. Experimental aspects of high-intensity transient signals in the detection of emboli. *J Clin Ultrasound*. 1995;23:81–87.
100. Babikian VL, Hyde C, Pochay V, Winter MR. Clinical correlates of high-intensity transient signals detected on transcranial doppler sonography in patients with cerebrovascular disease. *Stroke*. 1994;25:1570–1573.
101. Khaffaf N, Karnik R, Winkler WB, Valentin A, Slany J. Embolic stroke by compression maneuver during transcranial doppler sonography. *Stroke*. 1994;25:1056–1057.
102. Sitzer M, Muller W, Siebler M, Hort W, Kniemeyer HW, Jancke L, Steinmetz H. Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. *Stroke*. 1995;26:1231–1233.
103. Valton L, Larrue V, Arrue P, Geraud G, Bes A. Asymptomatic cerebral embolic signals in patients with carotid stenosis. Correlation with appearance of plaque ulceration on angiography. *Stroke*. 1995;26:813–815.
104. Siebler M, Nachtmann A, Sitzer M, Rose G, Kleinschmidt A, Rademacher J, Steinmetz H. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. *Stroke*. 1995;26:2184–2186.
105. Babikian VL, Wijman CA, Hyde C, Cantelmo NL, Winter MR, Baker E, Pochay V. Cerebral microembolism and early recurrent cerebral or retinal ischemic events. *Stroke*. 1997;28:1314–1318.
106. Valton L, Larrue V, le Traon AP, Massabuau P, Geraud G. Microembolic signals and risk of early recurrence in patients with stroke or transient ischemic attack. *Stroke*. 1998;29:2125–2128.
107. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke*. 1999;30:1440–1443.
108. Dimakakos PB, Arapoglou B, Markus PH. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke*. 2000;31:544–545.
109. Kang DW, Chu K, Ko SB, Kwon SJ, Yoon BW, Roh JK. Lesion patterns and mechanism of ischemia in internal carotid artery disease: a diffusion-weighted imaging study. *Arch Neurol*. 2002;59:1577–1582.
110. Tsiskaridze A, Devuyst G, de Freitas GR, van Melle G, Bogousslavsky J. Stroke with internal carotid artery stenosis. *Arch Neurol*. 2001;58:605–609.
111. Muller M, Reiche W, Langenscheidt P, Hassfeld J, Hagen T. Ischemia after carotid endarterectomy: comparison between transcranial doppler sonography and diffusion-weighted mr imaging. *AJNR Am J Neuroradiol*. 2000;21:47–54.
112. Kimura K, Minematsu K, Koga M, Arakawa R, Yasaka M, Yamagami H, Nagatsuka K, Naritomi H, Yamaguchi T. Microembolic signals and diffusion-weighted MR imaging abnormalities in acute ischemic stroke. *AJNR Am J Neuroradiol*. 2001;22:1037–1042.
113. Wong KS, Gao S, Chan YL, Hansberg T, Lam WW, Droste DW, Kay R, Ringelstein EB. Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: a diffusion-weighted imaging and microemboli monitoring study. *Ann Neurol*. 2002;52:74–81.

The Pathophysiology of Watershed Infarction in Internal Carotid Artery Disease: Review of Cerebral Perfusion Studies

Isabelle Momjian-Mayor and Jean-Claude Baron

Stroke. 2005;36:567-577; originally published online February 3, 2005;
doi: 10.1161/01.STR.0000155727.82242.e1
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628