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Relevance of the cerebral collateral circulation in ischaemic stroke: time is brain, but collaterals set the pace

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Summary

Blood supply to the brain is secured by an extensive collateral circulation system, which can be divided into primary routes, i.e., the Circle of Willis, and secondary routes, e.g., collaterals from the external to the internal carotid artery and leptomeningeal collaterals. Collateral flow is the basis for acute stroke treatment, since neurones will only survive long enough to be rescued with reperfusion therapies if there is sufficient collateral flow. Poor collateral flow is associated with worse outcome and faster growth of larger infarcts in acute stroke treatment. Therapeutic promotion of collateral flow theoretically offers the chance for outcome improvement, but randomised trials are lacking. The extent of collateral flow is highly variable between individuals. As a consequence, the speeds of infarct growth are highly variable, resulting in varying individual treatment time windows until the whole salvageable tissue has become infarcted. An ideal patient selection for reperfusion therapies should be based on imaging of the salvageable tissue, the so called penumbra. The penumbra can be approximately visualised by computed tomography (CT) and magnetic resonance imaging (MRI), but both methods are significantly inaccurate in about 25% of the patients. There is a need for improved penumbra imaging by CT and MRI, and first studies applying machine learning techniques have shown promising results.

Key words: *acute stroke, treatment, anaemia, haemoglobin decrease, infarct growth, haemodilution*

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The cerebral collateral system

Collateral blood circulation is common in most species as a system of vascular redundancy designed to preserve blood supply in the event of failure of the primary blood supplying system. In humans, collateral circulation can be found in most organs, and the blood supply to the brain especially is secured by an extensive collateral circulation system. The collateral circuits to the brain can be divided into primary and secondary routes. The primary route consists of the Circle of Willis, which mainly links the anterior with the posterior circulation and the nearby main cerebral arteries to each other (fig. 1). The secondary routes include all external to internal carotid artery connections through facial, maxillary, middle meningeal, and occipital arteries. The most common one is the connection through the ophthalmic artery: retrograde blood flow via the ophthalmic artery allows supply from the external carotid artery to the internal carotid artery (ICA) in the case of proximal occlusion of the ICA. In addition, the secondary routes comprise leptomeningeal collaterals, perforator collaterals, the tectal plexus and the ophthalmic plexus. Leptomeningeal collaterals are small pial arterioles connecting the territories of the middle cerebral artery (MCA) with those of the anterior (ACA) and posterior cerebral artery (PCA) (fig. 2). Leptomeningeal collaterals are very important in occlusions of the intracranial arteries. Perforator collaterals connect lenticulostriate and thalamostriate arteries with branches of the MCA and PCA and can be recruited in addition to leptomeningeal collaterals in MCA occlusions.
The extent of collaterals is highly variable between individuals, but there is also intraindividual variability during the lifetime: rarefaction of the collaterals is observed with aging and as a result of vascular risk factors [1].

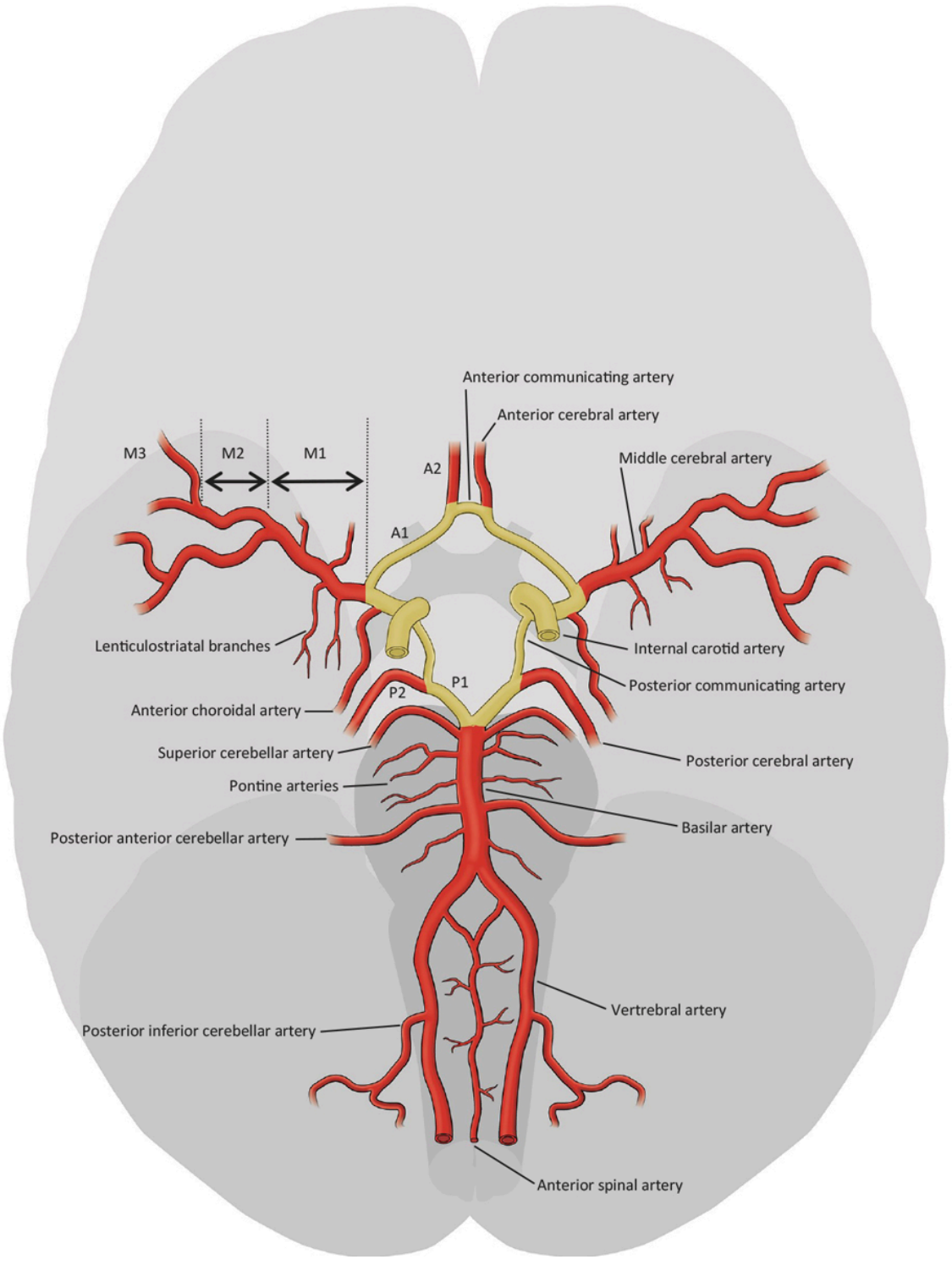
The role of collaterals in acute ischaemic stroke

Intravenous thrombolysis (IVT) and endovascular treatment (EVT) have been proven to have considerable therapeutic effect in acute ischaemic stroke in several large clinical trials [2–10]. The treatment effect of these reperfusion therapies is based on the penumbral concept, which assumes the existence of salvageable tissue due to gradual infarct growth within the territory of the occluded vessel (fig. 3) [11, 12]. Theoretical considerations quantify this gradual infarct growth to be 1.9 million neurones dying every minute in occlusion of one of the large arteries [13]. This is fast – but why do neurones not die all at once after a few minutes, given results from *in-vitro* experiments that have shown that neuronal cell death occurs already minutes after interruption of energy supply? Neuronal cell death can only be delayed by ongoing energy supply – that is, the whole penumbral concept as well as the therapeutic effect

of reperfusion therapies relies on collateral blood flow. Depending on the extent of collateral blood flow, neuronal death can be delayed in a variable manner or even prevented. The extent of collateral flow is highly variable between individuals, but it is usually greatest in the case of occlusion of the extracranial vessels: almost 60% of patients tolerate even complete ICA occlusion without infarct development because of sufficient blood supply through primary and secondary collateral circuits [14, 15]. The recruitment of inactive, vasoconstricted collaterals can take place extremely fast: it takes only 12 seconds after ICA occlusion in rats until maximal dilatation of the leptomeningeal collaterals [16].

The extent of collateral flow has major impact on the outcome of conservatively treated patients and of patients treated with IVT or EVT. Even at hospital admission, the severity of neurological deficits already depends on the extent of collaterals [17, 18], which is revealed by variable infarct sizes in baseline imaging, depending on the collateral quality [19, 20]. Several studies demonstrated that the

Figure 1: Intracranial vessels. Yellow: Circle of Willis (adapted from the Stroke Guidelines of the University Hospital of Bern 2017, www.stroke-center.ch).

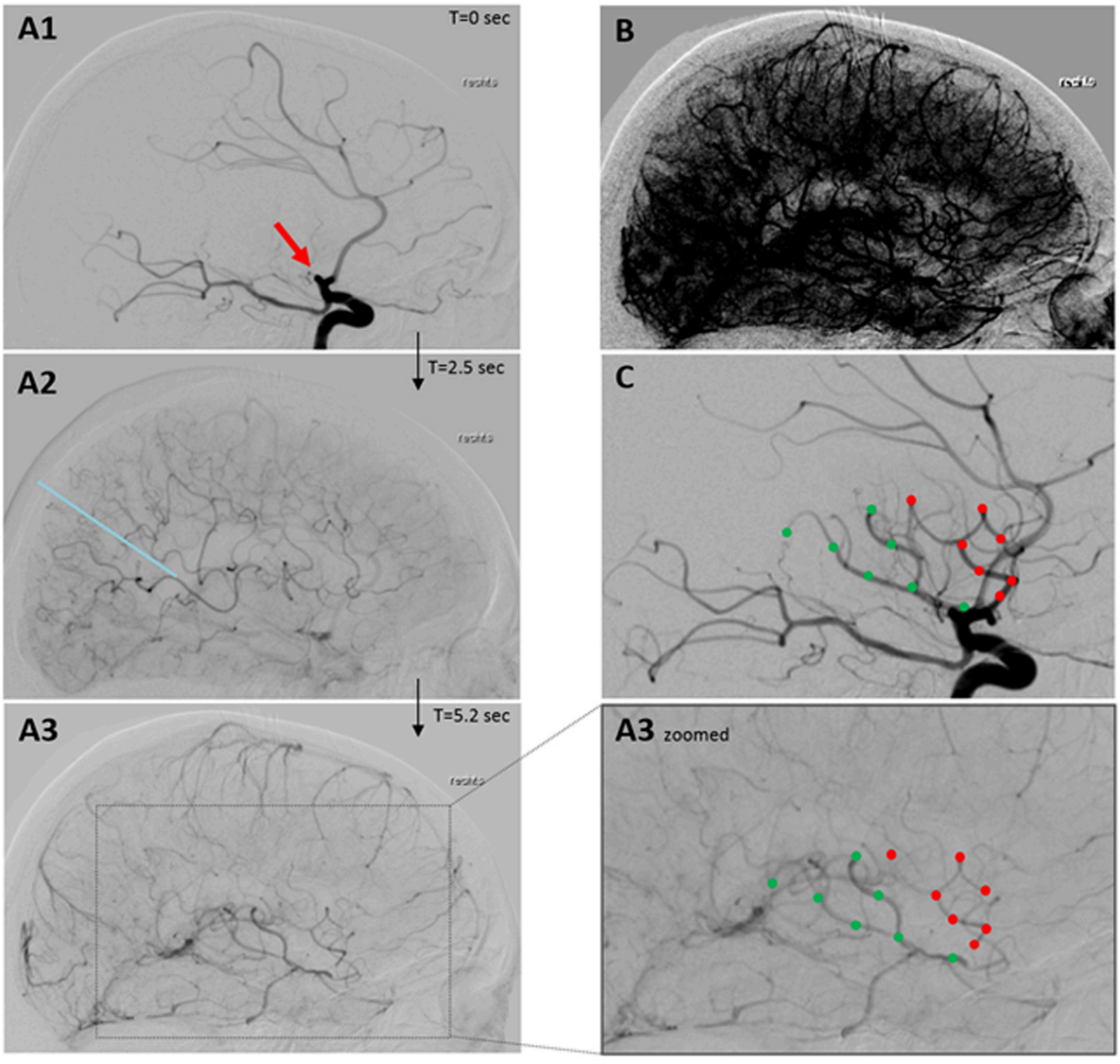


outcome after IVT and EVT is also highly dependent on the extent of collateral flow [21–33]: not only the volume of the final infarct [19, 20, 24, 34–38], but also the success of reperfusion [20, 27, 39, 40] are influenced by the collateral quality. In addition, the risk for symptomatic bleeding after reperfusion therapy seems to rise with poor collateral flow [30, 41, 42].

Implications of the collateral variability on time windows for acute stroke treatment

Reperfusion therapy by means of IVT and EVT is highly effective. In large randomised trials only 5–14 patients had to be treated with IVT and 3–7 patients with EVT to prevent one patient from death or dependency [2–10]. The therapeutic effect of these therapies is not only dependent on the success of reperfusion, but is also highly time dependent. Treatment time windows of 4.5 hours for IVT and 7.3 hours for EVT have been defined by pooled analysis of the patients treated in the large trials [43, 44]. Although patients on average may not benefit from later therapy, patient selection based on these time windows would neglect the large interindividual variability of the extent of collateral flow. This regimen would lead to the exclusion from therapy of many patients who would, in fact, benefit. Indeed, infarct growth is much less dependent on the elapsed time than on the quality of collaterals: good collaterals slow down infarct growth and poor collaterals accelerate it [19, 45–48]. Of course reperfusion treatment should always be initiated as early as possible because “time is brain”, but the collaterals set the pace of neuronal loss, and with this the individual time window until infarction of all tissue at risk. Figure 4 illustrates two patients in whom the approximated velocity of neuronal cell loss differed between 9000 neurones/min and more than 460 billion neurones/min. This large variability of the velocity of neuronal cell loss implies that there are probably many patients eligible for therapy far beyond time windows that were calculated on the average of patients. Patient selection based

Figure 2: Leptomeningeal collateral flow in occlusion of the proximal middle cerebral artery as seen in conventional angiography (sagittal plane). **(A1–A3)**: serial images after contrast agent application into the internal carotid artery showing proximal middle cerebral artery occlusion (red arrow in A1) with subsequent filling of leptomeningeal collaterals 2.5 sec thereafter fed by the anterior (above and right of blue line in A2) and posterior circulation. After 5.3 sec retrograde collateral flow filled the superior (red dots) and inferior branch (green dots) of the occluded middle cerebral artery (A3 + A3 zoomed). **(B)** After windowing A3 capillary filling visualised supply of the whole middle cerebral artery territory by collaterals. **(C)** The same branches filled retrogradely by collaterals in A3 are filled anterogradely after reperfusion of the occlusion. (Pictures: Stroke Centre Bern)



on restricted time windows would not only exclude from therapy eligible patients outside the time windows, but also all patients with wake-up stroke and with unknown symptom onset, who account for at least one third of all stroke patients. Therefore, patient selection for reperfusion therapy should be individualised by imaging salvageable tissue, rather than being restricted by strict time windows.

That imaging-based patient selection is a promising concept has recently been demonstrated by the DAWN trial (not yet published), which included patients with large artery occlusion between 6 and 24 hours after symptom onset for EVT, if they presented with a so called clinical-image mismatch: patients had to be clinically severely affected (NIHSS ≥10) but infarct core had to be restricted

Figure 3: Illustration of the penumbra concept. Infarct core (red): infarcted tissue. Penumbra (orange): salvageable tissue at risk for infarction in case of persistence vessel occlusion. Oligaemia (yellow): hypoperfused tissue without risk for infarction. Cerebral blood flow decreases in direction to the infarct core. Decreased blood flow can be compensated by an increased oxygen extraction fraction and vasodilation of collateral vessels sufficiently enough in the oligaemia but not in the penumbra. (Picture: Stroke Centre Bern)

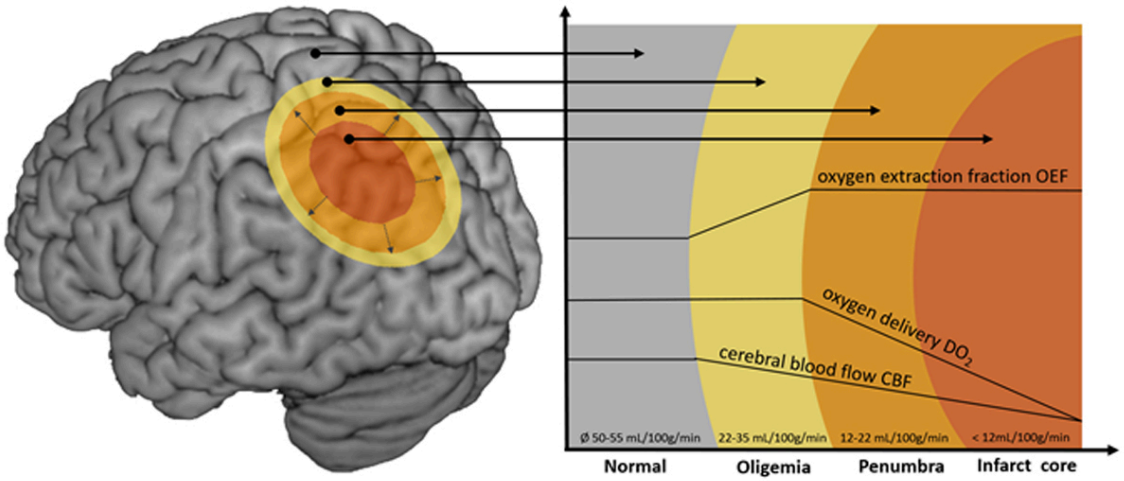
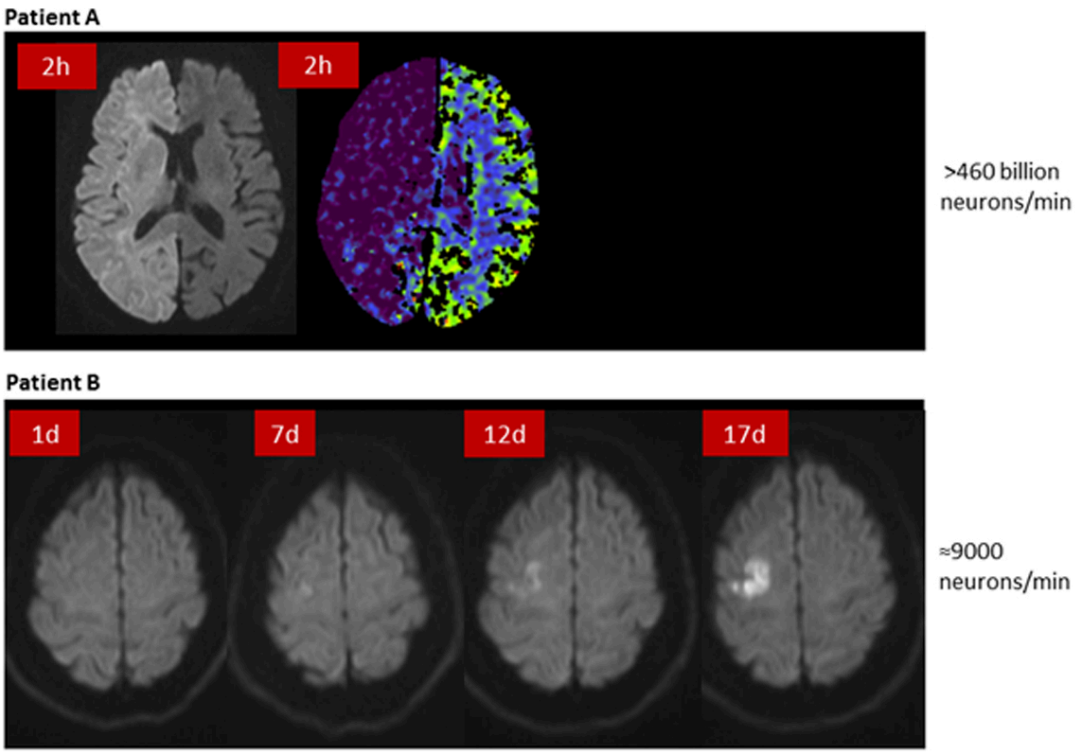


Figure 4: Variable velocities of infarct growth. Patient A: carotid T occlusion and fetal type posterior cerebral artery, 2 hours after symptom onset hyperintensity of the whole hemisphere in diffusion-weighted imaging (DWI) with corresponding hypodensity in CT perfusion (CBV). Patient B: persistent carotid occlusion, slow infarct growth in DWI over 17 days. Neuronal cell loss was estimated based on volumetric measurement of the lesion and the average neuronal density described in Saver et al. [13] (Pictures: Stroke Centre Bern)



(<21 cc if patients was ≥80 years, <31 cc if patients was <80 years and NIHSS ≥10 or <51 cc if patient was <80 years and NIHSS ≥20). The trial revealed a clear effect of reperfusion therapy in these selected patients: the number needed to treat was reported to be 2.8 for 90-day functional independence. Future trials will hopefully allow the inclusion of even more patients by a more detailed visualisation of salvageable tissue.

Assessment of cerebral collaterals and salvageable tissue

Collaterals can be visualised most accurately by use of conventional angiography, which is the gold standard due to its high temporal and spatial resolution [49–51]. Unfortunately, there are several systems for grading collateral flow, which hampers the comparability of study results. One of the scoring systems most often used is the one described by the Society of NeuroInterventional Surgery (formally ASITN/SIR) [52]. In clinical practice, therapeutic decisions are usually made in advance of conventional angiography, on the basis of noninvasive imaging with magnetic resonance (MR) or computed tomography (CT). Although grading of collaterals is also possible by CT and MR imaging, it is less accurate [53, 54]. Furthermore, there is more a need for an accurate visualisation of salvageable tissue at risk for infarction, rather than pure information on collateral flow.

Positron emission tomography (PET) is the gold standard for imaging of the penumbra because it allows the most accurate visualisation of the infarct core and the hypoperfused tissue [55]. A cerebral blood flow (CBF) below 12 ml/100g/min defines the area of infarct core, a flow of 12–22 ml/100g/min identifies the tissue at risk for infarction in the case of persistence vessel occlusion, and a flow greater than 22 ml/100g/min defines an area of oligaemia, i.e., hypoperfused tissue without risk for infarction [56]. Although very accurate, PET imaging is not a practicable technique in the acute setting of stroke. Both MR and CT allow approximation of the penumbra, but show a relevant inaccuracy of the imaging techniques used up to now [56–58]. The core is defined with MR imaging of the lesion in diffusion-weighted imaging (DWI) and the hypoperfused area by perfusion imaging. With CT, the core is visualised by means of cerebral blood volume (CBV) and the hypoperfused area by perfusion imaging. Visualisation of the infarct core with MRI is more accurate than with CT, but diffusion lesion reversal can occur because the DWI lesion may overestimate the infarct core and contain up to 25% false positive, surviving, tissue [59]. Definition of the core by use of quantitative analysis of the calculated Apparent Diffusion Coefficient (ADC) maps is more accurate [59].

Imaging of the hypoperfused tissue at risk by use of MR and CT perfusion imaging relies on surrogates of perfusion parameters calculated from nondeconvolved (e.g, time to peak TTP]) or deconvolved (e.g. CBF, mean transit time [MTT], time to maximum [Tmax]) tissue residue function (time contrast curve) of the intravascular contrast bolus [56]. Different maps computed from MR and CT imaging have been developed and compared with PET measurements. Recent studies indicate that Tmax thresholds of >6 sec improves the prediction of salvageable tissue compared with previous maps [60]. Nevertheless, estimation of the tissue at risk based on maps derived from simple thresholding is prone to errors in about 25% of patients, with variations of the predicted penumbra of up to 100 ml [61]. In most cases the penumbra is overestimated owing to inclusion of parts of the oligaemia. Newer studies applying machine learning techniques instead of using only the somewhat arbitrary thresholds of surrogate parameters have shown first promising results with improved accuracy of the penumbra imaging [62].

Potential treatment options for improving collateral flow

Given the association of poor collateral flow with poor outcome, and larger and faster infarct growth, therapeutic promotion of collateral flow may offer the chance to improve outcome beyond efforts to raise reperfusion success rates and to minimise treatment delay. Up to now, mainly *in-vivo* data support the potential benefit from promoting collateral flow [63, 64]. Possible treatment options include induced hypertension (e.g. by phenylephrine), selective cerebral vasodilation (e.g., by nitric oxide or sphenopalatine ganglion stimulation), external counterpulsation, and endovascular partial occlusion of the abdominal aorta [63, 64]. On the one hand, induced hypertension and partial occlusion of the abdominal aorta aim to improve collateral circulation by raising the perfusion pressure through an increased systemic pressure and flow diversion, respectively. External counterpulsation aims also to raise the perfusion pressure of collaterals, but through augmented diastolic flow. On the other hand, selective cerebral vasodilatation aims to increase collateral flow by reducing the vessel resistance within collateral arterioles.

Disclosure statement

Jan Gralla is the Global Principal Investigator of the SWIFT DIRECT Trial. No other potential conflict of interest relevant to this article was reported.

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