THE ROLE OF LEPTOMENINGEAL COLLATERAL FLOW IN ACUTE ISCHEMIC STROKE

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ABSTRACT

The importance of collateral flow through leptomeningeal anastomoses (LMA) is increasingly recognized in the physiopathology of acute ischemic stroke. We performed a review of the Medline database for studies in which collateral flow was correlated with clinical or imaging parameters in acute ischemic stroke. We also detail the anatomy of LMA, the various imaging modalities of collateral flow through LMA and current clinical trials investigating collateral flow augmentation treatments.

Keywords: collateral flow, leptomeningeal anastomoses (LMA), ischemic stroke

INTRODUCTION

The leptomeningeal anastomoses (LMA) are small caliber arteries that form an end to end connection between the distal branches of the major cerebral arteries. Their existence was first documented by Heubner in 1874. While trying to delineate the arterial territories in cadaveric brains, he observed that the injected product diffused in other arterial territories in the absence of Willis circle connections.

Ever since Heubner's initial observation, the presence and the functionality of LMA has been widely debated in the scientific community. In recent years however, an important body of evidence has accumulated, showing that collateral flow via LMA plays a key role in the survival of brain parenchyma after an arterial occlusion.

Being an important pathway of cerebral blow flow collateralization, LMA are involved in a variety of pathological processes: acute ischemic stroke, Moyamoyasyndrome, as well as chronic atherosclerotic intra and extra cranial stenotic or occlusive lesions. This article will concentrate on the role played by LMA in acute ischemic stroke.

ANATOMY OF LEPTOMENINGEAL ANASTOMOSES

The connections between the distal branches of the three major supratentorial arteries are illustrated in Fig. 1 and 2:

1. Frontal and parietal branches of the MCA anastomose with the homologue branches of the ACA.
2. Posterior parietal and temporal branches of the MCA anastomose with the homologue branches of the PCA.
3. The distal branches of the pericallosal artery (ACA) anastomose with the splenial and parieto-occipital branches of the PCA.

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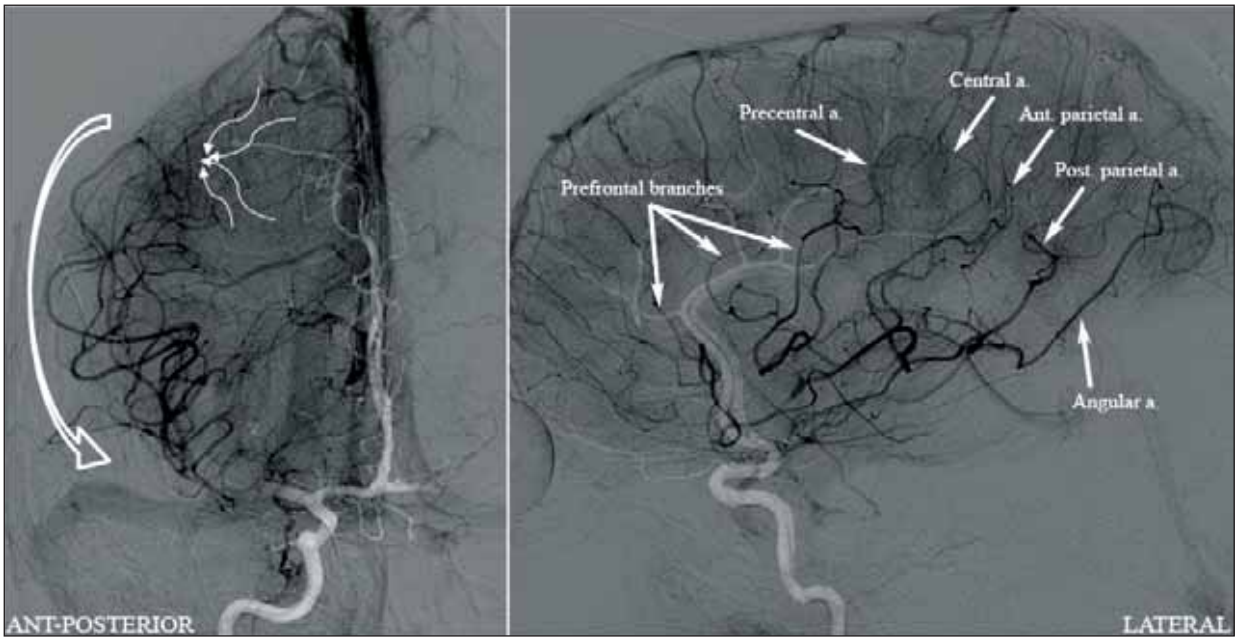

FIGURE 1. *Angiographic anatomy of ACA-MCA leptomeningeal anastomoses*
Late phase of internal carotid injection in a patient with acute right MCA occlusion.The images are re-masked in the arterial phase. Retrograde flow is seen in frontal and parietal branches of the MCA via leptomeningeal anastomoses between the ACA and MCA

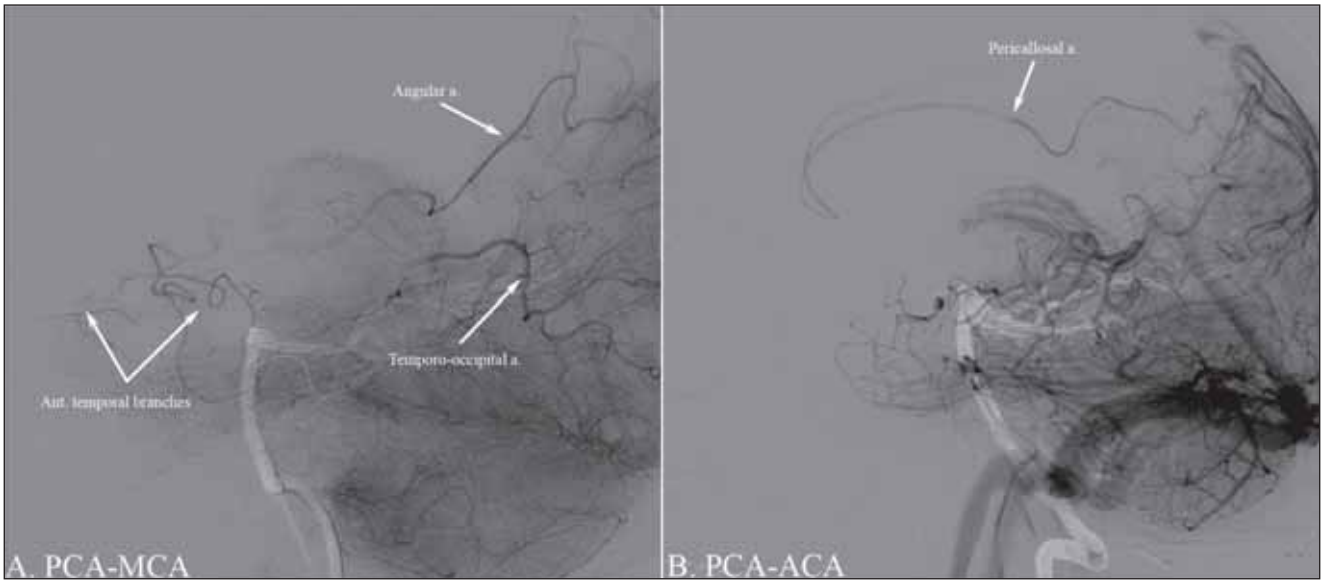

FIGURE 2. *Angiographic anatomy of PCA-MCA and PCA-ACA leptomeningeal anastomoses*
A. Retrograde flow inangular and temporal branches of the MCA via leptomeningeal anastomoses between the PCA and the MCA, seen on a vertebral artery injection in a patient with acute MCA occlusion
B. Retrograde flow in the ACA (pericallosal artery) via leptomeningeal anastomoses between PCA and ACA, seen on a vertebral artery injection in a patient with acute internal carotid terminus occlusion

There are relatively few descriptions or studies of pial collateral flow in the posterior fossa. However, during endovascular procedures that imply arterial occlusions, collateral flow was documented at the surface of the cerebellar cortex between the distal branches of the three cerebellar arteries, with similar functionality as in the supratentorial arteries.

EXPERIMENTAL STUDIES ON ANIMALS

The most frequently used animals in experimental studies of cerebrovascular disease were rats and monkeys. Studies were also performed on rabbits, cats, dogs and gerbils.

In 1958, Meyer (1) observed different flow restoration phases via LMA after MCA occlusion in

monkeys. He concluded that the collateral flow is barely sufficient to meet the metabolic demands necessary for tissue survival within the first 8 hours after MCA occlusion, varies from day to day, and becomes stable after 14 days. Symon (2) in experiments in dogs in 1960, observed that during an acute experimental MCA occlusion there was substantial blood flow entering its supply areas, mainly from the ACA. He also pointed out that the occlusion determined an infarction in the basal ganglia areas – a territory in which no collaterals were observed. The same author (3) (1961), in monkeys, observed that in MCA occlusions the amount of residual flow coming via LMA was dependent on the experimental conditions. He also observed a shift in the ACA and PCA territories due to MCA occlusion.

From further animal experiments, it was determined that a number of factors influence the functionality of LMA, such as variability (4,5), vascular dynamics (6), ischemic edema (7), age of the animal (8) and type of experimental occlusion (7). At the same time, it was found that LMA have an important role in the existence and outcome of the ischemic penumbra (9-11).

More recent studies reinforced these results by documenting the genetic variability of LMA in mice (12) and the degradation of LMA with advancing age (13).

Armitage et al (14) used laser-speckle contrast imaging after MCA occlusion in rats and found important variability in the presence and dynamic persistence of collateral flow. These results are complemented by Wang et al (15) who showed that initial arising of collateral channels does not ensure their persistence, and that collateral flow could be varied with distribution of regional blood flow in acute ischemic stroke.

PHYSIOPATHOLOGY IN THE ACUTE PHASE OF ISCHEMIC STROKE

From a physiological point of view, a LMA is an artery in which the blood can flow in both directions as a function of hemodynamic needs of the 2 territories it connects. The most important factor to influence flow direction is the pressure drop between the ends of the artery. The compensatory capacity of anastomosis is then inversely proportional to its hydraulic resistance – the fourth power of its radius. Therefore, size and number are an important determinant of the total capacity of LMA. Several animal (14,16) and early human pathological (17) studies have found an important genetically determined variability of collateral vessel number between individuals.

However, other factors influence collateral status. A recent study reported that age and metabolic syndromes including hyperuricemia were associated with poor leptomeningeal collateral status in patients with acute ischemic stroke (18). Several papers have found that the pre-morbid use of statins is associated with better collateral flow in patients with acute ischemic stroke (19-21). This data is consistent with the influences these factors could have on the local vascular inflammatory response during arteriogenesis. Additionally, hemodynamic factors like arterial blood pressure, central venous pressure, intracranial pressure and distal micro-emboli can alter the functionality of the collateral flow (22).

Important lessons can be learned from studies of collateral vessels dynamics in coronary and peripheral vasculatures. Two separate pathological processes have been identified after an arterial occlusion (23).

1. Arteriogenesis is the development of functional collateral flow from pre-existing arterial anastomoses. This process starts immediatelyafter the arterial occlusion when a pressure drop occurs distal to an occlusion and leads to opening of the anastomoses. It is induced by mechanical forces such as shear stress and circumferential wall stress, and its induction is not dependent of a hypoxia state. The initial increase of flow shear stress (FSS) exerted by the flowing blood activates the endothelium and stimulates a cascade of signaling events leading to the conductance of the collateral vessels. This involves endothelial cell activation, infiltration of inflammatory cells and subsequent inflammatory response leading to structural remodeling and increased diameter. As the collateral vessels grow in diameter, FSS falls and collateral flow decreases as a feedback autoregulatory mechanism. Arteriogenesis has been confirmed in the cerebral vasculature in animal models of cerebral ischemia (24,25).

2. Angiogenesis is a much slower process that involves the proliferation of endothelial cells and formation of new vessels. In addition, it can potentially increase the total resistance of the vascular bed of the afflicted artery and thus may be of limited value for the acute functional replacement of occluded arteries.

We can conclude that the existence and functional sustainability of collateral flowis genetically predetermined but also influenced by numerous hemodynamic, metabolic and immunological factors.

IMAGING MODALITIES

The leptomeningeal anastomoses have a small caliber, usually around 200-500 μm. Because of their size, the vessels themselves are not routinely visualized in conventional angiography and are below the spatial resolution of CT and MRI.

However, the **collateralflow** through these anastomoses can be evaluated on digital subtraction angiography (DSA), CT angiography, MRI and transcranial Doppler (TCD). In recent years, conventional angiography tends to be performed only in patients that are being considered for endovascular recanalization therapies. Because of their non-invasive nature, the other modalities are potentially accessible to a much larger group of patients.

CONVENTIONAL ANGIOGRAPHY

DSA remains the gold standard for collateral flow evaluation, given its high spatial resolution and the possibility of dynamic evaluation. Different grades of retrograde filling of branches distal to an occlusion can be visualized in late angiographic phases, after injection of the other cerebral vessels. The extent and the speed of collateral flow can be assessed selectively by successive injections of each vessel.

A recent systematic review (26) identified no less than 41 methods of collateral flow grading in angiography, in studies performed on acute and non-acute patient groups. Some of the grading criteria were:

- Rapidity and extent of retrograde collateral flow (21,27-30)
- Combination of occlusion site and extent of collateral flow (31-33)
- Zonal assessment based on ASPECTS areas (34,35)
- Number and/or rapidity of collateral vessel filling (36-46)
- Retrogade MCA flow to insula (47,48).

While most of these papers have not evaluated inter-observer reliability, the methods grading the anatomic extent of retrograde flow have showed good inter-observer agreement (47,49).

The most widely used grading scale was the one developed by the American Society of Interventional and Therapeutic Neuroradiology and Society of Interventional Radiology (ASITN/SIR) (27) (Table 1). This is a scale from 0 to 5 that rates the extent and speed of retrograde opacification of branches distal to an occlusion via the LMA. This method is being increasingly used in recent clinical trials for endovascular therapies because its simplicity, reproducibility and excellent inter-rater agreement (k = 0.89) (50).

TABLE 1. *The most commonly used angiographic collateral grading scale*

Angiographic collateral flow grading scale developed by the American Society of Interventional and Therapeutic Neuroradiology and Society of Interventional Radiology (ASITN/SIR)	
Grade 0	No collaterals visible to the ischemic site
Grade 1	Slow collaterals to the periphery of the ischemic site with persistence of some of the defect
Grade 2	Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
Grade 3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
Grade 4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

Another notable system proposed by Qureshi (31) incorporated the location of the arterial occlusion and the degree of retrograde collateral flow to obtain a severity score ranging from 0 to 5.

A different approach was taken by Kim et al (35), whoperformed a zonal grading of collateral flow from 0 to 3 in 15 cortical zones inspired from the ASPECTS score.

CT ANGIOGRAPHY

Although lacking dynamic information, CT angiography (CTA) source images alone (51) or in combination with MIP (52,53) and MPR (54-56) reconstructions can provide good visualization of the extent of collateral flow. Most studies evaluate the visualization of MCA branches distal to the occlusion grading from 0 to 3 or good/moderate/poor/none.

The addition of CT perfusion (CTP) to CTA adds important dynamic information to confirm that collateral flow is truly retrograde and demonstrates excellent interobserver agreement (57). Kim et al (58) found excellent correlation in collateral flow grading between multiphasic perfusion CT and conventional angiography.

More recently with the introduction of powerful multidetector scanners it became possible to realize a simultaneous acquisition of CTP and CTA (59). This also introduced the concept of 4D CT angiography and added the possibility of dynamic evaluation of collateral circulation on successive multiple acquisitions (60). Several studies showed that cu-

mulated MIP reconstructions on dynamic CTA have greater sensitivity in detecting collateral flow, which can be missed on conventional CTA scans if the acquisition is triggered too early (61-63). Additionally, 4D CTA can make the difference between slow anterograde flow in incomplete occlusions versus slow retrograde collateral flow in complete occlusions (61).

MRI SEQUENCES

Retrograde flow distal to an occlusion can be directly visualized as hyperintense vessels on FLAIR sequences (30,64-70) because of reduced velocity of flow that cancels the T2 flow-void effect**.** Additionally, in some cases, the same vessels are hypointense on T2 gradient echo sequences (71) reflecting intravascular deoxygenation due to increased oxygen extraction.

Campbell et al (72) used an interesting technique using anatomical background subtraction on perfusion MR source images to visualize flow in collateral vessels.

In addition, several methods allow for indirect estimation of collateral flow. Hermier et al (73) described areas of delayed perfusion observed on native perfusion MRI images, which reflect the extent of collateral flow. Other papers used perfusion MR to identify areas perfused by collateral vessels (74). Phase-contrast images allow the visualization of posterior to anterior circulation flow (75).

Arterial spin labeling (ASL) is a new noninvasive alternative MR perfusion imaging method that does not require exogenous contrast agents. It employs arterial blood as an endogenous contrast agent by magnetically labeling the inflowing blood by means of radiofrequency pulses. This method has not yet entered current clinical practice, but it has been documented to have similar results as with conventional contrast-enhanced MRI perfusion imaging. The greatest flaw of this method is its exquisite sensitivity to arterial arrival delays. However, the bright intravascular signal known as arterial transit artifact actually contains important information about late-arriving flow and thus is an accurate expression of collateral flow (39,76-78).

One of the other advantages of this modality is the possibility for selective labeling of a specific artery, allowing for the generation of selective perfusion maps for different arteries and delineation of cerebral arterial territories. Thus, is becomes possible to estimate the degree of collateral flow from different arteries (34,79).

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Collateral flow can estimated indirectly on TCD by quantifying relative (left to right differences) blood flow velocity and vessel pulsatility. These indices have been used as surrogate markers for collateral flow in a small number of studies (42,80-85).

Kim et al (42) found that detection of a difference of more than 30% comparative to the contralateral side in ACA and/or PCA had good sensitivity and specificity for detection of collateral flow in patients with M1 occlusions.

As this technique is non-invasive and reproducible, it can be used to quantify modifications in collateral flow before and after vasodilatatory stimuli, in order to assess the vascular reserve in chronic patients with stenotic or occlusive lesions.

PROGNOSTIC VALUE OF LMA IN ACUTE ISCHEMIC STROKE

- **Good collateral flow is a predictor of higher recanalization rates**

Table 2 summarizes the results of studies that have established that good collateral flow is a predictor of higher recanalization rates. This observation was validated in patients treated with endovascular therapies and with IV thrombolysis. A possible explanation is the better penetration of intrinsic and therapeutic thrombolytics into the thrombus via retrograde flow.

- **Good collateral flow is associated with smaller infarct volumes**

Table 3 summarizes the studies which showed that better collateral flow is associated with smaller initial and final infarct volumes in patients treated with intra-arterial (IA) therapies, intra-venous (IV) thrombolysis or without recanalization treatment. This finding strongly supports the hypothesis that collateral flow sustains the viability of cerebral parenchyma until therapeutic or endogenous thrombolysis occurs, or, alternatively, in some cases it can even provide definitive retrograde flow distal to a permanent occlusion.

- **Good collateral flow is predictive of better clinical outcome**

A large body of evidence (Table 4) has accumulated over the last 15 years showing that better collateral flow is an independent predictor of good clinical outcomes after an ischemic stroke. This is true for all groups of patients (treated with intra-arterial therapies, intra-venous thrombolysis, combined treatments or no recanalization treatment),

TABLE 2. *Collateral status versus recanalization rate*

Patient population	Collateral evaluation	Author (year)	No of patients	Prognostic significance of collaterals on recanalization rate
IA therapies	DSA	Liebeskind et al (100) (2014)	276	Beneficial
	DSA	Liebeskind et al (101) (2014)	72	Beneficial
	DSA	Marks et al (102) (2014)	60	Beneficial
	DSA	Nicoli et al (2014)	57	Beneficial
	DSA	Liebeskind et al (103) (2013)	119	Beneficial
	DSA	Rai et al (104) (2012)	89	Beneficial
	DSA	Bang et al (105) (2011)	222	Beneficial
	DSA	Qureshi et al (31) (2002)	60	Beneficial
	CTA	Nambiar et al (106) (2014)	84	Beneficial
IV thrombolysis	MRI – prolonged arterial tissue delay (indirect)	Nicoli et al (74) (2013)	64	Beneficial
	Dynamic CTA	Chen et al (63) (2014)	22	Beneficial
IV thrombolysis orno recanalization treatment	CTA	Miteff et al (57) (2009)	92	Beneficial
TOTAL			**1217**	

TABLE 3. *Collateral status versus infarct volume*

Patient population	Collateral evaluation	Author (year)	No of patients	Prognostic significance of collaterals on infarct volume
IA therapies	DSA	Marks et al (102) (2014)	60	TICI 0-2a patients had greater infarct growth with poor vs good collaterals
	DSA	Bang et al (105) (2011)	222	TICI 2b-3 patients had greater infarct growth with poor vs good collaterals
	DSA	Bang et al (29) (2008)	32	Poor collaterals correlated with larger infarct growth
	CTA	Angermaier et al (107) (2011)	25	Collateral grade correlated with final infarct volume
IV thrombolysis	DSA	Choi et al (108) (2011)	55	Collateral grade correlated with contrast enhanced CT ASPECTS score
	DSA	Mohammad et al (33) (2008)	56	Combined occlusion site and collateral score correlated with final infarct volume
	DSA	Christoforidis et al (47) (2005)	65	Good collaterals correlated with smaller final infarct volumes
	MRI-FLAIR	Lee et al (66) (2009)	52	Good collaterals associated with smaller initial and final infarct volume
	CTP source images	Calleja et al (109) (2013)	54	Good collaterals correlated with smaller final infarct volumes
IV thrombolysis or no recanalization treatment	CTA	Tan et al (53) (2009)	121	Good collaterals correlated with smaller final infarct volumes
IV, IA or no recanalization treatment	CTA	Souza et al (110) (2012)	197	Good collaterals correlated with smaller initial infarct volume
IA thrombolysis or heparin	DSA	Kim et al (35) (2012)	42	Good collaterals correlated with smaller final infarct volume
	CTA	Roberts et al (111) (2002)	162	Good collaterals correlated with smaller initial infarct volume
Without recanalization treatment	DSA	Shimoyama et al (112) (2013)	93	Poor collaterals correlated with larger baseline and final infarct volumes
N/A	MRI-FLAIR	Huang et al (68) (2012)	54	Lower initial infarct volume in patients with visible collaterals on FLAIR
	Contrast-enhanced CT	Jung et al (113) (2011)	11	Number of visible collaterals correlated with initial DWI-ASPECTS score
TOTAL			**1301**	

TABLE 4. *Collateral status versus clinical outcome*

Patient population	Collateral evaluation	Author (year)	No of patients	Prognostic significance of collaterals on clinical outcome
IA therapies	DSA	Liebeskind et al (100) (2014)	276	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	DSA	Kidwell et al (114) (2013)	118	After 3 hours, a favorable penumbral pattern may be a biomarker for good outcome because of the presence of better collaterals
	DSA	Liebeskind et al (103) (2013)	119	Good collaterals correlated with better NIHSS at discharge and 90 days mRS
	DSA	Liebeskind et al (115) (2013)	166	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	DSA	Pereria et al (116) (2013)	202	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	DSA	Liebeskind et al (101) (2014)	72	Collateral flow pattern is predictor of good outcome in carotid terminus occlusions
	DSA	Rai et al (104) (2012)	89	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	DSA	Galimanis et al (117) (2012)	623	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	DSA	Christoforidis et al (118) (2013)	112	Good collaterals favor rapid neurological improvement (> 50% of baseline NIHSS)
	DSA	Christoforidis et al (47) (2005)	53	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	DSA	Qureshi (31) (2002)	60	Combined score of occlusion site and collateral grade predictive of good recovery at 7 days (NIHSS ≤ 4)
	CTA	Seeta R et al (119) (2014)	87	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	CTA	Nambiar et al (106) (2014)	84	Patients with intermediate and good collaterals benefit from recanalization whereas patients with poor collaterals do not
	Dynamic CTA	Frolich et al (120) (2014)	82	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
IV thrombolysis	Dynamic CTA	Chen et al (63) (2014)	22	Collateral grade predictor of good clinical outcome (NIHSS 30 days and mRS ≤ 2)
	CTA	Brunner et al (121) (2012)	246	Collateral grade predictor of good clinical outcome (mRS≤2)
	CTP source images	Calleja et al (109) (2013)	54	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
IA or IA thrombolysis	DSA	Kucinski et al (122) (2003)	111	Collateral grade predictor of good clinical outcome (Barthel index)
IV or no recanalization treatment	Time invariant CTA	Smit et al (62) (2013)	40	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	CTA	Menon et al (123) (2011)	138	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	CTA	Tan et al (53) (2009)	121	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	CTA	Miteff et al (57) (2009)	92	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	CTA	Maas et al (124) (2009)	134	Poor collateral status associated with greater risk of in-hospital worsening
	CTA	Wildermuth et al (55) (1998)	40	Collateral grade predictor of clinical improvement at discharge
IV, IA or no recanalization treatment	CTA	Souza et al (110) (2012)	197	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	CTA	Lima et al (125) (2010)	196	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
N/A	CTA	Lee et al (126) (2013)	66	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
	MRI-FLAIR	Huang et al (68) (2012)	54	Collateral grade predictor of good clinical outcome (mRS ≤ 2)
TOTAL			**3654**	

even when recanalization status is not taken into account. The clinical repercussions are in keeping with the smaller infarct volumes observed in patients with better collaterals.

- **Poor collateral flow is predictive for more frequent hemorrhagic transformation**

Relatively less attention has been paid to the link between collateral flow and the risk of hemorrhagic transformation after recanalization therapies. It has been established that the degree of hypoperfusion in the ischemic territory influences the hemorrhagic risk (86,87). On the other hand, in the previous section we have seen that the degree of collateral flow was identified as a determinant of cerebral blood flow within the ischemic penumbra. These observations led to an intuitive connection between collateral flow and hemorrhagic transformation.

This connection has been confirmed in several studies, on patients treated with endovascular therapies, IV thrombolysis or conventional medical treatment (Table 5). Patients with poor collateral status are more at risk for hemorrhagic transformation. One study (49) found that these patients are at risk for larger volumes of hematoma compared to the group with more robust collateral flow. The subgroup of recanalized patients with poor collaterals seems to have a particularly high risk (50).

- **The link between collateral circulation and ischemic penumbra**

The interaction between collateral circulation and ischemic penumbra is complex and the variability in definitions of penumbral patterns on perfusion imaging has added to the difficulty of this evaluation. Table 6 summarizes the findings of studies that have investigated the link between collateral flow and perfusion imaging parameters in acute stroke.

Although it is not clear if collaterals influence total penumbral size, better collateral flow is correlated with higher absolute values of cerebral blood flow and smaller areas of severe hypoperfusion.

- **Collateral flow is dynamic and can determine infarct growth**

Campbell et al (72) evaluated collateral flow and infarct volumes on serial MRIs in the days that followed a stroke and showed that the collateral

TABLE 5. *Collateral status versus risk of hemorrhagic transformation*

Patient population	Collateral evaluation	Author (year)	No of patients	Prognostic significance of collaterals on the risk of hemorrhagic transformation (HT)
IA therapies	DSA	Bang et al (50) (2011)	222	Poor collaterals linked to more frequent HT
	DSA	Galimanis et al (117) (2012)	623	Poor collaterals linked to more frequent HT
	DSA	Christoforidis et al (49) (2009)	104	Poor collaterals linked to more frequent and larger volume of HT
IV thrombolysis	CTA	Brunner et al (121) (2012)	246	Poor collaterals linked to more frequent HT
No recanalisationtreatment	DSA	Shimoyama et al (112) (2013)	93	Poor collaterals linked to more frequent HT
TOTAL			**1288**	

TABLE 6. *The link between collateral status and ischemic penumbra*

Penumbra evaluation	Collateral evaluation	Author (year)	No of patients	Prognostic significance of collaterals on penumbral patterns
Perfusion MRI	DSA	Bang et al (29) (2008)	44	Good collaterals linked to larger areas of milder hypoperfusion
	DSA	Bang et al (28) (2008)	94	Good collaterals linked to larger areas of milder hypoperfusion
	MRI-FLAIR	Gawlitza et al (127) (2014)	33	Visible collaterals associated with larger DWI-PWI mismatch areas
	MRI-FLAIR	Haussen et al (67) (2013)	49	Visible collaterals associated with the presence of DWI-PWI mismatch
Perfusion CT	CTA	Kheradmand (128) et al (2013)	18	Collateral grade correlated with MTT/TTP mismatch
	DSA	Khatri et al (129) (2011)	16	No correlation between degree of collaterals and rCBF/ rCBV mismatch
TOTAL			**254**	

flow is dynamic and collateral failure leads to infarct growth. This result is in keeping with the findings of recent animal studies (14,15).

COLLATERAL FLOW ENHANCEMENT TREATMENTS

Efforts are being made to identify treatments that could enhance collateral flow in the acute or sub-acute stage of ischemic stroke. To the present day, none of these methods has obtained solid clinical results that could allow transition to current clinical practice.

Observations on stroke patients with patent foramen ovale have led to interesting theories on the potential role of the venous circulation during acute stroke. Microcirculatory venous collapse may lead to increased resistance in the ischemic core and thus participate to the failure of collateral flow (88,89). It could also help explain the no-reflow phenomenon encountered in some patients after recanalization. Venous collapse could be prevented by increasing the central venous pressure, in the same way alveolar recruitment is promoted by positive pressure ventilation.

1. Temporary aortic occlusion of the abdominal aorta at the suprarenal and infrarenal levels was tested to augment cerebral blood flow to the brain. Besides augmentation of cerebral arterial perfusion pressure, redistribution of blood in the upper extremity causes an increase in venous pressure that could prevent venous collapse in the ischemic area. Although the efficacy of NeuroFlo™ in ischemic stroke was not proven in the recently published SENTIS trial (90), two sub-analyses showed reduced mortality without an increase in severe disability (91) and a possible benefit in atrial fibrillation patients (92).

2. External counter-pulsation by applying diastole-synchronized compressions of the legs, usually in sessions of 1-hour per day, has been shown to increase cerebral blood flow velocities in patients with subacute ischemic stroke (93), however there is no data on functional outcomes and cerebral blood flow values.

3. Other treatments

Sphenopalatine ganglion stimulation increases intracranial blood flow and induces vasodilation through the parasympathetic innervation in the intracranial blood vessels. Based on encouraging preclinical data, the safety of sphenopalatine ganglion stimulation is currently being evaluated in human stroke patients (94). Mild induced arterial hypertension in the acute phase has shown promising results in animal studies, however human studies are restricted to several case reports (78). On the contrary, chronic hypertension has a deleterious effect on collateral recruitment (95). Among other volume expansion and hemodilution treatments, high-

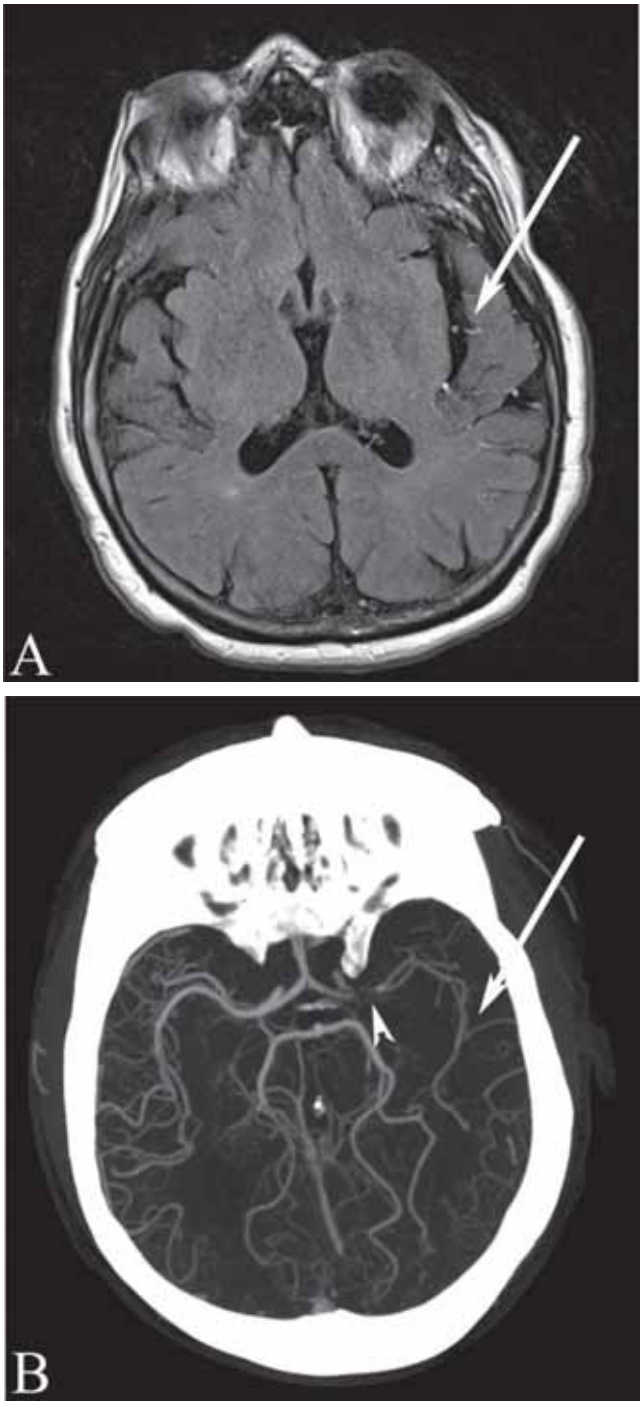

FIGURE 3. *Visualization of collateral flow on non-invasive imaging*
A. *MRI of a patient with acute left MCA occlusion.The distal MCA branches are hyperintense (arrow) on FLAIR sequences because of slow retrograde flow via leptomeningeal anastomoses ("spaghetti sign")*
B. *CT angiography (MIP reconstruction) of a patient with acute left carotid terminus occlusion (arrow head). Retrograde flow is seen in some of the distal left MCA branches (arrow) via leptomeningeal anastomoses*

dose albumin has failed to show a benefit on clinical outcome after acute stroke (96). Treatment with growth factors (notably G-CSF and GM-CSF) has been showed to promote leptomeningeal collateral growth and decrease infarct volume in rat stroke models (97).

DISCUSSION

It can be concluded that an important body of evidence supports the determinant role played by LMA in acute ischemic stroke. Good collateral flow is associated with smaller infarct volumes, better recanalization rates, less hemorrhagic transformation and better clinical outcomes.

Immediately after a cerebral arterial occlusion, the distal territory is retrogradely perfused via LMA. The efficacy of this process has an important inter-individual variability – some patients experience transitory neurological deficits or even remain completely asymptomatic, while others develop extensive infarctions. The time from symptom onset may not be equivalent to the time from arterial occlusion (98) – neurological symptoms could be the expression of a failing collateral supply. Animal (14,15) and human (72) studies have shown that collateral flow is dynamic and collateral failure is associated with infarct growth.

Understanding collateral flow dynamics could lead to a major shift in stroke treatment paradigms from criteria based on time from symptom onset to a system based on collateral grading and parenchymal viability. A recent study (99) has confirmed the potential role of collateral grading in extending the time window for recanalization treatments. Further research is needed on a larger scale, in order to implement these results in clinical practice.

CONCLUSION

Collateral flow is tightly linked with brain parenchymal survival after an acute ischemic lesion. By understanding the role of LMA in acute stroke, two avenues of research are opened. First, evaluation of collateral flow in the acute setting can improve the clinical results of revascularization treatments by helping identify patients who benefit best and possibly extending the currently accepted time window. Second, a new generation of stroke treatments can be developed, with the aim to improve collateral flow.

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