Progress Review

Anatomy and Functionality of Leptomeningeal Anastomoses
A Review

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Background—This review seeks to provide a structured presentation of existing knowledge of leptomeningeal anastomoses from anatomic and functional points of view and to identify problems and possible research directions to foster a better understanding of the subject and of stroke mechanisms.

Summary of Review—Available data show that leptomeningeal anastomoses may be important in understanding stroke mechanisms and that leptomeningeal anastomoses play an important role in penumbra outcome. However, the literature shows no consensus between statements on the existence of leptomeningeal anastomoses and compensatory capacity.

Conclusions—By analyzing the available literature and identifying the factors that contribute to this confusion, we found that variability and the functional consequences thereof are important but that quantitative data are lacking. Moreover, vascular remodeling is an issue to consider. (Stroke. 2003;34:2750-2762.)

Key Words: arterial occlusive diseases ■ collateral circulation ■ meningeal arteries

Since the introduction of the concept of the penumbra by Astrup et al1 in 1981, there is a new understanding of stroke mechanisms, but these mechanisms are not fully understood.2 One important factor that may lead to new methods of stroke treatment is a good understanding of the system of leptomeningeal anastomoses (LMA), which seems to have a role in saving part of the penumbral tissue.3–8 The first clear description of LMA was presented by Heubner9 in 1874. Since then, the importance of LMA in cerebrovascular ischemic disease is still a matter of dispute. A recent and authoritative stroke monograph10 only mentions the existence of LMA as part of the cerebrovascular circulation and scarcely discusses their importance in stroke pathophysiology.

Data from clinical literature show that, in similar middle cerebral artery (MCA) occlusions, there was a wide symptomatic interval ranging from ischemic events with clinical “restitutio ad integrum”11–13 to complete stroke in that territory.11,12 This diversity in clinical outcomes has been attributed to the interindividual variability of LMA, but convincing evidence regarding their compensatory capacity is not available.11,12,14–24 The interindividual variability of LMA led many authors to have divergent views about the existence of LMA and compensatory capacity.

It is likely that the existence of LMA and compensatory capacity was well documented clinically in patients with moyamoya disease who were almost symptom free, as long as the posterior cerebral arteries (PCAs) were free of severe stenosis and the territories of the anterior cerebral arteries (ACAs) and MCAs were filled retrogradely from the PCAs via the LMA.19,25–33 Another example of compensation is the absence of neurological symptoms after ACA, MCA, and PCA surgical occlusion for aneurysmal disease.34–36

The major trends in the literature on the subject of LMA follow a sinusoidal curve, as presented in Figure 1. The upper part of this plot shows the authors who had a positive view of the compensatory capacity of LMA, and the lower part shows the authors who had a negative view.

Some authors completely denied the presence of LMA and considered the ACA, MCA, and PCA as end arteries, functionally or even anatomically.37–45 These opinions were held because the LMA diameters were thought to be too small to be able to provide any communication between these arteries.46–53

Given the current state of knowledge concerning LMA, a review of this subject may be useful to the practitioners and investigators in this field. In this review we seek to provide a structured and comprehensive presentation of existing (and often conflicting) knowledge concerning human LMA from the point of view of presence and variability and from the point of view of compensatory capacity. One of our motives was to identify a line of investigation to promote further knowledge of LMA. In section 1, the known facts about the presence of LMA are presented from anatomic and clinical points of view. Section 2 shows, in a structured manner, the different views regarding the compensatory capacity of LMA. Section 3 discusses the possible function of LMA in animal experiments because not all of these results can be translated directly to humans. Finally, section 4 concludes the review

Received December 24, 2002; final revision received March 24, 2003; accepted March 28, 2003.

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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000095791.85737.65

2750
with a discussion of factors influencing the compensatory capacity of LMA, the relationship between the compensatory capacity of LMA and penumbra, and ways to assess the compensatory capacity of LMA in humans.

Section 1: Anatomic Evidence

We first consider the question of the existence and definition of LMA. A LMA is a pial artery that is a connecting branch between 2 major cerebral arteries supplying 2 different cortical territories. This section provides an overview of the anatomic evidence concerning LMA as gathered during more than 3 centuries after their first documented mention.

From a historical standpoint, LMA were first described by Sir Thomas Willis in *Cerebri Anatome* in 1684. They were also mentioned by Ruysch in 1699 and by Von Haller in the 18th century.

Heubner (1874) produced the first well-documented study demonstrating the presence of LMA. He attempted to establish the ACA, MCA, and PCA territories by injecting 1 of these arteries. Unexpectedly, the whole cerebral arterial tree was filled in the absence of anastomoses of the circle of Willis. Heubner was convinced of the existence of LMA and compensatory capacity. Moreover, he stated that LMA can reach a diameter of 1 mm. His contemporaries (Duret [1874], Charcot [1883], and Cohnheim [1872]) were not convinced of the importance of LMA as demonstrated by Heubner. Beevor (1909), Testut (in Vander Eecken and Adams [1919]), Poirer and Charpy (cited by Lazorthes et al), and Looten (in Lazorthes et al) took an intermediate position, ie, the LMA exist anatomically but do not have any physiological function.

In 1925, Fay (cited by Cobb) injected the isolated MCA of human cadaver brains with mercury and obtained the same result as Heubner, ie, the mercury filled the whole cerebral arterial tree. He therefore showed the existence of LMA on x-rays and considered LMA "important points of fusion" in the border zones of the 3 cerebral arteries.

Pfeifer (in Cobb) and Cobb (1931) investigated the capillary anastomoses. They observed that the cerebral vascular network is continuous, and Cobb concluded that "in the human brain there is an endless network of arterioles, capillaries and venules throughout the cortex, and similar networks in the ganglia and brain stem." He added, "The greatest anastomosis is in the capillary bed, there is much anastomosis between arterioles, and a definite but lesser amount between arterial trunks of larger size."

In 1927, Shellshear performed an experiment on a single human brain that was not completely perfused. He concluded the following on the constancy of the territories: "The arterial supply of the cerebral cortex is precise in its distribution, and might be used as an auxiliary to other methods of determining cerebral localization."

Vander Eecken and Adams were the first to provide a comprehensive anatomic description of LMA. They injected Schlesinger lead solution in 20 human cadaver brains, fixated the brain, and dissected the arteries under a magnifying glass. Figures 2, 3, 4, and 5 show the anatomy of LMA as described by Vander Eecken and Adams. They also defined the number and diameter of the arteries. They found interindividual variability in LMA in size, number, and localization and also found differences in LMA between the 2 hemispheres of the same brain.

In the 1960s, several authors studied the cerebral vascularization anatomic ally or postmortem radiographically. All
confirmed the presence of LMA.\textsuperscript{62–64} Moreover, Wollschläger and Wollschläger,\textsuperscript{65} who successfully injected 58 human cadaver brains, observed LMA, as described by Vander Eecken.\textsuperscript{14,15}

Lazorthes et al\textsuperscript{59} were some of the last anatomists to publish findings on LMA. Using 45 fresh cadaver human brains, they found anastomoses similar to those of Vander Eecken\textsuperscript{14,15} and also found several other anastomoses, eg, 1 at the level of the occipital lobe, where 3 branches of the cerebral arteries met: the artery of the gyrus angularis from MCA, the parietal inferior from ACA, and the occipital from PCA.

In recent years, both anatomic and angiographic studies confirmed the presence of LMA in every brain.\textsuperscript{66,67} The only exception was the work of Duvernoy,\textsuperscript{68–71} who performed cross-sectional studies (slice thickness=400 \( \mu \text{m} \)) on the cerebral vascularization after injection of the cerebral arteries with gelatin or resin. He did not observe any anastomosis of a caliber \( >90 \mu \text{m} \). It is possible that the 2-dimensional cross-sectional technique that Duvernoy used contributed to his failure to observe the larger anastomoses, compared with other techniques based on 3-dimensional visualization of the human arterial tree, such as that used by van der Zwan and Hillen.\textsuperscript{72} Van der Zwan and Hillen studied the variability of the vascular territories in human cadaver brains and observed anastomoses as large as 1 mm by injecting the cerebral arteries with resin colored with different pigments and maceration of the brain tissue. An example of LMA as visualized by van der Zwan and Hillen can be observed in Figure 6.

These studies, considered together, lead to the conclusion that LMA exist. However, a number of authors indicate the presence of interindividual variability in number and size. This interindividual variability results in confusion regarding the functional significance of LMA in stroke mechanisms.

### Section 2: Evidence of Functionality of LMA

We next consider the question of the functionality or compensatory capacity of LMA. From physical and physiological points of view, a LMA is an artery in which the blood can flow in both directions as a function of hemodynamic and metabolic needs of the 2 territories that are connected by it. The most important factor to influence flow direction is the pressure drop between the ends of the artery. The compensatory capacity of 1 LMA is then inversely proportional to its hydraulic resistance, ie, the fourth power of its radius. Therefore, size and number determine the total capacity of LMA.

This section provides a chronological overview of perpetual discussions of the functionality and possible role of LMA in different cerebrovascular diseases.

#### 1872–1930 Period

This is the first period when the compensatory capacity of LMA was suggested, denied, or not taken into account. As mentioned in section 1, Heubner\textsuperscript{9} (1874) concluded that LMA should have an important compensatory role in living people. Cohnheim\textsuperscript{58} (1872) maintained that an infarction can take place only in territories irrigated by end arteries and rejected the compensatory function of LMA. Duret\textsuperscript{47} (1874) concluded that LMA are too small to have functional significance and that the territories of the main cerebral arteries are separated completely. His conclusion\textsuperscript{47} was supported by Charcot\textsuperscript{46} (1883). Beevor\textsuperscript{48} (1909) took an intermediate position, ie, LMA are present anatomically, but their functionality is unclear. Testut (in Vander Eecken and Adams\textsuperscript{14}), Poirier and Charpy (in Lazorthes et al\textsuperscript{59}), and Looten (in Lazorthes et al\textsuperscript{59}) arrived at the same conclusion as Beevor.\textsuperscript{48} Fay (1925) (in Cobb\textsuperscript{60}) was convinced of the extensive possibility of compensation of LMA. Shellshear\textsuperscript{61} (1927), in an experiment on 1 poorly injected brain, concluded that the territories of the main cerebral arteries are fixed. Thus, from the beginning of these investigations, the compensatory capacity of LMA was questioned without documented evidence.

#### 1931–1959 Period

A period of positive views and evidence of the compensatory capacity of LMA was initiated by the remarkable results of the anatomic studies of Cobb,\textsuperscript{60} the experiments of De Seze,\textsuperscript{73} and the anatomicopathological results of Vander Eecken and Adams.\textsuperscript{14} Cobb (1931) concluded from his anatomic studies that the cerebral arterial tree is an endless network. De Seze (1931) did impressive postmortem work on the brains of animals and humans. Unfortunately, he published in a rather unknown and obscure source that is not cited often. He studied the influence of blood pressure on the prognosis of stroke patients by experimenting on postmortem stroke (n=2).
and stroke-free (n=17) patient brains at different pressures varying from 5 to 20 mm Hg. He radiographically observed the injected fluid flow direction in ACA or PCA that first filled the territory of the artery. Then the fluid started to fill the MCA branches retrogradely up to their origin from the MCA. His experiments led to the following conclusions: (1) All the MCA branches are connected to the branches of the ACA and/or PCA. (2) Age does not influence the permeability of the anastomoses. (3) In MCA complete occlusion, the liquid injected under pressure in ACA or PCA penetrates all its branches. (4) As a result of LMA, it is possible for the territory of a principal feeding artery to regain satisfying irrigation without recanalization of the nourishing artery.

These 2 studies initiated a positive period with respect to views on the functionality of LMA. The studies of Batson (1944), Vander Eecken (1953), and Gillilan (1959) were postmortem studies. Brain (1957) discussed, on anatomic grounds, the importance of the compensatory capacity of LMA in cerebrovascular diseases. The rest of the studies were angioGraphic (Ethelberg [1951], Mount and Tavers [1953], Rosegay and Welch [1954], Guiot and Le Besnerais [1955], Welch et al [1955], Gros et al [1956], Mount and Tavers [1957], Lehrer [1958], and Rovira et al [1958]). The results of these angiographic studies are presented in Tables 1, 2, and 3. Since most were carotid and not 4-vessel arteriographic studies, they focused on LMA between the ACA and MCA.

Vander Eecken (1953) was convinced that a vessel cannot exist without having any functionality, i.e., the caliber of a vessel depends on the amount of blood that flows through it. In agreement with this statement, he performed several studies on cadaver brains from patients suffering from stroke due to MCA occlusion and determined the following: (1) The infarced area was in most cases smaller than the occluded artery territory. (2) Infarction appeared in the subcortical areas, which were perfused by terminal arteries, i.e., no anastomoses existed between the arterial branches. (3) The rest of the MCA territory was more or less spared as a result of LMA that provided blood from ACA and/or PCA.

In conclusion, this period yielded positive, well-documented anatomic, anatomicopathological, and angiographic evidence of the importance of LMA in cerebrovascular disease.

**1960–1980 Period**

The introduction of angiography as an examination tool in cerebrovascular disease brought the investigators of the previous period to only positive conclusions regarding the compensatory capacity of LMA (Figure 1). However, in the early 1960s, scientific debate on the functionality of LMA began again with Tatelman (1960). He was convinced that the “functional end-artery” concept is wrong, but he concluded that the “lower incidence of collateral circulation in MCA occlusion is due to the lack of any large vascular communication in this area, with consequent poor collateral

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Occlusion</th>
<th>LMAs</th>
<th>Recovery</th>
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<tr>
<td>Rosegay</td>
<td>1</td>
<td>MCA</td>
<td>ACA*</td>
<td>Complete</td>
</tr>
<tr>
<td>Welch</td>
<td>2</td>
<td>Branch</td>
<td>ACA*</td>
<td>Improvement</td>
</tr>
<tr>
<td>Guiot</td>
<td>1</td>
<td>Branch</td>
<td>ACA and PCA</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Fasanò†</td>
<td>2</td>
<td>MCA</td>
<td>Yes</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Gros†</td>
<td>1</td>
<td>25 mm from origin</td>
<td>ACA*</td>
<td>Almost complete</td>
</tr>
<tr>
<td>Mount</td>
<td>1</td>
<td>MCA</td>
<td>ACA*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Rovira</td>
<td>2</td>
<td>MCA</td>
<td>ACA*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Lehrer</td>
<td>1</td>
<td>MCA</td>
<td>ACA*</td>
<td>Almost complete</td>
</tr>
<tr>
<td>Tatelman</td>
<td>19</td>
<td>MCA</td>
<td>ACA*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Lascelles</td>
<td>59</td>
<td>MCA</td>
<td>41 ACA*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Weidner</td>
<td>2</td>
<td>MCA</td>
<td>ACA*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Zappe</td>
<td>28</td>
<td>MCA</td>
<td>Yes 11*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Hawkins</td>
<td>18</td>
<td>MCA</td>
<td>Yes 14*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Wickbom†</td>
<td>20</td>
<td>MCA</td>
<td>Yes 19*</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Sindermann</td>
<td>63</td>
<td>MCA</td>
<td>Yes 80%</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Mirosa</td>
<td>18</td>
<td>MCA</td>
<td>Yes 10</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Adams</td>
<td>2</td>
<td>MCA</td>
<td>Yes</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Mull</td>
<td>6</td>
<td>MCA</td>
<td>Yes</td>
<td>Not discussed</td>
</tr>
</tbody>
</table>

*Vertebral angiography not performed.
†Cited by Gros et al.

It can be noted that most of the compensation is coming from the ACA due to the fact that in most of the cases vertebral angiography was not performed.

TABLE 1. Presence of LMAs on Arteriography of Patients With MCA Occlusion and Prognosis

Table 1 presents the presence of LMAs in patients with MCA occlusion and their recovery. It is evident that the majority of compensation comes from the ACA, especially in cases where vertebral angiography was not performed.
potential.” His statements were in contrast to the anatomic results of Kaplan,82 who suggested that the only significant collateral circulation takes place on the surface of the brain; these results were supported by the results of Fields83 (1971) and Mishkin and Schreiber84 (1974), who showed the angio-
graphic anatomy of LMA.

Berry85 (1961), Einsiedel-Lechtape et al22,86 (1977), and
Heiss87 (1977) concluded that LMA can limit the extent of damage. Potter88 (1959) and Jawad89 (1977) stated that “very little dilatation of peripheral collaterals”88 (LMA) can help to reduce the damage of a major vessel occlusion.

Jain90 (1964) stated in his anatomic results that the territo-
ries of the main cerebral arteries are well demarcated, and Lascelles and Burrows91 (1965), Sindermann et al92 (1969), and Mirosa et al93 (1980) found from clinical and angio-
graphic examinations that the visual presence of LMA on angiography does not appear to influence the prognosis of MCA occlusion.

Weidner et al84 (1965) stressed the importance of LMA and the necessity of understanding their compensatory capacity. Zatz et al95 (1965) was convinced that as a result of LMA, there is a possibility of major cerebral artery occlusion without consequent neurological deficit.

Zappe et al41 (1966), Ring40 (1976), and Yamaguchi96 (1977) defined the major cerebral arteries as functionally end arteries.

Until 1969, when Sindermann et al92 found a discrepancy between the presence and compensatory capacity of LMA, there were only positive views from scientists on the subject, eg, Hawkins97 (1966), Love et al98 (1966), and Dichgans and Voigt99 (1969).

In 1971, Zülch100 pointed out that a major cerebral artery occlusion induces a complete reversal of flow in its branches supplied by the other 2 patent arteries.

In 1978, Merkel et al101 observed the compensatory capac-
ity of LMA in stroke due to sickle cell disease. In 1979, Nádvornik and Đuroš102 termed the LMA “parasitical ves-

In conclusion, this period was represented by continuous debate on the compensatory capacity of LMA. There was no clear differentiation between the positive and negative opin-
ions that might lead to a definite conclusion about the compensatory capacity of LMA. This confusion was gener-
ated by variability in patients’ outcomes and the almost constant visual presence of LMA on arteriography. The most

### TABLE 2. Presence of LMAs on Arteriography of Patients With ACA, PCA, and ICA Occlusions and Prognosis

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
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<th>LMAs</th>
<th>Recovery</th>
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<td>ACA</td>
<td>MCA</td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>ACA</td>
<td>PCA</td>
<td>Death (HTA)</td>
</tr>
<tr>
<td>Rovira</td>
<td>1</td>
<td>ACA</td>
<td>MCA</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Tatelman</td>
<td>37</td>
<td>ACA</td>
<td>5 MCA</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Einsiedel</td>
<td>10</td>
<td>PCA bilateral</td>
<td>MCA</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Einsiedel</td>
<td>21</td>
<td>PCA</td>
<td>ACA and MCA</td>
<td>Recovery not correlated with presence of LMAs on angiography</td>
</tr>
<tr>
<td>Goto</td>
<td>14</td>
<td>PCA</td>
<td>13 MCA</td>
<td>Recovery: some complete, others to some extent, others not</td>
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<tr>
<td>Takagi</td>
<td></td>
<td>ICA</td>
<td>PCA</td>
<td>Several had good correlation between LMAs presence and prognosis</td>
</tr>
<tr>
<td>Mull</td>
<td>24</td>
<td>ICA</td>
<td>20</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Archer</td>
<td>2</td>
<td>BA occlusion</td>
<td>MCA</td>
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### TABLE 3. Presence of LMAs in Aneurysmal Disease

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<th>Author</th>
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<th>LMAs</th>
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<td>Rosegay</td>
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<td>MCA</td>
<td>Yes</td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>ACA</td>
<td>Yes</td>
<td>Bad course (HTA)</td>
</tr>
<tr>
<td>Guiot</td>
<td>1</td>
<td>MCA</td>
<td>Yes</td>
<td>Complete in 10 days</td>
</tr>
<tr>
<td>Mount</td>
<td>1</td>
<td>Both ACAs</td>
<td>MCA</td>
<td>Not discussed</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>ICA</td>
<td>PCA</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Weidner</td>
<td></td>
<td>MCA</td>
<td>No</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Drake (1994)</td>
<td></td>
<td>ACA</td>
<td>Yes</td>
<td>Good outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCA</td>
<td>Yes</td>
<td>Good outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCA</td>
<td>Yes</td>
<td>Good outcome</td>
</tr>
<tr>
<td>Drake (1997)</td>
<td>4</td>
<td>MCA</td>
<td>Yes</td>
<td>Bypass occluded, no symptoms</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>ACA</td>
<td>MCA and PCA</td>
<td>Excellent outcome</td>
</tr>
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</table>
realistic way to identify LMA on angiography is on the lateral view, whereas the anteroposterior view may lead to overprojection and consequently to overestimation of LMA.

1981 to Present

This period was marked by the introduction of new imaging techniques such as transcranial Doppler ultrasonography (TCD), CT, nuclear medicine techniques, and MRI to study cerebral vascularization and circulation and by the introduction of the concept of the penumbra in the evolution of stroke. Views on the compensatory capacity of LMA were contradictory, and the introduction of these new techniques did not shed more light on the subject.

Takagi and Shinomara,103 in 1981, using angiography and CT, concluded that the dimensions of the infarction do not always depend on the collateral flow. In the same year, Zülch106 published a monograph on cerebrovascular pathology and pathogenesis, in which he pointed out the importance of LMA in ACA, MCA, or PCA occlusion. Fukuyama et al105 (1983) studied LMA by nuclear medicine techniques and concluded that cortical infarction occurs in cases with inadequate development of LMA despite an angiographically normal circle of Willis. In this way, he introduced the concept of vascular dynamics, which was also observed by Adams106 (1983) and Hasegawa107 (1992) and explained by Naritomi et al108 (1985). Bozzao et al109 (1989) stated that the presence of LMA in the late phases of an ischemic lesion does not indicate presence in the early phases. Nakano et al110 (1995) observed LMA in all of their patients with MCA stenosis, and Yamashita et al111 (1996) concluded that LMA develop to some extent immediately after occlusion and continue to develop later. Hoksbergen et al.110 using TCD (1999), stated that LMA are “theoretically present, but not developed in absence of extracranial cerebrovascular disease.” In contrast, in 1984, Corston et al112 observed patients with stroke due to MCA stenosis, ie, with no vascular adaptation due to MCA stenosis. They determined that carotid obstruction would not lead to development of LMA between ACA and MCA because both of them were affected. The remodeling effect would take place between PCA and MCA or ACA, and these anastomoses cannot be visualized by carotid angiography.

In 1984, Aaslid et al.42 in TCD studies, used the concept of functional end artery in the case of MCA, a concept that was maintained by Lindergaard et al.39 (1985), Sorensen et al.41 (1989), Bode and Harders.44 (1988), Pansera.38 (1990), and Ungerboeck et al.37 (1995). Day suggested that LMA are “too small in their protective capacities”; Harders and Gilsbach.53 (1987) and Aaslid et al.52 (1989) arrived at the same conclusion; Muller and Schimrigk.51 (1996) defined the LMA as “the most compromised collateral supply”; and Derdeyn et al.113 (1998) concluded that LMA are not adequate to maintain normal cerebral hemodynamics in major cerebral artery occlusion, a conclusion sustained by Aaslid.114 in 1999.

Ikeda et al.115 (1985), who expected the presence of retrograde flow in cases of ACA occlusion, did not observe LMA flow on angiography.

In 1986, Olsen et al.116 observed LMA on angiography only in noninfarcted areas. Their observation was strengthened by the suggestion of Leblanc et al.117 (1987) that LMA represent an important compensatory mechanism in cerebrovascular disease and by the conclusions of Ueda et al.118 (1992) and Yamashita et al.119 (1992). Weiller et al.120 (1990, 1993) (in a combined clinical, single-photon emission CT, and TCD study) considered that LMA form a rich collateral network that can prevent infarction due to MCA stenosis or occlusion. Kaps et al.121 (1990), Brass et al.122 (1989), Bode and Harders.44 (1989), and Ueda et al.118 (1992) found on TCD an increase in flow velocities in the ipsilateral ACA and PCA during MCA occlusion. Angeleno et al.123 (1990) (in a combined study) observed only internal border zone infarctions and considered that the cortical border zone was spared as a result of the functionality of LMA. The importance of LMA in flow compensation after major cerebral artery occlusion was also suggested by Yamauchi et al.123 (1992) in ICA severe stenosis, Touho et al.124 (1995) in a case of bilateral MCA occlusion associated with left PCA stenosis, Lyer et al.125 (1997), Mull et al.126 (1997), Urbach et al.127 (1997), Min et al.128 (2000), Oppermann et al.129 (2000), and Nimishita et al.130 (2001), who concluded that subcortical infarction does not extend to cortical areas if LMA are efficient.

A different perspective on the hemodynamic functionality of LMA came from Viñuela et al.131 (1986) and Enam and Malik.132 (1999), who observed refilling of arteriovenous malformations in conditions of complete occlusion of feeding vessels as a result of LMA and other vessels.

Saito et al.133 (1987) and Fieschi et al.134 (1989) concluded that LMA do not influence the prognosis of patients with cerebrovascular disease.

Fujita et al.135 (1989), Choksey et al.135 (1993), Drake et al.136,137 (1994, 1997), and Taylor et al.136 (2000) again observed the importance of LMA in aneurysmal disease (Table 3). Choksey et al.135 suggested that “the chronic presence of a giant aneurysm so distorts the distal MCA branches that blood flow in them falls slowly over a period of years. This leads to the development of LMA from the territory of anterior and posterior cerebral arteries.” Drake et al.134 were astonished by the compensatory possibility of LMA in surgical major cerebral artery occlusion due to aneurysmal disease. They based their conclusions on follow-up observations of patients with installed extracranial-intracranial bypass before surgical occlusion. The bypass was completely occluded at the follow-up patient examinations. The aforementioned patients had no neurological symptoms.

Ogata et al.137 (1989) suggested that LMA can determine the transformation of a pale infarct to a hemorrhagic one.

The positive influence of rheological blood factors on the compensatory capacity of LMA was observed by Carey et al.138 (1990) and Wildermuth et al.139 (1998).


Ringelstein et al.143 (1992) hypothesized the presence of a relationship between penumbra, recanalization, and therapeutic window and the role of LMA in MCA occlusion. They suggested that LMA “maintain a certain degree of cortical perfusion, critically elevating tissue in the ischemic penumbra from the level of irreversible cell death.” Moreover, they considered that early recanalization can only be efficient if
LMA might define “the temporal width of the therapeutic window.”

Von Kummer et al.143 (1995) concluded that LMA are important in the prognosis of cerebrovascular ischemic disease, and Wildermuth et al.139 (1998) and Lee et al.144 (2000) found a positive correlation between recovery after thrombolytic therapy and the presence of efficient LMA.

Kakinuma et al.145 (1999) and Lownie et al.36 (2000) suggested that LMA are important in cerebrovascular disease but that their function is not fully understood.

Finally, Klijn et al.146 (2000) found a correlation between ICA occlusion, presence of collateral flow of LMA, and recurrence of infarction (Figure 7).

When all these results are considered, we can draw 4 conclusions. First, this section shows the marked absence of consensus between investigators on the subject of LMA. Second, it shows the lack of understanding regarding the compensatory capacity of LMA. Third, it shows that each new diagnostic tool led to positive and negative conclusions regarding the compensatory capacity of LMA. Fourth, it shows the necessity of a comprehensive functional study on the compensatory capacity of LMA in cerebrovascular disease.

Our hypothesis is that LMA have a great capacity for compensation if several conditions are met. These conditions can clearly influence the patient’s outcome in cerebrovascular disease, and more research must be done to understand the relationship between stroke mechanisms and the compensatory capacity of LMA.

Given the above conclusions, a brief overview of animal experiments on the compensatory capacity of LMA (section 3) will further illuminate problems encountered in clinical practice in cerebrovascular disease.

Section 3: Evidence of Functionality of LMA From Animal Experiments

The third question regards the conditions necessary for optimal functionality of LMA. The advantage of animal experiments, compared with human LMA studies, is the possibility of performing them in the living anesthetized or unanesthetized animal. However, one must be aware of certain differences between the cerebrovascular systems (and reactions to different factors) of humans and animals. Animal experiments provide the possibility of measuring, in vivo, different parameters that are not accessible in living humans and also of manipulating conditions during the experiments. This possibility of different in vivo measurements correlated with postmortem brain evaluation makes the animal experiments a valuable means to explain several phenomena and reactions observed in the human cerebral circulation under different stress conditions, eg, decreased blood pressure due to major vessel occlusion or due to severe stenosis.

This section presents the most important differences between human and animal cerebrovascular systems and provides an overview of the results of animal experiments that may lead to better understanding of human cerebrovascular disease.

Differences Between Animal and Human Cerebrovascular Systems

Certain anatomic features in animals are not present in the human cerebral circulation. Some of these features can influence the validity of the results of animal experiments when they are extrapolated to the human cerebrovascular system. However, the major implications are true for the human cerebrovascular system as well.

The most frequently used animals in experimental studies of cerebrovascular disease are rats and monkeys. However, studies were also performed on rabbits, cats, dogs, and gerbils. The most important difference between the cerebrovascular system of the rat and monkey and the human system is the presence of a single ACA in the animals. The results of the flow measurements that are made to investigate the compensatory function of LMA are not influenced by this feature, as translated to humans, because of the presence of the anterior communicating artery in humans, which equalizes the pressure at the level of the emergence of the second segment of the ACA. The cerebral arterial system of cats and rabbits presents a rete mirabile caroticum that connects the internal carotid artery with the arteries on the surface of the brain. This feature represents another collateral system between the internal carotid artery and the cerebral arteries and consequently influences flow measurements designed to investigate the functionality of LMA.

Results of Animal Studies

A chronological view is presented of the animal experiments that were performed to investigate the compensatory capability of LMA. The investigators who studied LMA in animals had no doubt about their presence; they only tried to understand their compensatory capacity in cerebrovascular disease and the factors that can influence this capacity.

In 1954, Meyer et al.147 (cats) concluded that oxygen availability after a major cerebral artery occlusion depends on vessel size and collateral circulation. Meyer et al.147 Denny-Brown and Meyer148 (1957) (monkeys), Symon et al.149 (1963) (monkeys), Ishikawa et al.150 (1965) (monkeys), Symon151 (1968) (monkeys), Sundt and Waltz152 (1971)
(monkeys), and Tulleken et al.153 (1978) (cats and monkeys) suggested that systemic blood pressure is important for maintaining flow through the anastomoses. They stated that the pressure gradient between healthy territories and the occluded artery is associated with local vasodilatation in the downstream occlusion territory. Meyer et al.147 also supposed that the diameter of LMA is influenced by the metabolic products generated by the ischemic area. Their supposition147 was contradicted by the findings of Denny-Brown and Meyer148 and Symon et al.149 Denny-Brown and Meyer148 were convinced that the flow from ACA and PCA through LMA can overtake the whole territory of an occluded MCA. In 1958, Meyer,154 in monkeys, observed different flow restoration phases via LMA after MCA occlusion. 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,155 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. Symon156 (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. The amount of territorial shift from ACA or PCA was dependent on the initial (ie, before occlusion) dimensions of the territories. In 1968, Symon151 opposed Cohnheim’s58 theory on end arteries and pointed out that flow via LMA is established immediately after occlusion and that there is a chronic adaptation of LMA by hypertrophy. Ott et al.,157 in 1975, observed in baboons that some flow was still preserved in the occluded MCA territory and assumed that this flow was coming via LMA. Tulleken et al.153 did a comparative study in cats and monkeys on LMA flow adaptations in response to different factors. He observed that hypertension associated with hypercapnia resulted in a great increase in flow in LMA in MCA occlusion in monkeys, whereas in cats the effect was not as strong.

From animal experiments, it was determined that a number of factors influence the functionality of LMA, such as variability,58,159 vascular dynamics,160 age of the animal,161 size,162,163 ischemic edema,164 and type of experimental occlusion.165 At the same time, it was found that LMA have an important role in the existence and outcome of the penumbra.166–168

In conclusion, the aforementioned animal models showed that the compensatory capacity of LMA depends on different factors, including LMA diameter, systemic blood pressure, and local metabolism. The authors of these studies also observed the vascular adaptation of the collaterals. Finally, LMA may have an important role in penumbra evolution.

**Discussion**

In this review we have presented different views of the LMA system. First, in section 1, the LMA system was described from an anatomic point of view. Section 2 presented the results emerging from clinical practice in relation to the functionality of this system. Finally, the advantages, limitations, and findings regarding the compensatory capacity of LMA from animal experiments were discussed in section 3. However, there are still several important issues regarding the role of LMA in stroke prevention.

The following section attempts to provide further information on several aspects of this topic. First, we show the important pathophysiological factors that can improve or decrease the functionality of LMA. Next, we will discuss the implications of good functioning anastomoses on penumbra. Finally, we analyze several research directions that can provide a better understanding of this controversial subject.

**Section 4: Additional Factors Affecting the Role of LMA in Stroke Prevention**

**Factors Influencing the Compensatory Capacity of LMA**

**Variability in Diameter and Number of LMA**

The variability in number and diameter of LMA can affect the compensatory capacity. Rosegay and Welch13 concluded that some patients can have a meningeal anastomotic bed that can be double that of other patients. Gros et al.12 stated that “the presence of collateral circulation [LMA] is not constant, but not an exceptional fact.” Guiot and Le Besnerais24 concluded that the capacity of LMA depends on the individual variation of these anastomoses. Animal experiments clearly showed that the variability of LMA affects the outcome of the animal after MCA occlusion.150 The importance of this variability was also stated by Quiring169 and Fields170: “The collateral flow will be adequate provided the sum of the squares of the cross-sections of the collateral arteries is equivalent to, or greater than, the square of the cross-section of the occluded primary artery.”170 This definition of compensatory capacity stresses the necessity of reliable anatomic evaluation of the morphology of the anastomoses and the range of interindividual variability.

**Systemic Blood Pressure**

Occlusion of an artery results in a decrease in pressure in that territory. Because the arteries around the diseased artery have higher pressure, a pressure gradient appears between the healthy artery and the territory of the occluded artery. This pressure gradient will cause blood to flow from the healthy arteries to the territory of the occluded artery via the LMA. The pressure gradient magnitude, and thus the flow rate, is influenced by the systemic blood pressure. This statement was suggested by the results of clinical studies11,73,81,84,98,171 and was confirmed by animal experiments.148,149 An important observation made by Symon et al.149 in monkeys is that, in cases of an established collateral flow through LMA, systemic blood pressure greatly influences flow maintenance to deficient areas. Denny-Brown and Meyer148 observed the occurrence of transient ischemic attacks in monkeys when, after an experimental MCA occlusion, systemic blood pressure was reduced. They also observed that reduction of systemic blood pressure under the transient ischemic attack limit led to the appearance of transient paralysis, which disappeared after restoration of systemic blood pressure values.
In a study of the influence of blood pressure on the ischemic event, De Seze\textsuperscript{73} observed that hypertensive patients who presented with an increase in blood pressure after stroke had a better outcome after stroke, ranging from partial to complete recovery. The opposite observation was also valid, ie, hypertensive and normotensive patients who presented with a decrease in blood pressure after the ischemic event had a poor prognosis, ranging from almost no recovery to death.

In conclusion, systemic blood pressure has a great influence on the compensatory capacity of LMA, and differences can emerge between patients who have a fall in blood pressure after the ischemic event and patients who have maintained or even increased their systemic blood pressure.

**Vascular Dynamics**

An occlusion can occur gradually, as in the case of evolution of a stenosis to occlusion, or suddenly, as in the case of thromboembolic occlusion. In the first case, several authors\textsuperscript{12,76,83,85,94,100,101,105,172,173,195,196} stated that the LMA have enough time to develop and the compensatory capacity will be better than in sudden occlusion, when the anastomoses are not adapted to react promptly. This assumption is confirmed by the presence of compensatory LMA in other cerebrovascular diseases, such as the presence of an aneurysm or moyamoya disease. We have mentioned the hypothesis of Choksey et al\textsuperscript{135} (see section 2) in the case of aneurysm. For moyamoya disease, its definition includes the concept of slowly progressive disease that allows time for the anastomoses to develop (ie, increase in size and/or number) for better compensation. The vascular remodeling of small arteries in moyamoya disease was clearly modeled by Han.\textsuperscript{173} In conclusion, if an artery has time to develop, it will provide more compensatory flow. Thus, in sudden arterial occlusion, the lack of adaptation of LMA represents a limiting factor for recovery.

It is difficult to define in a patient the type of occlusion that resulted in the ischemic event if there is no knowledge about the patient’s history. These facts can explain the difference in prognoses between patients with similar arterial lesions. Moreover, they stress the necessity of knowledge of the anatomy of LMA and the need for a way to predict the reactions of LMA in different pathological situations, such as the possibility of test balloon MCA occlusion, and in mathematical models.

**Age of Patient**

Several authors stressed the importance of the patient’s age as an independent factor in the compensatory capacity of LMA.\textsuperscript{24,76,85,94} They also regarded the presence of atherosclerosis as a determinant of stiffness of anastomoses and of cerebral arteries as a disadvantage.\textsuperscript{24} Finally, they considered the functional state of the circulation of aged patients as altered and the compensatory capacity as very low.\textsuperscript{24,76,85,91} In treating an aged patient with a cerebrovascular disorder, the clinician must determine the influence of time on cerebral vascularization. We do not know the effects of age on vascular demodulation, amount of peripheral circulation, and LMA.

These are the main factors, as reviewed in the literature, that can influence the compensatory capacity of LMA. This discussion clearly shows that the pressure gradient between healthy arteries and the territory of the occluded artery associated with adequate systemic blood pressure is the most important factor that can positively influence the flow through the LMA and determine better clinical evolution. Furthermore, it is important to know the approximate dimensions of the anastomoses and the patient’s status before the ischemic event.

**LMA and Penumbra**

Astrup et al\textsuperscript{1} introduced the concept of the penumbra in 1981. Since then, many studies were performed to understand this phenomenon and to prevent its evolution toward the necrotic core of infarction. It is our opinion that the very presence of penumbra suggests the apparition of flow through the LMA. In animal experiments, Morawetz et al\textsuperscript{158} suggested that LMA can help to save the penumbral tissue. Several studies performed before the introduction of the concept of penumbra in clinical practice have confirmed this supposition. These studies suggested a shift in the territories of the ACA and PCA after MCA occlusion. Symon\textsuperscript{156} concluded that part of the territory of the occluded MCA would be taken over by ACA or PCA depending on the corresponding pressure gradients. He also observed the shift phenomenon in vertebral artery occlusion after a fall in blood pressure in the PCA. He further observed that flow started in the posterior branches of the MCA, overtaking part of the PCA territory. In addition, Hinton et al\textsuperscript{174} suggested that in MCA stenosis in humans, the retrograde flow from ACA and PCA to MCA via LMA would determine a border zone shift. Van der Zwan et al\textsuperscript{175} observed this shift during experiments on fresh human cadaver brains.

It is well known from the studies of van der Zwan et al\textsuperscript{175} that there is an interindividual variability in space between the ACA, MCA, and PCA territories (Figure 8). This interindividual variability depends on the amount of blood that flows through each artery and is determined by the presence of LMA. Evidence from the study of Symon\textsuperscript{156} suggests an interindividual variability of the territories that is related to variability in time and adaptation to local flow requirements.

**Conclusions**

This review showed that there is great interindividual variability in distribution, size, and number of LMA. Various
authors found this variability, but no study shows the range of this variability and ties variability to compensatory capacity. Furthermore, there is no consensus about functionality and capacity for compensation. Moreover, this review discussed animal experiments that may improve understanding of the role of LMA in pathology. Finally, it showed the important factors that can determine good functioning of the anastomoses.

In conclusion, we identified the need for a comprehensive study of LMA concerning their distribution, size, and number and the influence of these parameters on hemodynamics. On the basis of these findings, we are presently conducting a morphological and functional study on fresh human cadaver brains to assess the functionality of LMA. These experiments will provide the necessary data for validation of mathematical simulations that can predict the amount of compensation of LMA in patients.

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Anatomy and Functionality of Leptomeningeal Anastomoses: A Review
Mariana Brozici, Albert van der Zwan and Berend Hillen

Stroke. 2003;34:2750-2762; originally published online October 23, 2003;
doi: 10.1161/01.STR.0000095791.85737.65
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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