Mixed perfusion: A combined blood supply to the brain tissue by multiple arteries

Perfusion mixte : un apport sanguin combiné du tissu cérébral par des artères multiples

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\textbf{Summary} From intra-arterial angiography studies and recently developed imaging techniques capable of non-invasively visualizing the flow territories of the cerebral arteries at brain tissue level, it is known that brain regions can be fed by multiple arteries simultaneously. This indicates a mixing of blood from separate supplying arteries before reaching the brain tissue. Herein, we aim to explore the various manners blood from different arteries may mix in both healthy individuals and in patients with steno-occlusive disease. Furthermore, the impact of cerebrovascular interventions on the blood flow patterns and its effect on the mixing of the blood supply is discussed. More accurate knowledge and understanding of the vascular sources of tissue perfusion, and potential mixing, may result in more efficient vascular therapies and interventions targeted specifically to affected brain tissue areas.

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\textbf{Introduction}

Since the first description of the territorial distribution of blood by the brain arteries in 1874 by Henri Duret, various anatomical atlases have shown schematic drawings of the vascularisation of the brain \cite{1}. In these drawings the vascular origin of the blood supply to specific brain regions is illustrated by dedicating a color to the distribution territories of the major cerebral arteries \cite{2–4}. During the past two decades, with the introduction of magnetic resonance imaging (MRI) and computed tomography (CT), this concept of a relatively fixed territorial distribution has strongly influenced patient management. For instance, in the clinical workup of patients with stroke and multivessel disease it is used to establish which artery is causing the symptoms.

There are however several sources that suggest that these templates are an oversimplification. In an extensive article reviewing the literature of territorial distribution of the major cerebral arteries many discrepancies were

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described between the various studies [5] and post-mortem investigations have shown that the topographic variability was significantly greater than previously assumed [6,7]. In addition, from traditional catheter angiography examinations of the cerebral arteries it is known that a certain overlap between perfusion territories is possible. New imaging techniques that are able to visualize the individual flow territories of the cerebral arteries at brain tissue level have recently shown that it is possible to identify areas simultaneously fed with freshly oxygenated blood from multiple arteries [8—10]. In this review we aim to explore the various ways freshly oxygenated blood may mix, both in healthy individuals and in patients with obstructive cerebrovascular disease.

**Methods of assessing mixed perfusion**

Our knowledge of the vascularisation and the territorial distribution of blood from the brain feeding arteries is derived from a wide variety of techniques. Initial descriptions of the vascularisation are based on cadaver studies in which the arteries are injected with a solidifying material [1,7]. To study the separate distribution territories of the brain feeding arteries, and prevent overflow of injection material through preexisting anastomoses, differently color dyes are simultaneously injected into the efferent vessels [11].

With the introduction of modern imaging methods, it was possible to visualize the cerebral hemodynamics in more detail. First in cadaver studies, in which after injection of radiopaque substances x-ray was used to visualize the brains vasculature within its surrounding tissue [12]. And later in vivo, with imaging techniques such as CT, MR and intra-arterial digital subtraction angiography (DSA). Both CT and MR angiography can be used to visualize the cerebral arteries, but are unable to reliably image smaller vessels and distinguish possible mixing at brain tissue level. Intra-arterial DSA has the advantage that both the proximal and distal arteries can be assessed. Through selective injection the brain feeding arteries it can furthermore visualize potential overlap. Intra-arterial DSA is however invasive and offers no correlation with cross-sectional anatomical images.

A recently developed perfusion technique is arterial spin labeling (ASL) MRI. ASL-MRI measures perfusion throughout the brain by magnetically labeling blood with radiofrequency pulses [13—15]. It does not require gadolinium-based contrast agents. Using selective labeling techniques, ASL-MRI can also image the individual perfusion territories of the cerebral arteries and collateral vessels [16,17]. Selective ASL-MRI can furthermore depict brain tissue areas that are simultaneously fed by multiple arteries [8—10].

**Mixed perfusion in healthy individuals**

This section describes and illustrates the various ways oxygenated blood from different arteries may mix before reaching the brain tissue in healthy individuals (Table 1). We will distinguish mixing at two distinct levels. The first is below and at the level of the circle of Willis, and the second is at the level of the distal branches of the supplying arteries. Between these two levels different patterns of mixing may be recognized. Mixing at or below the level of the circle of Willis can occur between the internal carotid arteries (ICAs), or the vertebrobasilar arteries and the ICA. Above the level of the circle of Willis mixing can occur between the left and right anterior cerebral arteries, the middle cerebral arteries and the posterior cerebral arteries.

**Brain region predominantly supplied by the anterior cerebral artery**

At the level of the circle of Willis mixing of the blood supply to the distribution area of the anterior cerebral artery (ACA) may occur when both ICAs contribute blood flow to one hemisphere. This can take place when there is cross-flow through the anterior communicating artery (ACoA) and both ICAs feed the postcommunicating part of the ACA (A2 segment). This does not only occur in patients with obstructive cerebrovascular disease, but also in healthy individuals when there is a partial dominance of one the precommunicating part of the ACA (A1 segment) [18]. Due to an asymmetry, which can vary from a functionally hypoplastic to a slight asymmetrical A1 segment on one side, the affected A2 segment may be fed by a combination of blood from both the ipsi and contralateral A1 segment (Fig. 1A). These asymmetries can frequently be found in healthy individuals, as hypoplasia of the A1 segment has been reported in up to 22% of all brains [19—24]. Even with fully symmetrical A1 segments and a balanced blood pressure across the ACoA there may be mixing, as magnetic resonance angiography (MRA) scans have shown flow-weighted signal in the ACoA with a symmetrical anterior circle of Willis configuration, indicating the presence of cross-flow [18]. Only with an absent ACoA (in between 1 to 7%), or with an anatomical variant of the circle of Willis with absence of the A1 segment and contralateral feeding of both ACAs by one carotid artery (in between 1 to 18%), there will be no mixing at the circle of Willis [22,23,25,26].

At the level of the distal branches of the ACA mixing may occur due to crossing of the arterial branches over the midline to the contralateral hemisphere. With a reported prevalence of 12 to 64%, this additional blood supply from the contralateral ICA can frequently be found in healthy individuals [24,27—29]. Further mixing may occur more distally due to one of the various anatomical variants. The clearest example is the anatomical variant with an azygous pericallosal artery. This is present in 1 to 5% of all individuals when both A1 segments converge into one common trunk, distributing a mix of the two supplying arteries to both hemispheres [22,29,29,30]. Another example of mixing associated with an anatomical variant is the bi-hemispheric ACA. This frequently occurring anatomical anomaly, with a reported prevalence between 2 and 18% [27,29], is constituted by a pericallosal artery branching from the ACoA simultaneously supplying the medial portions of both hemispheres.

**Brain region predominantly supplied by the middle cerebral artery**

In healthy individuals there is only a limited amount of possibilities for the blood to mix before supplying the perfusion...
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Most important patterns of mixed perfusion in healthy individuals.</th>
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<tr>
<td></td>
<td>Mixing if present</td>
</tr>
<tr>
<td>Anterior cerebral artery territory</td>
<td>Hypoplastic A1 segment</td>
</tr>
<tr>
<td></td>
<td>Symmetrical circle of Willis</td>
</tr>
<tr>
<td></td>
<td>Crossing branches</td>
</tr>
<tr>
<td></td>
<td>Azygos pericallosal artery</td>
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<td></td>
<td>Bi-hemispheric ACA</td>
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<tr>
<td>Middle cerebral artery territory</td>
<td>Latent PCoA</td>
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<tr>
<td>Posterior cerebral artery territory</td>
<td>Basilar artery</td>
</tr>
<tr>
<td></td>
<td>Trigeminal artery</td>
</tr>
<tr>
<td></td>
<td>Patent PCoA</td>
</tr>
<tr>
<td></td>
<td>Transitional configuration</td>
</tr>
<tr>
<td></td>
<td>Partial fetal type</td>
</tr>
<tr>
<td></td>
<td>Adult configuration</td>
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</tbody>
</table>
area of the middle cerebral artery (MCA). At the level of the circle of Willis mixing may occur due to latent collateral blood flow through the posterior communicating artery (PCoA). In healthy individuals the presence of a functional PCoA has been reported in 78 to 98% [19,22,25,31], and with an observed posterior to anterior flow direction of between 8 and 14% [19,31,32], there may frequently be an additional contribution from the posterior circulation to the MCA.

Brain region predominantly supplied by the posterior cerebral artery

In the posterior circulation of the brain there is the unique situation of a mixing more proximal to the circle of Willis in the vertebrobasilar arterial system. In most individuals the vertebral arteries (VAs) are unequal of size and one VA will dominate the contribution of blood supply to the basilar artery. In the majority, approximately 50%, this will be the left VA, in 25% the right VA and in the remaining 25% the arteries are equal in size [33,34]. The most extreme variant is when the distal VA segment is functionally hypoplastic or nonexistent, which occurs in approximately 15%, and ends in the posterior inferior cerebellar artery [33]. In such case there is limited to no mixing of the blood supplied to the basilar artery.

Occasionally an embryonic anastomosis between the ICA and posterior circulation, ordinarily only present in early fetal life, will persist into adulthood leading to a functional connection between the ICA and the vertebrobasilar arterial system. The most frequent embryonic anastomosis between the ICA and vertebrobasilar arteries (VBAs) that persists into adulthood is the trigeminal artery, with a prevalence of 0.1 to 0.8% [26,35–37]. The brain tissue perfused by the posterior cerebral artery (PCA) will receive due to this anastomosis a combined arterial contribution from both the ICA and VAs.

At the level of the circle of Willis mixing of the blood supply may occur between the ICA and the posterior circulation. This may take place when both the ICA, through the PCoA, and the basilar artery feed the postcommunicating part of the PCA (P2 segment). There are three separate configurations of the posterior part of the circle of Willis that may result in such combined contribution to the P2 segment. The first is the transitional configuration, with a prevalence of 7 – 40%, in which the precommunicating part of the PCA (P1 segment) and the PCoA are of equal size and both make an equal contribution to the P2 segment of the PCA (Fig. 1B) [38]. The second configuration is a partial fetal (FTP) or also known as the embryogenic configuration (Fig. 1B). With a partial FTP there is a small P1 segment and the P2 segment is predominantly fed by the PCoA (prevalence between 5 and 36%) [39,40]. Finally there is the adult configuration, in which the P1 segment is larger than the PCoA. Due to the high prevalence, between 50 and 76%, this is normally designated as the non-variant circle of Willis [38].

Mixed perfusion in obstructive cerebrovascular disease

This section describes and illustrates the various ways blood from different arteries may mix before reaching the brain tissue in patients with steno-occlusive disease (Table 2). Several changes occur to both the cerebral metabolism and circulation when there is an obstructive lesion in one of the large extracranial or smaller intracranial arteries. In comparison to healthy individuals the degree and pattern of mixing will differ depending on which supplying artery or arteries are affected, to which degree and with the amount of collateral blood flow recruitment. Initially, as a result of the obstructive lesion the cerebral blood pressure will reduce in the affected arterial flow territory [41]. To maintain cerebral perfusion, blood flow is recruited either through the primary collateral pathways via the circle of Willis and through the secondary collateral pathways via leptomeningeal and ophthalmic vessels [42–44]. Due to the decline in blood flow and this functional rerouting of blood flow there will be a shift in the origin of the blood supplied to the affected brain tissue [45,46]. To establish the degree
**Table 2** Most important manners of mixing in patients with obstructive cerebrovascular disease.

<table>
<thead>
<tr>
<th></th>
<th>Present with stenosis or occlusion</th>
<th>Mixing between</th>
<th>By means of</th>
<th>Prevalence (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral artery territory</td>
<td>ICA stenosis</td>
<td>ICA/contralateral ICA</td>
<td>ACoA cross-flow</td>
<td>11 — 80</td>
<td>[43,47–49]</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis/occlusion</td>
<td>(contralateral) ICA/posterior circulation</td>
<td>Posterior PCoA</td>
<td>22 — 58</td>
<td>[23,47,51]</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis/occlusion</td>
<td>(contralateral) ICA/posterior circulation</td>
<td>Leptomeningeal arteries</td>
<td>Up to 80</td>
<td>[42,43,52,53]</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis/occlusion</td>
<td>(contralateral) ICA/ECA</td>
<td>Reversed ophalmic artery flow</td>
<td>40 to 77</td>
<td>[42,43,52,53]</td>
</tr>
<tr>
<td>Middle cerebral artery territory</td>
<td>ICA stenosis</td>
<td>ICA/contralateral ICA</td>
<td>Reversed A1 segment flow</td>
<td>23 — 58</td>
<td>[47,50]</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis/occlusion</td>
<td>(contralateral) ICA/posterior circulation</td>
<td>Posterior PCoA</td>
<td>22 — 58</td>
<td>[23,47,51]</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis/occlusion</td>
<td>(contralateral) ICA/posterior circulation</td>
<td>Leptomeningeal arteries</td>
<td>Up to 80</td>
<td>[42,43,52,53]</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis/occlusion</td>
<td>Posterior circulation/contralateral ICA</td>
<td>Reversed A1 segment and PCoA flow</td>
<td>12 — 58</td>
<td>[42,43,51,55,56]</td>
</tr>
<tr>
<td></td>
<td>VA stenosis/occlusion</td>
<td>Posterior circulation/ipsilateral ICA</td>
<td>Anterior PCoA flow or/and leptomeningeal vessels</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
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and pattern of mixed perfusion one must know both the various manners of mixing in healthy individuals and the possible hemodynamic effects that an obstructive lesion may have.

### Brain region predominantly supplied by the anterior cerebral artery

For the brain region predominantly supplied by the ACA, an obstructive lesion of the ICA will result in several hemodynamic changes. Regarding the collateralization, additional blood flow to this region can be recruited from various sources: the contralateral ICA through the ACoA, the posterior circulation through the PCoA and/or leptomeningeal collaterals, or from the external carotid artery (ECA) by means of reversed flow in the ophthalmic artery. In patients with a severe carotid stenosis this will lead to mixing between the remaining blood flow through the affected ICA and the recruited collateral blood flow. In between 11 and 80% of all patients with a stenosis collateral blood flow has been observed through the ACoA [43,47–49], indicating a combined feeding of the A2 segment by both the affected and the contralateral ICA. When there is an insufficient capacity of collateral flow via the ACoA, flow recruitment from the posterior circulation via the PCoA has been reported in 10 to 43% [23,47,49,50], leading to a potential combined contribution to the A2 by the affected and contralateral ICA, and the posterior circulation. Only with a complete obstruction will there be no possibility of mixing with the remaining flow from the affected ICA. However, there still is the possibility of mixing between recruited collateral circulation (Fig. 2). Simultaneous collateralization from both the ACoA and the PCoA has been reported in between 22 to 58% of patients with a unilateral ICA obstruction [23,47,51]. Furthermore, secondary collateral blood flow may be recruited the posterior circulation and ECA, via leptomeningeal vessels (large interindividual variability, up to 80%) and the ophthalmic artery (in between 40 to 77%) [42,43,52,53].

### Brain region predominantly supplied by the middle cerebral artery

In relation to the brain region predominantly fed through the MCA an obstructive lesion of the ICA may lead to recruitment of primary collateral flow through the A1 segment and PCoA, and from the secondary collaterals as previously described. In patients with a severe carotid stenosis this may lead to mixing between the remaining blood flow through the ICA, contralateral ICA, posterior circulation and ECA (Fig. 3) [54]. Blood flow from the contralateral ICA to the MCA may occur due to a reverse in the flow direction of the A1, and has been observed in 23 to 58% of all patients with a unilateral stenosis [47,50]. In the case of a complete occlusion there will evidently no mixing between the remaining flow through the affected ICA and collateral pathways. However, in these patients simultaneous collateral flow recruitment from both the A1 segment and the PCoA has been observed in 12 to 58%, leading to a mixing of the contralateral ICA and posterior circulation (Fig. 4) [42,43,51,55,56]. Furthermore, in patients with a partial FTP, where the posterior circulation is partially supplied by the ICA [57,58], a stenosis or occlusion of the ICA may lead to an increase in the relative contribution to the PCA from the posterior circulation.

### Brain region predominantly supplied by the posterior cerebral artery

Regarding the posterior circulation, where the two VAs unite to form the basilar artery, a unilateral vertebral obstruction will lead to a reduced mixing of the blood supply to the posterior circulation. At the level of the circle of Willis, collateral blood flow may be recruited through the PCoA in patients with a stenosis, leading to a combined perfusion to the P2 segment by both the affected vertebral vessels and the ICA [59,60]. Above the circle of Willis peripheral mixing may occur due to the recruitment of leptomeningeal collaterals. For instance after an acute obstruction of the PCA by a thrombus, collateral leptomeningeal flow recruitment from both theACA and MCA branches may result in a mixed collateral brain tissue perfusion distal to the obstruction.

### Effect of cerebrovascular interventions

In patients with steno-occlusive disease cerebrovascular interventions are routinely performed to prevent progression and reduce the risk of stroke. Due to the changes in flow through the affected artery and collateral circulation this will directly affect the pattern and degree of mixing of the blood. In this section we will describe and illustrate the impact of the various interventions on the blood flow routes and its effect on the mixing of blood supplied to the brain tissue.

The two main therapeutic interventions in steno-occlusive disease are carotid endarterectomy (CEA) and
carotid angioplasty with stent placement (CAS) [61]. Both treatments are targeted at the obstructive lesion and will lead to an increase in blood flow through the affected artery. CEA in patients with a stenosis has been described to lead to a twofold increase in blood flow through the affected ICA [62], with a decrease in the amount of collateralization [49,63,64]. Due to these changes there will be a normalization of the hemodynamic flow patterns to the pre-obstructive state. This has also been described at tissue level in studies after both CEA and CAS using an MRI technique able of visualizing the territorial distribution of the arteries individually [10,65]. With interventions targeted more distally the effect of hemodynamic changes on mixing will be more localized. For instance, after an intra-arterial thrombolysis of a thrombus in the MCA, there will be an increase of the flow through the affected MCA, reducing the amount of leptomeningeal collateral blood flow recruitment and amount of combined contribution. It is important to note that interventions will not always lead to a decrease of mixing. For instance, in patients with an ICA occlusion, endarterectomy of a severe stenosis of the contralateral carotid artery had been reported to lead to increased collateral flow to the occluded side and cerebral hemodynamic improvement not only on the side of surgery but also on the side of the ICA occlusion [66].

Extracranial to intracranial bypass surgery is another therapeutic option in patients with ICA occlusion and severely impaired cerebral hemodynamics. Although the effectiveness of this treatment is still to be demonstrated [67], the bypass augments the cerebral blood supply, leading to mixing between the previously recruited collateral blood and extracranial circulation. This additional blood supply
by the extracranial to intracranial bypass has been demonstrated at brain tissue level using duplex and MRI techniques [68].

Implications

The concept of a relatively constant pattern of territorial distribution of the brain feeding arteries has had a major impact in clinical practice. In patients with acute stroke, the location of a cerebral infarct is a determinant in the differential diagnosis of hemodynamic watershed infarctions and thromboembolic ischemia [69,70]. Besides the normal variation of perfusion territories, a possible combined supply of blood from multiple vessels may complicate the correct neuroradiological diagnosis of ischemic lesions. Especially in patients with cerebrovascular disease this is an issue, as a steno-occlusive lesion leads to recruitment of blood flow through additional collateral pathways. Resulting in a shift of the perfusion-territories of the major brain feeding arteries [44,45]. Furthermore, when multiple vessels are supplying brain tissue with critically low perfusion, therapeutic interventions targeted at all sources of blood supply may enhance therapeutic success. For instance, in a patient with a symptomatic ICA stenosis and inadequate collateral blood supply circle of Willis, the ECA may supply additional blood through reversed flow in the ophthalmic artery.

Information about the perfusion territories of these arteries may help identify symptomatic brain tissue that is fed from sources and target an optimal revascularization strategy.

Conclusion

In this review we discussed and illustrated the possibilities of a combined perfusion to the brain tissue by multiple arteries. This concept is discussed in relation to the proximal and distal cerebral vasculature both in healthy subjects and in patients with cerebrovascular disease. We conclude that because of mixing of the cerebral blood supply to a single brain area occurs frequently, especially in cerebrovascular disease, the standard maps of brain tissue perfusion may be unreliable in individual patients. In the future, more accurate knowledge of the vascular sources of tissue perfusion may result in more efficient vascular therapies and interventions that are targeted specifically to affected brain tissue areas. Imaging methods capable of assessing the origin of blood supply at brain tissue level may enable better understanding of the vascular sources of tissue perfusion, both in health and disease.

Conflicts of interest

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References


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