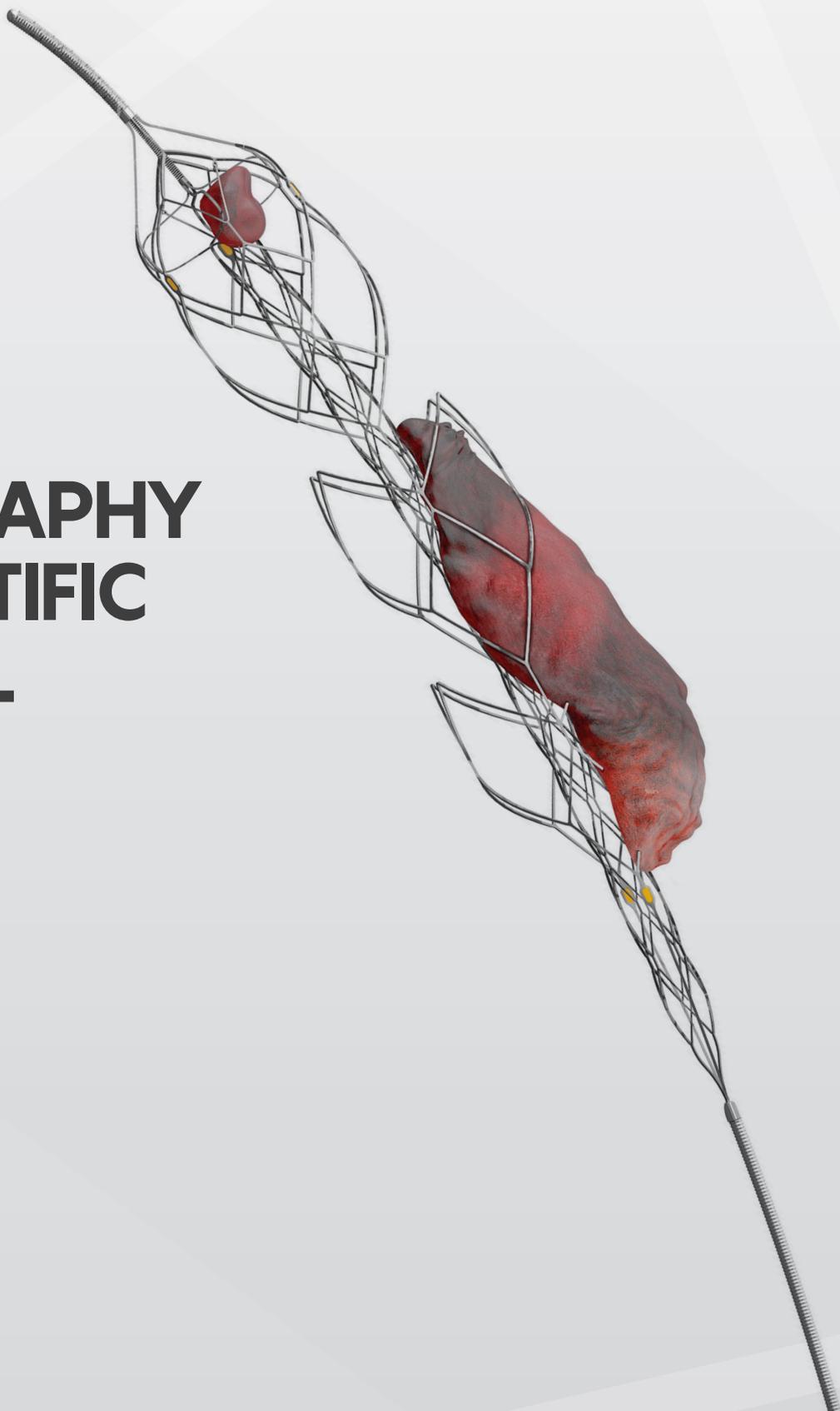


EMBOTRAP[®] II

revascularization device

BIBLIOGRAPHY OF SCIENTIFIC JOURNAL ARTICLES



CERENOVUS

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Neuravi Thromboembolic Initiative (NTI)

The following articles, presentations, and posters resulted from the NTI and collaborative work with academic institutions and stroke centres in chronological order.

- Johnson S, McCarthy R, Fahy B, Mereuta OM, Fitzgerald S, Gaudirc J, Remadi JP, Shotar E, Sourour NA, Doyle K, Gilvarry M, McGarry P, McHugh PE, Clarençon F. **Development of an in vitro model of calcified cerebral emboli in acute ischemic stroke for mechanical thrombectomy evaluation.** J Neurointerv Surg [Internet]. 2020; 0:1–6. Available from: <https://jn.is.bmj.com/content/early/2020/01/03/neurintsurg-2019-015595>

Calcified clots occur in 1–3% of all cases but are among the most difficult clots to recanalize. Ex-vivo human calcified material was mechanically characterized to generate realistic clot analogs, which are significantly stiffer than typical thrombi. Recanalization was attempted using an in-vitro closed loop vascular model and calcified analogues to test four different treatment strategies, up to a maximum of three passes (n=11 tests, n= 29 passes). The results showed that out of 29 passes, 25 passes (86%) failed. The most successful technique was a combination of BGC, IC and stent retriever (n=3 success, n=3 failed). Therefore, better modelling of difficult clots can be insightful for techniques evaluation and device development.

This is the first reported calcified clot analogue that accurately represents the behavior of calcified tissue. This model provides a valuable test platform for the evaluation of future purpose-designed devices and procedural techniques for this challenging situation.

- Johnson S, Chueh J, Gounis MJ, McCarthy R, McGarry JP, McHugh PE, Gilvarry M. **Mechanical behavior of in vitro blood clots and the implications of acute ischemic stroke treatment.** J Neurointerv Surg [Internet]. 2019; 0:1–6. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/31780453>

This novel study investigates how platelet-driven contraction affects the blood clot mechanical behavior and microstructure. A range of clots analogues with varying hematocrits were created in two groups: platelet rich and platelet poor. Overall, PCC (platelet-contracted clots) were found to be stiffer than NCC (non-contracted clots), more compacted in their microstructure, and more challenging to thrombectomy. This relationship was maintained across all hematocrits, but no significant differences were found in histology between PCC and NCC with the same hematocrit.

The paper presents an evolution of better modelling NTI clots to be even more realistic. The study allowed us to understand the impact of other blood components (platelets) on the clot mechanical behavior, showing that PCCs present a significantly greater challenge than NCCs. The study brings important insights to our previous research in understanding how clots behave.

- Bretzner M, Lopes R, McCarthy R, Corseaux D, Auger F, Gunning G, Beauval N, Bongiovanni A, Tardivel M, Cordonnier C, Pruvo JP, Susen S, Leclerc X, Kuchcinski G. **Texture parameters of R2* maps are correlated with iron concentration and red blood cells count in clot analogs: A 7-T micro-MRI study.** J Neuroradiology [Internet]. 2019. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/31726073>

This article investigated if the RBC component of clot composition can be predicted using 7-T MRI. Three clot types (n=12 total) were produced (RBC-poor, RBC-intermediate and RBC-rich) and 3D R2* maps were generated using well known MR sequences in a phantom. Each clot was then analyzed histologically for RBC content and using absorption spectrometry for iron concentration. The results showed a strong correlation between the R2* maps (first and second order parameters), RBC content and iron concentration. This gives important indicators that, using MRI, it is possible to accurately identify RBC rich clots.

A collaboration between NTI and Centre Hospitalier Universitaire de Lille that brings out a novel imaging marker for clot concentration prediction. The work presented is in line with current research attempting to predict clot before treatment to select treatment strategy in acute ischemic stroke.

- Duffy S, Weafer F, Alone A, Rainsford E, McCarthy R. **An in-vitro study to examine changes in clot properties from exposure to recombinant tissue plasminogen activator and predict possible implications for mechanical thrombectomy in stroke.** Oral abstract at 15th WFITN Congress (2019); Oct 21–24; Naples, Italy.

This study presents an in-vitro thrombolysis model to evaluate changes in the microstructure and mechanical properties of thrombi with different histology after fibrinolysis using rtPA. Six human clot analogues (n= 18 total) with varied RBC and fibrin composition were produced and placed in a silicon flow loop for two hours with circulating human plasma and rt-PA (0.9mg/kg). The results showed clots with increasing RBC content were correlated with greater degradation. By analyzing the SEM images, fibrin cleavage and disruption were found throughout the entire RBC-rich clots, but only at the face in contact with plasma for fibrin-rich clots. Furthermore, fibrinolysis of thrombi did not significantly alter their stiffness.

This study gives important insights of how rtPA can impact the mechanical properties and behaviour of clots. It is in-line with current clinical studies focused on possible implications of rtPA for mechanical thrombectomy in stroke.

- Bourcier R, Pautre R, Mirza M, Castets C, Darcourt J, Labreuche J, Detraz L, Desal H, Serfaty JM, Toquet C. **MRI Quantitative T2* Mapping to Predict Dominant Composition of In Vitro Thrombus**. AJNR Am J Neuroradiol. [Internet]. 2019; 40(1):59–64. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/30635330>

In order to predict clot composition before mechanical thrombectomy, MR techniques were utilized with in-vitro clots. Seven types of clot analogs (n = 35 total), with varying RBC concentrations were produced and analyzed using T2* mapping and confirmed histologically. The values of thrombus T2* relaxation time (TT2* RT) were higher for fibrin-dominant thrombi compared to RBC-dominant thrombi showing an inverse correlation with RBC content. Therefore, MR could be used reliably to quantify RBC content.

This study is a collaboration between NTI and Nantes University Hospital in France that provides an imaging biomarker of thrombus composition accessible in clinical routine. Analyzing the proportion of RBCs in thrombus may be insightful in selecting a treatment strategy for AIS.

- Duffy S, McCarthy R, Farrell M, Thomas S, Brennan P, Power S, O'Hare A, Morris L, Rainsford E, MacCarthy E, Thornton J, Gilvarry M. **Per-Pass Analysis of Thrombus Composition in Patients With Acute Ischemic Stroke Undergoing Mechanical Thrombectomy**. Stroke. 2019:1156–1163. doi:10.1161/strokeaha.118.023419

In this novel study, the thrombus composition of all fragments retrieved during thrombectomy of 60 consecutive AIS patients were histologically analyzed for each pass (total 138 passes). In the first 2 passes, the ratio of fibrin:RBC was 1:1, which significantly increased to 2:1 (ie, twice as much fibrin as RBCs) if completed in more than 2 passes. This remained consistent across all etiologies.

For the first time, thrombus histology was characterized per pass, unlike all other studies that combine thrombus material for the entire case. The insight that the ratio of fibrin:RBCs doubles after 2 passes is consistent with NTI research that suggests fibrin clots have inherent properties that could make them more difficult to retrieve. This method of analysis sets a new standard for understanding the challenges of thrombectomy and can offer greater insights into procedure progression than the combined “per-case” analysis.

- Weafer FM, Duffy S, Machado I, Gunning G, Mordasini P, Roche E, McHugh PE, Gilvarry M. **Characterization of strut indentation during mechanical thrombectomy in acute ischemic stroke clot analogs**. J Neurointerv Surg [Internet]. 2019; 0:1–7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/30661030>

Five ovine clot analogs ranging from fibrin rich to erythrocyte rich were used to investigate the impact of “embedding time”. A specialized fixture was created to simulate the indentation of a single strut of the EMBOTRAP device. All clots displayed viscoelastic behavior, where the indenter continued to creep into the clot over 5 minutes. Since the fibrin rich clots were twice as stiff, initial indentation was greater in the RBC-rich clots. However, SEM images revealed fibrin strands continued to stretch in fibrin-rich clots improving strut integration over time. In addition, micro-CT analysis showed EMBOTRAP’s open cell design may improve clot integration.

This article attempts to understand the mechanics that occur during the “embedding time” in mechanical thrombectomy. While all clots display a similar viscoelastic property, fibrin rich clots are stiffer, and may continue to embed into the device over 5 minutes, lending support to the idea of embedding time particularly in fibrin rich clots. This may be overcome by the EMBOTRAP’s unique design in allowing the clot to integrate into the device in the open gaps. However, the challenge to revascularize fibrin rich clots continues to be an area of research for NTI and an unmet need that CERENOVUS is committed to solve.

- Bourcier R, Alexandre PL, Eugène F, Delasalle-Guyomarch B, Guillon B, Kerleroux B, Saleme S, Marnat G, Boucemi S, Mirza M, Ferré JC, Papagiannaki C, Desal H. **Is bridging therapy still required in stroke due to carotid artery terminus occlusions?** J Neurointerv Surg [Internet]. 2017; 0:1–5.

To investigate the impact of IVT on internal carotid artery terminus occlusions (ICA-O), 141 consecutive ICA-O patients were split into two groups: MT alone [n=56] or bridging therapy (BT) [n=85]. The results showed no significant difference in the rate of recanalization success (mTICI 2b/3), distal emboli, average number of passes and clinical outcomes (mRS score ≤2) between the groups. However, patients that received BT had longer time from stroke onset to groin puncture. Therefore, IVT provided no apparent benefits to patients with ICA-O, but may delay care and increase the risk of symptomatic ICH.

This paper is a collaboration between NTI and Nantes University Hospital in France. It is the first to present results of MT with or without IVT in a large number of patients with very proximal occlusions. The results are aligned with recent studies investigated the need for IVT in MT.

- Gunning GM, McArdle K, Mirza M, Duffy S, Gilvarry M, Brouwer PA. **Clot friction variation with fibrin content; implications for resistance to thrombectomy.** J Neurointerv Surg [Internet]. 2017;372(1):1019–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28044009>

The purpose of this study was to characterize the friction properties of clots of various composition. The underlying hypothesis is that increased friction between the clot and the vessel or catheter wall may contribute to difficulty in removing the clot, which may account for recanalization challenges in some patients. In the study, it was found that clots with 20% or less RBC content had a significant increase in the coefficient of friction, which could make these clots more difficult to retrieve.

This article characterizes in detail one of the mechanical properties of clot – the coefficient of friction. By using analogs and bench testing, this study supports the hypothesis that fibrin content may be an underlying factor behind challenging occlusions. Challenging occlusions are an area of unmet need – and CERENOVUS is committed to understanding them and advancing technologies and techniques to aid in revascularizing these cases.

- Johnson S, Duffy S, Gunning G, Gilvarry M, McGarry JP, McHugh PE. **Review of Mechanical Testing and Modelling of Thrombus Material for Vascular Implant and Device Design.** Annals of Biomedical Engineering. 2017. p. 2494–508.

This article is a review of the literature on mechanical testing and modelling of thrombus. Some interesting points are: mechanical properties and characteristics of thrombi are strongly dependant on their structural and molecular origins, the fibrin network is a highly complex 3D structure with microstructural properties such as fibrin diameter / thickness, concentration, and branch point density, thrombus has been characterized as a viscoelastic material, thrombus testing is many times conducted on in-vitro clot analogs, constitutive and computational models have been created, but detailed models are lacking.

This article presents a review of mechanical testing in thrombus modelling. It is a foundational paper that presents the current state of knowledge and future topics important to modelling thrombi.

- Bourcier R, Lili D, Serfaty JM, Delasalle BG, Mirza M, Derraz I, Toulgoat F, Naggara O, Toquet C, Desal H. **MRI Interscanner Agreement of the Association between the Susceptibility Vessel Sign and Histologic Composition of Thrombi** J Neuroimaging. 2017; 27 (6):577–582. doi: 10.1111/jon.12464

Using MRI, the susceptibility vessel sign (SVS) has previously been related to red blood cell dominant thrombi, and may have implications to mechanical thrombectomy. In-vitro blood clots (produced by NTI) were created with a variation of composition, and assessed for SVS under 4 different MRI machines by nine radiologists and compared to their histological composition. While the study found that the SVS is a reliable and reproducible tool, with an excellent interobserver and intraobserver agreement, it's diagnostic accuracy varies significantly with the type of MRI scanner, and thus can have significant implications to multi-centre studies.

A collaboration between NTI and Nantes University Hospital in France that resulted in a novel publication looking at the variability of MRI scanners. A first step in creating algorithms to detect clot compositions using pre-interventional imaging.

- Chueh J-Y, Marosfoi MG, Brooks OW, King RM, Puri AS, Gounis MJ. **Novel Distal Emboli Protection Technology: The EMBOTRAP®.** Interv Neurol [Internet]. 2017;6(3–4):268–76. Available from: <https://www.wkarger.com/Article/FullText/480668>

Distal and new territory embolization is a known complication of mechanical thrombectomy, and in this study Dr. Gounis tested the hypothesis that this risk can be modified through choice of stentriever device. The study was done in UMass, using their open loop flow model and friable clots. The results of the study show that EMBOTRAP®II (5x21mm) yielded a statistically significant reduction in the generation ($p=0.0096$) and rate ($p=0.031$) of distal embolization of large fragments compared to the Solitaire control device, and a trend towards reduced new territory embolization of small clot fragments ($p=0.0656$).

An independent study by the lab in University of Massachusetts to investigate the ability of the EMBOTRAP® to retain fragments using in-vitro models. For large fragments greater than 1000um (ie, 1mm), the EMBOTRAP® released 15% fragments vs 55% for the Solitaire device. This significant difference may help to explain high mTICI 2c-3 and first-pass results of the EMBOTRAP® clinically.

- Meyer SF De, Andersson T, Baxter B, Bendzus M, Brouwer P, Brinjikji W, Campbell BC, Costalat V, Dávalos A, Demchuk A, Dippel D, Fiehler J, Fischer U, Gilvarry M, Gounis M, Gralla J, Jansen O, Jovin T, Kallmes D, Khatri P, Lees KR, López-Cancio E, Majoie C, Marquering H, Narata AP, Nogueira R, Ringleb P, Siddiqui A, Szikora I, Vale D, von Kummer R, Yoo AJ, Hacke W, Liebeskind DS. **Analyses of thrombi in acute ischemic stroke : A consensus statement on current knowledge and future directions.** *Int J Stroke.* 2017;12(6):606–14. doi: 10.1177/1747493017709671

The first Clot Summit was held in Heidelberg, Germany in 2015. This consensus statement was published in 2017 including 34 authors on behalf of the Clot Summit Group. The article presents 5 main topics: standardization of the terminology of clots, thrombus composition analysis, thrombus physical properties, imaging techniques to determine thrombus characteristics, and the use of in-vitro modelling to evaluate effectiveness of techniques. The current knowledge, and recommendations for future research are discussed.

Consensus statement of the first Clot Summit held in Heidelberg, Germany in 2015.

- Brinjikji W, Duffy S, Burrows A, Hacke W, Liebeskind D, Majoie CBLM, Dippel DWJ, Siddiqui AH, Khatri P, Baxter B, Nogueira R, Gounis M, Jovin T, Kallmes DF. **Correlation of imaging and histopathology of thrombi in acute ischemic stroke with etiology and outcome: a systematic review.** *J Neurointerv Surg.* 2017; 9 (6): 529–534. doi: 10.1136/neurintsurg-2016-012391

This systematic literature review and meta-analysis looks at imaging and histology of clots in stroke. No significant differences in clot composition were found based on clot etiology. Imaging indicates that hyper density is associated with a greater proportion of red blood cells. The article highlights the paucity of data on clots in stroke, and the need for further research on thrombi in stroke.

This is another foundational article, detailing what is known today and areas of research interest – and also underlining that this area of research is important in treating stroke patients.

- Yoo AJ, Andersson T. **Thrombectomy in Acute Ischemic Stroke : Challenges to Procedural Success.** *J Stroke.* 2017;19(2):121–30. doi: 10.5853/jos.2017.00752

With reperfusion (mTICI 2b–3) rates reaching up to 90%, a more useful endpoint in future trials will be near to near-complete reperfusion (mTICI 2c–3), which is approaching 50%. This article discusses procedural challenges to recanalize the remaining population and improve reperfusion success, including vascular access, thrombus–vessel interaction, and interaction with devices. CERENOVUS made significant contributions to the review of this article, including figures and videos.

A collaborative publication with NTI to discuss the clinical challenges to procedural success.

- Borggrefe J, Kottlors J, Mirza M, Neuhaus V-F, Abdullayev N, Maus V, Kabbasch C, Maintz D, Mpotsaris A. **Differentiation of Clot Composition Using Conventional and Dual-Energy Computed Tomography.** *Clin Neuroradiol* [Internet]. 2017; Available from: <http://link.springer.com/10.1007/s00062-017-0599-3>

There is an established association between red blood cell content and density on unenhanced CT of occluding clots in stroke. However, no marker for fibrin content is currently established. This article investigated the use of dual-energy CT to detect the fibrin content of clots. The fibrin clots were left in contrast solution for different times, and then imaged. It was shown that fibrin-rich clots absorb more contrast over time and increase measured density on CT scans. This has the potential to determine exact clot composition prior to treatment.

A collaboration between NTI and Köln University in Germany that resulted in a novel publication to investigate the detection of fibrin rich clots pre-interventionally. These types of publications represent the collaborative approach of NTI to continually build our knowledge and advance treatment in acute ischemic stroke.

- Narata AP, Filipiak I, Bibi R, Cottier PJ, Janot K. **Abstract TP35: Estimation of Red Blood Cells in the Thrombus Using MRI. A Phantom Study with Predetermined Thrombus Components.** *Stroke.* 2017;48(suppl_1):ATP35. doi:10.1161/str.48.suppl_1.tp35

The purpose of this work is to assess if MRI imaging can distinguish between clots of various composition, which could be used to provide information on clot composition prior to intervention. In this study, in vitro MRI imaging of five clot analogs with known composition was performed, along with histological analysis of the clot. The study showed that thrombus composition can be evaluated by standard MRI protocol.

This indicates there is potential for imaging to provide an indication of clot composition. Further research is needed to assess applicability in a clinical vs. research setting.

- Duffy S, Farrell M, McArdle K, Thornton J, Vale D, Rainsford E, Morris L, Liebeskind DS, MacCarthy E, Gilvarry M. **Novel methodology to replicate clot analogs with diverse composition in acute ischemic stroke.** J Neurointerv Surg [Internet]. 2016 Apr;1–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/27127231/>

The paper outlines a range of clot analogs developed by CERENOVUS through NTI to replicate the types of clots that cause stroke, for use in both device development and technique evaluations using in-vitro models. This publication is a comprehensive validation of the NTI clot analogues, through a comparison of their composition to clots retrieved from stroke patients.

This article helps to detail the scientific methodology that has gone into developing clots for in-vitro modeling. The compositional and histological assessments illustrate the significant range of clots. This is a foundational article as some centers are now working to more thoroughly analyze and understand clots that are retrieved from stroke patients. Through collaborations and the Clot Summit group, CERENOVUS is actively involved in these efforts and the search for correlations between procedural factors and clot characteristics.

- Gilvarry M, Vale D, **E-096 Role of In-Vitro Modeling in Addressing Challenging Occlusions**, Journal of NeuroInterventional Surgery Jul 2016, 8 (Suppl1) A93; DOI: 10.1136/neurintsurg-2016-012589.168

Clots retrieved from challenging stroke cases were used to reverse engineer clot analogs in order to simulate challenging clinical cases. Clots with higher fibrin content require a greater number of passes required to recanalize a vessel, due to their higher frictional properties. In Vitro modeling of challenging cases in this way may help in optimizing procedural techniques as well as designing improved devices.

Challenging occlusions are an area of unmet need — and CERENOVUS is committed to understanding them and advancing technologies and techniques in-vitro to aid in revascularizing these cases. Despite significant advances in endovascular therapy, approximately 25% of occlusions do not achieve TIC1 2b-3 reperfusion or require multiple passes.

- Brinjikji W, Duffy S, Kallmes D, **P-011 Imaging and Histopathology of Thrombi in Acute Ischemic Stroke: Systematic Review & Meta-analysis**, Journal of NeuroInterventional Surgery Jul 2016, 8 (Suppl 1) A33; DOI: 10.1136/neurintsurg-2016-012589.53
Poster presentation preceding JNIS publication referenced above

- L Bailey, M Gilvarry, M Holian, A Tzafiriri, J Stanley, E Edelman, **E-080 Preclinical Evaluation of Mechanical Thrombectomy Devices in a Swine Clot Model**, Bailey et al, Journal of NeuroInterventional Surgery Jul 2016, 8 (Suppl 1) A84; DOI: 10.1136/neurintsurg-2016-012589.152.

Poster primarily highlighting the ability to consistently model stroke in an animal model. The EMBOTRAP® device and a control device (commercially approved) were tested, demonstrating high rates of TIC1 2b-3 recanalization of both firm and soft clots with EMBOTRAP®.

- Andersson T, **E-033 Variety of clot types and their implication on technique during endovascular stroke therapy**, Andersson, Journal of NeuroInterventional Surgery Jul 2015, 7 (Suppl1) A57; DOI: 10.1136/neurintsurg-2015-011917.108

Karolinska case series combined with in vitro testing to assess impact of clot type on mechanical thrombectomy technique. Fresh, less organized clot may fragment, presenting an embolization risk. Fibrin-rich mature clot may not deform to enter an intermediate catheter, potentially causing retrieval difficulties. Based on case series predominately using flow arrest, good outcomes were achieved in 88% of cases where a balloon guide was used as compared to 61% overall. Data indicates stent-retriever with a balloon guide presents best opportunity for good outcomes.

Poster highlighting the clinical relevance of the NTI work on different clot types — and the implications for technique. The emphasis on achieving TIC1 2b-3 in as few passes as possible, while minimizing embolization and vessel trauma. Supports the importance of making the first pass count.

- Gilvarry M, ESOC-1167, 08. **Neurointervention – Clot Physical Behavior in Acute Ischemic Stroke — Implications of Clot-Device Interaction in Recanalization Therapy**, International Journal of Stroke, vol. 10, 2_suppl: pp. 1-76. First Published April 15, 2015; DOI: 10.1111/ijss.12478

The clots causing stroke vary significantly, and different characteristics have implications for stroke therapy. Friction testing of clot analogues demonstrates that as the percentage of fibrin to red blood cells increases, so does the coefficient of friction. Compression can further increase friction. Indentation testing suggests that the degree of embedding into a clot depends upon the clot structure.

This is one of the first podium presentations on the NTI work — overviewing the challenge when striving to retrieve a range of clots, and presenting mechanical properties of a variety of clots.

EMBOTRAP®

The following publications evaluate the EMBOTRAP® device clinically. Their order is based on the universal evidence-based medicine pyramid, and chronologically for the same level.

- Zaidat OO, Bozorgchami H, Ribó M, Saver JL, Mattle HP, Chapot R, Narata AP, Francois O, Jadhav AP, Grossberg JA, Riedel CH, Tomasello A, Clark WM, Nordmeyer H, Lin E, Nogueira RG, Yoo AJ, Jovin TG, Siddiqui AH, Bernard T, Claffey M, Andersson T. **Primary Results of the Multicenter ARISE II Study (Analysis of Revascularization in Ischemic Stroke With EMBOTRAP®)**. *Stroke*. 2018 May;49(5):1107-1115. doi: 10.1161/STROKEAHA.117.020125. Epub 2018 Apr 11.

First presented at the International Stroke Congress in LA, February 2018.

This was a single-arm, prospective, multicentre study comparing the EMBOTRAP® device to a performance goal using SWIFT (Solitaire) and TREVO-2 (Trepo) trials. Patients at 11 US and 8 European sites were eligible for inclusion if presenting with LVO and moderate to severe neurological deficit within 8 hours of symptom-onset. Between October 2015 and February 2017, 227 patients were enrolled and treated with the EMBOTRAP® device. The primary end point (mTICI 2b-3 within 3 passes) was achieved in 80.2%, and mTICI 2c-3 within 3 passes in 65%. At the end of all interventions, mTICI 2b-3 was achieved in 92.5%, and mTICI 2c-3 in 76%. The rate of first pass success (mTICI 2b-3 after a single pass) was 51.5%. Functional independence at 90 days (mRS 0-2) was 67%.

- Narata AP, Amelot A, Zaidat OO, Saver JL, Bozorgchami H, Mattle HP, Ribo M, Andersson T. **Benefit of M2 Thrombectomy in ARISE II (Analysis of Revascularization in Ischemic Stroke with EMBOTRAP)**. Oral communication and poster presented at International Stroke Conference 2020; 2020 Feb 19-21; Los Angeles, CA, USA.

This study is a sub-analysis of the ARISE II trial comparing M2 and M1 occlusions to characterize the outcomes of revascularization with EMBOTRAP in small vessels. Of 227 patients, 25% (n=57) had M2 occlusions, with 35.1% of them in the distal M2. The results showed that M2 occlusions had similar efficacy and safety to M1 occlusions. The recanalization rates for M2 and M1 groups are: final mTICI 2b-3 is 91.2% and 92.1%, first pass mTICI 2c-3 (FPE) is 38.6% and 38.1% and first pass mTICI 2b-3 (mFPE) is 49.1% and 51.6%, respectively. The functional independence at 90 days (mRS 0-2) is 70.2% for M2 and 69.7% for M1. There were no serious adverse device events (SADE) for both groups.

- Andersson T, Ribo M, Mattle HP, Ehm A, Crivera C, Cameron HL, Qadeer RA, Zaidat OO. **Procedural and Hospitalization-Related Economic Impact of First Pass Effect (FPE) in Endovascular Stroke Treatment with the EMBOTRAP II Device from the ARISE II Study – a European Economic Analysis**. Oral abstract at 15th WFITN Congress (2019); Oct 21-24; Naples, Italy.

In total four different oral abstracts (short-term and long-term, Europe and USA) were presented. Two at WFITN in 2019 by Andersson et al., and two at SNIS in 2019 by Zaidat et al.

This is the first analysis of its kind to assess the short and long-term economic impact of First Pass Effect (FPE). It is based on healthcare resource costs in six European countries (France, Germany, Italy, Spain, Sweden and UK) and US, using ARISE II data, in which EMBOTRAP device was used. The results were presented at the 15th WFITN Congress (2019) and 16th SNIS Annual Meeting (2019), showing the European and US analysis, respectively. The analysis showed that patients achieving FPE had a significantly shorter hospital length of stay and fewer days spent in the intensive care and standard beds, and required less devices compared to non-FPE ones. Also, patients with FPE achieved better functional outcomes and were associated with lower estimated costs for annual care, leading to potential per-patient cost-savings across all-countries.

- Mattle HP, Scarrott C, Claffey M, Thornton J, Macho J, Riedel C, Söderman M, Bonafé A, Piotin M, Newell J, Andersson T; **ARISE I Study Group. Analysis of revascularisation in ischaemic stroke with EMBOTRAP (ARISE I study) and meta-analysis of thrombectomy**. *Interv Neuroradiol*. 2018 Dec 18:1591019918817406. doi: 10.1177/1591019918817406.

The ARISE I study is an open label, single arm, multicentre (6 European centers), prospective observational study that enrolled 40 patients and was terminated in favour of ARISE II. In the 40 patients, successful reperfusion (mTICI 2b-3) was achieved in 85% of patients after all passes (75% after 3 passes), and compared better (though not statistically) to a meta-analysis of 8 RCTs in thrombectomy. Good clinical outcomes (mRS 0-2 in 90 days) were 64%, also non-significantly superior to the RCT meta-analysis. No patients had sICH, while only 2 patients died (mRS 6) in the entire cohort.

- Brouwer PA, Yeo LLL, Holmberg A, Andersson T, Kolloch J, KuntzeSöderqvist Å, Ohlsson M, Holmin S, Mpotsaris A, Gontu VK, Bhogal P, Soderman M. **Thrombectomy using the EMBOTRAP® device: core laboratory-assessed results in 201 consecutive patients in a real-world setting**. *J Neurointerv Surg* [Internet]. 2018; 10(10): 964-968. Available from: <http://jn.is.bmj.com/lookup/doi/10.1136/neurintsurg-2018-013765>

First presented at ABC-WIN in Val D'Isere, France, January 2017 for the first 166 patients.

Between October 2013 to March 2017, 201 consecutive patients treated with EMBOTRAP® were analysed in this publication. All images were core-lab validated, and clinical evaluations were performed by independent neurologists entered into a national registry. 7 different INRs at the Karolinska Institute with varying experience and techniques performed thrombectomy using EMBOTRAP®. There was no specific inclusion or exclusion criteria, and patients with carotid stenosis, intracranial disease, multiple occlusions, co-morbidities, etc were all included, as long as there was a possible benefit from treatment. mTICI 2b-3 was achieved in 84.6% with a median of 2 attempts, with 52.8% of the population achieving good functional outcome (mRS 0-2) at 3 months.

- Bourcier R, Abed D, Piotin M, Redjem H, Ferré JC, Eugène F, Raoult H, Mirza M, Chapot R, Desal H, Nordmeyer H. **Multicenter initial experience with the EMBOTRAP® device in acute anterior ischemic stroke.** *J Neuroradiol* [Internet]. 2018; 45(4):230-235. Available from: <https://doi.org/10.1016/j.neurad.2018.01.052>

First presented in SFNR, France, in March 2017

A multi-centre (3 in France, 1 in Germany) retrospective analysis of 80 consecutive patients treated with EMBOTRAP® from June 2015 to December 2016. Successful recanalization was achieved in 72 patients (90%). When considering the use of a second thrombectomy device as a failure (ie, all rescues were treated as failures), 65 patients (81%) were successfully recanalized, including 56% with mTICI 3. Furthermore, 50% complete (mTICI 3) recanalization was achieved within 1 or 2 passes. Good clinical outcome occurred in 49 patients (63%). Median procedure time (groin to recanalization) was 35 minutes. Safety metrics: distal embolization in previously unaffected territory, 5 patients (6%); vasospasms, 3 patients (4%); vessel perforations, 0 patients (0%); intracranial haemorrhage on CT at day 1, 17 patients (21%); subarachnoid haemorrhage, 0 patients (0%); sICH, 5 patients (6%).

- Valente I, Nappini S, Renieri L, Pedicelli A, Lozupone E, Colosimo C, Mangiafico S, Limbucci N. **Initial experience with the novel EMBOTRAP II clot-retrieving device for the treatment of ischaemic stroke.** *Interv Neuroradiol* [Internet]. 2019; 0 (00): 1-6. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/30714502>

This article reports the experience of two Italian centers using EMBOTRAP II in 29 patients with acute ischaemic stroke due to large vessel occlusions (LVO), with clinical follow-up. Successful reperfusion (mTICI 2b-3) was achieved in 76% of patients when treated only with EMBOTRAP, and 86% when all devices considered. The mean number of passes until achieving maximal reperfusion with EMBOTRAP II alone was 1.86 (SD±1.16). mTICI 2b-C in first-pass was obtained in 34% of the cases while first-pass mTICI 3 was achieved in 28% of the cases. Overall, 55% of the patients had a good clinical outcome (mRS 0-2 at 90 days). The authors considered EMBOTRAP II a safe and effective mechanical thrombectomy device with reperfusion rates comparable to that obtained with other stent retrievers.

- Söderman M, Brouwer PA, Andersson T, Thornton J, **ESOC-1262, 08. Neurointervention – EMBOTRAP® revascularization device: Initial experience in 49 patients from two European centers,** *International Journal of Stroke*, vol. 10, 2_suppl: p. 157. First Published April 15, 2015; DOI: 10.1111/ijss.12479

Karolinska and Beaumont case series of initial EMBOTRAP® cases, with clinical follow-up. EMBOTRAP® alone achieved 86% TICI 2b-3 reperfusion, while overall 93% of patients achieved TICI 2b-3. Of those revascularized with EMBOTRAP® alone, half of the cases were completed in one pass and 77% of those patients had a good clinical outcome. Overall 66% of the patients in had a good outcome (mRS 0-2 at 90 days).

- Kabbasch C, Mpotsaris A, Liebig T, Söderman M, Holtmannspötter M, Cronqvist M, Thornton J, Mendes Pereira V, Andersson T, **First-in-Man Procedural Experience with the Novel EMBOTRAP® Revascularization Device for the Treatment of Ischemic Stroke — A European Multicenter series,** *Clin Neuroradiol* 2016 Jun; 26(2): 221-8; DOI: 10.1007/s00062-014-0352-0

Case series of initial EMBOTRAP® cases from 5 centers involved in the first-in-human cases. Evaluation included all-comers treated based on the practice standards of each center. A procedural recanalization rate of 95% TICI 2b-3 was achieved, with a 73% rate for the EMBOTRAP®. Additional devices beyond EMBOTRAP® were used in 11 patients. Clinical follow up was not done as part of the study; however 90d clinical data was reported for a subset of patients.

This first-in-human experience is from the early EMBOTRAP® users using a variety of techniques. Some of the techniques used are less common practice today.

- Janot K, Zhu F, Kerleroux B, Boulouis G, Shotar E, Premat K, Eugene F, Dargazanli C, Chalumeau V, L'Allinec V, Benhassen W, Marnat G, Lebras A, Detraz L, Ognard J, Personnic T, Chivot C, Cappucci M, Forestier G, Soize S, Bourdain F, Consoli A, Labreuche J, Desal H, Lapergue B, Rouchaud A, Bourcier R. **Adaptive endovascular to the CloT MRI in large intracranial vessel occlusion" (VECTOR): Study protocol of a randomized control trial.** *J. Neuroradiology* [Internet]. 2019. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/31726072>

Recent studies suggest that positive susceptibility vessel sign (SVS+) in MRI is associated with RBC-rich clots. This is a methods paper of the VECTOR trial, which is a randomized control trial (RCT) designed to compare, in case of SVS+ occlusions, a first-line co-aspiration strategy with EMBOTRAP versus a contact aspiration alone. This is the first RCT that is using an imaging marker to determine the treatment technique to maximize the rate of early successful reperfusion. The hypothesis is that EMBOTRAP's unique design will help in the stabilization of friable clots and allow a more efficient retrieving of SVS+ clots in a lower number of passes.

Device Reviews and Case Series that included EMBOTRAP®

- Yeo LL, Andersson T, Holmberg Å, Mpotsaris A, Söderman M, Holmin S, Bhogal P, Cunli Y, Gopinathan A, Tan BY, Gontu V, Kolloch J, KuntzeSöderqvist Å, Brouwer PA, Cornelissen S. **Posterior communicating and anterior communicating arteries on pre-thrombectomy computed tomography scans are associated with good outcomes irrespective of leptomeningeal collateral status.** *Interv Neuroradiol.* 2019 Feb 25;1591019919831215. doi: 10.1177/1591019919831215

A novel study that looked at 147 consecutive cases with EMBOTRAP only to investigate the impact of collateral blood flow in the Circle of Willis on clinical outcome after thrombectomy.

- Yeo LLL, Cervo A, Gopinathan A, Cunli Y, Holmberg A, Söderman M, Holmin S, Bhogal P, Gontu V, Mpotsaris A, Andersson T, Cornelissen SA. **Very Late Leptomeningeal Collaterals-Potential New Way to Subdivide Modified Thrombolysis in Cerebral Ischemia (mTICI) 2B.** *Clin Neuroradiol.* 2018 Nov 26. doi: 10.1007/s00062-018-0747-4.

Using a series of 177 consecutive cases treated with EMBOTRAP, this interesting study investigates the influence of very late leptomeningeal collaterals (VLLC), namely that their presence is associated with mortality and poor clinical outcome, suggesting a radiological marker to subdivide mTICI 2b patients.

- Kaneko N, Komuro Y, Yokota H, Tateshima S. **Stent retrievers with segmented design improve the efficacy of thrombectomy in tortuous vessels.** *J Neurointerv Surg.* 2019 Feb;11(2):119-122. doi: 10.1136/neurintsurg-2018-014061. Epub 2018 Jul 24.

Bench-top evaluation of 4 devices (Versi, EMBOTRAP, Solitarie, and Trevo) in mild, moderate, and severe tortuous anatomies with 1 type of porcine-based clot model. Showed the segmented device (Versi and EMBOTRAP) resulted in higher success rates in tortuous models compared to conventional devices.

- Cornelissen SA, Andersson T, Holmberg A, Brouwer PA, Söderman M, Bhogal P, Yeo LLL. **Intracranial Stenting after Failure of Thrombectomy with the EMBOTRAP® Device.** *Clin Neuroradiol.* 2018 May 29. doi: 10.1007/s00062-018-0697-x.

From among the 201 consecutively treated patients with EMBOTRAP in this single center experience, 26 patients remain non-reperused, and 12 (46%) of them were treated with an intracranial stent after failed thrombectomy. A comparison of stented vs non-stented group revealed superior clinical outcomes (3-fold rate of mRS 0-2, no mortalities and no sICH) for the stented group.

- Yeo LLL, Holmberg A, Mpotsaris A, Söderman M, Holmin S, Kuntze Söderqvist A, Ohlsson M, Bhogal P, Gontu V, Andersson T, Brouwer PA. **Posterior Circulation Occlusions May Be Associated with Distal Emboli During Thrombectomy : Factors for Distal Embolization and a Review of the Literature.** *Clin Neuroradiol.* 2018 Mar 22. doi: 10.1007/s00062-018-0679-z.

From among 167 consecutively treated patients with EMBOTRAP®, the only independent predictor of distal emboli on multivariate analysis was having a posterior occlusion. This suggests a possible improvement in techniques in posterior occlusion may be warranted.

- Chartrain AG, Awad AJ, Mascitelli JR, Shoirah H, Oxley TJ, Feng R, et al. **Novel and emerging technologies for endovascular thrombectomy.** 2017;42(April):1-7.

In this review of emerging technologies for endovascular thrombectomy, the EMBOTRAP® is described in detail, and clinical evidence until the point of publication is presented

- Hameed A, Zafar H, Mylotte D, Sharif F. **Recent Trends in Clot Retrieval Devices: A Review.** *Cardiol Ther.* 2017;6(2):193-202. doi:10.1007/s40119-017-0098-2

In this review of new clot retrieval devices, a description of the EMBOTRAP® is provided, and a mention of the ongoing ARISE II clinical trial.

- **Maus V, Behme D, Kabbasch C, Borggreffe J, Tsochkas I, Nikoubashman O, et al. Maximizing First-Pass Complete Reperfusion with SAVE. Clin Neuroradiol [Internet]. 2017;**
Available from: <http://link.springer.com/10.1007/s00062-017-0566-z>

EMBOTRAP® used in 2 of the 32 cases (both TIC1 3)

- **Renú A, Laredo C, Lopez-Rueda A, Llull L, Tudela R, San-Roman L, et al. Vessel Wall Enhancement and Blood-Cerebrospinal Fluid Barrier Disruption after Mechanical Thrombectomy in Acute Ischemic Stroke. Stroke. 2017;**

Out of 60 cases, EMBOTRAP® was used in 9 cases.

Some common references on Clot Science and EMBOTRAP

The following is a list of the most commonly referred articles on Clot Science (NTI and others) and EMBOTRAP. This list is not complete nor extensive.

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- Liebeskind, D. S., Sanossian, N., Yong, W. H., Starkman, S., Tsang, M. P., Moya, A. L., ... Saver, J. L. (2011). CT and MRI early vessel signs reflect clot composition in acute stroke. *Stroke; a Journal of Cerebral Circulation*, 42(5), 1237–43. <https://doi.org/10.1161/STROKEAHA.110.605576>
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- Riedel, C. H., Jensen, U., Rohr, A., Tietke, M., Alfke, K., Ulmer, S., & Jansen, O. (2010). Assessment of thrombus in acute middle cerebral artery occlusion using thin-slice nonenhanced computed tomography reconstructions. *Stroke*, 41(8), 1659–1664. <https://doi.org/10.1161/STROKEAHA.110.580662>

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- Liebeskind, D. S., Sanossian, N., Yong, W. H., Starkman, S., Tsang, M. P., Moya, A. L., ... Saver, J. L. (2011). CT and MRI early vessel signs reflect clot composition in acute stroke. *Stroke; a Journal of Cerebral Circulation*, 42(5), 1237–43. <https://doi.org/10.1161/STROKEAHA.110.605576>

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