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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Stroke Newsletter" which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

1. Intravenous thrombolysis and endovascular thrombectomy are enhanced with mobile stroke care.
2. Acute ischemic stroke caused by basilar artery occlusion: endovascular therapy with or without intravenous alteplase.
3. A Comprehensive Mendelian Randomization Study on Cardiac Risk Factors for Stroke.
4. A case report on transcranial direct electrical stimulation for hand function in a stroke patient with significant upper limb paralysis due to blockage of the lenticulostriate artery.

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Intravenous thrombolysis and endovascular thrombectomy are enhanced with mobile stroke care

Stroke is a leading cause of disability and death in affluent countries. The approved treatment for ischemic stroke is thrombolysis with alteplase within the first hours of symptom onset to recanalize blocked arteries. However, implementing recanalising therapy within this tight therapeutic window is problematic. For the treatment of acute ischemic stroke, current guidelines advocate thrombolysis as soon as possible.[1] In 2003, Fassbender et al. proposed the notion of a mobile stroke unit (MSU), including regular ambulance equipment, a CT scanner, point-of-care laboratory equipment, telemedicine capabilities, and the ability to deliver tissue plasminogen activator as crucial components (tPA). Mobile stroke units (MSUs) are ambulances with a computed tomography (CT) scanner that can perform thrombolysis before the patient arrives at the hospital. Mobile stroke units reduce time to treatment, enhance prehospital triage, and raise thrombolysis rates.[2] Mobile stroke care has been demonstrated to speed up intravenous thrombolysis in multiple studies. There is conflicting evidence that MSU helps patients with major artery blockage undergo endovascular thrombectomy. Because most MSU research do not disclose clinical outcomes, the influence of mobile stroke on clinical outcomes is unknown.[3]

This study hypothesised that the MSU was linked to faster intravenous and intra-arterial thrombolysis times, and that this shorter treatment time would result in better long-term functional outcomes.

On weekdays, MSU operates for 8 hours and is dispatched with a separate emergency medical services (EMS) unit for all cases involving suspected stroke. The healthcare system provides a particularly qualified registered nurse (RN) and CT technologist, as well as a paramedic and emergency medical technician, to staff the MSU. Patients with signs and symptoms of a major artery blockage who have had their symptoms for less than 24 hours are taken to one of two regional comprehensive stroke centres. The MSU notified the interventional team ahead of time to allow for early planning for probable emergency treatment. After the dates of this analysis, CT angiography (CTA) was introduced on the MSU. A small percentage of patients (5%), which are not included in the data, were moved to out-of-network facilities.

The MSU was sent 1489 times (2.6 per day) during its 568 days of operation and transported 300 patients (20 percent of dispatches). 57 MSU patients received intravenous tissue plasminogen activator (tPA), and the average time from 911 call to tPA was 42.5 minutes (±9.2), while EMS transported 73 patients who received tPA in 99.4 minutes (±35.7) ($p<0.001$). Seven MSU patients (12%) received tPA between 3.5 and 4.5 hours after their last known well and would have been outside the window if they had received EMS care. Endovascular

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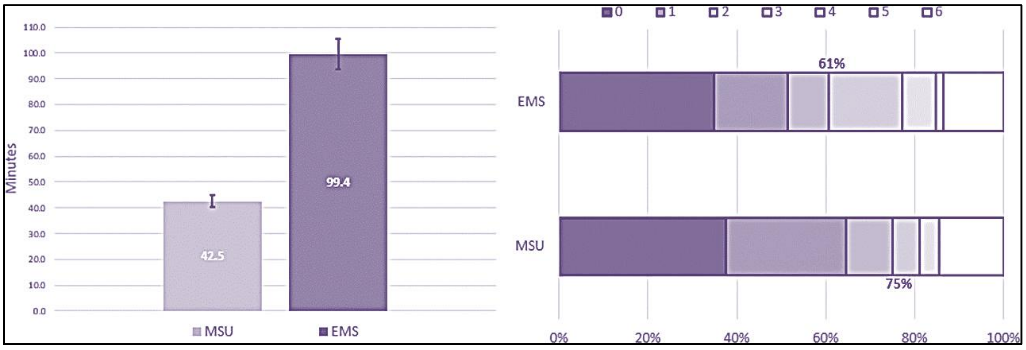
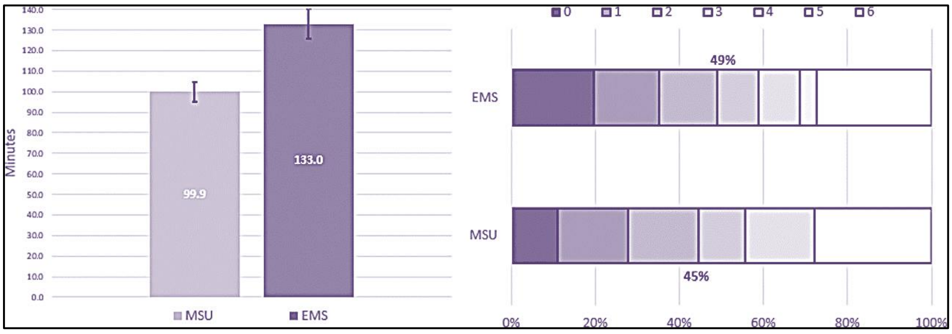
thrombectomy (ET) was done on 21 MSU patients with an average 911 call-to-groin puncture time of 99.9 minutes (±18.1), while EMS transported 54 patients for ET in 133.0 minutes (±37.0) (p=0.0002). In patients undergoing intravenous thrombolysis or endovascular thrombectomy, there was no difference in modified Rankin score between MSU and standard EMS at 90-day clinic followup, whether scored as a binary or ordinal variable.



Average time from emergency alert to tPA administration for patients triaged by mobile stroke unit versus traditional EMS services (p<0.0001, left).



Average time from emergency alert to groin access for patients triaged by mobile stroke unit vs traditional EMS services (p=0.0002, left).

In this single-institution retrospective investigation, individuals treated by MSU had considerably faster intravenous thrombolysis times than those treated by traditional EMS. The study further showed that, even without on-board CTA capacity, MSU care speeds up endovascular thrombectomy. MSU patients who received intravenous tPA had greater rates of functional independence at 3 months than those who were evacuated by EMS, albeit the differences were not statistically significant. Zhao H et al reported that, the Melbourne MSU significantly decreased time to reperfusion treatments, with the more potent impact of early EVT having the greatest projected disability avoidance. These data underscore the advantages of prehospital notification and direct triage to EVT centres, as well as the MSU's ability to streamline workflow upon arrival.[4] Lin E et al demonstrated the world's first 24-hour MSU, with IV- tissue plasminogen activator delivery rates and timeframes comparable to other MSUs, as well as quick triage and treatment of neurologic emergencies in the field, including status epilepticus. With the growing number of MSUs around the world, more data will be used to develop uniform protocols that EMS may use across the world.[5] The various geographies from which MSU and EMS patients came is a unique shortcoming of this study.

In conclusion, for both intravenous and intra-arterial thrombolysis, mobile stroke care was linked to faster call-to-tPA and call-to-groin times. Faster MSU treatment times result in better outcomes, according to emerging evidence from larger studies, as we witnessed in patients getting intravenous tPA.

Highlights: Mobile stroke units (MSUs) are ambulances with a computed tomography (CT) scanner that can perform thrombolysis before the patient arrives at the hospital. Mobile stroke units reduce time to treatment, enhance prehospital triage, and raise thrombolysis rates.

Reference:

1. Walter S, et al . Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. Lancet Neurol. 2012 May;11(5):397-404. doi: 10.1016/S1474-4422(12)70057-1. Epub 2012 Apr 11. Erratum in: Lancet Neurol. 2012 Jun;11(6):483.
2. Ebinger M, Siegerink B, Kunz A, Wendt M, Weber JE, Schwabauer E, Geisler F, Freitag E, Lange J, Behrens J, Erdur H. Association between dispatch of mobile stroke units and functional outcomes among patients with acute ischemic stroke in Berlin. JAMA. 2021 Feb 2;325(5):454-66.
3. Bender MT, Mattingly TK, Rahmani R, et alMobile stroke care expedites intravenous thrombolysis and endovascular thrombectomyStroke and Vascular Neurology 2021;svn-2021-001119.
4. Zhao H, Coote S, Easton D, Langenberg F, Stephenson M, Smith K, Bernard S, Cadilhac DA, Kim J, Bladin CF, Churilov L. Melbourne mobile stroke unit and reperfusion therapy: greater clinical impact of thrombectomy than thrombolysis. Stroke. 2020 Mar;51(3):922-30.
5. Lin E,Calderon V,Goins-Whitmore J, et al World's first 24/7 mobile stroke unit: initial 6-month experience at Mercy health in Toledo, Ohio. Front Neurol 2018;**9**:283.

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Acute ischemic stroke caused by basilar artery occlusion: Endovascular therapy with or without intravenous Alteplase

Many major and minor vessels in the posterior circulation are supplied by the vertebral and basilar arteries. Most of the strokes are caused by occlusions in the posterior circulation arteries. Clinical manifestations of occlusion of the basilar artery range from minor transitory symptoms to life-threatening strokes. Basilar artery occlusion, a rare condition found in 8% of patients with symptomatic vertebrobasilar area ischaemia and responsible for about 1% of all strokes.[1] Patients with acute ischemic stroke (AIS) with anterior-circulation large vessel occlusion (LVO) could benefit from intravenous thrombolysis (IVT) and endovascular therapy (EVT) up to 24 hours after the onset of the stroke, according to pivotal randomised controlled trials (RCTs).[2] Direct endovascular therapy (DEVT) was found to be non-inferior to bridging treatment within 4.5 hours of commencement in patients with AIS and an anterior-circulation LVO in recent RCTs. However, in individuals with posterior-circulation LVO, the effect of IVT first followed by EVT is unknown. The beginning of basilar artery occlusion (BAO) is minimal at first, and it progresses quickly. Patients with BAO can experience symptoms ranging from isolated cranial nerve palsies or hemiplegia to a locked-in condition or coma due to varying degrees of brainstem involvement.[3] The aim of this study was to evaluate the functional outcomes of EVT with and without intravenous thrombolysis (IVT) in patients who have had an AIS owing to BAO.

This was a prospective cohort study. This study included patients with AIS treated with EVT within 24 hours of stroke onset in RESCUE-RE and met the following criteria. Baseline information, process details, EVT procedure, perioperative treatment, and primary and secondary outcomes were all collected prospectively. On admission, the National Institutes of Health Stroke Scale (NIHSS) score was utilised to determine the severity of the stroke. Based on the occlusion site, BAO was categorised into distal, intermediate, and proximal BAO. Both the Basilar Artery on Computed Tomography Angiography (BATMAN) score and the Posterior Circulation Collateral Score were used to assess the posterior-circulation collateral condition (PC-CS). Functional independence after 90 days was the primary outcome of the study. The adjusted OR (aOR) from the multivariable logistic regression was used to evaluate all outcomes. A meta-analysis of all previously published crucial trials on functional independence after EVT in patients with BAO was also conducted.

Of the 310 patients with BAO who were included, 241 (78%) received direct EVT and 69 (22%) received IVT+EVT. Direct EVT was linked to a poorer functional result (aOR, 0.46 (95% CI 0.24 to 0.85), p=0.01). IVT+EVT was linked to a decreased percentage of patients who required three stent retrieval passes (10.14 percent vs 20.75 percent). A potential positive

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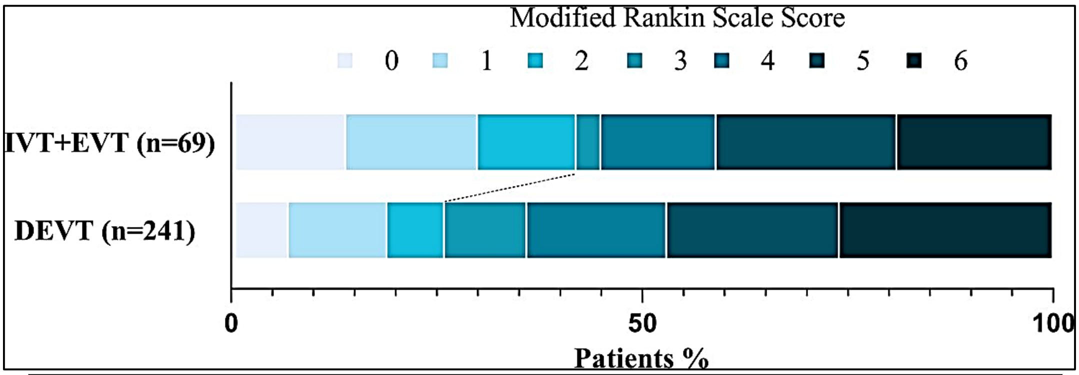
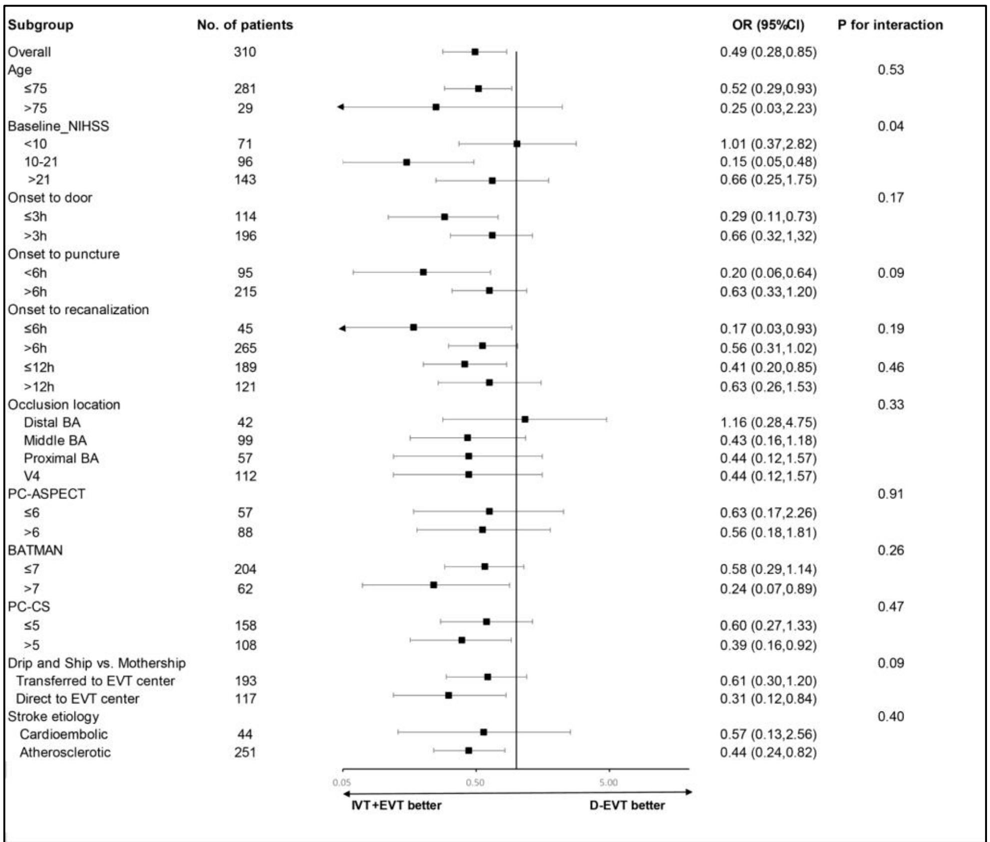
link between bridging with IVT first and functional independence was discovered in the meta-analysis regression (r=0.14 (95 percent CI 0.05 to 0.24), p<0.01).



At 90 days, the mRS score was distributed. DEVT stands for direct endovascular therapy; EVT stands for endovascular therapy; IVT stands for intravenous thrombolysis; and mRS stands for modified Rankin Scale.



Subgroup analysis. Forest plot showing the difference in the primary clinical outcome across all subgroups.

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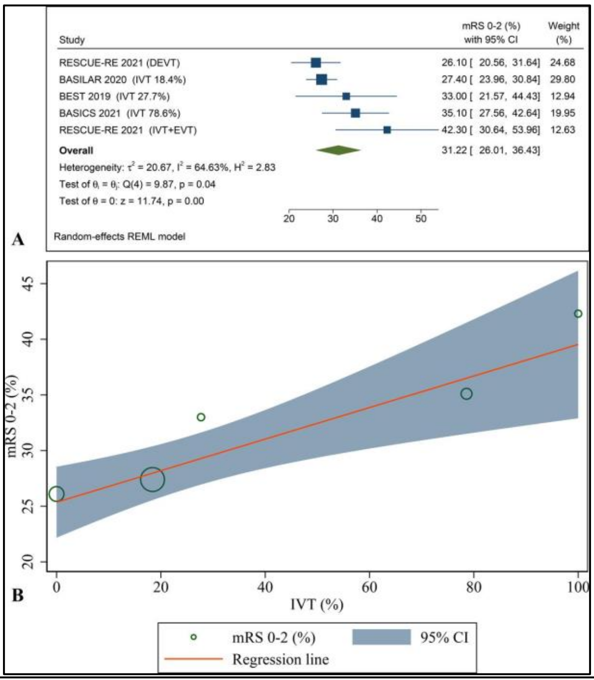

(A) Meta-analysis of each arm of RESCUE-RE and the EVT arms of pivotal EVT trials on BAO using the restricted maximum likelihood random-effects method. (B) Meta-analysis regression of IVT (%) in each arm of RESCUE-RE and the EVT arms of pivotal EVT trials on BAO on the functional independence using restricted maximum likelihood random-effects method.

Previous research on the effectiveness of EVT versus regular medical treatment in patients with AIS caused by BAO came up with mixed results. An original investigation revealed that EVT given within 24 hours of the predicted occlusion period is linked to better functional outcomes and lower death in patients with acute BAO.[4] Yang P et al demonstrated that within a 20% margin of error, endovascular thrombectomy alone was noninferior to endovascular thrombectomy preceded by intravenous alteplase administered within 4.5 hours after symptom onset in patients with acute ischemic stroke from large-vessel obstruction in terms of functional outcome.[5] This study found that combining EVT with IVT first (bridging) was associated with a better clinical outcome in patients with BAO treated within 24 hours of onset, as the first multicentre cohort study comparing the effectiveness and safety of IVT+EVT versus DEVT in patients with BAO treated within 24 hours of onset. Furthermore, a regression meta-analysis found a possible link between the proportion of patients receiving bridging treatment and greater functional independence in BAO patients. As a result, the research added to the body of evidence supporting the use of bridging treatment.[3]

Patients with BAO-AIS who were treated within 24 hours of onset with either bridging therapy or DEVT had a substantial difference in functional outcome. After correcting for relevant confounders, the data demonstrated that bridging therapy may result in better functional outcomes at 90 days than EVT alone, particularly in individuals with a low NIHSS score (10–21) at commencement. IVT may provide additional benefits in the beginning. A potential positive association between IVT first and functional independence was also discovered in the regression meta-analysis. Overall, the findings of this study suggested that bridging therapy could be beneficial for BAO and improved functional outcomes. To corroborate these findings, more RCTs are needed.

Highlights: combining EVT with IVT first (bridging) was associated with a better clinical outcome in patients with BAO treated within 24 hours of onset.

Reference:

1. Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. Lancet Neurol. 2011 Nov;10(11):1002-14.
2. Goyal M, Menon BK, van Zwam WH, *et al* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;**387**:1723–31.
3. Nie X, Wang D, Pu Y, *et al*Endovascular treatment with or without intravenous alteplase for acute ischaemic stroke due to basilar artery occlusion*Stroke and Vascular Neurology* 2021;svn-2021-001242
4. Zi W, Qiu Z, Wu D, Li F, Liu H, Liu W, Huang W, Shi Z, Bai Y, Liu Z, Wang L. Assessment of endovascular treatment for acute basilar artery occlusion via a nationwide prospective registry. JAMA neurology. 2020 May 1;77(5):561-73.
5. Yang P, et al; DIRECT-MT Investigators. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. N Engl J Med. 2020 May 21;382(21):1981-1993.

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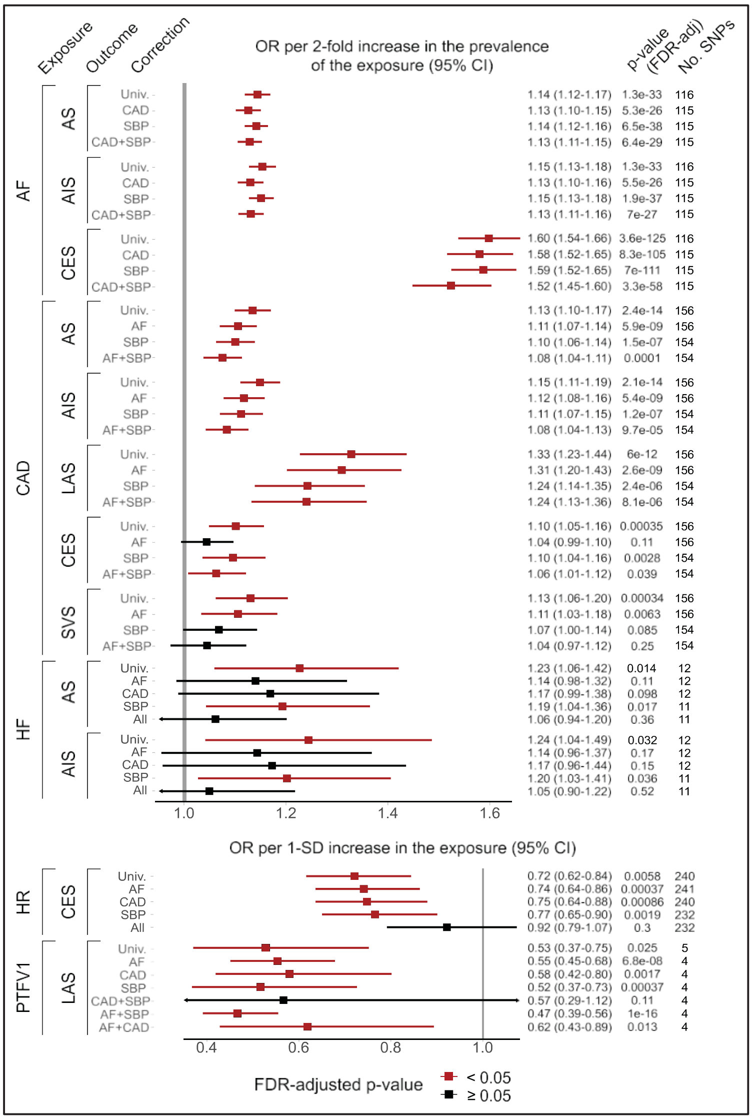
A Comprehensive Mendelian Randomization Study on Cardiac Risk Factors for Stroke

Although hypertension is the most significant risk factor for stroke, age and the presence of other risk factors can alter or intensify the effect of high blood pressure on stroke. At all blood pressure levels, impaired heart function, whether overt or occult, increases the risk of stroke. Coronary heart disease, cardiac failure, and especially atrial fibrillation are all linked to an elevated risk of stroke in hypertensive people.[1] There are many strategies for treating stroke caused by cardiac failure, however has certain limitations. Based on genetic data, Mendelian Randomization (MR) can help to elucidate probable causal relationships. MR, particularly multivariable, is less prone to bias than observational research because genetic variants are randomly assigned at conception. Recent genome-wide association studies (GWASs) covering a wide range of cardiac characteristics provide an opportunity to investigate causal associations with stroke in a comprehensive manner.[2] The aim of this study was to conduct a large-scale, systematic magnetic resonance imaging (MRI) assessment of cardiac characteristics and their impact on stroke and stroke subtypes.

In a 2-sample Mendelian Randomization technique, 66 cardiac features were studied, including cardiovascular illnesses, magnetic resonance imaging–derived cardiac imaging, echocardiographic imaging, and electrocardiographic measurements, as well as blood biomarkers. In data from the MEGASTROKE consortium (40585 cases/406111 controls), genetic predisposition to each attribute was investigated for relationships with stroke risk and stroke subtypes. Adjustment for putative pleiotropic or mediating effects linked to atrial fibrillation, coronary artery disease, and systolic blood pressure was done using multivariable Mendelian Randomization.

The results of sensitivity analyses were consistent. The study showed evidence for directional pleiotropy in 15 of 330 correlations in main analyses, and MR-PRESSO14 detected several outliers. The study found that when the main findings were adjusted for AF, CAD, and systolic blood pressure(SBP) in a multivariable MR, the correlations between heart failure (HF) and both any stroke (AS) and any ischemic stroke (AIS), as well as between heart rate (HR) and cardioembolic stroke (CES), was attenuated toward the null. P wave terminal force in lead V1 (PTFV1) had an inverse relationship with large artery stroke(LAS) that was independent of AF but nonsignificant after adjusting for CAD and SBP.



Multivariate associations between selected cardiac traits and stroke

An independent replication in the UKBiobank verified the links between AS and AIS and a genetic propensity to AF and CAD. The results of the study's studies in causative classification system defined stroke subtypes mostly validated our findings based on the TOAST classification, while also indicating links between genetic predisposition to AF and CAD and stroke from unknown causes.

The study found strong independent links between genetic predisposition to AF and CES, as well as CAD, a surrogate for systemic atherosclerosis, and LAS. The data-driven investigation of 64 additional genetically predicted cardiac features found links between HF and reduced HR and the risk of stroke. However, in multivariable MR, these associations were reduced, implying pleiotropic or mediating effects involving AF, CAD, and SBP. The MR investigation discovered evidence of possible inverse relationships between genetically predicted RHR and AF and cardioembolic stroke. Other CVD outcomes were not significantly linked with genetically predicted RHR, but weak relationships could not be ruled out.[3] Hopewell JC et al validated that Mendelian randomization studies for stroke has both strengths and limitations. MR establishes the causality, provides additional biological insights and can assess causality of novel risk factors. On the other hand, MR gives lack of suitable genetic variants that results in in weak instrument bias and linkage disequilibrium.[4]

In conclusion, beyond recognised clinical risk factors, available genetic data do not suggest significant impact of cardiac characteristics on the risk of stroke. Our findings underline the importance of thoroughly controlling for confounding and other potential biases in research looking at putative stroke risk factors.

Highlights: Mendelian Randomization is a method for determining causal relationships in observational data that can be compared to a randomised trial with genetic variants i.e., influencing a risk factor acting as a randomised treatment. If a genetic variant is connected with both the risk factor and the result of interest, then the risk factor is a cause of the outcome under certain circumstances.

Reference:

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991 Aug;22(8):983-8.
2. Frerich S, Malik R, Georgakis MK, Sinner MF, Kittner SJ, Mitchell BD, Dichgans M. Cardiac Risk Factors for Stroke: A Comprehensive Mendelian Randomization Study. Stroke. 2021 Dec 16:STROKEAHA121036306.
3. Larsson SC, Drca N, Mason AM, Burgess S. Resting heart rate and car-diovascular disease. Circ Genom Precis Med. 2019;12:e002459.
4. Hopewell JC et al. Emerging risk factors for stroke.2016 April 19:STROKEAHA.115.010646.

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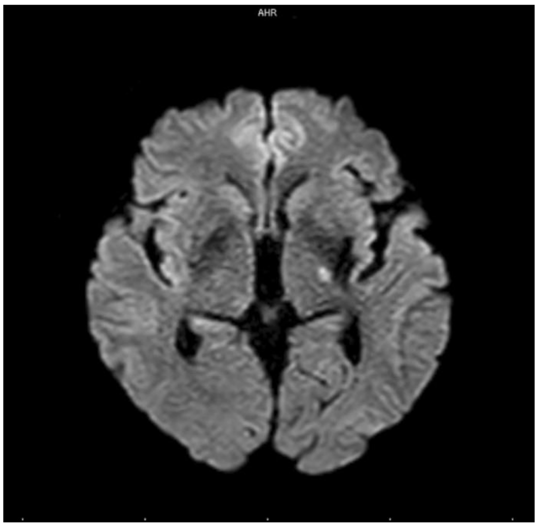
A case report on transcranial direct electrical stimulation for hand function in a stroke patient with significant upper limb paralysis due to blockage of the lenticulostriate artery

Stroke is a serious health disease that affects people all around the world. Stroke is the third leading cause of death and the leading cause of acquired adult disability in high-income countries. The well-known complication of stroke is motor impairment, [1] specifically, the Upper limb disability that affects 50–80% of people in the acute phase and 40–50% of people in the chronic phase.[2] Majority of stroke patients survive the initial injury, the most significant impact on patients is frequently in the form of long-term impairment, activity limitation, and diminished involvement that can affect quality of life by reducing activities of daily living.[1] As a result, there is a need for effective therapies for severe upper limb paralysis. A noninvasive brain stimulation technique known as transcranial direct current stimulation (tDCS) is gaining attention as a stroke therapy. A weak direct current (1–2 mA) is applied to a stroke patient's scalp via transcranial direct current stimulation (tDCS). It enhances function by reducing interhemispheric inhibition between the affected and unaffected hemispheres.[3]

The aim of this study was to report how transcranial direct current stimulation helped a patient with lenticulostriate artery blockage improve the function and frequency of use of his paralysed hand.

Due to lenticulostriate artery blockage, a man in his forties suffered a left internal hindfoot perforator branch infarction and severe right upper and lower limb paralysis. Multiple interventions for his paralysed hand, including robot therapy, had no discernible effect on his hand function or frequency of use in daily life. For six weeks, transcranial direct current stimulation was combined with upper limb functional activities for 20 minutes five times each week. As a result, the Fugl–Meyer Assessment (FMA) of the Upper Extremities' hand items improved, discomfort around the shoulder joint decreased. The paralysed hand's frequency of use and quality of movement were also improved.



A lesion of the left posterior limb of the internal capsule was identified as a left entropion perforator branch infarction on diffusion-weighted imaging of the head

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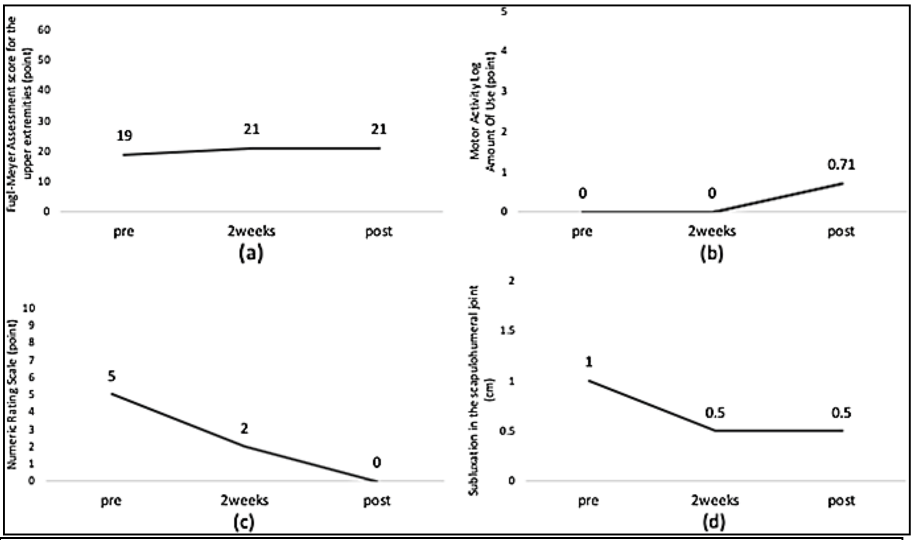

Changes in each upper extremity functional assessment

Transcranial direct current stimulation combined with upper limb functional training increased the function and frequency of use of a paralysed hand in a patient who had upper limb paralysis due to LSA blockage of the left medial hindfoot perforator branch.[3] Subthreshold depolarization is caused by anodal stimulation, which promotes neuronal excitement. Subthreshold polarisation is induced by cathodal stimulation, which inhibits neuronal activity.[4] Elsner B et al demonstrated that transcranial direct current stimulation, specially, cathode stimulation is the effective treatment regimen to improve the activities of daily living in people with stroke.[5] Morris et al. suggest using the ability to produce voluntary finger extension motions as a criterion for introducing task-oriented practise into constraint-induced movement therapy.[6]

In conclusion, the function and frequency of use of a paralysed hand were improved after a combined intervention employing tDCS and upper limb functional training, according to this case report. As a result, combining tDCS with the present approach of upper limb functional training to improve hand function in patients with severe upper limb paralysis could be an effective intervention strategy.

Highlights: During stroke rehabilitation, transcranial direct current stimulation is an effective adjuvant therapy. It stimulates the brain with a mild and continuous direct current that can either boost or reduce cortical excitability, with effects lasting up to several hours after stimulation.

References:

1. Langhorne P, et al. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009;8(8):741–54.
2. Hussain N, Alt Murphy M, Sunnerhagen KS. Upper Limb Kinematics in Stroke and Healthy Controls Using Target-to-Target Task in Virtual Reality. Front Neurol. 2018 May 9;9:300.
3. Hirayama, K., Fuchigami, T. & Morioka, S. Transcranial direct electrical stimulation for hand function in a stroke patient with severe upper limb paralysis due to lenticulostriate artery occlusion: a case report. *J Med Case Reports* **15,** 582 (2021).
4. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
5. Elsner, B., Kwakkel, G., Kugler, J. *et al.* Transcranial direct current stimulation (tDCS) for improving capacity in activities and arm function after stroke: a network meta-analysis of randomised controlled trials. *J NeuroEngineering Rehabil* **14,** 95 (2017).
6. Morris DM, Taub E, Mark VW. Constraint-induced movement therapy: characterizing the intervention protocol. Eura Medicophys. 2006;42(3):257–68.