The human brain accounts for about 2% of the total body weight, but it consumes about 15% of cardiac output and about 20% of the total body energy at rest [1]. The neurovascular coupling in the brain is a mechanism that increases the blood flow in the part of the brain where neurons are the most active [1]. If, for whatever reason, the blood flow drops below the threshold and there is a loss of ionic homeostasis and anoxic depolarization, consequent neuronal necrosis, i.e. brain infarction develops. Complete arrest of blood supply, or inadequate supply of neurons with glucose and oxygen, leads to metabolic and neuronal disorders (within 30 seconds), then functional disorders occur (after 1 minute), and finally (after 5 minutes) irreversible changes and neuronal death occur; this leads to brain infarction, which clinically manifests as ischemic stroke [2]. If the flow of oxygenated blood is re-established quickly enough, the neuronal damage is reversible.

**Acute ischemic stroke**

Stroke is one of the leading causes of morbidity and mortality in the world [3]. Ischemic stroke occurs due to sudden occlusion of a cerebral artery, usually as a result of progressive atherosclerosis or embolization [3, 4]. The attitude towards the treatment of patients with acute ischemic stroke (AIS) was predominantly nihilistic till 1993, when, based on the results of the National Institute of Neurological Disorders and Stroke rt-PA (NINDS) study, stroke was defined as an emergency medical condition of the utmost importance [5]. At the end of the twentieth century, intravenous thrombolysis was introduced in the treatment of AIS and now it is a standard treatment of patients within the first 4.5 hours after the onset of symptoms [6]. The last decade was marked by studies employing the endovascular treatment of intracranial and extracranial occlusions, and it was only recently that several studies confirmed that mechanical thrombectomy following the endovascular approach is superior to standard treatment with or without intravenous thrombolysis [7]. However, the outcomes after these treatments are still variable and do not depend only on the method, but also on specific biological characteristics of the patient [8].

The main goal of the treatment of patients with AIS is recanalization of the previously occluded artery, but sometimes, even despite treatment, patients do not have a favorable outcome. In patients with AIS, one of the most significant and independent factors in the prediction of the clinical outcome is the status of the collateral circulation [9, 10]. In the daily clinical practice and the need to start the treatment for AIS as quickly as possible, vascular neurologists and intervention radiologists often have insufficient time to thoroughly evaluate the pretreatment status of the patient’s collateral blood flow. Subsequent analyses showed that a favorable clinical response could not be expected even despite a successful recanalization in patients with poorly developed collaterals [11]. Collateral cerebral circulation is a physiological pathway of specific endogenous connections of blood vessels that protect the brain parenchyma from damage in case of ischemia [12]. The degree of development of collateral circulation also affects the size of the infarct lesion. All these findings have put the relationship between collaterals and the possibility of predicting the evolution of infarction and clinical outcome after AIS in the focus of scientific interest in recent years [8, 13].

**Collateral cerebral blood flow**

Collateral cerebral blood flow includes the establishment of arterio-arterial anastomosis, which...
supplies oxygen and nutrients to the part of the brain where the primary source of blood supply was interrupted [14]. Two main pathways of the collateral circulation are extra- and intracranial pathways [15]. The extracranial sources consist of a large number of branches of the external carotid artery that develop in case of a chronic, atherosclerotic steno-occlusive disease of the internal carotid artery, in most cases through the ophthalmic artery; however, facial, maxillary, middle meningeal, occipital, as well as unnamed dural vessels may take part in the supply of endocranial arteries [16]. Intracranial collaterals can be divided into primary and secondary. Primary collateral circulation is actually a continuously active part of the arterial network at the base of the brain, i.e. the circle of Willis, which connects the anterior and posterior circulations. Secondary collateral circulation consists of non-linear leptomeningeal anastomoses, which connect distal areas of large cerebral arteries and become extremely significant in case of acute cerebral artery occlusion [14]. In cerebral arterial occlusion, leptomeningeal collaterals are recruited to remodel small cortical arterioles, whereas in chronic occlusions there is also neo-collateralization [17]. Depending on the metabolic activity of neurons, different regions of the brain have different blood flow rates at different times. In acute brain infarction, when cerebral arterial occlusion occurs, the cerebral blood flow decreases significantly, and neuronal death occurs in a few minutes, while in case of hypoperfusion and a slightly greater cerebral flow, neurons become dysfunctional but still viable [18, 19]. This actually takes place in the penumbra, i.e. the brain tissue surrounding the acute infarction, which can potentially be saved if there is timely reperfusion, either following recanalization or due to the collaterals [19, 20]. The degree of collateral formation affects the size of the penumbra, as well as the time needed for its adequate perfusion.

Digital subtraction angiography (DSA) is a gold standard for the anatomic evaluation of collateral circulation [8]. This technique enables spatial and temporal visualization of collateral circulation, providing also feedback about dilatation and phases of filling collaterals. However, it has drawbacks in terms of invasiveness, application of contrast, radiation, inability to show the brain parenchyma, and the additional time needed to perform it, which is sometimes crucial in the treatment of patients with AIS [17, 21]. In contrast to DSA, non-invasive techniques have a limited resolution in the assessment of leptomeningeal or other secondary collaterals [8]. Computed tomography angiography (CTA), a non-invasive, fast, simple and available method is most frequently used today, both in the detection of occlusion site or in the assessment of collateral cerebral circulation in AIS [8, 21]. It implies the application of intravenous contrast, spiral computed tomography (CT) imaging and subsequent three-dimensional reconstruction. Evaluation of collateral circulation using magnetic resonance angiography (MRA) is limited to proximal segments of arteries of the circle of Willis [21, 22]. Slow flow velocity at the site of occlusion, a hyperintense signal in collateral blood vessels, can also be visualized using fluid attenuation inversion recovery (FLAIR) sequences, but without the possibility to quantify the flow [21]. Contrast MRA shows slower flow in the distal branches better, while post-contrast time of flight (TOF) sequences can enhance the retrograde supply/filling through the leptomeningeal arteries [22]. The dynamic, contrast MRA provides precise information on both the occlusion site and the development of collateral circulation and its hemodynamic status; therefore, it can be used as a non-invasive method in the assessment of patients with AIS who are candidates for endovascular interventions [23]. Arterial spin-labeling (ASL) MRI sequence encompasses elements of collaterals quantification and ischemic tissue perfusion through leptomeningeal collaterals, which makes it very useful in the outcome prediction after AIS [22, 23]. Transcranial Doppler (TCD) provides data on cerebral circulation and cerebral autoregulation [8, 21]. Transcranial Doppler has been used primarily in the evaluation of collateral pathways via the arteries of the circle of Willis [24]. Assessment of cerebral vasomotor reactivity using TCD provides information on autoregulation and the collateral status. The main disadvantage of TCD, as well as of other ultrasonography methods, is that the interpretation of findings depends on the examiner [21, 24].

Evaluation of collaterals in the outcome prediction after AIS

In the last two decades, numerous published data have emphasized the importance of the status of collateral circulation in the outcome assessment after AIS [14]. Considerations about the role of collateral circulation in perfusion of ischemic tissue and consequent replacement and bridging of occlusion sites have become an essential part of the assessment of the vascular status of every patient with AIS [25]. The American Society of Interventional and Therapeutic Neuroradiology and the Association of Interventional Radiology differentiated five degrees of collaterals, based on the DSA findings [10]. Grades 0 and 1 indicate only marginal flow, grade 2 indicates partial filling of the ischemic zone, while
grades 3 and 4 indicate well-developed collaterals with varying degrees of perfusion of the whole vascular territory of the occluded vessel. Assessment of collaterals has become crucial in the prediction of treatment outcome in patients with AIS [17]. Patients with well-developed collaterals were shown to have smaller infarctions after treatment [15, 17], as opposed to patients with poorly developed collaterals, who had worse outcomes [26, 27], leading to the conclusion that the initiation of AIS treatment may have lower impact on the outcome than the collateral status. Micro-vascular parenchymal perfusion [15] is also important for complete restoration of the ischemic tissue. In physiological conditions, the diameter of the blood vessel is the main regulator of cerebral blood flow, while in blood vessel occlusion most of the penumbra perfusion originates from collaterals, which enables retrograde perfusion of the penetrating arterioles of the ischemic penumbra after AIS [28]. Determination of the capillary index score using DSA may enable estimation of the degree of perfusion [29]. To determine the capillary index score, the ischemic area is divided into three identical parts, and each is scored 0 or 1, depending on whether there is no capillary network in that part, or the capillary network is normal. The sum of points for the three parts gives the capillary index score, which can be 0 – 3 [29]. Scores 2 and 3 indicate that a larger ischemic region is potentially viable for recovery after a successful recanalization. A recently published meta-analysis showed that patients with AIS who underwent endovascular treatment and had a higher capillary index also had higher rates of favorable neurological outcome and significantly lower rates of intracranial bleeding after treatment [29].

All of these findings show that adequate assessment of collaterals and hypoperfused tissue may extend the therapeutic window for administration of either intravenous systemic (thrombolytic) therapy or endovascular treatment [30]. Therefore, the well-developed collaterals slow down the loss of penumbra tissue, that is, they “buy time” for the administration of therapy in patients with AIS [31]. Sometimes, even without a successful recanalization, complete reperfusion can occur due to collateral circulation [32]. On the other hand, poorly developed collaterals, even in case of rapid recanalization and reperfusion, may be predictors of poor outcome and a potential cause of hemorrhagic transformation [33]. Although time is the most important factor in terms of AIS treatment, the status of collateral circulation affects the time-dependent treatment efficacy [14]. Generally, the outcome for patients with poor collaterals is directly dependent on the time of initiation of the endovascular treatment, while in patients with good collaterals, the time of initiation of the treatment bears no such significance [34]. On the other hand, the capacity of collateral circulation in AIS has been shown to weaken with time, i.e. it is more likely that patients with AIS will have good collaterals if they are treated within a shorter time interval from the onset of symptoms [35]. All this leads to the conclusion that if enhanced involvement of collaterals in AIS was possible, the time for initiation of reperfusion treatment could be extended [14].

Today, it is clear that well-developed collateral blood flow in patients with AIS slows down the cascade of metabolic degeneration in the penumbra tissue and is associated with smaller brain infarctions, better reperfusion of ischemic tissue and more favorable outcomes after intravenous thrombolysis and/or mechanical thrombectomy [10, 18]. However, collateral blood flow in AIS is dynamic and over time can become insufficient (collapse of collateral blood flow); therefore, it is still recommended that the therapy should not be delayed but started as soon as possible. Determination of the occlusion site is now a standard in the diagnostic protocol for patients with AIS, and for the purpose of selecting patients for endovascular procedures it is also necessary to evaluate the collateral status of cerebral blood flow, which provides higher probability of predicting favorable outcome, as well as patients at risk for hemorrhagic complications [9, 33, 36].

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