Vascular medicine and thrombectomy in stroke

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Abstract: The treatment of stroke caused by intracranial vessel occlusion with intravenous recombinant tissue plasminogen activator (rt-PA) was the only evidence-based treatment option for a long time. Nevertheless the response rate was disappointing in large vessel occlusions. Five studies that evaluated the efficacy of mechanical thrombectomy published in 2015 proved a significant clinical benefit for selected patients suffering from acute ischemic stroke. These results are the basis for extensive technical, institutional, and personal structural changes in the neurovascular field of stroke treatment. This review gives an overview of the current status of mechanical thrombectomy and future expectations and challenges are discussed.

Keywords: ADAPT, intravenous thrombolysis, mechanical thrombectomy, stent retriever, stroke

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Introduction

Stroke is one of the leading causes of disability and mortality in industrial nations.[1] The majority of strokes are ischemic with about 80% caused by arterio-arterial embolism or cardiac embolism. Dissections of intracranial or cervical arteries represent a further often underestimated cause of cerebral infarction especially in the younger population.[2]

A prompt and complete restoration of blood flow in the affected artery is the key factor for a favorable neurological outcome – 'time is brain'.

The intra-arterial approach to restore the blood flow in intracerebral artery occlusions is not new. In 1982 Zeumer and colleagues presented a publication on local fibrinolytic therapy in basilar artery occlusion as a promising therapeutic option.[3] However, the benefit of endovascular therapy remained unproven though technical options have developed drastically in recent years. The possibility of directly extracting the occluding thrombus from the intracranial artery with a self-expandable and retrievable stent was found by chance in 2008.[4] From then on the introduction of numerous innovative endovascular tools lead to a widespread application of endovascular stroke treatment with promising recanalization rates, but nevertheless intravenous recombinant tissue plasminogen activator (rt-PA) remained the only evidence-based therapeutic option.

In 2015 five randomized clinical trials revealed high recanalization rates in acute proximal occlusions of the anterior circulation. An analysis of the clinical results proved the significant superiority of mechanical thrombectomy in combination with intravenous thrombolysis in acute stroke compared with intravenous thrombolysis alone.[5–9] New-generation stent retrievers were applied in these studies, which might be one explanation for the promising angiographic and clinical results. A meta-analysis of these studies with the pooled data from 1287 patients showed that 46.0% of patients undergoing mechanical thrombectomy reached an independent functional outcome (Modified Rankin Scale [mRS] 0–2 at 90 days) compared with 26.5% treated with best medical treatment alone.[10]

The results and emerging consequences of these studies have had a fundamental impact on the multidisciplinary organization of stroke treatment. From a neurovascular point of view the impact of the positive thrombectomy studies was many times higher than the paradigm shift in the

treatment of ruptured aneurysms following the results of the International Subarachnoid Aneurysm Trial study in 2002.[11]

How should eligible patients for mechanical thrombectomy be selected?

Around 80% of the estimated annual 260,000 strokes in Germany are ischemic in nature, of these, 25% meet the inclusion criteria for treatment with rt-PA and 5–10% are suitable for mechanical thrombectomy.[12]

The identification of patients that will benefit from mechanical thrombectomy needs a multidisciplinary setting. A prompt and reliable clinical assessment followed by a classification of the National Institutes of Health Stroke Scale (NIHSS) and a determination of prestroke clinical status, modified Rankin Scale (mRS) and an assured identification of the time spread from stroke onset are mandatory requirements for a successful image-based selection of patients. Clinical and image-based selection criteria for patients eligible for mechanical thrombectomy have been published in the European Recommendations on Organization of Interventional Care in Acute Stroke (EROICAS).[13] These recommendations are based on the previously mentioned evidence-based studies. The recommendations are grouped according to level of evidence. High-level evidence recommendations include a good prestroke functional level, a time frame from symptom onset to groin puncture of 6 h, and no application of an upper age limit. With regard to the standard imaging protocol, a subanalysis of computed tomography (CT) perfusion data from the MR CLEAN study showed that this method can be useful in predicting functional outcome. However, CT perfusion was not reliable in identifying patients that would benefit from mechanical thrombectomy.[14] These findings contributed to a change in our institutional imaging protocol. Patients admitted within 6 h of symptom onset are examined using a conventional CT scan including CT angiography without CT perfusion. In cases of vessel occlusions, the patient is referred for mechanical thrombectomy without additional diagnostic imaging. In patients with a time frame of more than 4.5 h CT perfusion can be helpful in identifying patients that may benefit from endovascular therapy according to the mismatch concept combined with an extended indication for additional intravenous thrombolysis. The decision to use endovascular treatment is then reached by consensus between the neurologist and the interventionist. Our institutional standard is based on the selection criteria for mechanical thrombectomy taken from successful trials that were summarized by Evans and colleagues in 2017.[15] These include the following:

(1) large vessel occlusions of the anterior circulation
(2) severe clinical deficit at the time of treatment measured by NIHSS score (NIHSS $>$ 5 or a lower score that is functionally significant for the patient)
(3) mild clinical deficit from a proven large vessel occlusion is not a contraindication for mechanical thrombectomy and bears a high risk of clinical deterioration
(4) lack of extensive ischemic change on plain CT
(5) prestroke clinical status and lack of relevant comorbidities
(6) age over 80 years alone is not a contraindication for treatment

There is limited evidence to date for mechanical thrombectomy in M2 and basilar artery occlusions, nevertheless our current standard is to proceed as with anterior large vessel occlusions.[16]

Who should treat patients eligible for mechanical thrombectomy?

Neuroradiologists are confronted with the task of transferring new evidence into a permanent and appropriate neuroendovascular supply process, therefore personal and institutional requirements need to be defined. Prompt and accurate patient selection is crucial in order to achieve a good clinical outcome but this is less effective with an inadequately trained operator.[17] A well-trained interventionist should have performed a defined number of stroke cases (over 100 intra- and extracranial interventions) on his own. Furthermore, the neurointerventionist should be familiar not only with mechanical thrombectomy but also with the endovascular techniques necessary to deal with the complications that may occur.

The German Society of Interventional Radiology and Minimally Invasive Therapy (DeGIR) and the German Society of Neuroradiology (DGNR)

defined performance requirements that are summarized in different modules. Endovascular stroke treatment is included in module E. Certified teaching courses including a final examination are needed to receive the relevant certification. The requirements for module E are summarized as follows:

(1) at least 1 year's practical experience in interventional neuroradiology
(2) DeGIR and DGNR membership
(3) attendance on certified DeGIR/DGNR courses
(4) regular weekly attendance of radiological conferences
(5) interdisciplinary residential therapy of treated patients
(6) at least 100 extra- and intracranial neurovascular interventions performed independently
(7) successful oral and written examination

Endovascular stroke treatment should be carried out in certified neurovascular centers including a continuous neuroendovascular service with a certified stroke unit.

Because not all hospitals with stroke units can provide a permanent and complete stroke treatment facility the question of quick and effective organization of patient transportation arises. Is the clinical outcome of patients directly referred to neuroendovascular stroke centers different from those secondarily transferred? The concept of this 'drip-and-shift' system was analyzed by Weber and colleagues in 2016. They compared consecutive stroke patients directly admitted and treated with thrombectomy in a neurointerventional center with patients secondarily referred to a neurointerventional center from other hospitals. The in-hospital mortality and the 3-month mortality were not significantly different in both groups. They concluded that the drip-and-shift thrombectomy concept can be effectively organized in a metropolitan stroke network.[18] These findings result from an analysis of patients treated in a densely populated area with a well-appointed infrastructure regarding the number of hospitals and the distances between them. The results are therefore not transferable to all areas of Germany. This underlines the need for structured and quality-assured training, not only of neuroradiologists as already implemented, but also of all disciplines including paramedics that work in the field of interdisciplinary stroke treatment.

How should mechanical thrombectomy be performed?

The primary aim of endovascular stroke treatment is a rapid and complete recanalization of the occluded artery. The first device available for the mechanical retrieval of thrombus was the MERCI Retriever (Concentric Medical, Mountain View, CA, USA) in 2004, which consisted of a nitinol spiral.[19] Several similar devices were introduced thereafter ranging from concepts with cages or micro brushes to a combination of an aspiration catheter with a wire for the fragmentation of the thrombus.[4] With the Solitaire Stent AB (ev3, Irvine, CA, USA), a self-expanding electrolytically detachable device for the stent-assisted coiling of intracranial aneurysms entered the market in 2004. Following the ability of the Solitaire to act as a clot retriever it was modified to a nondetachable version exclusively designed as a stent retriever named Solitaire FR (flow restoration). Several stent retrievers of different sizes and shapes were introduced by different companies all with the aim of sole mechanical retrieval. In the early phase of mechanical thrombectomy guiding catheters were too stiff to enter the tortuous anomalies of the carotid or vertebral arteries and could therefore not be placed close to the occluding thrombus. Therefore mechanical thrombectomy was more of a mechanical extraction of the clot than an aspiration. This changed with the introduction of highly flexible intermediate catheters that could be navigated directly to the occlusion. Thrombectomy results from a combination of manual or machine aspiration with the intermediate or aspiration catheter and mechanical retrieval with a stent retriever. This approach advanced to the A Direct Aspiration First Pass Technique (ADAPT), which aspirated the thrombus from the intracranial artery without the need for a stent retriever and also without the need to penetrate the thrombus with a microcatheter beforehand.[20] This technique might have a lower incidence of distal emboli followed by mechanical thrombectomy and any potential endothelial damage caused by the passage of the stent retriever will not occur.[21] Nevertheless ADAPT does not work in every case since individual anatomies and different types of thrombi require a range of thrombectomy devices and techniques.

Our current standard concept consists of an initial approach with aspiration alone. We use an 8 French guiding catheter in combination with a highly flexible aspiration catheter of a diameter

close to the size of the occluded vessel with the intention of complete suction of the entire thrombus. If this fails we combine this with a stent retriever placed inside the thrombus.

The fundamental aim of endovascular stroke treatment is complete restoration of blood flow not only at the site of occlusion but in the entire dependent vascular territory (score of 3 in the thrombolysis in cerebral infarction grading system), since the above-mentioned studies proved a positive correlation between higher recanalization grades and a good clinical outcome. Therefore we try to achieve a complete recanalization in all cases. The recanalization of secondarily occluded, more distally located arteries became more successful and safer with the introduction of smaller stent retrievers with a lower radial force that required smaller microcatheters and the availability of highly flexible aspiration catheters of smaller diameters.[22,23]

In cases of tandem occlusions of the cervical carotid artery and an intracranial vessel occlusion with an underlying high-grade stenosis of the proximal carotid artery, the endovascular access to the intracranial occlusion is hindered. The operator has to treat the occlusion or stenosis of the carotid artery by percutaneous transluminal angioplasty before the intracranial occlusion can be cleared. If stent placement is performed before treatment of the intracranial occlusion one has to avoid a passage of the stent with the retriever which might result in an interaction of the devices followed by severe vascular damage.[24]

Balloon guide catheters act as proximal protection systems due to their ability to block the blood flow in the target artery during mechanical thrombectomy. A combination of flow arrest with simultaneous aspiration may reduce the rate of iatrogenic thromboembolic complications.[25]

There is still controversy on the issue of general anesthesia compared with conscious sedation during endovascular treatment of acute stroke. The main argument against general anesthesia is the time loss and the occurrence of lower systolic blood pressure that results in a worse clinical outcome.[26] Nevertheless we prefer to perform all endovascular stroke treatments under general anesthesia with a continuous systolic blood pressure of more than 150 mmHg since the entire procedure is technically easier and because of this, faster. Previously published data reveal a similar safety profile for the different types of anesthesia.[27,28]

Goyal and colleagues analyzed the impact of high blood pressure levels after mechanical thrombectomy and hyperglycemia on admission on the clinical outcome of patients with large vessel occlusions. They found an increased likelihood of mortality and functional dependence at 3 months in patients with high systolic blood pressure and hyperglycemia. These data underline the imperative of a multidisciplinary supervision of patients not only in the acute phase.[29,30]

Future expectations and challenges

The main task involves the implementation of a nationwide infrastructure that allows for a comprehensive 24 h multidisciplinary stroke treatment. As described above training programs for interventional radiologists and the implementation of certified stroke centers are already in existence with growing numbers. There has been a debate on the possibilities of expanding the number of interventionists for endovascular stroke treatment by other specialties. The direct process of thrombus aspiration, whether by aspiration alone or in combination with mechanical thrombectomy, is not the crucial technical step in endovascular stroke treatment. The quick and safe catheterization of the often highly tortuous and elongated vessels in elderly patients and the management of complications that may occur require a high level of experience in neuroendovascular techniques.[31] Therefore we believe that a high quality standard with clinical results in line with those of clinical trials can only be guaranteed with experienced interventional neuroradiologists.

Further research is needed to expand the evidence for mechanical thrombectomy in the posterior circulation, in wake-up strokes, and in the time window between 6 h and 12 h. Clinical trials have already been initiated to answer these questions. Initial results from the DAWN study revealed a better outcome of wake-up stroke patients undergoing endovascular treatment within 6–24 h from time last seen at 3 months compared with subjects treated with standard medical therapy alone.[32]

Another two recently published studies found high grades of good clinical outcomes and low

complication rates in patients treated by mechanical thrombectomy outside the recent guidelines for endovascular management of emergent large vessel occlusions and top-tier evidence. These data indicated no increased risk of intracerebral hemorrhages in patients that would have been excluded from mechanical thrombectomy if top-tier criteria were upheld due to a NIHSS score of less than 6, a premorbid mRS score (greater than 2), an M2 occlusion, an occlusion in the posterior circulation, or a symptom to groin puncture time of more than 360 min.[33,34]

The significance of mechanical thrombectomy in combination with intravenous thrombolysis as the current standard needs to be compared with that of sole mechanical thrombectomy in the future. A meta-analysis by Tsivgoulis and colleagues analyzed the efficacy of endovascular therapy for acute ischemic stroke with and without pretreatment intravenous thrombolysis. They could not document a significant effect of intravenous therapy on the 3-month functional outcome. Their findings underline the efficacy of endovascular therapy independent of an intravenous pretreatment.[35,36] These data may indicate the future value of endovascular treatment as a standalone therapy in acute ischemic stroke.

Conclusion

The angiographic and clinical success of mechanical recanalization in acute stroke is impressive.[37] Future challenges are the implementation of a comprehensive 24 h interdisciplinary stroke treatment at highly experienced neurovascular centers rather than the introduction of further devices for mechanical thrombectomy.

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Conflict of interest statement

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