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 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. 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%.

Although the pathological and imaging characteristics 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, hemodynamic failure is classically thought to cause WS infarcts in ICA disease. Susceptibility of the WS areas is thought to result from their situation of “distal field,” where perfusion pressure is lowest, 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, 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. This interpretation is further supported by radiologic studies showing that WS infarcts distal to ICA disease are more likely with a noncompetent circle of Willis. In contrast, embolism from ICA disease...
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 Torvik2 and Torvik and Skullerud4 were the first to report that most of the occlusions observed in the leptomeningeal arteries over WS infaracts 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 al20 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 Deck21 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 al22 found atheromatous embolism to cause WS 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 infarct, a recent pathological study25 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 clinicoradiological 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
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 protective35,36 or without effect37 regarding the pathophysiology of IWS and CWS infarcts are another important issue. To facilitate reading, the findings made the important distinction between CR and CSO infarcts, which, as will be seen, turned out to be crucial. Within IWS infarcts, however, only a minority of studies directly compared them, which, as will be seen, its pathophysiology appears less controversial than the former.

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 II42,43). 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
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, 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. \(^{49,50,51}\) 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, \(^{52,53}\) 1 used SPECT, \(^{54}\) 1 combined SPECT and TCD, \(^{55}\) and 4 used PET. \(^{56,57,58,59}\) They involved relatively small numbers

### TABLE 1. PET Studies

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

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; MCA, 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.
of symptomatic patients (range, 7 to 37). Seven of these studies considered patients with ICAO only,\textsuperscript{52,54–60} whereas 2 enrolled patients with either severe ICA stenosis or ICA occlusion.\textsuperscript{53,58} All studies except 1 (the PET study of Derdeyn et al 2000\textsuperscript{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.\textsuperscript{57,59} In contrast, the third study, that of Derdeyn et al,\textsuperscript{60} concluded that the IWS is not more susceptible than the cortical MCA areas to hemodynamic compromise, even though 9 patients

### TABLE 2. SPECT and Xenon-CT Studies

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

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

### TABLE 3. TCD Studies

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Reference</th>
<th>Patient</th>
<th>ICA Disease (No.)</th>
<th>Infarct Location (No.)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringelstein et al 1988</td>
<td>47</td>
<td>55</td>
<td>Occlusion uni (40)/bil (15)</td>
<td>LFI (20) TI (14)</td>
<td>WS infarcts related to hemodynamic impairment</td>
</tr>
<tr>
<td>Weiller et al 1991</td>
<td>56</td>
<td>37</td>
<td>Occlusion (28)</td>
<td>IWS (17) MCAT (20)</td>
<td>IWS infarcts related to hemodynamic impairment</td>
</tr>
<tr>
<td>Provinciali et al 1993</td>
<td>46</td>
<td>30</td>
<td>Occlusion</td>
<td>IWS (12) CWS (2) MCAT (16)</td>
<td>WS infarcts related to hemodynamic impairment</td>
</tr>
<tr>
<td>Baumgartner et al 1994</td>
<td>70</td>
<td>112</td>
<td>Stenosis/occlusion</td>
<td>AWS (9) TI (26)</td>
<td>AWS infarct typically related to hemodynamic impairment</td>
</tr>
<tr>
<td>Ringelstein et al 1994</td>
<td>54</td>
<td>64</td>
<td>Occlusion</td>
<td>IWS (n=18) Territorial (n=28) No infarct (n=20)</td>
<td>Selective vulnerability of IWS to hemodynamic impairment</td>
</tr>
<tr>
<td>Krapf et al 1998</td>
<td>53</td>
<td>11</td>
<td>Occlusion (7)/bil (3)</td>
<td>CSO (11) AWS (2)</td>
<td>Rosary-like CSO infarct typical for the presence of hemodynamic impairment</td>
</tr>
<tr>
<td>Bisschops et al 2003</td>
<td>37</td>
<td>70</td>
<td>ICAO</td>
<td>ICA0</td>
<td>Significant association with hemodynamic impairment for IWS only</td>
</tr>
</tbody>
</table>

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, 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 explicitly indicate the rosary-like pattern as typical for the presence of hemodynamic compromise. Furthermore, 1 study 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. In 1 study only 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, all symptomatc patients had IWS infarcts as well.

Of these 14 studies, 10 assessed patients with TIAs only and no CWS infarcts; 2 assessed patients with CWS infarcts and 2 enrolled patients both with and without CWS infarcts. There were 8 PET studies, 1 SPECT study, 1 Xenon CT study, 2 TCD studies, and 2 perfusion MR studies. All but 1 study found a hemodynamic compromise in the CWS areas. This was true 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), more frequently than the posterior watershed (PWS). Four studies assessed the CWS hemodynamics before and after successful revascularization, either extracranial–intracranial bypass or carotid endarterectomy, 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, they are of particular significance because they directly compared the 2 WS areas. In 3 studies, patients with isolated IWS or CWS infarcts were studied and their hemodynamic status compared, whereas in the fourth study the comparison was made between CWS and IWS ROIs. Methods used were SPECT, PET, TCD. 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 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. There are 2 additional important observations from this series of studies. Arakawa et al found that although misery perfusion could affect both the IWS and the CWS, it never affected the CWS alone. Moriwaki et al 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 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 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 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 at follow-up. An interesting information provided in Yamauchi et al is that three-fourths of the patients 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 studies and a number of retrospective studies not using PET. 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.
**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 infaracts), 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 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.

**TABLE 4. MR Perfusion Studies**

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Reference</th>
<th>Patient</th>
<th>ICA Disease (No.)</th>
<th>ROI</th>
<th>Infarct Location</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detre et al 1998</td>
<td>49</td>
<td>11</td>
<td>Stenosis uni/bilat</td>
<td>ACAT, MCAT, PCAT</td>
<td>AWS + PWS</td>
<td>WS uniquely sensitive to hemodynamic compromise</td>
</tr>
<tr>
<td>Wiart et al 2000</td>
<td>72</td>
<td>13</td>
<td>Stenosis &gt;80%</td>
<td>MCAT, AWS, PWS, CSO</td>
<td>IWS</td>
<td>Selective hemodynamic compromise in AWS</td>
</tr>
<tr>
<td>Chaves et al 2000</td>
<td>50</td>
<td>17</td>
<td>Stenosis (5) occlusion (2)</td>
<td>Visual assessment</td>
<td>CWS</td>
<td>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</td>
</tr>
<tr>
<td>Nasel et al 2001</td>
<td>73</td>
<td>34</td>
<td>Uni (24)</td>
<td>ACAT, MCAT,</td>
<td>CWS</td>
<td>CWS infarcts related to hemodynamic compromise</td>
</tr>
<tr>
<td>Szabo et al 2001</td>
<td>51</td>
<td>102</td>
<td>Stenosis &gt;50% (42)</td>
<td>Visual assessment</td>
<td>MCAT</td>
<td>WS infarcts related to hemodynamic compromise in high-grade ICAS; in low-grade ICAS, no hemodynamic compromise (related to micro-embolism?)</td>
</tr>
</tbody>
</table>

CSC indicates cortico-subcortical.


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.37,63,64,66,68,69,72 In agreement with this observation, most CWS infarcts observed in combination with IWS infarcts involved the postulated AWS.9,53 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. Conversely, stenosis or occlusion of the vertebro-basilar system, or a fetal-type PCA, may favor the 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 studies37,65,74–76 (2 from the same team65,76) 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 al75 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.26,98

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 artery26–101 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 Hennerici26 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 al51 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 microemboli.
bolus together with the lack of characterization of the collateral blood supply.

Although a few studies have combined DWI and TCD detection of MES, none has focused on the pathophysiology of WS infarction so far. However, the study of Wong et al 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 would apply not only to the CWS but also to the IWS areas, which would be consistent with the recent pathological study of Lammie.

Despite its overall appeal, however, Caplan’s mixed hypoperfusion/embolism 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, 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. 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 microembolism 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


The Pathophysiology of Watershed Infarction in Internal Carotid Artery Disease: Review of Cerebral Perfusion Studies
Isabelle Momjian-Mayor and Jean-Claude Baron

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