The History of Endovascular Stroke Treatment: From Local Intraarterial Fibrinolysis to Stent Retriever Thrombectomy

Die Geschichte der endovaskulären Schlaganfallbehandlung: Von der lokalen intraarteriellen Fibrinolyse zur Stent Retriever-Thrombektomie

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ABSTRACT

Background Acute thromboembolic occlusions of large intracranial arteries are associated with high rates of permanent disability and mortality. Intravenous thrombolysis (IVT) in these patients resulted in an inadequate rate of recanalization and has had limited clinical success. Various endovascular procedures have been attempted to remove intracranial thrombi and reopen occluded vessels. These technical innovations led to the publication of initial case reports, but the methods ultimately did not endure. Endovascular treatment of acute cerebral ischemia was performed only rarely and in selected centers as part of individualized curative attempts. The Solitaire stent was originally developed to treat intracranial aneurysms through stent-assisted coil occlusion. The suggestion that this stent could also be used for intracranial thrombectomy was made as early as 2003 and was clinically confirmed in 2008. Releasing a Solitaire stent into an embolically occluded large cerebral artery, with an incubation time of approximately 3 minutes and slow retraction of the stent, has led to unprecedented success rates of thrombus removal and (sub)total recanalization in more than 90 % of patients.

Methods This review article aimed to describe the steps in the development of endovascular stroke therapy, beginning with intra-arterial thrombolysis and early technical innovations leading to the eventual success of stent retriever thrombectomy.

Conclusion The potential for mechanical recanalization of acutely occluded large cerebral arteries could not be fully exploited until the advent of stent retriever thrombectomy. The entire concept of stroke treatment fundamentally changed after complete and rapid recanalization first became possible. Randomized controlled trials have shown superiority of stent retriever thrombectomy over IVT. An unparalleled boom in endovascular stroke therapy followed.

Key Points

- The history of endovascular stroke treatment was marked by setbacks in the first three decades.
- Stent retriever thrombectomy is the first procedure enabling recanalization of acute large intracranial artery occlusions in more than 90 % of patients.
- Stent retriever thrombectomy has transformed stroke care and neuroradiology in unprecedented ways.
- Further technical improvements will enable even faster, safer, complete recanalization in the near future.
- Further improvements in clinical outcomes will probably be determined by aspects beyond endovascular methods alone.

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ZUSAMMENFASSUNG

Hintergrund Akute thrombembolische Verschlüsse großer intrakranieller Arterien sind assoziiert mit einer hohen Rate an bleibender Behinderung und Mortalität. Die intravenöse Thrombolyse (IVT) führt bei diesen Patienten nur zu einer unzureichenden Rate an Rekanalisationen und ist von begrenztem klinischem Erfolg. Mit unterschiedlichen endovaskulären Verfahren wurde daher versucht, intrakranielle Thromben zu entfernen. Mehrere technische Neuerungen führten zwar zu ersten Fallbeschreibungen, hatten aber letztlich keinen Bestand. Die endovaskuläre Behandlung der akuten zerebralen Ischämie blieb eine in wenigen Zentren seltene und als individueller Heilversuch durchgeführte Prozedur. Der Solitaire Stent wurde ursprünglich entwickelt zur Behandlung intrakranieller Aneurysmen durch Stent-assistierte Coil-Okklusion. Die bereits 2003 geäußerte Vermutung, dass dieser Stent auch zur intrakraniellen Thrombektomie verwendet werden kann, wurde von uns 2008 klinisch bestätigt. Durch die Freisetzung eines Solitaire-Stents in einer embolisch verschlossenen großen Hirnarterie, einer Inkubationszeit von etwa 3 Minuten, und einem langsamen Rückzug des Stents, gelingt jetzt erstmalig die Thrombus-Entfernung und Rekanalisation in über 90 % der Patienten.

Methode Der vorliegende Beitrag schildert die Entwicklungsschritte der endovaskulären Schlaganfallbehandlung von der intra-arteriellen Thrombolyse über frühe technische Innovationen bis hin zum Erfolg der Stent-basierten Thrombektomie.

Schlussfolgerung Erst durch die Stent-basierte Thrombektomie konnte das Potenzial der mechanischen Rekanalisation akut verschlossener Hirnarterien in vollem Umfang ausgenutzt werden. Diese Beobachtung hat das gesamte Konzept der Schlaganfallbehandlung grundlegend verändert. Eine (häufig) komplette und rasche Rekanalisation wurde erstmalig möglich. Randomisierte kontrollierte Studien zeigten eine eindeutige Überlegenheit in Bezug auf Patientenunabhängigkeit und Mortalität gegenüber der IVT. Es folgte ein unvergleichlicher Boom in der endovaskulären Schlaganfalltherapie.

Kernaussagen

- Die Geschichte der endovaskulären Schlaganfallbehandlung war in den ersten Jahrzehnten von Rückschlägen geprägt.
- Die Stent Retriever-Thrombektomie ist das erste Verfahren überhaupt, das eine Rekanalisation großer intrakranieller Verschlüsse von Hirnarterien in über 90 % der Patienten ermöglicht.
- Die Stent Retriever-Thrombektomie hat die Schlaganfallversorgung und die Neuroradiologie in ungeahnter Weise verändert.
- Weitere technische Verbesserungen werden in naher Zukunft schnellere, sichere, vollständige Rekanalisationen ermöglichen.
- Über eine weitere Verbesserung des klinischen Ausgangs werden wahrscheinlich nicht nur endovaskuläre Methoden entscheiden.

Introduction

Acute occlusion of large brain-supplying arteries was recognized as a frequent cause of ischemic stroke by 1658 [1]. Intravenous thrombolysis (IVT) was the first therapeutic procedure established for this condition [2–5]. However, its ability to recanalize large thrombi was low, and embolic occlusion of large vessels remained associated with poor outcomes, often permanent disability or death, despite IVT [6]. Over the past 65 years, interventional (neuro)radiologists have sought methods to reopen acutely occluded intracranial vessels in an image-guided manner by using catheters [7–39]. While individual success cases have been published, none of these methods was proven to be sufficiently simple, safe, and effective to become established as a first-line treatment.

The misappropriated use for thrombectomy of a detachable stent originally intended for assisted coil occlusion of intracranial aneurysms changed many things [40, 41]. After initial setbacks arising from methodologically flawed studies, randomized controlled trials (RCTs) confirmed the safety and high efficacy of stent retriever thrombectomy [42].

Mechanical thrombectomy has revolutionized both stroke treatment and interventional neuroradiology more than any other prior therapeutic concept. Intracranial thrombectomy became the most common procedure performed in many interventional departments between 2013 and 2023 [43]. Here, we describe the historical development from local intra-arterial fibrinolysis to stent retriever thrombectomy as a history of ideas.

Local Intra-arterial Fibrinolysis

The first attempt to induce intracranial recanalization by catheter intervention is attributed to Sussman and Fitch (1958) [7], who described a patient receiving intra-arterial thrombolysis (IAT) for an occluded internal carotid artery. Sussman and Fitch and, 24 years later, Zeumer (in patients with basilar artery thrombosis via proximal catheters in the vertebral artery) infused fibrinolysin and streptokinase, respectively, into distal embolically occluded brain-supplying vessels from a supraaortic position [7, 8]. In a further development, toward the end of the 1980 s, microcatheters were inserted further distally, reaching near the actual site of occlusion, thus enabling local application of the thrombolytic agent [9, 10]. A phase 2 trial (Prolysis in Acute Cerebral Thromboembolism, PROACT) demonstrated the feasibility and efficacy of local IAT (recombinant pro-urokinase in combination with intravenous

heparin) with concomitantly increased rates of intracerebral hemorrhage [11]. This effect was independent of the choice of thrombolytic agent [12]. In 1999, PROACT II demonstrated the superiority of IAT compared to heparin in terms of functional independence (modified Rankin Scale [mRS] 0–2) in patients with acute middle cerebral artery (MCA) occlusion. However, the risk of intracerebral hemorrhage persisted [13]. Retrospective data on vertebrobasilar occlusions also yielded promising results, including a significant decrease in previously high mortality [12, 14, 15]. Problems and obstacles such as low adoption of the method, the timing and duration of the intervention, and a lack of training facilities hindered global application [15]. Moreover, superiority compared to intravenous thrombolysis could not be demonstrated [16].

Latency Phase

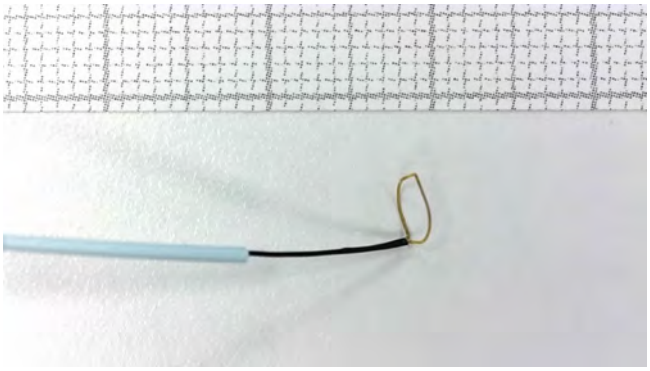
Initially, no significant advances in endovascular procedures occurred in the 1990 s. One reason was the focus on IVT as a promising recanalizing therapeutic option for ischemic stroke [3]. Randomized controlled trials indicated the superiority of intravenous thrombolysis compared to placebo in terms of patient outcomes (mRS 0–2; good functional outcome) in a time window as long as 4.5 hours after symptom onset (for acute anterior circulation ischemic stroke) [2–5]. A major factor determining outcomes is early recanalization of the acutely occluded vessel [3]. However, the ability of IVT to recanalize acute occlusions of large cerebral vessels remained limited, at approximately 40 %, and morbidity and mortality in patients with acute stroke remained high [3, 5].

Starting in the late 1990 s, innovative new endovascular therapy options were increasingly developed for patients with severe stroke and poor response to IVT. Nakano et al. (1998) described primary percutaneous transluminal angioplasty for acute MCA occlusion by using a Stealth balloon catheter (Target Therapeutics, Fremont, CA, USA) in ten patients with stenosis and thromboembolic MCA occlusion [17] (▶ **Fig. 1**).

A small balloon diameter (2–2.5 mm) and very low inflation pressure (2–3 atm) prevented vascular injury. However, the recanalization was based on thrombus fragmentation rather than removal. From a current perspective, the resultant distal occlusion of many small vessels is unacceptable. However, percutaneous transluminal angioplasty remains an important option when an atherosclerotic stenosis underlies an intracranial vessel occlusion. The dedicated balloon catheters (e. g., pITA, phenox, Bochum, Germany) available for this purpose are technically adapted derivatives of originally coronary devices for intracranial use.

Microsnares were developed to remove foreign bodies (e. g., coils) from cerebral vessels (▶ **Fig. 2**). Wikholm (1998) and Chopko et al. (2000) described the use of microsnares for endovascular embolectomy [32, 33]. The technical procedure is analogous to foreign body removal. The occluded vessel is catheterized with a microcatheter distal to the occlusion plane. Here, the microsnare is deployed by slight retraction of the microcatheter. Because of its shape memory features, the microsnare opens and bends slightly against the longitudinal axis of the catheterized vessel. Slow retraction of the microcatheter and microsnare is performed to encircle the thrombus. The microcatheter is then advanced slightly, and the loop is partially closed, sufficient to grasp but not dissect the thrombus. This method thus requires extensive experience and great skill. These technical challenges have prevented this method's widespread adoption. Recanalization with a microsnare is now considered when a vessel is occluded by an organized or heavily calcified thrombus that cannot be captured with a stent retriever.

▶ **Fig. 1** Stealth balloon catheter originally developed for the treatment of cerebral vasospasm.

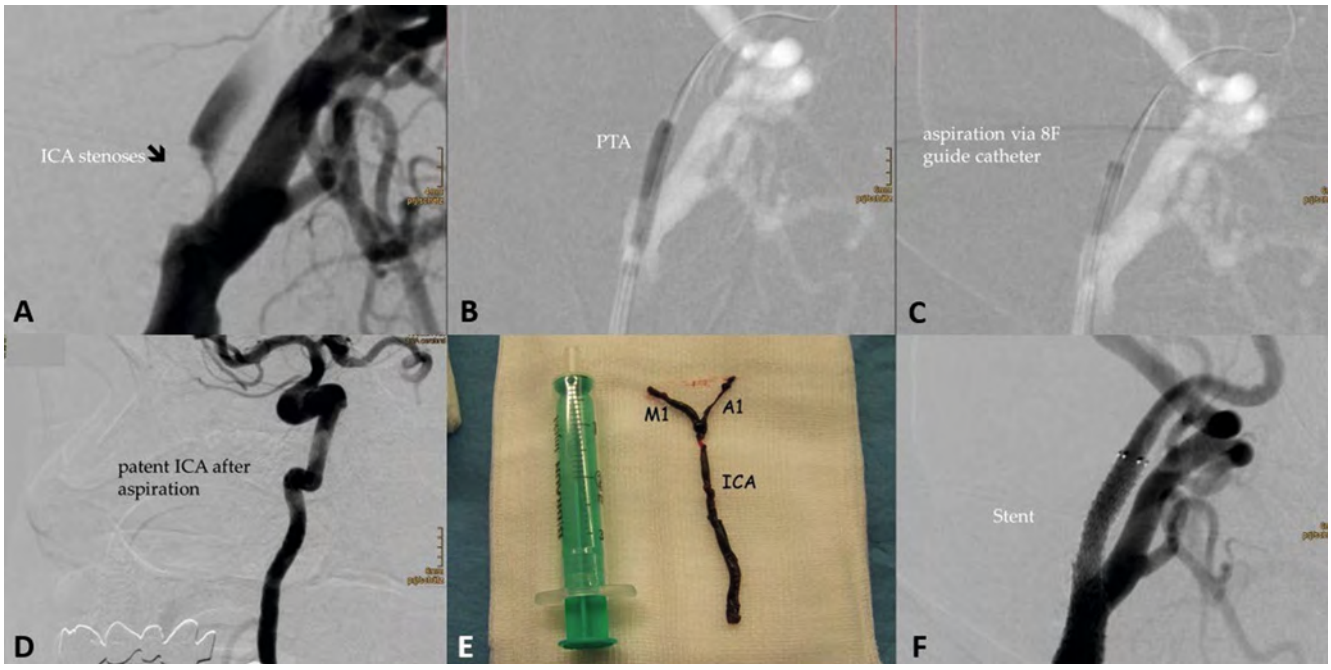


▶ **Fig. 2** "Goose neck" microsnare (Microvena, White Bear Lake, MN, USA).

The first case reports of direct thrombus aspiration were published in 2002. Lutsep et al. (2002) were able to remove large amounts of thrombus from the internal carotid artery by using commercially available guiding catheters [18]. For the posterior circulation, Chapot et al. (2002) successfully used 4F or 5F catheters for diagnostic angiography [19]. At that time, because no dedicated aspiration catheters were available, aspiration thrombectomy was limited to select patients with favorable anatomical conditions (▶ **Fig. 3**).

Corkscrews, Brushes, and Baskets: Mechanical Thrombectomy

In the early 2000 s, the first dedicated devices based on direct interaction with the blood clot were developed. With these devices,



▶ **Fig. 3** Recanalization of an internal carotid artery (ICA) with proximal atherosclerotic stenosis and distal thrombus formation. Contrast medium injection of the common carotid artery shows the proximal ICA stenosis (**A**). An undersized (2.5 mm) balloon angioplasty (**B**) allows insertion of an 8F guide catheter into the proximal ICA (**C**). Contrast injection of the ICA after aspiration with a 50 cc syringe confirmed the patency of this vessel (**D**). (**E**) depicts the removed thrombus. The proximal stenosis was dilated to 4 mm and sealed with a self-expanding stent (**F**).

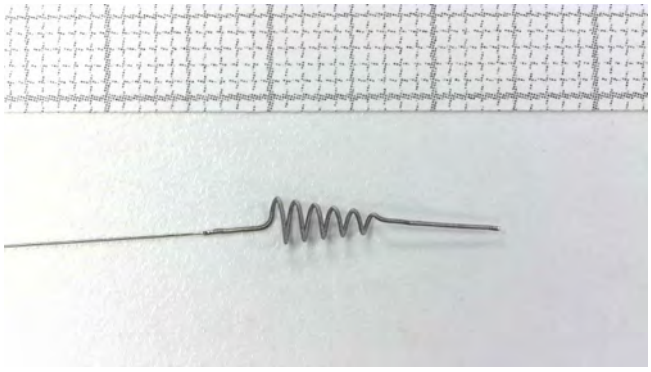
the blood clot is grasped and then retrieved from the occluded vessel. Unlike microsnares and balloon catheters, these devices were designed for this purpose. This time period marked the beginning of mechanical thrombectomy.

Wensel and Gobin had filed a patent application for the concept of using a coil for endovascular removal of intracranial thrombi in 1996 (later US Patent No. 6,530,935 B2). They claimed the use of a wire with shape memory features, which is inserted in a stretched state through a microcatheter into the target vessel under X-ray fluoroscopy. Then the distal end of the wire exits into the thrombus and takes the shape of a spiral. This spiral "grasps" the thrombus, which is then removed from the body together with the microcatheter and the "retriever" [20] (▶ **Fig. 4**).

The "Mechanical Embolus Removal in Cerebral Ischemia" (MERCI) device (Concentric Medical, Mountain View, CA, USA) was first used clinically in 2001 and received FDA approval for the US market in 2004 [23]. Fragmentation of the thrombus during thrombus passage or retraction, associated with distal embolization, has been reported to occur in as many as 35 % of cases [21]. Retrospective cohort studies have indicated recanalization rates of 50–65 %, a 32 % rate of good functional outcomes (mRS 0–2), and a mortality rate of 35.2 % [22].

The Neuronet (Guidant, Santa Clara, CA, USA) from 2002 was a self-expanding basket firmly connected to a guidewire, which was advanced via a microcatheter and used to retract the thrombus in toto [24]. The Neuronet was never commercially available.

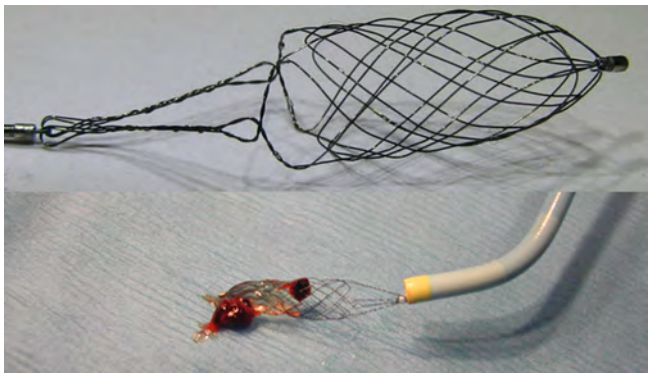
The CATCH device, described and initiated by Chapot in 2005 (Balt, Montmorency, France) [25, 26], works in a similar manner and is a stent-like, distally closed wire structure (▶ **Fig. 5**).



▶ **Fig. 4** MERCI retriever (Concentric Medical, Mountain View, CA, USA).

It is also advanced via a microcatheter distal to the thrombus, where it is released. A braided nitinol basket is proximally attached at two points to an insertion wire and is distally occluded. The device "captures" the thrombus and is withdrawn together with the microcatheter under aspiration. Proximal occlusion with BGC has not been used [25, 26]. The CATCH device was approved in the European Union (Conformité Européenne, CE mark). Mourand et al. (2011) have achieved sufficient recanalization in 65 % of patients with the CATCH device together with other treatment modalities, such as intra-arterial and intravenous fibrinolysis [26].

The phenox clot retriever (pCR, CE mark in 2006; phenox GmbH, Bochum, Germany) consisted of a core wire compound surrounded by a palisade of perpendicularly oriented stiff polyamide microfilaments [27]. The BONnet (CE mark in 2010; phenox



▶ **Fig. 5** CATCH device (Balt Extrusion).

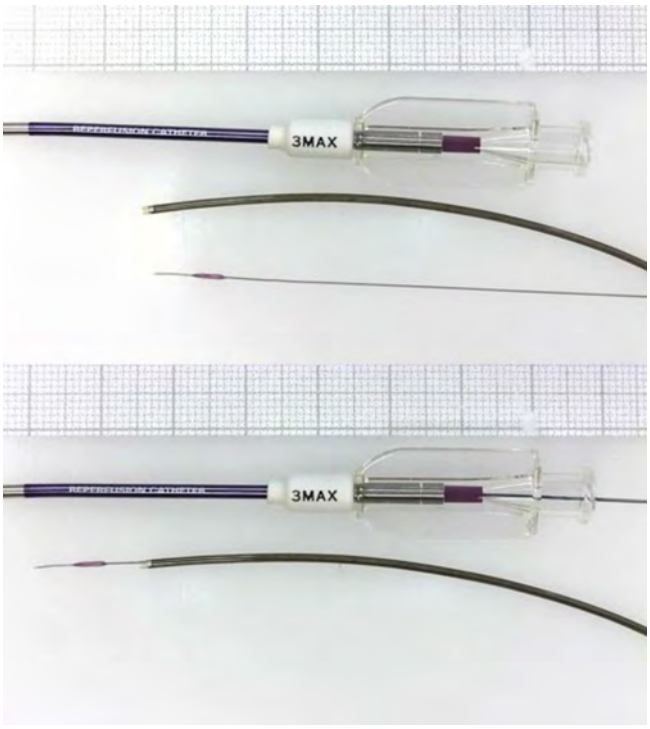
▶ **Fig. 6** pCR and BONnet (phenox GmbH).

GmbH, Bochum, Germany) was a braided nitinol basket eccentrically connected to an insertion wire. Its handling was similar to that of the other mechanical thrombectomy instruments (▶ **Fig. 6**). Both devices were introduced through a microcatheter, deployed distally to the thrombus, and then pulled back under continuous aspiration.

All the above thrombectomy devices of the pre-Solitaire era were able to remove intracranial thrombi, had good safety profiles, were sometimes complicated to use, and did not achieve a rate of adequate recanalization > 60 %.

Fragmentation, Thrombus Destruction, and Aspiration

The Penumbra system (Penumbra, Alameda, CA, USA), patent by Bose et al. (2004, US 609 028 P), uses a different approach to thrombus extraction [28]. An aspiration catheter is passed over a guide catheter just *proximal* to the blood clot. An aspiration pump is connected to this aspiration catheter. A thin wire with a teardrop-shaped distal distension ("separator") is inserted through this catheter via a hemostatic valve. With the distal end of the aspiration catheter in front of the thrombus, the thrombus is fragmented under continuous aspiration by gentle movement of the separator back and forth through the thrombus. Consequently, the thrombus is fragmented, and the resulting fragments are aspirated (▶ **Fig. 7**).



▶ **Fig. 7** Penumbra system (Penumbra, Alameda, CA, USA): Aspiration catheter and separator.

In cases of persistent residual thrombus, direct thrombus extraction can be performed via a "thrombus removal ring" under flow arrest through a proximal balloon guide catheter [28]. With the Penumbra system, complete recanalization (TIMI 3 [Thrombolysis in Myocardial Infarction] and TICI 3 [Thrombolysis in Cerebral Infarction]) has been achieved in as many as 70 % of cases [29, 30]. The CE mark was granted in 2007, and FDA approval followed in 2008. The Penumbra system is indicated for endovascular stroke therapy within 8 hours after symptom onset for patients with occlusion of the MCA (M1 and M2 segment), as well as the basilar artery or a vertebral artery [31].

The AngioJet system (Possis Medical, Minneapolis, MN, USA) is a rheolytic thrombectomy device using high-pressure saline jets that generate clot fragments, which are consecutively sucked into the access catheter [34]. Complications have been reported to include dissection and difficult intracranial navigation. Consequently, the AngioJet has not been further investigated for ischemic stroke [34, 35].

Endovascular photoacoustic recanalization (EPAR; Endovasix Inc, Belmont, CA, USA), a laser- and catheter-based procedure for thrombus fragmentation (mechanical thrombolysis), was introduced in 2001 [36]. Here, the emulsification of the thrombus appears to be attributable to a conversion of photonic energy to acoustic energy at the fiberoptic tip of the EPAR microcatheter. The EPAR microcatheter is pulled (in a guiding catheter) from distal to the occlusion, through the thrombus, to proximal to the occlusion [37]. Retrospective data have indicated recanalization rates between 40 % and 60 % [37]. In direct laser procedures (LaTIS, Minneapolis, MA, USA), contrast agent is intended to act

as a light guide to transport energy from the catheter in situ to the thrombus [38]. Neither approach was pursued further.

The EKOS device (Bothell, Washington, USA) was introduced as an ultrasound-assisted procedure with the goal of augmenting locally applied IAT (via EKOS catheter) [39]. A single-lumen microcatheter with a piezoelectric ultrasound element at the distal end was designed to locally enhance the interaction of IVT with thrombi (by passaging fibrin separation). The positive results of the pilot study could not be confirmed [39, 44].

Temporary Bypass

Kelley et al. (2008) have presented the concept of a temporary bypass [45]. After unsuccessful IAT (MCA, M1 segment), an enterprise stent (Codman Neurovascular, Raynham, MA, USA) was placed via a microcatheter within and distal to the thrombus. As the stent expanded, the thrombus was displaced, and blood flow was restored. IA thrombolytics were applied during and after the procedure (as the stent was reconstrained and removed after 20 minutes). The thrombus material between the stent and the vessel wall had dissolved or migrated distally but was not removed from the body [45]. Ferrera has filed a patent application for a stent-like structure (Iriis Plus) designed to be used as a temporary bypass (2012, U.S. 8,088,140 B2) (▶ **Fig. 8**). This device was a particularly dense stent (▶ **Fig. 6**). Neither the temporary bypass procedure nor the Iriis Plus device (MindFrame, Irvine, CA, USA) could prevail over the stent retriever thrombectomy.

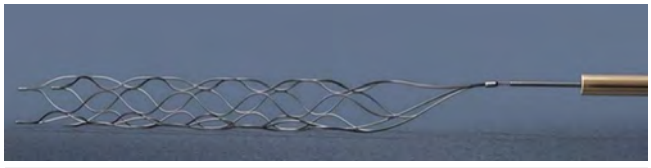
Stent Retriever Thrombectomy

In three RCTs from 2013, first-generation thrombectomy devices (MERCI retriever; Penumbra system; or IAT in the setting of EKOS or with a standard microcatheter) did not gain acceptance [44, 46, 47]. No superiority compared to IVT was demonstrated, although modern thrombectomy devices were also used in two of the three studies (e. g., Solitaire stent retriever; Covidien/now Medtronic, Dublin, Ireland), in small numbers (IMS III: 1.5 %; SYNTHESIS: 11 %).The Solitaire stent was originally designed for assisted coil occlusion of intracranial aneurysms (▶ **Fig. 9**).

Technical development was guided by experience in the use of the Neuroform stent (Stryker, Kalamazoo, MI, USA) and Enterprise stent (Cerenovus, Irvine, CA, USA) in aneurysm treatment. The Solitaire stent was designed to be retrievable after complete deployment, and its open cell design enables superior position correction compared to that with the Neuroform stent. For easier passage of the microcatheter through the stent into the aneurysm, the cells of the Solitaire were designed to be larger than those of the Enterprise stent. For more reliable coil retention in the aneurysm than that with the Neuroform stent, the stent structure was designed to be more stable. These properties ultimately determined the suitability of the Solitaire stent also for mechanical thrombectomy:

- The stent retriever needed to be retrievable at least into the guide or aspiration catheter.
- Sufficiently large cells were required to allow the thrombus to migrate into the deployed stent.

▶ **Fig. 8** Iriis Plus (Mindframe Inc., Irvine, CA, USA).



▶ **Fig. 9** Solitaire stent (developed at Dendron GmbH, Bochum, Germany; today Medtronic, Dublin, Ireland).

- A stable stent structure was required to “peel off” the thrombus adherent to the vessel wall.

The suitability of the Solitaire stent for foreign body and thrombus removal was discussed when this device was first described in 2003 [40]. Between 2002 and 2007, after the acquisition of Dendron by MTI/ev3, the Solitaire stent was not produced for internal company reasons. In 2008, small quantities of the stent were available with the CE mark still valid. Use of the Solitaire stent for thrombectomy was rumored to have been considered or attempted with unknown results. Subsequent investigations by Covidien (the new owner, later acquired by Medtronic) revealed that no stent retriever thrombectomy had been successful with a Solitaire stent before March 8, 2008. With the first technically and clinically successful stent retriever thrombectomy that day, all parties involved were aware that a long-awaited breakthrough had been achieved [41] (▶ **Fig. 10**).

▶ **Fig. 10** The first thrombus removed from a middle cerebral artery with a Solitaire stent.

In subsequent years, numerous other stent retrievers were developed to the stage of market readiness (e. g., Trevo, Concentric Medical, Mountain View, CA, USA; EmboTrap, Neuravi, Galway, Ireland) [48, 49]. In 2015, several RCTs and subsequent meta-analyses demonstrated significant superiority of stent retriever thrombectomy compared to IVT for acute ischemic stroke due to the occlusion of large intracranial vessels [42]. pRESET (phenox GmbH, Bochum, Germany) was the first stent retriever approved by the FDA on the basis of comparison with the Solitaire stent in a randomized controlled trial (ClinicalTrials.gov: NCT03994822) [50].

The successful use of the Solitaire stent in the first stent retriever thrombectomy was performed in an otherwise hopeless situation outside of the approval of this medical device at that time as compassionate use. A major aspect of the "discovery" of stent retriever thrombectomy was serendipitous. In specialized neurovascular centers, a rate of > 90 % sufficient recanalization with < 3 % complications is currently expected (2023). Despite this unprecedented technical success rate, poor clinical outcomes have been observed. Out-of-study and "all comers" treatment will each have one-third of patients receiving thrombectomy survive independently, with disability, or still die [43]. Closing the gap between the technical success of thrombectomy and the poor clinical outcomes will be the next challenge in stroke treatment. In a separate article, we will present new technical developments and concepts beyond stent retriever thrombectomy.

Conflict of Interest

HH is co-inventor of the Solitaire Stent and the pRESET stent retriever, co-founder and shareholder of phenox GmbH and Femtos GmbH. The other authors declare that they have no conclicts of interest regarding the content of this manuscript.

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