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Modern Aspects of Endovascular Thrombectomy of Acute Ischemic Stroke. Selection Criteria for Endovascular Thrombectomy. Prediction of Treatment Outcomes

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ABSTRACT Endovascular thrombectomy (ET) effectively and safely recanalizes the occluded artery and restores the ischemic area in patients with acute ischemic stroke (IS), improving the clinical prognosis of stroke in the anterior and posterior circulation system, expanding the time therapeutic window from no more than 6 to 24 hours, greatly increasing the chances of functional independence and survival. However, some patients develop an unfavorable postoperative outcome, complications and "ineffectiveness" of revascularization. The thrombectomy result depends not only on the patient selection criteria, timing and success of the procedure, but on many other factors as well. Despite the advances in stroke treatment, the issues of neuroimaging and patient selection for ET remain relevant; the pathophysiological mechanisms of the influence of some factors on the effectiveness of the procedure are not completely clear; the causes of "uneffective" revascularization, unfavorable outcome and mortality after ET are unclear. An analysis of global experience in treating ischemic stroke with ET showed the heterogeneity of the patient selection criteria, clinical and neuroimaging variables, prognostic factors and treatment outcomes, which makes it difficult to draw a general conclusion and requires further targeted research. The article discusses the issues of patient selection, pathophysiological mechanisms of the influence of some risk factors on the outcome of ischemic stroke and the causes of unfavorable outcome and death after ET.

Keywords: endovascular thrombectomy, prognosis scales, patient selection criteria, revascularization, risk factors for prognosis and death

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AH — arterial hypertension
AF — atrial fibrillation

ASPECTS — Alberta Score Program Early CT Score
BBB — blood-brain barrier
BMI — body mass index
BP — blood pressure
CA — cerebral artery
CI — confidence interval
CC — collateral circulation
CIC — core of cerebral infarction
CM — cerebral microangiopathy
CT — computed tomography
CVD — cardiovascular diseases
DT — drug therapy
ET — endovascular thrombectomy
FI — functional independence
HbA1C — glycated hemoglobin
HG — hyperglycemia
HLP — hyperlipoproteinemia
ICGR — ischemic core growth rate
ICH — intracranial hemorrhage
IHD — ischemic heart disease
IS — ischemic stroke
LC — leptomeningeal collaterals
MRI — magnetic resonance imaging
mRS — modified Rankin Scale
NIHSS — National Institutes of Health Stroke Scale
OR — odds ratio
PSD — pre-stroke disability
RCTs — randomized clinical trials
RF — risk factor
RD — risk of death
RT — reperfusion therapy
rtPA — recombinant tissue plasminogen activator
RR — relative risk
SBP — systolic blood pressure
SD — diabetes mellitus
SvO_2 — cerebral venous blood saturation
TICI — Treatment in Cerebral Ischemia
vWF — factor Von Willebrand

INTRODUCTION

Randomized controlled trials (RCTs) have proven the efficacy and safety of endovascular thrombectomy (ET) in the treatment of acute ischemic stroke (IS) [1–3]. Rapid and effective recanalization of the occluded artery and restoration of ischemic zone perfusion improved the clinical prognosis of patients with stroke in the anterior and posterior circulation systems [4, 5] while maintaining the effect of treatment for a long time [6]. ET made it possible to extend the time therapeutic window from no more than 6 to 24 hours, repeatedly increasing the chances of functional independence (FI) (modified Rankin Scale (mRS) score not higher than 2) and patient survival [2, 6]. Improvements in endovascular devices targeting smaller vessels have allowed ET to be performed on more distal segments of the middle cerebral artery (MCA) (M2–M4), anterior (A1–A2), posterior MCA (P1–P3), superior cerebellar artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery, both as a primary intervention and as a salvage procedure [3].

Endovascular mechanical revascularization according to the TICI (Treatment in Cerebral Ischemia) 2b–3 scale is the main goal of treatment of acute IS [3, 6]. TICI 2b–3 revascularization was achieved in more than 86% of patients with IS and in 76, 84, and 88% of cases in the DEFUSE 3, DAWN , and SWIFT-PRIME studies [7]. Three months after ET, a favorable outcome was noted in 37% of patients, mortality was 29% [8]. FN after ET, when compared with drug therapy (DT), was determined in 44–45% and 17–18.9% of patients (odds ratio - OR - 2.67; 95% confidence interval (CI), from 1.60 to 4.48; p <0.001), respectively; Mortality was 14–16.8% and 20–26% (p = 0.05); the rate of reperfusion and vascular recanalization was higher with mechanical reperfusion, but the rate of symptomatic intracerebral hemorrhage (ICH) did not differ significantly between the groups (7% and 4%, respectively ; p = 0.75) [9]. A prospective randomized study, which was prematurely stopped due to the effectiveness of ET, showed that in patients with stroke due to occlusion of the internal carotid artery or the first segment of the middle cerebral artery within 24 hours after the onset of the disease, FN was in 20% of cases (with DT 7%; relative risk 2.97; 95% CI from 1.60 to 5.51) of patients [10]. In the MR CLEAN Registry study, clinical outcomes of treatment were improved by accelerating the hospital workflow and increasing the frequency and quality of reperfusion [6]. The introduction of new interventional methods and devices, experience and advanced training of both individual interventional specialists and the entire team, and a reduction in the duration of patient logistics have improved the treatment outcomes for acute ischemic stroke.

At the same time, after 3 months, an unfavorable outcome (mRS score 3–6 points) was noted in ~60% of patients with successful recanalization of the occluded artery and reperfusion of the ischemic zone. The results of reperfusion depended not only on the early ET, but also on such factors as age, previous stroke, comorbidity, time of patient admission for reperfusion, size of the cerebral infarction core (CIC), and rapid early detection of ET complications (the risk of complications after mechanical thrombectomy with consequences for patients is ~15%) [11]. "Failure" recanalization (defined as functional dependence with successful reperfusion) is observed in 29–77% of cases [12–13]. Independent predictors of adverse outcomes after successful recanalization were female gender, older age with comorbidities, high NIHSS (National Institutes of Health Stroke Scale) score at admission, and the number of tractions per procedure [14]. When comparing the results of ET successful (mTICI 2 b –3) and complete (mTICI 2 c –3) recanalization, the most favorable outcome and low risk of death (RD) are observed in patients with a single traction per procedure. G. Deng et al . [13], having analyzed 12 studies, showed that female gender, history of hypertension and diabetes mellitus (DM), high systolic blood pressure (SBP) and blood glucose level on admission, occlusion of the internal carotid artery and post-procedural ICH are predictors of "ineffective" recanalization. High mortality within 90 days after reperfusion persisted in more than 51% of patients with acute vertebrobasilar artery occlusion; Predictors of unfavorable outcome were NIHSS (OR more than 36 compared with those remaining alive, no more than 11 = 9.01, $p < 0.001$), time from onset of disease to puncture (OR more than 441 min compared with no more than 210 min = 2.71, $p = 0.023$) and duration of the procedure (OR more than 145 min versus no more than 59 min = 2.77, $p = 0.031$) [15]. Assessment of collateral circulation (CC) is a simple way to identify patients in whom reperfusion therapy (RT) is effective even at later stages. A positive clinical outcome is observed with good CC, absence of leukoaraiosis, early thrombectomy, high ASPECTS values and low NIHSS values [16]. In a patient with good CC, the CIC is absent or small, and RT with prolonged vessel occlusion leads to complete neurological recovery [17].

Identification of patients with high DR in ET is important for predicting treatment outcome and planning future clinical trials. Analyzing the experience of stroke treatment with ET, heterogeneity of patient selection criteria and interventions used, as well as treatment outcomes, is noteworthy, which makes it difficult to draw a general conclusion [18]. Issues of candidate selection for mechanical reperfusion, use of thrombolytic drugs before the ET procedure, thrombectomy and anesthesia methods, distal embolism, the role of advanced neuroimaging, treatment of patients with a large infarct focus and patients with milder stroke symptoms remain unresolved [8].

The aim of this study is to examine the experience of treating acute ischemic stroke using ET (patient selection criteria, pathophysiological mechanisms of the influence of certain risk factors (RF) on the outcome of the disease and the reasons for the unfavorable prognosis of mechanical reperfusion).

PREDICTION OF ENDOVASCULAR THROMBECTOMY OUTCOMES

1. Patient selection for endovascular thrombectomy and predictors of clinical outcome

Correct selection of patients for ET and timely, successful reperfusion are the "key" to a favorable functional outcome. An increase in the patient's "door-to-puncture" delay by 1 hour results in a loss of 0.92 years of life, and each second results in a loss of 2.2 hours of healthy life [19]. The prognosis of stroke varies significantly in different subgroups of patients. The outcome of endovascular treatment depends on the correct selection of the patient taking into account his/her gender and age, risk factors, stroke subtype, and concomitant diseases (ischemic heart disease (IHD), atrial fibrillation (AF), diabetes, and previous stroke) [20].

A preoperative and postoperative prognostic model has been developed for patients with IS who underwent ET. The preoperative model is designed to predict the clinical outcome before ET and support

the decision to perform surgery. The postoperative model allows determining the prognostic accuracy of the clinical outcome after mechanical reperfusion [21–22]. The multivariate preoperative prediction model includes clinical variables (age, baseline NIHSS, SBP, treatment with intravenous recombinant tissue plasminogen activator (rtPA), previous IS, DM, pre-stroke mRS), imaging markers (occlusion site, collateral index), and the time from stroke onset to ET. The outcome and potential benefit of ET are usually assessed at 3 months using mRS in a dichotomous analysis: 0–2 points are defined as a favorable outcome, 3–6 points as an unfavorable outcome. The MR PREDICTS prognostic model can be used as an adjunct to clinical assessment. The best scales in predicting the functional outcome of ET are THRIVE-c and MR PREDICTS [21].

To determine the effectiveness of treatment, the following are taken into account : NIHSS upon admission, patient age; presence of signs of diabetes/hyperglycemia (HG), arterial collaterals; infarction size and signs of disruption/damage to the blood-brain barrier (BBB). However, even with known clinical and instrumental studies, predicting the outcome in individual patients remains a difficult task. The most valuable are the results of vascular imaging of the head and neck, necessary for searching for occlusion of large vessels; the state of leptomeningeal collaterals (LC) and the circle of Willis; for patients with late admission, perfusion visualization can additionally provide information on the "ischemic penumbra" [16, 22]. In the DEFUSE-3 and DAWN studies, neuroimaging with perfusion computed tomography (CT) or magnetic resonance - imaging (MRI) using automated software demonstrated the existence of potentially reversible ischemia, allowing the therapeutic time window to be extended to 24 hours for large vessel occlusion stroke [22]. Collateral status assessment on admission is essential for selection for ET, especially when MRI and CT perfusion are unavailable.

Many treatment centers use different neuroimaging methods to select patients for ET. Some centers triage patients solely based on CT images, while others include parameters of non-contrast CT and CT perfusion or MR perfusion in their decision algorithms [23]. In the DEFUSE 3 and DAWN trials , selection of patients in the late therapeutic window was based on CT perfusion or diffusion-perfusion mismatch with automated image analysis. Some studies have demonstrated better thrombectomy results when selection is based on perfusion CT [22]. Using parameters (cerebral blood volume, cerebral blood flow, etc.), it is possible to assess the degree of hypoperfused “ischemic core” and hypoperfusion, and with timely reperfusion, the viability of the “penumbra”. In the study by A. Sarrajetal [24], high FI rates and chances of ET were observed in patients with CT and perfusion CTA SPECTS values of at least 6, regional cerebral blood flow (less than 30%) less than 70 ml with a mismatch coefficient of at least 1.2 and a mismatch volume of at least 10 ml. Patients with less favorable neuroimaging profiles had a high rate of unfavorable outcome. The researchers note that when using only one neuroimaging method, the number of patients requiring ET is reduced.

The reperfusion rate varies depending on the use of different methods of patient selection for ET: 1) CIC study based on age, NIHSS and infarct volume; 2) “ischemic penumbra” study based on infarct volume less than 70 ml, ischemic tissue to initial infarct volume ratio of at least 1.8, and absolute volume of potentially reversible ischemia; 3) CC status. One in four patients was classified as suitable for ET, and one in five as ineligible by all three selection methods [25]. S. Nannoni et al. [26] Among 925 late admitted patients with IS and complete neuroimaging, 2.5%, 5.1% met the criteria of the DAWN , DEFUSE -3 study, and 11.1% were patients with anterior circulation stroke with discrepancy between the clinical picture and neuroimaging results (NIHSS 5–9 and ASPECTS at least 8; or NIHSS at least 10 and ASPECTS at least 7; or NIHSS at least 20 and ASPECTS at least 5). The inclusion of this group allowed us to double the number of patients on ET, in whom a favorable outcome was observed in 58% of cases.

The inclusion of various variables to predict the outcome of ET is controversial. Age, gender, pre-stroke mRS score, NIHSS score, CC, postoperative

TICI score and several other factors are used to construct a nomogram to predict the likelihood of poor outcome in patients after ET. It is suggested that prognostic factors such as age, gender, comorbidities, NHISS score, blood glycated hemoglobin (HbA1C), creatinine, neuroimaging results and occlusion location cannot predict the outcome in patients with IS. This is probably associated with some interventional factors (procedure duration, surgical technique, recanalization) that affect the prognosis [16]. M. A. Mutke et al. [27] believe that in ET, prediction of poor outcome (mRS score of 5 or 6 points) is possible based on baseline clinical variables alone, and the speed and volume of thrombectomy do not affect the prognosis. In another study, the most relevant predictors of lack of treatment effect were identified as: clinical variables (severe stroke, older age, cancer, pre-stroke disability (PSD), laboratory parameters (severity of HS, blood levels of C-reactive protein and creatinine), imaging biomarkers and the time from disease onset to hospitalization [16–18, 28]. For the development of an unfavorable outcome, the most important factors are the patient's age, stroke severity (NIHSS), the degree of disability before stroke (premorbid value according to mRS), as well as the time from disease onset to imaging.

The main prognostic factor for a favorable outcome in the Japanese population is considered to be the introduction of ET as a progressive method of treating IS with an OR of 2.95 (95% CI [1.41–6.46], p = 0.005) [29]. In the study by FA Wollenweberetal [8], statistically significant predictors of a favorable outcome were young age (OR, 1.06; 95% CI [1.05–1.07]), no interhospital transfer (OR, 1.39; 95% CI [1.03–1.88]), mild stroke (OR, 1.10; 95% CI [1.08–1.13]), smaller cerebral infarction (CI) size (OR, 1.26; 95% CI [1.15–1.39]), use of alteplase (OR, 1.49; 95% CI [1.08–2.06]), and successful reperfusion (OR (1.08–2.06) 1.69; 95% CI [1.45–1.96]). When comparing the treatment outcomes of patients with single and multiple tractions during a single thrombectomy procedure, successful revascularization with a single traction was more effective and safe (favorable outcomes were observed in 49.7% (95% CI [40.5–58.9]%) and 34.7% (95% CI [26.8–42.7]%); mortality at 3 months was 13.8% (95% CI [10.8–16.9]%) and 26.0% (95% CI [17.7–34.2]%), respectively [14]. Among patients with a single traction during the ET procedure, there were significantly more people discharged from the hospital after 90 days (33.6% versus 19.4%, p = 0.001); FI were 51.7% and 40.8% (p = 0.032) and there was low mortality (18.0% versus 27.5%, p = 0.032). p = 0.027) when compared with the results of multiple tractions [30].

2. Prognostic risk factors. Pathophysiological mechanisms

2.1. Age

With increasing life expectancy, the number of patients with concomitant cardiovascular diseases (CVD), acute ischemic stroke, cerebrovascular accident, and frailty increases. In the older age - group, cerebral autoregulation and cerebral crises are impaired, cerebral atrophy and leukoaraiosis increase, which should be considered an independent risk factor for "ineffective" recanalization [31]. Patients with ischemic stroke over 85 years old account for 17–30% and are characterized by a high frequency of disability, mortality, and length of hospital stay [32]. Age of at least 80 years is an independent predictor of unfavorable outcome (mRS 2–6) and mortality after thrombectomy. In individuals aged 80 years and older, a favorable outcome (mRS 0–2) of thrombectomy is observed in 20–30% of cases, and an unfavorable outcome in 57%; The 3-month and 1-year mortality rates are 32% and 41%, respectively [33]. However, with successful recanalization, their functional outcome is better than that of younger patients. With unsuccessful recanalization, an increased risk of complications and a low survival rate are observed among patients with frailty and comorbidity. Frailty increases the likelihood of an unfavorable outcome of ET (79%) and death; 35% of patients remain alive one year after ET [20, 25]. R.V. McDonough et al. [32] studied the effect of age on the outcome of ET treatment. Good functional results were observed more often in patients over 85 years of age than in those with conservative treatment. Each decade of life increased the likelihood of 90-day mortality after ET by 1.5 times. Despite this,

thrombectomy should be offered to elderly patients, since its clinical benefit has been demonstrated by RCTs in various age groups [1].

Young patients had statistically significantly lower NIHSS scores (14 vs. 16, p < 0.001) and fewer concomitant CVDs than older patients. Clinical outcome was better in younger than in older patients (acOR for modified Rankin Scale change: 1.8; 95% CI [1.5–2.2]; FI (mRS score 0–2) was 69% vs. 39% (adjusted OR 2.1, 95% CI [1.6–2.8]) [1], respectively, and mortality was 7% vs. 32% (adjusted OR 0.2, 95% CI [0.1–0.3]). Symptomatic ICH occurred less frequently in younger patients (3% vs. 6%, adjusted OR 0.5; 95% CI [0.2–1.00]) [34]. Patients aged 18–49 years treated with ET were 4 times more likely to achieve FI than patients aged 65–80 years.

2.2. Pre-stroke disability and comorbidity

ICD was diagnosed in 45% of patients with IS [3], mainly in older individuals with multiple comorbidities. Most of the diseases are CVD and stroke. One third of patients dependent on care had a previous stroke and had several risk factors (old age, severe and complicated course of stroke, high frequency of hypertension and diabetes), which led to an unfavorable outcome [35]. In individuals with diabetes, a high NIHSS score and a low ASPECTS score, the chances of a favorable outcome after ET were low, and diabetes reduced the chances of a favorable outcome sixfold. Given the unfavorable prognosis and ineffectiveness of ET, patients with PSC were excluded from the RCTs. As the premorbid mRS (a scale often used to describe disability before stroke and is a reliable predictor of post-stroke prognosis) increases, the frequency of unfavorable outcomes (complications, length of hospital stay, and mortality) increases. A. Adamou et al. [36], comparing the effectiveness of ET in patients with and without PSC, revealed a high frequency of unfavorable clinical outcome and mortality in patients with disabilities. In the study of S. Salwietal [37], one third of patients had moderate (mRS 2–3) DII, in whom mortality after 90 days was higher (14.3% versus 40.3%, OR 4.06 [2.82–5.86], p <0.001) than in individuals with minimal (mRS , 0–1) DII (adjusted OR 2.83 [1.84–4.37], p <0.001). A favorable outcome of treatment in patients with DII should be considered a return to the pre-stroke baseline level of the mRS indicator (pre-stroke functional status), and an increase in the mRS indicator on the 90th day compared to its baseline level should be considered an unfavorable outcome. An analysis of the results of 13 observational studies revealed a high probability of return to the pre-stroke mRS value (relative risk (RR) 1.86; 95% CI [1.28–2.70]) and a lower probability of mortality (RR 0.75; 95% CI [0.58–0.97]) in patients with ET compared with standard treatment. The frequency of return to the pre-stroke mRS value in patients with a pre-stroke mRS score of 2–4 was 20% [38]. ET contributed to early neurological improvement in 41% of individuals with DIS; after 3 months, functionality returned to the baseline level in 1 out of 4 patients; mortality was 36% [37]. In the study by EG Florentetal [39], the pre-stroke functional state of individuals with DIS did not worsen; Three months after ET, every fourth patient had a favorable outcome and no functional differences were found compared to patients without disabilities. The use of ET in patients with PSC led to better functional results and a favorable outcome (return to the initial mRS status after 3 months) in 28.0 and 10.9% of cases in the PSC group (p < 0.01, statistically significant). Similar results were obtained 90 days after ET, when the functional status returned to the initial pre-stroke level in a third of patients with DIS and stroke in the anterior circulation system. The researchers believe that PSC should not be considered as an exclusion criterion for thrombectomy [40]. The role of polymorbidity in predicting the outcome of stroke and the effectiveness of ET is ambiguous [3]. The prevalence of hypertension, hyperlipoproteinemia (HLP), coronary heart disease, and AF was the same in surviving and deceased patients after thrombectomy. In the DEFUSE 3 trial, outcome was not associated with comorbidities and traditional demographic predictors [41]. However, a high probability of “futile” recanalization was observed in patients with hypertension, diabetes, AF, coronary artery disease, previous stroke, and an NIHSS score of at least 20 [13]. In patients with diabetes, coronary artery disease, and high NIHSS scores, recanalization was not clinically successful. Unfavorable functional -

outcome of ET was observed in individuals with hypertension, diabetes, hypertrophy, asymptomatic carotid artery stenosis, and peripheral and coronary artery disease.

2.3. Overweight

Excess body weight may have a protective effect by providing patients with metabolic reserves. The protective effects of adipose tissue block the release of inflammatory cytokines during a catabolic state. A retrospective analysis of the MR CLEAN trial assessed the relationship between body mass index (BMI) and outcome after ET in patients with IS. The obesity paradox was a better functional outcome, lower mortality and stroke progression in patients with a higher BMI. Post-stroke mortality was low in patients with BMI and obesity, and its high rates were observed among underweight patients [42]. However, young individuals with elevated BMI/obesity (about 50%) had a higher fatal outcome [43].

2.4. Arterial hypertension

The pathophysiological mechanisms of the influence of blood pressure (BP) on the outcomes of IS after ET are not fully understood, and the exact range of BP before and after the procedure is unknown. The optimal target BP, which simultaneously avoids cerebral perfusion impairment, remains unknown (class I; level of evidence B) [2]. In the early stage of IS, 80% of patients have elevated BP (more than 140/90 mm Hg), which serves as a compensatory response to maintain cerebral perfusion. Before the recanalization procedure, elevated BP, increasing cerebral blood flow, protects the ischemic penumbra, but adversely affects the state of the CC, thereby reducing the frequency of successful recanalization. In elderly patients with hypertension, due to the duration of hypertension and critical damage to the vascular wall, elongation/tortuosity and stiffness of the arteries are one of the reasons for unsuccessful recanalization. In stroke with occlusion of large arteries, high and low SBP is a predictor of an unfavorable outcome [17]. In the study by M. Hu et al. [44], the optimal SBP during hospitalization should be 135–150 mmHg. A U- shaped relationship was determined between the average SBP value and the functional outcome 3 months after ischemic stroke, i.e., both high and low SBP lead to an unfavorable prognosis.

The risk of adverse outcome and death after ET is associated with high SBP, and the likelihood of adverse outcome is reduced by normal BP after thrombectomy. An association was found between elevated BP after ET and adverse outcome regardless of the recanalization outcome. A history of hypertension and stenosis of extracranial arteries impair cerebral autoregulation. SBP may spontaneously decrease after ET regardless of the recanalization outcome, and in patients with unsuccessful recanalization it decreases slightly, but eventually reaches a level similar to that in patients after successful recanalization within 24 hours. Hypertension after achieving reperfusion damages the BBB, leading to hemorrhagic transformation of the brain. At the same time, due to increased vascular permeability, the infarction focus and ischemic penumbra are at risk of reperfusion injury. Models of ischemia-reperfusion injury confirm a decrease in BP in patients after reperfusion and suggest that simple antihypertensive treatment may not be sufficient [45]. In patients with successful reperfusion after ET and poor CC, high BP variability influenced outcome [46]. High SBP levels ($p = 0.008$) before and after ET ($p = 0.009$) were observed in patients who died within 3 months after stroke.

To date, there are no recommendations for optimal BP management in the acute phase of ischemic stroke treated with ET. A 10% intraprocedural drop in BP from baseline and mean BP below 100 mmHg were associated with adverse outcome. High SBP during the 24 hours after the procedure is associated with adverse outcome. BP below 140/90 mmHg is associated with favorable outcome after ET [17]. According to a post-hoc analysis of the ASTER trial, BP variations during ET correlate with adverse outcomes regardless of any concomitant status. An ongoing RCT is attempting to confirm the beneficial effect of increasing SBP by 20%, but not less than 160 mmHg, before completion of ET [46]. A recent multicenter study compared different SBP targets after successful ET and showed that patients treated with a SBP target below 140

mmHg had higher odds of FI compared with those treated with the guideline-recommended SBP target (below 180 mmHg) [47].

2.5. Hyperglycemia

Blood glucose levels change dynamically and depend on factors such as stress response and stroke worsening. In HG, the risk of adverse outcome increases regardless of endovascular treatment of ischemic stroke [17]. HG induces anaerobic metabolism, formation of mitochondrial reactive oxygen species, lactic acidosis, and formation of free radicals, thereby acting as a catalyst for cell lysis in the ischemic penumbra. In patients with HG, the infarct area continues to grow after 24 and 72 hours of hospitalization. HG is observed in 75% of patients in the first 48 hours of acute ischemic stroke. It is assumed that this is a primarily adaptive response that has a neuroprotective effect due to the delay of energy-dependent ion transport and a decrease in the transmembrane ion gradient, as a result of which neuronal depolarization slows down and they maintain their functional activity. However, persistent HG in the acute period is a risk factor for death [48]. Stress HG exacerbates cerebral injury by increasing acidosis in the ischemic penumbra and may directly contribute to adverse outcomes through mechanisms including induction of endothelial apoptosis, endothelial dysfunction, oxidative stress, and procoagulant state. Stress HG, measured by glucose/HbA1c ratio, is associated with an increased risk of ICH [49]. The mechanisms of injury in acute HG include early adhesion and accumulation of platelets and leukocytes in cerebral cortex microvessels, as well as leukocyte extravasation, BBB disruption, and postcapillary microthrombosis. Non-diabetic patients are more susceptible to glucose fluctuations, while those with diabetes have high tolerance. This indicated that acute HG may be a predisposing factor for adverse functional outcome. Chronic HG is toxic to neurons, cerebral vessels, and BBB; causes cerebral vascular damage through mechanisms independent of thromboinflammatory changes. It leads to the formation of advanced glycation end products, increased oxidative damage, and vascular complications characteristic of diabetes. Endothelial damage occurs due to the deposition of advanced glycation end products in the vessel wall [50]. In addition, poor glycemic control causes morning blood pressure rises, which can synergistically accelerate vascular damage by enhancing inflammation in atherosclerotic lesions. In chronic HG, small cerebral vessels are damaged, making the brain unable to compensate for acute ischemic damage. This is probably why the unfavorable prognosis in diabetes is associated with poorly developed CC, which leads to an increase in infarct volume, unfavorable clinical outcomes due to increasing cerebral edema and hemorrhagic transformation of the affected tissue. At the same time, high glucose levels reduce the likelihood of a good outcome in patients with well-developed collaterals, but their effect on the outcome is less significant for patients with underdeveloped collaterals. With well-developed CC, more intensive glucose control is required [70]. In the study by M. Zhang et al. [51], for every 1 mmol/L increase in blood glucose on admission, the risk of early neurological deterioration after ET increases by 14.2%.

High fasting glucose levels 24 hours after ET increase the risk of poor outcome at 3 months. Despite successful reperfusion by thrombectomy, HG leads to poor outcomes and increased intracranial large vessel occlusion infarction [52]. Increased HG (HbA1c) levels are associated with decreased FI (OR=0.76; 95% CI [0.60–0.96]; p =0.02), increased incidence of ICH (OR=1.33; 95% CI [1.03–1.71]; p =0.03) and mortality (OR=1.26; 95% CI 1.01 to 1.57; p =0.04) [53]. With successful reperfusion of ET, the negative consequences of HG are reduced. Patients with HbA1C ⩾6.0% had poor 3-month mRS score , higher incidence of ICH and mortality than those with HbA1C <6.0%. Higher HbA1C and serum glucose on admission were independent predictors of poor clinical outcomes in patients with large artery occlusion treated with ET. The incidence of favorable outcome was reduced in patients with HbA1c >8.0% compared with HbA1c <6.5%. In patients with anterior circulation atherosclerotic stroke, a target HbA1c <6.5% should be strictly followed [54].

2.6. Fever

Fever (over 37.5°C) within 6 hours of stroke onset occurs in 20% of acutely ill patients. Fever after successful mechanical reperfusion is associated with poor neurological outcome and infarction enlargement [16–17]. Fever increases glutamate release and free radical formation, which disrupts the blood-brain barrier and promotes edema and increases tissue oxygen demand by increasing cerebral metabolic rate.

A 1°C increase in body temperature reduces FI by 34% and increases mortality by 65%. Hyperthermia leads to a tenfold increase in hospital mortality and an eightfold increase in the length of stay in the intensive care unit. Mild hyperthermia (37.6–38°C) increases the length of hospital stay but not mortality. Hyperthermia before ET is a predictor of reduced FI and mortality at 3 months [55]. Hyperthermia is associated with larger infarct volume, stroke severity, and poor functional outcome. A relationship was found between fever and increased infarct volume on the second and third days of ischemic stroke. Hypothermia is a reliable neuroprotector. Lower temperature before ET is an independent predictor of a favorable outcome and may stimulate future studies to examine whether therapeutic hypothermia performed at the prehospital stage or during interhospital transfer can improve patient outcomes. More pragmatic methods of reducing brain temperature, such as noninvasive head cooling, are recommended. Rapid intraischemic hypothermia has more pronounced protective effects than delayed or postischemic hypothermia.

2.7. Cerebral microangiopathy, or disease of small cerebral vessels

Cerebral microangiopathy (CM), or small cerebral vessel disease, results in decreased cerebral blood flow, impaired cerebral autoregulation, and increased BBB permeability. CM markers include small subcortical infarcts, white matter hyperintensity, lacunae, dilated perivascular space , cerebral microbleeds, and cerebral atrophy. CM was the cause of stroke in 25% of cases and doubled the risk of recurrent stroke. Leukoaraiosis is considered a neuroimaging marker of small cerebral vessel pathology. In a study by L. Zheng [56], 16.4% of patients with anterior circulation ischemic stroke were diagnosed with CM (moderate to severe), which increases the risk of neurological deterioration. Long-term hypoperfusion of the brain in elderly people, uncontrolled hypertension, smoking, diabetes, sleep apnea syndrome, arteriosclerosis, etc., causing endothelial dysfunction and insufficiency of these vessels, contribute to a decrease in the density of microvessels, a deficiency of CC and, ultimately, to a decrease in the functional reserve in the most metabolically active nuclei of the brain and white matter networks. CM in patients with ICH increases the risk of mortality and recurrent stroke by 150% and 44%, respectively [57]. CM can serve as a visualizing marker of cerebral vascular reserve. Even with successful recanalization, CM can be considered as an independent risk factor for an unfavorable clinical outcome and a predictor of fatal outcomes in IS, but it should not be used as a criterion for refusing ET [58].

2.8. Leptomeningeal collaterals and the core of cerebral infarction

Collateral status is the main determinant of how quickly the ischemic penumbra will progress to an irreversible infarction. In some patients, progression may occur within an hour, while in others it may take more than 24 hours, since the degree of collateral flow varies greatly among individuals. As a consequence , the rate of infarction growth is highly variable. LCs maintain the blood supply to the ischemic penumbra until the occluded vessel is revascularized. In the first 6.5 hours after the onset of symptoms of ischemic stroke, collateral status does not change, but reducing the time from onset to recanalization should remain a priority for all patients, regardless of collateral status [59]. Patients with well-developed LCs have a high efficacy of ET with a reduction in the final volume of CIC, a favorable neurological outcome, and a low incidence of hemorrhagic transformation of the brain. Assessment of LC is a simple way to identify patients who may benefit from effective RT even at later stages, and their study can help in making decisions on treatment tactics in the late therapeutic window [60].

Good collateral status, absence of leukoariosis, early thrombectomy, high ASPECTS values, and low NIHSS scores contribute to a favorable outcome [17–18]. In most patients with anterior circulation stroke and low NIHSS scores , the absence of collaterals correlates with a larger final infarct volume and worse long-term functional outcome. Patients with slowly progressive stroke had more LC, high FI values, and were 3.5-fold more likely to achieve reperfusion compared with patients with rapidly progressive stroke [61]. Well-developed LC were observed in individuals with lower baseline glucose levels or absence of diabetes and a higher probability of angiographic reperfusion after ET. In the DAWN trial (therapeutic window of at least 6 hours), 90 days after ET, well-developed LCs with small foci, slow infarction progression and higher FI rates were found [62]. However, in the DEFUSE 3 trial, in well-developed LCs, small CIC size and its growth were not associated with EF, mortality and ET efficacy [60]. Presumably, patients with a small core, moderate or well-developed CIC, admitted for endovascular treatment in an extended time window, will benefit most from recanalization of the ischemic penumbra [63].

Collateral blood flow is a factor influencing the growth of the ischemic core. The extent of irreversible damage, called CIC, plays a key role in the selection of patients for ET. CIC undergoes a sudden decrease in blood flow, free radical overproduction, calcium overload, and necrosis in the first hours of IS. The rate of CIC growth is a determinant of the clinical outcome of ET. Collaterals regulate the rate and severity of cerebral ischemia, distinguishing between rapid and slow progression and the corresponding therapeutic options. The selection of patients for ET is based solely on the size of the core and/or its size ratio with the penumbra, which represents the lesion tissue potentially subject to salvage, and the infarct center. CIC and deficit lesion volumes are important imaging biomarkers that have been successfully applied to select the treatment option for IS in several RCTs (DAWN , DEFUSE 3, EXTEND) [64]. Measurements of the volume of the CIC and the volume of the ischemic penumbra are considered effective predictors of clinical outcome in patients undergoing ET. Endovascular therapy is more effective in patients with a small infarct focus and a large penumbra. In the study by MS Koopman et al. [65], adverse outcome after ET was dependent on age, NIHSS score , and the volume of the CIC. With a volume of at least 70 ml, high rates of mortality, ICH, and less frequently, FI were observed.

The rate of ischemic core growth (ICGR) depends on the degree of development of the pulmonary circulation, which varies in patients with stroke. Slowly progressing ICGR had high FI rates and a 3.5-fold higher probability of achieving a modified Rankin Scale score of 0–2 with ET (aOR = 2.94 [95% CI [1.53–5.61], p = 0.001) compared with rapidly progressing ones, who had significantly worse clinical outcomes in both the early and late time windows. The probability of a good outcome decreased by 14% for each 5 mL/h increase in RiC (aOR , 0.87 [0.80–0.94], p < 0.001) [61]. ET is more effective in patients with a small infarct focus and a large penumbra, whereas patients with a large ischemic focus are at risk of developing an unfavorable clinical outcome after ET. In patients who undergo ET within the recovery time window (<6 hours), the ischemic brain area, particularly the penumbral region, will be reperfused and spared, but the IMI will not. Despite successful recanalization, infarct growth continues . Although restoration of blood flow alleviates hypoxia, subsequent irreversible cell death may still occur. The mechanisms of infarct growth and progression include ischemic reperfusion injury, cerebral edema, delayed or failure to achieve complete reperfusion or reocclusion of vessels after ET, distal embolization, and infarction in a new territory. Ischemic reperfusion injury is the result of multiple processes including endothelial activation, oxidative stress, inflammatory responses causing leukocyte infiltration, platelet activation, and disruption of the blood-brain barrier causing apoptosis, cerebral edema, and hemorrhagic transformation. A potential neuroprotective strategy to slow infarct growth after reperfusion in patients with large vessel occlusion is to treat cerebral edema before reperfusion. Early reocclusion occurs in 2 to 11%. In patients with initially small infarct volume, with rapid and

successful reperfusion, and in patients admitted in the early time window, slower infarct growth was observed [66].

2.9. Cerebral venous blood saturation

Long-term hypoxia of cerebral tissue leads to functional damage of the nervous system. Cerebral venous oxygen saturation (SvO2) is an indicator reflecting the functional activity of brain tissue. Measuring cerebral SvO_2 in patients with ischemic stroke is necessary to assess stroke severity, treatment, and prognosis. A decrease in cerebral blood flow velocity leads to a decrease in local cerebral SvO_2; when blood flow is restored without improving cerebral SvO_2, nervous function is not restored. Cerebral SvO_2 and its changes after treatment in hypoxic regions are associated with patient prognosis. Cerebral SvO_2 is measured by positron emission tomography, which is considered the gold standard, and it can be used as a new independent imaging indicator. Reduction in infarct volume was only part of the effects of endovascular treatment. Prognosis depends on infarction localization. The volume of hypoxic regions does not have a significant correlation with NIHSS and mRS scores. Correlation analysis with NIHSS and mRS scores showed that cerebral SvO_2 in hypoxic regions can serve as an important imaging indicator for assessing the clinical status and early prognosis [67].

2.10. Characteristics of a thrombus

The histological, biochemical and structural composition of the thrombus has a significant impact on the success rates of treatment. Thrombi with a high red blood cell content are generally associated with favorable outcomes, such as more successful recanalization, shorter intervention time and increased rtPA sensitivity. On the other hand, fibrin-rich thrombi have a less favorable outcome, mainly due to their increased stiffness and resistance to both mechanical thrombectomy and thrombolysis [68]. All DT techniques are associated with a risk of peri-interventional thrombus fragmentation and subsequent downstream embolism, which prevents complete recanalization and reduces the rate of neurological improvement. Clots that can be easily retrieved are more vulnerable to peri-operative thrombus fragmentation; they typically have higher red blood cell levels and lower fibrin amounts. Therefore, understanding the variables that contribute to fragmentation may be useful to maximize the therapeutic effect. The most important factors for predicting the number of tractions per ET procedure required for successful recanalization are the fibrin and red blood cell content in the thrombus, von Willebrand factor (vWF) [69]. Of 137 collected thrombi during mechanical thrombectomy, the overall mean percentages of red blood cells, white blood cells, platelets, fibrin and vWF in thrombi were 45.83%, 3.58%, 22.23%, 28.27% and 16.23%, respectively. The delayed surgery group (more than 4 hours) had higher thrombus fractions of white blood cells ($p = 0.02$), fibrin ($p = 0.02$) and vWF ($p = 0.03$) compared with the early group. Longer time to recanalization was associated with increased numbers of white blood cells, fibrin and vWF in thrombi, reflecting possible maturation of thrombus components in situ . Increased fibrin and vWF content reduce the likelihood of revascularization by changing the mechanical properties of the thrombus [70].

CONCLUSION

The aim of stroke treatment is to prevent the transition of ischemic penumbra to infarction and, consequently, to decrease the size of cerebral infarction and to improve the functional outcome of patients. Endovascular thrombectomy is the main prognostic factor for a favorable outcome of ischemic stroke in different age groups. The combination of endovascular thrombectomy and drug therapy in individuals with and without pre-stroke disability is safe and effective compared with standard drug therapy. It is extremely difficult to identify patients in whom early reperfusion treatment is futile or may cause more harm than good. Despite the efficacy and safety of endovascular thrombectomy, some patients experience postoperative unfavorable outcome due to unresolved issues of patient selection for mechanical reperfusion; poorly understood mechanisms of pathophysiology of some factors; the role of advanced neuroimaging has not been studied and the lack of scales for preoperative and postoperative prediction of treatment outcome.

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