

Letter to Editor

Acute Stroke and the Collateral Cascade: Can we Improve the Outcome?

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The collaterals in acute stroke play an important role in determining the outcome, regardless of the stroke's aetiology. The normal cerebral blood flow is 50-60 millilitre/100 gram/minute, and below 10 millilitre/100 gram/minute, rapid structural injury occurs in the brain. However, when cerebral blood flow is between 10 and 25 millilitres per 100 grams per minute, functional impairment occurs while the penumbra remains structurally salvageable. In addition, during this period, collateral flow can maintain perfusion for hours and sometimes even days [1].

We can divide the collateral cascade into two axes. Axis I includes arterial pressure distribution. Firstly, the circle of Willis (the first level of axis I) plays a crucial role. A complete circle of Willis (COW) (present in around 12% of the population) is advantageous. This advantage is because an intact ACOM (anterior communicating artery) and PCOM (posterior communicating artery) act as a helping channel directing blood to or from the anterior/posterior circulation, depending on which circulation (part of the brain) is in crisis. The next variation is non-isolated COW (most common in the population: 57%). In this scenario, either ACOM or PCOM is absent. Finally, isolated COW, where both ACOM and PCOM are absent, indicates the worst possible prognosis (present in approximately 31% of patients) [1].

Secondly, the secondary level of axis I involves leptomeningeal collaterals that connect the anterior cerebral artery, middle cerebral artery, and posterior cerebral artery. The collateral flow depends on a pressure-driven system. It depends on cerebral pressure (CPP), while CPP is the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP). These collaterals open when there is a vessel obstruction leading to a distal pressure drop and the flow is driven by pressure gradient (not dilatation). Thus, there is immediate retrograde flow as a compensatory mechanism.

Thirdly, the tertiary level of axis I: external carotid artery (ECA)-internal carotid artery (ICA) collaterals. For example, there is slower recruitment of the ophthalmic artery (retrograde), the superficial temporal artery, and other branches of the external carotid artery (ECA). This phenomenon is more relevant in chronic disease [1].

The collateral failure may be secondary to hypotension, dehydration, hyperglycaemia, inflammation, endothelial dysfunction and failure of autoregulation [1].

Next comes axis II, or microvascular instability. This determines whether blood flow delivers oxygen to tissue. Normally there occurs homogenous capillary transit time, efficient oxygen extraction and coordinated pericytes, endothelium and RBC deformability. Ischaemia leads to increased capillary transit time heterogeneity. Blood flow in some capillaries becomes too fast (shunting) and slow in some. Thus, there may be a mismatch between flow and extraction. Although cerebral blood flow may look satisfactory, tissue becomes hypoxic.

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The mechanism of microvascular failure occurs due to:

1. Pericyte dysfunction leads to persistent capillary narrowing.
2. Microvascular dysfunction leads to neutrophil adhesion – 20-30% capillary stalls. This dysfunction leads to traffic jams in microcirculation.
3. Glycocalyx breakdown leads to loss of the endothelial surface layer. These lead to decreased functional capillary density, increased flow heterogeneity, and increased leukocyte adhesion.
4. There occurs decreased deformability of RBC and increased aggregation, thereby worsening heterogeneity.

As there is cerebral oedema post-stroke, there is decreased perfusion, which leads to decreased collateral flow, affecting pial collaterals and penetrating arterioles [2].

Thus, there is increased ischaemia and an inflammatory cascade inviting more oedema, and a vicious cycle begins. Therefore, it is crucial to establish blood flow as soon as possible, either through thrombolysis or endovascular therapy, to reduce ischaemia and to promptly implement antioedema measures that can break this cycle and maintain the patency of the collaterals. On the other hand, patent collaterals can only ensure a positive outcome of acute stroke intervention.

It is understandable from the role of axis II that even though there is an establishment of perfusion in the salvageable parenchyma, neurological improvement is not obvious if there is increased microvascular instability. This phenomenon can be detected in a CT angiogram of the brain by noting the asymmetric or poor venous drainage: reduced venous filling score (e.g., COVES) [3].

Improvement of the microvascular stability requires improvement of metabolic conditions, avoidance of high temperatures, lifestyle modifications (like avoiding smoking and a sedentary lifestyle), and standard stroke therapy. However, more research on therapeutics which may decrease vascular stiffness, increase oxygen extraction, prevent pericyte glycocalyx dysfunction, and improve RBC deformability is required. Statins, cellular modulators like cilastazole and dipyridamole, and antioxidants are probably promising agents in this regard.

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