Reduction in Distal Emboli With Proximal Flow Control During Mechanical Thrombectomy
A Quantitative In Vitro Study
Ju-Yu Chueh, PhD; Anna Luisa Kühn, MD, PhD; Ajit S. Puri, MD; Scott D. Wilson, BS; Ajay K. Wakhloo, MD, PhD, FAHA; Matthew J. Gounis, PhD

Background and Purpose—To evaluate the impact of proximal flow control on efficacy and safety of mechanical thrombectomy in an in vitro middle cerebral artery occlusion.

Methods—Three independent variables, including clot type, device (Merci Retriever, Solitaire FR, and Trevo devices), and use of a balloon guide catheter, were used to ascertain the impact of proximal flow control on the size and number of distal emboli generated during thrombectomy. Secondary end points were the recanalization rate and amount of flow restored.

Results—Use of the balloon guide catheter during thrombectomy of the fragile, hard clot significantly reduced the formation of large distal emboli with a diameter >1 mm, regardless of the device used (P<0.01). Applying aspiration via the balloon guide catheter in place of the conventional guide catheter resulted in a significant increase of flow reversal (P<0.0001). Prior to thrombectomy, deployment of the stent-trievers produced immediate flow restoration through the soft and hard clot occlusions, 69.2±27.3 and 45.5±22.8 mL/min, respectively, that was preserved after the balloon inflation because of collateral flow via the posterior communication artery. After deployment but before thrombectomy, no flow was restored when using the Merci Retriever. After thrombectomy, complete flow restoration was achieved in a majority of cases. The Merci Retriever required more thrombectomy attempts to achieve hard clot removal compared with the stent-trievers when the conventional guide catheter was used (1.5 versus 1.1).

Conclusions—The risk of distal embolization was significantly reduced with the use of the balloon guide catheter. (Stroke. 2013;44:1396-1401.)

Key Words: acute ischemic stroke ▪ embolism ▪ experimental ▪ interventional treatment ▪ mechanical thrombectomy

Treatment of acute ischemic stroke with the administration of intravenous recombinant tissue plasminogen activator or intra-arterial endovascular mechanical thrombectomy aims to restore blood flow to the brain. Several clinical trials have shown that improvements in thrombectomy technology have subsequently produced increases in the recanalization rate. The results of the prospective, nonrandomized Multi-MERCI (Mechanical Embolus Removal in Cerebral Ischemia) trial concluded that primary recanalization was achieved in 57.3% patients treated with the Merci L5-Retriever compared with 45.5% with the older generation Merci X5/X6-Retriever (P=0.25). In 2009, the Penumbra Pivotal Stroke Trial investigators reported a recanalization rate of 81.6% with an aspiration system. The latest class of thrombectomy technology, the stent-trievers (Solitaire FR and Trevo), has shown recanalization rates approaching 90%. Despite great strides in the ability of the device to achieve recanalization, there may be an opportunity to improve good clinical outcome, defined as modified Rankin Scale ≤2 at 90-days, that is currently ≈40% of patients treated with intra-arterial endovascular thrombectomy. Besides vessel recanalization, many other parameters, including presence of distal emboli, site of vascular occlusion, baseline National Institutes of Health Stroke Scale, comorbidities, and time to recanalization, serve as potential predictive markers for neurological outcomes and mortality. Among them, clot fragmentation during treatment with subsequent distal shower of emboli is a procedure-related adverse event, which may be technically modified. In this study, we hypothesize that applying temporary proximal flow arrest along with aspiration during clot retrieval can minimize downstream emboli regardless of the clot type. These findings potentially

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can be translated into the clinical setting with improvement of postprocedural outcomes.

Materials and Methods

We used a model system previously reported\(^1\) to evaluate systematically the impact of proximal flow control with a Balloon Guide Catheter (BGC) during mechanical thrombectomy. Briefly, a vascular replica, which represented the geometry of human internal carotid artery (ICA), posterior communication artery, and middle cerebral artery (MCA), was constructed according to a small batch processing method described elsewhere (Figure 1A).\(^14\) The silicone replica was connected to a flow loop, which contained a peristaltic roller pump, Starling resistor chambers, and a data acquisition system (Dewetron, Charlestown, RI). A filter funnel was attached to the saline reservoir in an effort to reduce particle introduction into the system.\(^15\)

To mimic realistic human cerebrovascular hemodynamics, the flow of the filtered saline pumped out from the reservoir simulated the common carotid artery flow.\(^15\) The mock common carotid artery divided to mimic the external carotid artery and ICA, and the latter was connected to the silicone replica. Collateral flow derived from the external carotid artery joined distal to the MCA model to maintain a realistic pressure gradient. Flow sensors (Transonic Systems, Ithaca, NY) monitored the common carotid artery and MCA flow throughout the experiment. Negative flow values during aspiration indicate retrograde flow. Pressure transducers (Validyne Engineering, Northridge, CA) were used to record the proximal and distal MCA pressure (Figure 1B).

Two experimental clot models, hard and soft clots, were prepared to create the MCA occlusion. The hard, inelastic clot was generated by thrombin-induced clotting of bovine blood (2.5 National Institutes of Health Unit thrombin/mL blood) with addition of barium sulfate (1 g/10 mL blood). On the other hand, human blood was mixed with thrombin (2.5 National Institutes of Health Unit thrombin/mL blood) to form the soft, elastic clot.\(^16\) Clot with a diameter of 4.7 mm and a length of 1 cm was injected into the flow loop to create an MCA occlusion. During thrombectomy, saline that flowed through the vascular replica was collected in an empty container for particle analysis.

The Merci V-Series Retrievers (Concentric Medical, Mountain View, CA), and the Trevo (Concentric Medical) and Solitaire FR (eV3 Neurovascular, Irvine, CA) stent-treivers were used to achieve recanalization according to the instructions for use. In the Merci group, the Merci V2.0-soft Retriever was used as the primary recanalization tool (Table I in the online-only Data Supplement). If the occlusion persisted, Merci V2.0-firm, V2.5-soft, or V2.5-firm was used. Eight replicates were carried out for each experiment. The maximum number of thrombectomy attempts was limited to 3.

An 8F BGC (Concentric Medical) was placed proximal to the occlusion in the ICA and delivered the microcatheter that was navigated over the wire to the distal end of the occlusive clot. The guide wire was withdrawn followed by device delivery for thrombectomy. Before the retriever retraction, the balloon was inflated to arrest the clot and delivered the microcatheter that was navigated as described previously.\(^13\)

Clot fragments generated during thrombectomy and washed into the collection reservoir were analyzed. The visible clot fragments (>1 mm) were first separated from the collected sample by a 10-mL graduated pipette. The number and the Feret diameter, which is the longest dimension of the particle of the aforesaid fragments, were recorded. Characterization of the microemboli suspended in the collected sample was conducted by using the Coulter Principle (Multisizer4 Coulter Counter, Beckman-Coulter, Brea, CA).\(^13\) We selected apertures (400 μm and 2000 μm) that measure all particles with sizes ranging from 8 to 1200 μm. According to the measurable particle size ranges for the selected apertures, the results of particulate analysis were grouped into 3 categories based on fragment diameter: >1 mm, between 200 and 1000 μm, and <200 μm.

The primary endpoint was the risk of the embolic shower as indicated by the number of clot fragments and their size distribution. A secondary endpoint was the recanalization rate and the amount of flow restored.

Statistical Analysis

Data were presented as means±SD. Differences in size and number of distal emboli between experimental groups were further analyzed using 1-way ANOVA with Tukey analysis. Additionally, particles generated were summed for each size threshold, and the impact of BGC use was compared using a 2-sided Fisher exact analysis. Statistical significance was set at \(P<0.05\).

Results

Before clot introduction, common carotid artery, MCA, and posterior communication artery flow were 340±15.1, 131±2.7, and 11.4±2.7 mL/min, respectively. Mean pressure of the proximal MCA waveform was 73.7±5.2 mmHg. The pressure gradient between the proximal and distal MCA was 5.6±4.2 mmHg. A complete occlusion of the MCA was confirmed by both flow reduction acquired by the flow sensor and angiography (Figure 2).

Size and Number of Distal Emboli

There was a significant decrease in large clot fragments (>1 mm) with the BGC (\(P<0.01\)) for all devices and clot models tested. The majority of the visible emboli (>1 mm) was produced in the hard clot groups with the absence of the proximal flow control regardless of the device used (Figures 3A and 4A). The rate of forming clot fragments >1 mm from the hard clot model was reduced by 18-fold with the use of BGC (\(P<0.01\)). However, the BGC offered only 2-fold improvement in soft clot fragmentation >1 mm (Figures 3A and 4A). There were 1.8x more fragments in this range compared to Solitaire thrombectomy compared with use of the Trevo device; however, this difference was not significant (Figure I in the online-only Data Supplement).

In the medium range of fragments (200 to 1000 μm), the use of BGC significantly reduced the rate of distal
fragmentation of the hard clot model ($P<0.0001$). However, the BGC had little (Figure 3A) or no (Figure 4A) effect on soft clot fragmentation in this size range. The mean particle diameter was between 200 and 300 μm, and was not dependent on the device used or the BGC (Figures 3B and 4B).

There was a significant increase in the number of particles having a diameter between 8 and 200 μm generated during thrombectomy using the soft clot model ($P<0.0001$), regardless of BGC assistance or device used compared with that of the hard clot model (Figures 3C and 4C). The average particle diameter in this range was <10 μm in all groups (Figures 3D and 4D).
Recanalization Rate and Flow Restoration

The recanalization rate of the Trevo device was 100%. The Solitaire and Merci devices cleared the majority of the occlusions except one in each group (recanalization rate = 97%). In 1 out of 8 experiments with the Solitaire device in the hard clot model without BGC group, a clot fragment was retained in one of the MCA branches after 3 attempts of mechanical thrombectomy, resulting in a partial flow restoration (74.1%). Partial clot removal also occurred when the conventional guide catheter was used in 1 Merci experiment; however, the small residual hard clot did not obstruct any flow. The mean number of retrieval attempts in all groups was between 1 and 1.2 in each group. The Merci device was less efficient in hard clot removal compared with the Trevo and Solitaire devices (mean thrombectomy attempt: 1.5 versus 1.1).

Unlike the Merci device, use of Trevo or Solitaire FR devices was found to be effective for immediate MCA flow restoration (Figure 5A). There was a significant increase in partial flow restoration after use of the Trevo device or Solitaire device in the soft clot group compared with the hard clot group, 69.2±27.3 and 45.5±22.8 mL/min, respectively (P=0.0003). Similarly, a significant increase was noted when the standard guide catheter was used (66.3±28.9 mL/min) in place of the BGC (44.1±19.4 mL/min; P=0.007).

A mean flow rate of 48.1±10.4 mL/min was measured in the MCA after balloon occlusion in the cases treated with Trevo and Solitaire FR devices. There was no significant difference between the MCA flow before and after balloon inflation (44.1±19.4 versus 48.1±10.4 mL/min) when stent-trievers were used (P>0.05; Figure 5B). When the ICA flow was blocked by the balloon catheter, applying aspiration resulted in flow reversal in the MCA (−84.9±66.4 mL/min). On average, aspiration through the standard guide catheter caused mild MCA flow reversal (−33.2±47.7 mL/min; Figure 6).
Discussion

Mechanical thrombectomy with continuous aspiration and temporary proximal flow reversal by using BGC is technically feasible and effective in the prevention of hard clot fragmentation in a mock MCA occlusion model. These findings are consistent with the previous clinical experience in which inflation of the balloon on the BGC as a proximal protection is recommended for clearance of thromboembolic occlusions. Use of thrombectomy devices not only generates visible clot fragments but also thousands of microemboli. The underlying problem is that these microemboli may not be noticeable on angiographic imaging, however, their existence could be related to the poor clinical outcomes. So far, we are unable to precisely conclude the neurological consequences to which these significant numbers of disrupted clots could lead. However, based on the previous research, we have learned the following: (1) a presumable inverse relationship exists between the size and number of the disrupted clots required to create cerebral ischemia and infarction, (2) most distal protection devices for carotid stenting have a pore size between 100 and 200 µm, suggesting particles with size <100 to 200 µm are less likely to result in severe embolic stroke, and (3) other than the fibrinolytic system and hemodynamic forces, recanalization of cerebral microvascular occlusion could be achieved by embolus extravasation. As documented in a recent clinical report, among all the clot debris, a small fraction were larger fragments with size between 200 and 1600 µm. The number of these particles was significantly less than that of the small debris; however, they are thought to lead to significant cerebral occlusions. To better determine the tolerance of the brain to the emboli, clearly, more research is needed. At this juncture, our goal is to characterize shed emboli and find adjunctive devices and techniques to reduce clot fragmentation.

Results of previous studies have demonstrated that emboli retrieved from stroke patients are either soft and elastic or hard and aged clots containing denatured fibrin that is prone to fragment. To conduct a comprehensive assessment of the impact of BGC on recanalization rate and risk of embolic shower, both hard and soft clots were used to create the MCA occlusions for device evaluation. It was found that there was a significant reduction in generation of large clot fragments during the procedure under the protection of proximal flow control with the BGC. Flow data suggest that augmented flow reversal with aspiration through the BGC may be the primary mechanism by which the number of large distal emboli was reduced.

In the Merci thrombectomy experiments, use of the BGC moderately reduced the number of distal microemboli (<200 µm) that fragmented from the soft clot model. However, this observation was not repeated in the experiments with the stent-trievers. This is most likely attributable to immediate partial flow restoration, when the stent is used within the occlusive soft clot, and fluid shear forces carry small emboli downstream. The soft clot emboli in this size range had a mean diameter <10 µm.

Flow arrest is usually applied at the discretion of the interventionalist. Major concern of using BGC during the thrombectomy procedure includes patients’ tolerance to temporary flow arrest and addition of complexity and time required to place a BGC. The results of this study showed that in the cases with collateral flow through the posterior communication artery, partial MCA flow can be immediately re-established after the stent-triever is deployed and was not affected by inflation of the BGC. We were not aware of significant differences in time required to use an 8F BGC and a conventional guide catheter in the ICA; on the contrary, lower mean number of passes and a trend toward shorter mean procedure time were observed during hard clot removal with assistance of BGC (P<0.05).

Although the proposed occlusion model offered a reproducible testing environment and allowed us to manipulate one variable (proximal flow control) at a time, vascular response to mechanical thrombectomy cannot be studied in this experimental design. The absence of the abovementioned pathological processes, the use of new generation clot retrievers, and the selection of a single occlusion site (MCA occlusion) may be associated with the high-recanalization rate reported in this study.

Conclusions

Systematic evaluation of the BGC effects on the risk of embolic shower and MCA flow restoration was performed by using the Merci Retriever and 2 different stent-trievers. Proximal flow control reduced the number of thrombectomy attempts and increased the recanalization rate in the hard clot occlusions. Flow reversal was observed during aspiration when the balloon was inflated. The risk of distal embolization was reduced with the use of temporary flow arrest with a BGC.

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Disclosures

Dr Gounis has been a consultant per hour for Codman Neurovascular, Stryker Neurovascular, Surpass Inc, and Surpass Medical; and has received research support from the National Institutes of Health (NIH), Codman Neurovascular, Concentric Medical, Neurointerventional Therapeutics, Sanofi-aventis, Stryker Neurovascular, and Thrombolytic Science Inc. Dr Wakhloo is a board member of Surpass Medical and
consultant with Johnson & Johnson, Codman Neurovascular, and Stryker Neurovascular. Dr. Wakhloo has received grants and has grants pending with NIH and Philips Healthcare, respectively; has received payment for Lectures (including service on Speakers Bureaus) from the Harvard Medical School, Baptist Healthcare Miami; has held stock/stock options in Surpass Medical; and has met with travel/accommodations/meeting expenses unrelated to activities listed with NIH and Philips Healthcare, respectively; has received consultant with Johnson & Johnson, Codman Neurovascular, and Stryker Neurovascular, and Covidien et al. Dr. Wilson has been an employee of Concentric Medical. The other authors have no conflicts to report.

References

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SUPPLEMENTAL MATERIAL

Supplemental Tables

Table 1 Study design

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Supplemental Figures

Figure 1. Large particle fragmentation ≥200μm for each device. (SC – soft clot, HC – hard clot, CGC – conventional guide catheter, BGC – balloon guide catheter)