A narrative review of the pathophysiology of ischemic stroke in carotid plaques: a distinction versus a compromise between hemodynamic and embolic mechanism

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Contributions: (I) Conception and design: None; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Atherosclerotic carotid artery stenosis causes about 10–20% of all ischemic strokes through two main mechanisms: hemodynamic impairment in case of significant stenosis and thromboembolism from an atherosclerotic plaque regardless of the degree of stenosis. The latter is the most frequent mechanism and appear to result from embolization from a vulnerable atherosclerotic plaque or acute occlusion of the carotid artery and propagation of thrombus distally. Downstream infarcts may occur in a territory of major cerebral artery or at the most distal areas between two territories of major cerebral arteries, the so-called watershed (WS), or border zone area. Although WS infarcts, especially deep WS infarct, were historically thought to be due to hemodynamic compromise, the role of microembolism has also been documented, both mechanisms may act synergistically to promote WS infarcts. Routine and more advanced imaging techniques may provide information on the underlying mechanism involved in ipsilateral ischemic stroke. A better understanding of ischemic stroke pathogenesis in carotid stenosis may limit the use of routine non-selective shunt, whose benefit-risk balance is debated, to patients with hemodynamic impairment.

After reviewing existing evidence underpinning the contribution of the two mechanisms in downstream ischemic stroke and the various imaging techniques available to investigate them, we will focus on the pathogenesis of WS infarcts that remains debated.

Keywords: Stroke; carotid stenosis; watershed infarct (WS infarct)

Prior studies have estimated that up to 20–25% of ischemic strokes are caused by large-artery atherosclerosis (1-3). Carotid artery disease is believed to be responsible for anywhere between 10 and 20% of ischemic stroke (4). The degree of stenosis is a relevant risk factor of ipsilateral ischemic stroke (5). This criterion has been used to select

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patients in randomized clinical trials and is consequently considered when making treatment decisions in patients with carotid disease (6,7). However, the importance of hemodynamic factors in the pathogenesis of focal cerebral ischemia is still debated. While it is likely that some ischemic strokes associated with carotid artery disease result from hypoperfusion, the majority of such strokes appear to result from embolization from a vulnerable atherosclerotic plaque or acute occlusion of the carotid artery and propagation of thrombus distally (8-10). Routine and more advanced imaging techniques may provide information on the underlying mechanism involved in ipsilateral ischemic stroke (11-13). Downstream infarcts may affect watershed (WS) or border zone area, that are the most distal areas between two territories of major cerebral arteries (14). Some studies suggested that WS infarct, especially deep WS infarct, are related to hemodynamic compromise, but this hypothesis has been challenged by evidence on the contribution of microembolism in this setting (15). We aimed to review existing evidence and imaging modalities supporting the contribution of these two mechanisms, especially in the pathogenesis of WS infarcts, in which they may act synergistically.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/atm-20-7490).

Hemodynamic impairment downstream to carotid stenosis

Generalities about brain perfusion: cerebral autoregulation and vascular reserve

The cerebral blood flow (CBF) is about 50 mL/100 g/minutes (16-18). Cerebral autoregulation maintains a constant CBF in case of increased brain functional activity or a significant drop of systemic blood pressure (from 50 to 170 mmHg) (19). Cerebrovascular reserve is the ability of the brain to increase cerebral blood volume (CBV) via collateral network development to maintain a constant CBF. In case of severe decrease of CBF related to unilateral severe carotid artery stenosis, adaptative mechanisms are involved. First (grade I) a vasodilatation of arterioles occurs, which is traduced by an increase of mean transit time (MTT) and CBV while a normal oxygen extraction fraction (OEF) is maintained. If this mechanism is exhausted (grade II), OEF increases in order to maintain the cerebral metabolic rate of oxygen ($CMRO_2$) (20). At the end, when these

compensatory mechanisms are exhausted and CBF and $CMRO_2$ decreased, irreversible damage then takes place: this is ischemia (*Figure 1*) (21,22).

Many different methods are available to evaluate brain perfusion: transcranial doppler (TCD), positron emission tomography (PET), xenon-CT (Xe-CT), single-photon emission computed tomography (SPECT), CT-angiography (CTA), MR-angiography (MRA), perfusion CT (CTP), MR perfusion (MRP) and conventional cerebral angiography (16,23). PET is the gold standard to estimate cerebrovascular reserve. It uses an oxygen-15 radiotracer and can provide estimations of CBV, CBF, $CMRO_2$ and MTT (21). TCD is used to evaluate vasomotor reactivity (VMR) in the middle cerebral artery (MCA) before and after the administration of either CO_2 or acetazolamide. A reduced VMR is a marker of impaired cerebral perfusion and poor collateral circulation. SPECT also evaluates hemodynamic reserve by measuring regional VMR after administration of CO_2 or acetazolamide. In physiological conditions, administration of acetazolamide increases blood flow by as much as 80%. CT or MR perfusion-based methods are easily accessible in clinical practice and maps of CBF, CBV, MTT and time to peak (TTP) may be provided to estimate brain perfusion (16,24).

Evidence of hemodynamic impairment in case of carotid artery stenosis

Hemodynamic and cerebrovascular reactivity (CVR) studies

Cerebral perfusion pressure is not systematically compromised downstream of carotid plaques. It is only in case of significant stenosis that brain hemodynamic may be impaired (25).

PET studies on patients with severe carotid stenosis show a decrease of CBF, CBF/CBV ratio, $CMRO_2$ and an increase in MTT, CBV, and OEF in the ipsilateral hemisphere (26,27).

Many studies using acetazolamide (24) or 99mTc-HMPAO SPECT before and after injection of dipyridamole (28,29) showed a reduced resting CBF and an altered CVR ipsilateral to the carotid stenosis after injection. More recently, multimodal MRI perfusion studies showed that CBF and CVR were decreased ipsilaterally to the stenosis (30). Lythgoe *et al.* found a significant increase in mean MTT and CBV, and a significant decrease in mean CBF ipsilateral MCA territory in carotid stenosis patients, compared with both the contralateral MCA territory
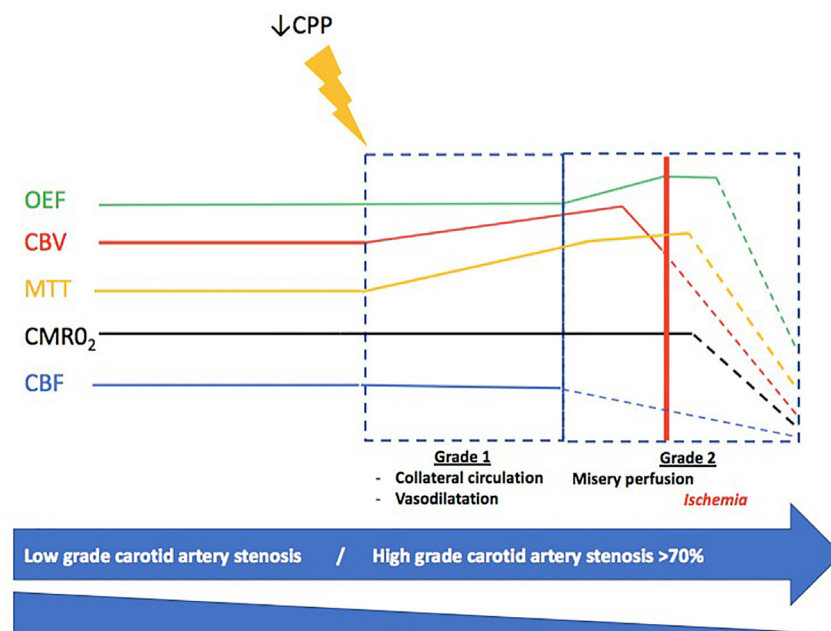
Figure 1 Illustration of cerebrovascular reserve in case of a CPP decrease due to high grade carotid artery stenosis. CPP, cerebral perfusion pressure; CBF, cerebral blood flow; CBV, cerebral blood volume; CMR02, cerebral metabolic rate of O2; MTT, mean transit time; OEF, oxygen extraction fraction.

and the control group (31). In a multimodal imaging study, CBF, mean flow velocity in MCA ipsilateral artery and VMR were significantly decreased in case of carotid stenosis (32). These results were confirmed by two other studies showing a decrease in CVR ipsilateral to carotid stenosis (33,34). Finally a Xe/CT study found a decreased vasoreactivity to C02 in patients with carotid stenosis but no effect on CBF versus contralateral hemisphere (35).

An alteration of CVR, evaluated by apnea-induced hypercapnia and transcranial doppler was significantly associated with an increased risk of stroke in a prospective study (36). For Blaser *et al.* exhausted CVR was the major risk factor of stroke recurrence in case of symptomatic carotid stenosis (37). Webster *et al.* and Yonas *et al.* also showed in Xe-CT studies an association between a decreased CVR and risk of stroke in patients with severe carotid stenosis (38,39). These results were corroborated by two other studies using CT perfusion and doppler ultrasound (40,41). A meta-analysis has identified an increased OEF as an independent predictor of stroke in carotid stenosis or occlusion (42).

Moreover, many studies with different methods of brain perfusion or vasoreactivity evaluation showed an improvement of brain hemodynamic after endarterectomy

or stenting (43-49).

These data suggest that hemodynamic impairment may play a role in the occurrence of stroke in patients with carotid stenosis.

Influence of collateral circulation

Some factors have been identified to explain patient susceptibility to ischemic stroke occurrence downstream to carotid stenosis. The most relevant protective factor seems to be the presence and the quality of collateral circulation. Collateral circulation is a compensatory pathway which can be recruited to preserve brain perfusion in case of acute or chronic hypoperfusion. Its protective role depends on several factors as anatomical variations, blood pressure, age and rate of development of steno-occlusive disease (16). Primary collateral pathways involved in carotid artery stenosis are represented by the circle of Willis. It is necessary to distinguish the anterior pathway with the anterior communicating artery and the A1 segment of the anterior cerebral artery (ACA) and the posterior communicating pathway with the posterior communicating artery and the P1 segment of the posterior cerebral artery (PCA). Secondary pathways are extra Willisian collaterals like retrograde flow via the external carotid and ophthalmic

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artery and leptomeningeal collateral flow via the PCA (50).

Fang *et al.* demonstrated that in patients with unilateral carotid stenosis, blood flow velocity in the contralateral commune carotid artery was higher than in the ipsilateral commune carotid artery (51). Furthermore, patients with bilateral carotid artery stenosis had higher blood flow velocity in vertebral arteries than control patients or patients with unilateral carotid artery stenosis. These data are in favor of compensatory mechanisms via collateral pathways in case of carotid stenosis. In a doppler study, CVR tended to be less important in patients without collateral circulation (52). There was a majority of patients with a reduced CVR ipsilateral to carotid stenosis.

These arguments highlight role of hemodynamic impairment in ischemic strokes downstream to carotid stenosis.

Influence of degree of stenosis

There is a relationship between the severity of symptomatic or asymptomatic carotid stenosis and the risk of ipsilateral ischemic stroke (53). Tomura *et al.* assessed the correlation between carotid stenosis degree and cerebral reserve alteration (54). They observed no significant association between CBF and stenosis degree but a small but significant association between CVR alteration and degree of stenosis. Jongen *et al.* showed that a higher degree of carotid artery stenosis was associated with a decreased CBF and an increased MTT (55). An association between doppler CO_2 vasoreactivity alteration and degree of stenosis was also reported but these results might be biased by the recruitment of patients who had experienced recent stroke or transient ischemic attack (TIA) (37).

Microembolic mechanism from vulnerable carotid plaques

Beyond the degree of stenosis and its potential hemodynamic impairment, carotid plaques, especially vulnerable plaques, cause mostly downstream ischemic stroke through a microembolic mechanism (8,9).

This hypothesis is supported by data coming from TCD studies. TCD is a validated tool to detect cerebral microembolic signals (MES) using a probe placed in front of the ipsilateral middle cerebral artery (56). MES detection is predictive of ischemic stroke/TIA occurrence in patients with carotid stenosis both in asymptomatic (57) and symptomatic patients (58). A severe degree of carotid stenosis appears to be associated with a higher detection of MES (59,60), whereas optimizing medical treatment may decrease their detection (61).

Plaques that are more prone to cause distal embolization and subsequent TIA and stroke occurrence are qualified as vulnerable (62). Plaque features of vulnerability include a large lipid-rich necrotic core, a thin or ruptured fibrous cap, ulcerations and intraplaque hemorrhage and the presence of inflammatory cells (63). Several approaches have been developed to identify imaging markers of plaque vulnerability from routine to advanced techniques, using ultrasound, CTA, MRI or other imaging techniques (*Figure 2*) (11,12). Carotid stenosis progression is also considered as a marker of vulnerability (64). The prevalence of vulnerable plaques on the basis of various imaging criteria account for about 25% of all asymptomatic carotid plaques (65). Plaques classified as vulnerable were associated with a higher risk of an ipsilateral ischemic event (65). This relationship was also observed in case of <50% luminal narrowing plaques among patients with cryptogenic stroke (66) and, more specifically those with embolic stroke of undetermined source (67).

Among routine imaging, two-dimensional ultrasound is often used as first-line imaging and provide information on carotid plaque echostructure, besides the degree of stenosis. Echolucency that corresponds to lipid-rich necrotic core or intraplaque hemorrhage has been established as a stroke risk marker (68-70) as well as higher juxta-luminal hypoechoic black size (71,72) and plaque area (72). Other risk markers as ulceration (73) and neovascularization (74,75) may be assessed using three-dimensional and contrast-enhanced ultrasound.

CTA, which is widely available, may approach plaque vulnerability with a high degree of agreement with histologic examination (76) and high-resolution MRI (77). Soft plaque, plaque ulceration, increased common carotid artery wall thickness and lack of calcifications on CTA have been associated with the risk of ipsilateral stroke (78).

Advanced imaging as high resolution MRI and PET/CT or PET/MRI studies of carotid plaques now offer the possibility to better characterize plaque composition and risk features (12). High resolution MRI is an accurate, sensitive and specific method for determining the plaque characteristics of vulnerability, as the lipid rich necrotic core, thin and/or ruptured fibrous cap and intraplaque hemorrhage compared to histological findings (79,80). High resolution contrast-enhanced MRI can also detect increased plaque permeability, a hallmark of neoangiogenesis (81). The inflammatory plaque component was mainly evaluated
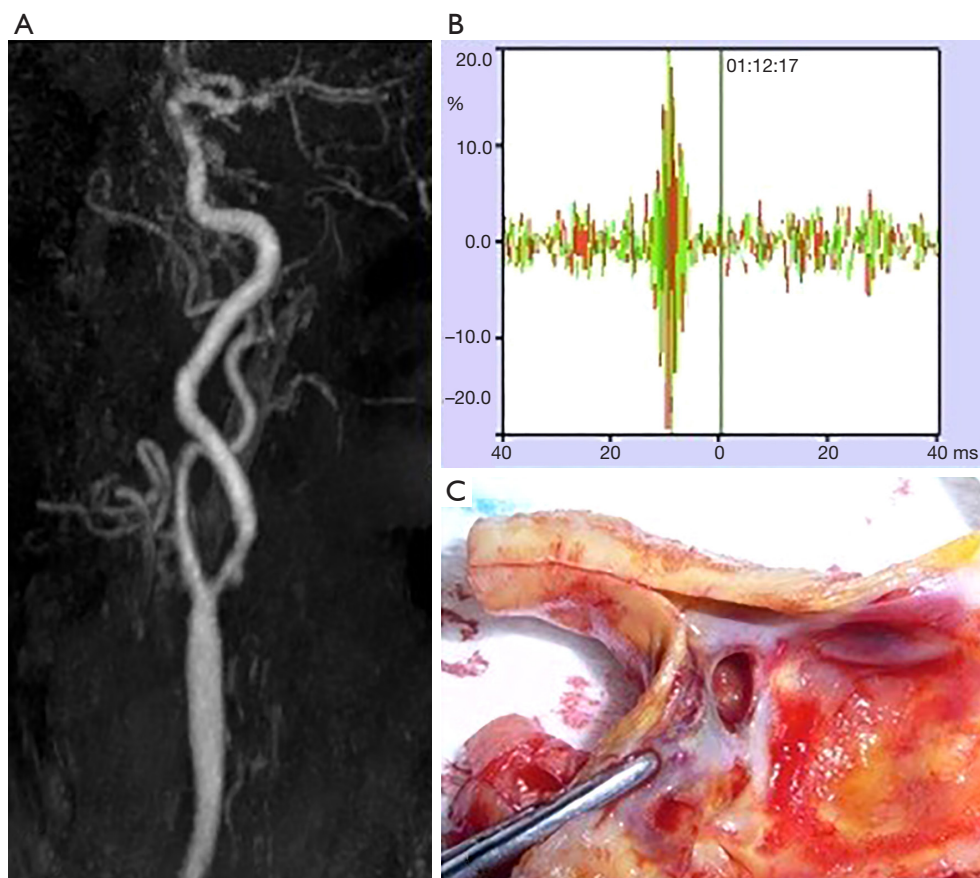
Figure 2 Illustrative case of a 73-year-old woman with a transient ischemic attack. Angio-MR MIP (maximum intensity projection) reconstruction (A) highlighting the presence of a plaque ulceration of the right internal carotid artery (image courtesy of Sara Boccalini). Transcranial Doppler (B) showing a cerebral microembolic signal in the right middle cerebral artery. Surgical specimen confirming the presence of ulceration (C).

with 18F-fluorodeoxyglucose (FDG) PET/CT (82). Indeed, FDG uptake has been recognized as a marker of stroke risk and correlated with MES (83). Inflammation imaging of atherosclerosis is an active research field and new tracers are currently under clinical evaluation using hybrid imaging, PET/CT or PET/MRI (84). Among the other factors of plaque vulnerability, intraplaque neoangiogenesis and hypoxia are associated with an increased risk. Hypoxia can be evaluated by 18F-fluoromisonidazole (FMISO) PET and was correlated with FDG uptake (85). Thus, FDG PET/MRI can explore the link between MRI vulnerable plaque features and inflammation (84). In a small study of 18 patients using 18F-FDG PET/MRI, non-stenotic carotid plaques were diagnosed as the cause of embolic stroke of unknown origin (86). Microcalcification is the hallmark of active atherosclerosis and is linked to acute

events. It can be evaluated by PET/CT or PET/MRI using 18F-sodium fluoride (NaF) (87). Two recent studies used both NaF and FDG PET tracers to evaluate the association of active microcalcification and inflammation in culprit plaques (88,89). The study by Fujimoto *et al.* conducted in 28 patients assessed the relationship between these tracers and the severity of ischemic brain disease on MRI and concluded that NaF uptake appeared more discriminant than FDG (89).

WS infarct pattern

In 1959, German neurosurgeons Wilhelm Tönnis and Wolfgang Schiefer endorsed the Schneider's concept of "letzte Wiese" to explain the manifestation of circulatory disturbances in the border zones between the 3 large
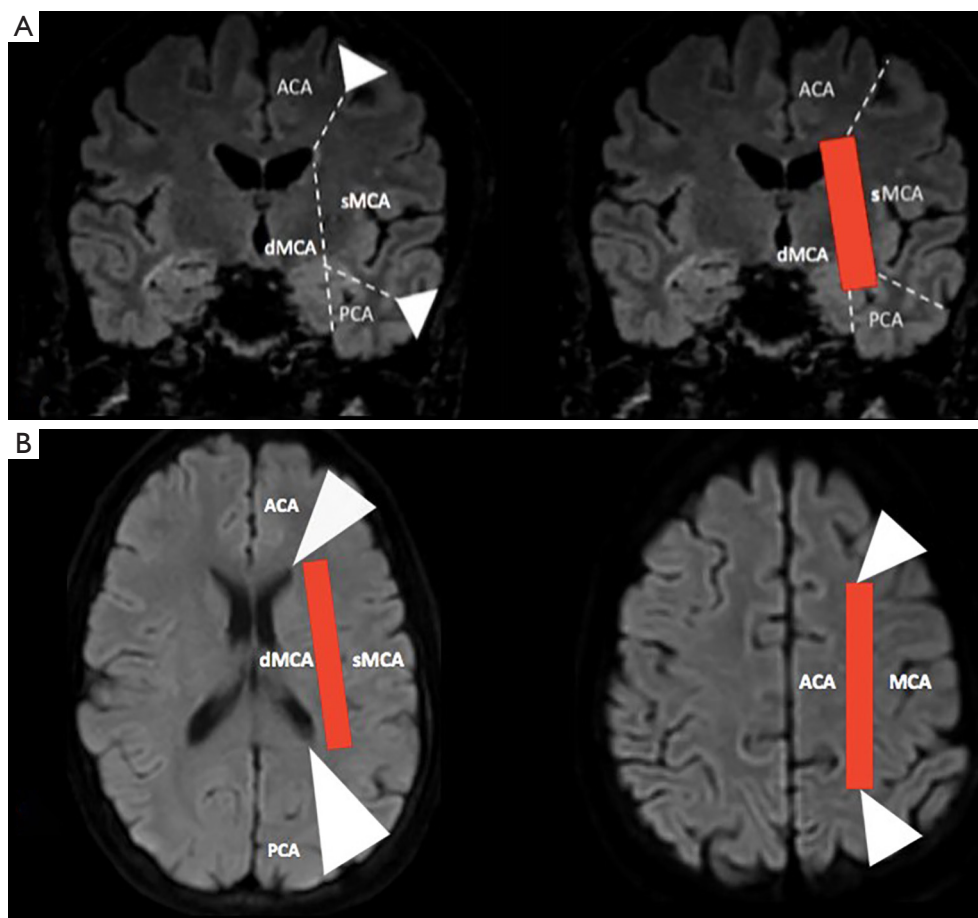
Figure 3 Schematic representation of watershed area. Coronal (A) and axial (B) representation of cortical (white) and internal (red) watershed area. ACA, anterior cerebral artery; MCA, middle cerebral artery; dMCA, deep MCA; sMCA, superficial MCA; PCA, posterior cerebral artery.

cerebral arteries and in basal ganglia and internal capsule (90).

WS or border zones correspond to the most distal areas between two territories of major cerebral arteries (14,15). Cortical WS zones are located between the cortical territories of the ACA, MCA, and PCA. Deep or internal WS zones are located in the white matter along and slightly above the lateral ventricle, between the superficial systems of the MCA and ACA, or between the deep and the superficial arterial systems of the MCA (*Figures 3* and *4*) (91). Deep WS zones are divided into confluent and partial infarcts either as a single lesion or in "rosary-like" pattern in the centrum semiovale. However, WS zones and vascular territories have variable spatial distribution in healthy individuals (92,93) and even more markedly in those with artery stenosis or occlusion (94) in

whom collateral pathways is recruited in a highly individual pattern to compensate for diminished blood flow. An individual WS zone mapping using multimodal MRI has been proposed to take into account this inter-individual spatial variability (95,96).

WS, or border-zone, infarcts account for about 10% of all infarcts and for up to about 60% of infarcts in patients with carotid artery stenosis or occlusion (97-101). The pathogenesis of WS infarcts remains debated. WS infarcts, and particularly deep WS and the rosary-like pattern, were historically thought to be due to hemodynamic compromise in the setting of carotid artery stenosis or occlusion as supplying by distal arterial branches with lowest perfusion pressure (102). Indeed, they were observed early in the clinical setting of severe systemic hypotension (2,103,104). Several PET, SPECT, MRI and TCD sonography
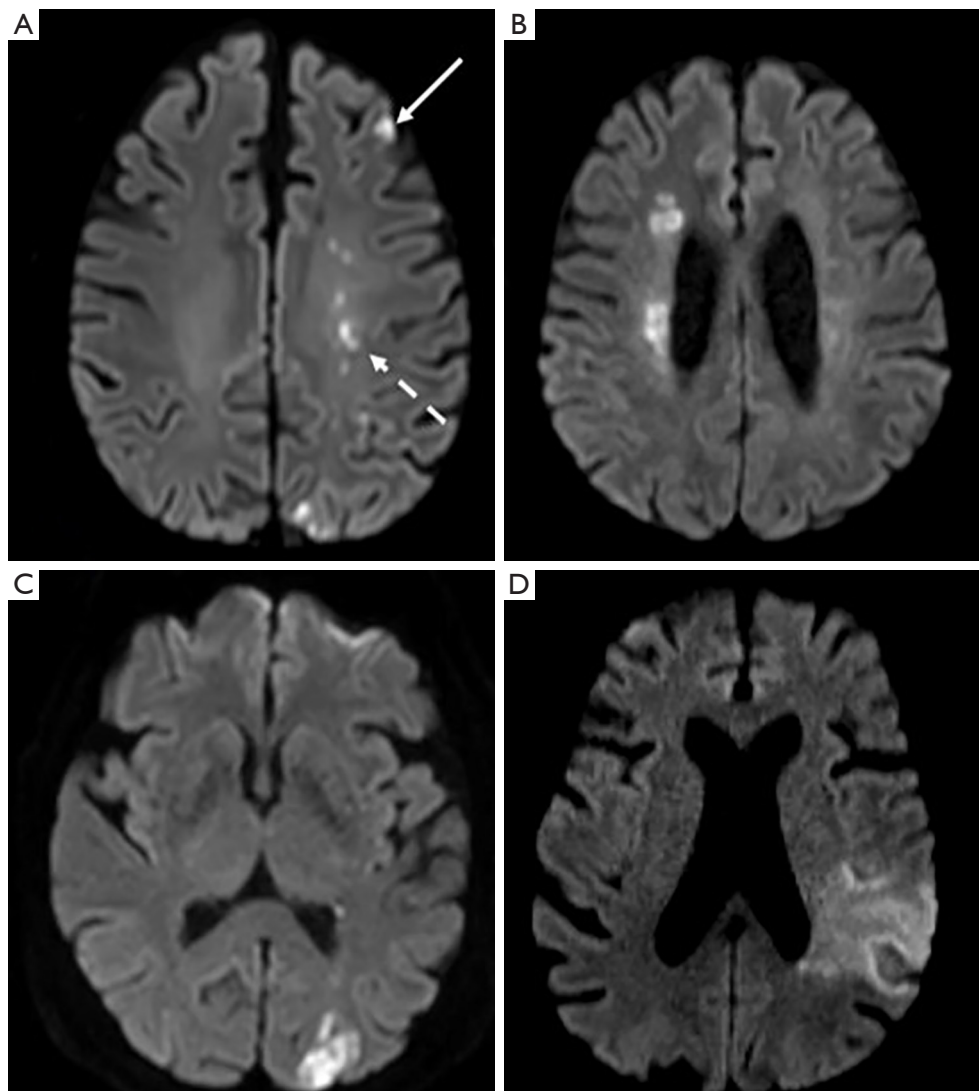
Figure 4 Axial slices of diffusion-weighted MRI showing anterior cortical (full arrow) and internal (dotted arrow) watershed infarcts (A), internal (full arrow) watershed infarcts (B), posterior cortical watershed infarcts (C) and a territorial infarct in the middle cerebral artery territory (D).

studies have demonstrated hemodynamic impairment in these zones as reduced regional CBF, reduced perfusion reserve, and an elevated regional OEF (13,105-107). The relationship between a noncompetent circle of Willis (108-110) or a reduced MCA intensity on 3D TOF MRA (111) and WS infarcts, in particular in deep WS infarcts, also argued for this hypothesis. The supposedly stronger role of hemodynamic impairment in deep WS infarcts was reinforced by the fact that deep WS infarcts had more likely a higher degree of stenosis or occlusion in either the middle cerebral or internal carotid artery (101)

and were mainly due to large artery atherosclerosis (112) than cortical WS infarcts.

However, evidence of the role of embolism in the pathophysiology of WS infarcts has been documented early in autopsy studies showing the presence of microemboli including cholesterol crystals in arteries supplying WS zones (98,113-116). In addition, the perfusion with suspensions of glass microspheres of the brains of cadavers resulted in distribution of these microspheres into the WS zones as well as various arterial territories (117). The preferential distribution pattern of the microspheres into

the WS zones was affected by their diameters, as observed in rodents (118). An experimental study conducted in non-human primates showed that subsequent WS infarcts affected both cortical and deep WS zones (119). In a clinical study, ipsilateral MES were common in patients with recent WS infarct related to carotid artery stenosis or occlusion thus demonstrating an embolic mechanism from the plaque (120). In the same way, carotid intraplaque hemorrhage, a marker of plaque instability, tended to be associated with WS infarcts in the absence of severe hemodynamic impairment (121). Emboli may also come upstream from the carotid artery. Thus, cardioembolism was considered as the most frequent cause of cortical WS infarcts and accounted for about 15% of deep WS infarcts (112).

A dichotomized approach is nevertheless likely too simplistic. Caplan *et al.* proposed that hemodynamic compromise and embolism may be intimately intertwined. Thus, reduced perfusion may hamper washout or clearance of emboli, particularly within the WS zone or make this brain area, with marginal perfusion, more vulnerable to the effect of microemboli (122). In any case, these two mechanisms appear to contribute, solely or synergistically, to all subtypes of deep WS infarcts according to studies combining brain perfusion mapping and MES assessment in patients with recently symptomatic carotid stenosis (83,123).

Conclusions

While some ischemic strokes associated with carotid artery disease may result from hypoperfusion, most of them are related to embolism from a vulnerable plaque. The contribution of these different pathways in patients with carotid plaque cannot be inferred from infarct pattern but may be explored using routine and more advanced imaging techniques. A better understanding of ischemic stroke pathogenesis in carotid stenosis may limit the use of routine non-selective shunt, whose benefit-risk balance is debated, to patients with hemodynamic impairment (124).

Acknowledgments

Footnote

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