Prehospital Detection of Large Vessel Occlusion Stroke With Electroencephalography: Results of the ELECTRA-STROKE Study

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ABSTRACT

Background and objectives

Endovascular thrombectomy (EVT) is standard treatment for anterior large vessel occlusion stroke (LVO-a stroke). Prehospital diagnosis of LVO-a stroke would reduce time-to-EVT by allowing direct transportation to an EVT-capable hospital. We aim to evaluate the diagnostic accuracy of dry electrode electroencephalography (EEG) for detection of LVO-a stroke in the prehospital setting.

Methods

ELECTRA-STROKE was an investigator-initiated, prospective, multi-center, diagnostic study, performed in the prehospital setting. Adult patients were eligible if they had suspected stroke (as assessed by the attending paramedic), and symptom onset <24 hours. A single dry electrode EEG recording (8 electrodes) was performed by the paramedic. Primary endpoint was the diagnostic accuracy of the theta/alpha frequency ratio for LVO-a stroke (intracranial ICA, A1, M1 or proximal M2 occlusion) among patients with EEG data of sufficient quality, expressed as the area under the receiver operating characteristic curve (AUC). Secondary endpoints were diagnostic accuracies of other EEG features quantifying frequency band power and the pairwise derived Brain Symmetry Index. Neuroimaging was assessed by a neuroradiologist blinded to EEG results.

Results

Between August 2020 and September 2022, 311 patients were included. Median EEG duration time was 151 (IQR 151-152) seconds. For 212/311 (68%) patients, EEG data were of sufficient quality for analysis. Median age was 74 (IQR 66-81) years, 90/212 (42%) were women, and median baseline NIHSS was 1 (IQR 0-4). Six (3%) patients had an LVO-a
stroke, 109/212 (51%) a non-LVO-a ischemic stroke, 32/212 (15%) a transient ischemic attack, 8/212 (4%) a hemorrhagic stroke, and 57/212 (27%) a stroke mimic. AUC for the theta/alpha ratio was 0.80 (95% CI 0.58-1.00). Of the secondary endpoints, the pairwise derived Brain Symmetry Index in the delta frequency band had highest diagnostic accuracy (AUC 0.91 [95% CI 0.73-1.00]; sensitivity 80% [95% CI 38%-96%]; specificity 93% [95% CI 88%-96%]; positive likelihood ratio 11.0 [95% CI 5.5-21.7]).

Discussion

The data from this study suggest that dry electrode EEG has potential to detect LVO-a stroke among patients with suspected stroke in the prehospital setting. Towards future implementation of EEG in prehospital stroke care, EEG data quality needs to be improved.

Trial registration

ClinicalTrials.gov identifier: NCT03699397.

Classification of Evidence

This study provides Class II evidence that prehospital dry electrode scalp EEG accurately detects LVO-a stroke among patients with suspected acute stroke.
INTRODUCTION

Endovascular thrombectomy (EVT) is standard treatment for patients with an anterior circulation large vessel occlusion stroke (LVO-a stroke).\(^1\) EVT must be initiated as soon as possible, as patient outcome after EVT is highly time-dependent.\(^2\)\(^-\)\(^4\) A large group of LVO-a stroke patients (45-83\%) is initially transported to a non-EVT capable primary stroke center, necessitating interhospital transfer to a comprehensive stroke center.\(^5\)\(^-\)\(^9\) On average, this so-called drip-and-ship workflow delays initiation of EVT by 39-114 minutes, and is associated with a 7.8-21.4\% lower chance of functional independence at 90 days.\(^5\)\(^,\)\(^7\)\(^-\)\(^9\)\(^,\)\(^11\)

A triage instrument that can quickly and reliably identify patients with an LVO-a stroke in the prehospital setting would allow direct transportation of these patients to a comprehensive stroke center, which could substantially shorten EVT treatment initiation times. Several methods for prehospital detection of LVO-a stroke currently exist, including clinical stroke scales and mobile stroke units.\(^12\)\(^-\)\(^18\) However, none of these methods have been implemented on a widespread scale and inadequate prehospital stroke triage remains an important issue in acute care organization. Electroencephalography (EEG) is a promising technique for prehospital stroke triage because it is highly sensitive to reduction of the cerebral blood flow almost immediately after onset.\(^19\)\(^-\)\(^23\) Previous studies have shown that EEG can discriminate between LVO-a stroke patients and other suspected stroke patients in an in-hospital setting\(^24\)\(^-\)\(^26\), but studies in the prehospital setting have not been performed. The primary aim of the ELECTRA-STROKE study was to determine the diagnostic accuracy of dry electrode EEG for LVO-a stroke detection in the prehospital setting, expressed as the area under the receiver operating characteristic curve of the theta/alpha ratio.
METHODS

Study design and population

ELECTRA-STROKE was a prospective, investigator-initiated, multicenter, diagnostic study, consisting of an in-hospital and a prehospital phase. Results of the in-hospital phase have been published previously. Here, we report the results of the prehospital phase.

The study was carried out by two ambulance services (Ambulance Amsterdam and Witte Kruis Ambulancezorg Alkmaar) and three receiving hospitals in the Dutch province of North Holland (Amsterdam UMC, OLVG Hospital and Noordwest Ziekenhuisgroep). Patient recruitment took place between August 2020 and September 2022.

We included adult patients with a clinically suspected stroke as judged by the ambulance paramedic and onset of symptoms or time last seen well less than 24 hours before start of the EEG recording. Patients with a wound or active infection of the scalp in the dry electrode cap placement area and patients with a (suspected) COVID-19 infection were excluded.

Standard protocol approvals, registrations, and patient consents

The study protocol (eSAP) was approved by the institutional review board of the Amsterdam University Medical Centers and by each participating hospital. The study protocol was published previously. The study was monitored by the Clinical Research Unit of the Amsterdam University Medical Centers. Because of the emergency setting of the study, we used a deferred informed consent procedure in line with national legislation and with approval of the institutional review board. Written informed consent was obtained from all patients or their legal representatives after EEG acquisition.
Study procedures

A single EEG recording was performed using a dry electrode EEG cap with eight electrodes covering the vascular territory of the middle cerebral artery (FC3, FC4, CP3, CP4, FT7, FT8, TP7 and TP8; Waveguard touch, Eemagine, Berlin, Germany) and a compatible EEG amplifier (eego amplifier EE-411, Eemagine, Berlin, Germany). EEG data were acquired at a sample frequency of 500 Hz using clinical EEG software (NeuroCenter EEG, Clinical Science Systems, Leiden, The Netherlands). EEG recordings were performed in the prehospital setting by ambulance paramedics who attended a 1-hour training in performing dry electrode EEG recordings for the purpose of this study. A portable and lightweight bag was used to store all equipment required for the EEG recording (Figure 1). In December 2020 (Witte Kruis Ambulancezorg Alkmaar) and February 2021 (Ambulance Amsterdam) we adapted the acquisition software to provide visual feedback on the electrode-skin impedances to guide optimization of the electrode-skin contact. We time-limited both the impedance optimization step (1.5 minutes) and the EEG recording step (2.5-3.0 minutes) to minimize delay in the prehospital workflow. As of January 2021, we collected information on the length of the hair of the patients in whom an EEG recording was performed by ambulance paramedics of Witte Kruis Ambulancezorg Alkmaar.

Routine stroke work-up included a non-contrast computed tomography (CT) and, if indicated, CT angiography and CT perfusion were performed in the receiving hospital.

Definitions and outcomes

The primary endpoint of the study was the diagnostic accuracy of dry electrode EEG to discriminate LVO-a stroke from all other strokes and stroke mimics, expressed as the area under the ROC curve (AUC), of the theta/alpha ratio. The theta/alpha ratio was defined as:

\[ TAR = \frac{P(\theta) - P(\alpha)}{P(\theta) + P(\alpha)} \]  

(1)
with $P(\theta)$ the power in the theta frequency band (4-8 Hz) and $P(\alpha)$ the power in the alpha frequency band (8-13 Hz). The theta/alpha ratio was chosen as this EEG feature had highest diagnostic accuracy for LVO-a stroke detection in the first 100 patients included in the hospital phase of the study.$^{26}$ Besides the AUC, sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratio were determined.

Secondary endpoints, which should be considered exploratory only, were: the diagnostic accuracies of the relative delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-18 Hz) power, the normalized delta/alpha ratio, the normalized (delta+theta)/(alpha+beta) ratio, and the pairwise derived Brain Symmetry Index, and the logistical and technical feasibility of paramedics performing an EEG recording with a dry electrode cap in the prehospital setting in patients with a suspected stroke. Definitions of the EEG features are included in the eAppendix 1. We quantified the logistical and technical feasibility by calculating the percentage of patients with EEG data of sufficient quality for analysis, and the percentage of clean EEG data per patient. To account for learning effects and hard- and software improvements, we compared the percentage of clean EEG data of the first 50 EEG recordings to the percentage of clean EEG data of the last 50 EEG recordings performed in the study. The principal safety outcome was the occurrence of device-related adverse events.

We defined an LVO-a stroke as an occlusion of the intracranial part of the internal carotid artery, the first or proximal second segment of the middle cerebral artery (M1 and proximal M2, respectively), or the first segment of the anterior cerebral artery (A1). The occlusion location was determined by an adjudication committee - consisting of a neuroradiologist (MK) and a stroke neurologist (JC) - based on CT angiography data. The adjudication committee was blinded for EEG results. In case a patient was not clinically suspected of having an LVO-a stroke and therefore did not undergo CT angiography, the patient was scored as not having an LVO-a stroke.
Data analysis

EEG data were re-referenced to a 12-channel bipolar montage with 6 bipolar channels located at each hemisphere and bandpass filtered between 0.5 and 35 Hz using a 3th order Butterworth filter. Artifacts were detected and rejected per 2-second bipolar channel segment using an automatic Convolutional Neural Network algorithm specifically developed for detection of artifacts in dry electrode EEG data (Van Stigt et al., submitted). The pairwise derived Brain Symmetry Index was calculated using EEG channels located on both hemispheres. All other EEG features were calculated per hemisphere. For patients with a stroke, we kept the ipsilesional EEG features, and for patients with a stroke mimic, we averaged the EEG features over both hemispheres (if available). Further details are provided in the eMethods.

Statistical analysis

The sample size was calculated based on an expected specificity of dry electrode EEG for LVO-a stroke of 70%. At the start of the study, the sample size was set at 222, based on an expected incidence of LVO-a stroke of 7% and a dropout rate of 20%. An interim analysis, based on 137 suspected stroke patients in whom a dry electrode EEG recording was performed in the prehospital setting, showed an actual incidence of LVO-a stroke of 5% and a dropout rate of 58%. Patients were considered a dropout if EEG data were of insufficient quality, time of symptom onset was more than 24 hours before the start of the EEG recording, or no informed consent was provided. A revised incidence of LVO-a stroke of 5%, an alpha of 0.05 and a maximum margin of error of 7% indicated that 174 patients with a suspected were required. As EEG data quality improved over time, we assumed a dropout rate of
55% when recalculating the sample size. Considering this dropout rate, our revised estimation resulted in a sample size of 386 patients with a suspected stroke.

The diagnostic accuracies of all features were evaluated by calculating areas under the ROC-curves. Two cutoff values were determined as the highest sensitivity at a specificity of \( \geq 70\% \) and \( \geq 80\% \) for LVO-a stroke, respectively. The latter is defined as optimal cutoff. For both cutoff values, the sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratio are reported with 95% confidence intervals. The 95% confidence intervals were estimated using the method of Hanley and McNeil\(^{30} \) for the AUC, the Wilson interval\(^{31} \) for the sensitivity, specificity, positive predictive value, and negative predictive value, and the method of Simel et al.\(^{32} \) for the positive likelihood ratio.

Baseline characteristics and EEG feature values of patients with an LVO-a stroke and those without an LVO-a stroke were compared using the independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and chi-square test (if any of the cells had expected count \( \geq 5 \)) or Fisher’s exact test (if any of the cells had expected count <5) for categorical variables. Percentages of clean EEG data of the first and last 50 EEG recordings were compared using the Mann-Whitney U test. A P-value \( \leq 0.05 \) was considered statistically significant.

Data were analyzed with Python (Python Software Foundation, Wilmington, Delaware, United States; version 3.8).

**Data availability**

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data, even in coded form.
RESULTS

Ambulance paramedics performed a dry electrode EEG recording in 386 patients, of whom 75/386 (19%) were subsequently excluded because no informed consent could be obtained (n=65), symptom onset >24 hours (n=9), or absence of symptoms during EEG recording (n=1; Figure 2). Of the 311 patients included in the study, 99 (32%) were excluded from analysis because of insufficient quality of the EEG data (n=94) or the absence of EEG data due to technical failure (n=5). The median (IQR) percentage of clean EEG data over all patients was 14% (4%-39%). Data quality improved over time (median [IQR] percentage of clean EEG data of the first 50 EEG recordings vs. the last 50 EEG recordings: 11% [9%-12%] vs. 26% [25%-27%], P<0.001). A comparison of baseline characteristics between patients included and excluded in the analysis are reported in Table 1. Excluded patients were more often female (59% vs. 42%, P=0.01) and more often had an LVO-a stroke (9% vs. 3%, P=0.02). Patients who were excluded from analysis also more often had long hair (32% vs. 15%, P=0.07).

Of the 212 patients included in data analysis, 6 (3%) had an LVO-a stroke, 109 (51%) a non-LVO-a ischemic stroke, 32 (15%) a TIA, 8 (4%) a hemorrhagic stroke, and 57 (27%) a stroke mimic. Patients with an LVO-a stroke had a higher median NIHSS (15 vs. 1, P<0.001), more often received IVT and EVT (67% vs. 16%, P=0.008 and 83% vs. 2%, P<0.001, respectively) and had lower onset- to-EEG time (median: 46 vs. 139 minutes, P=0.05) (Table 2). EEG recordings were performed before initiation of any reperfusion therapy in all patients. No device-related adverse events were reported.

For the frequency band powers and pairwise derived Brain Symmetry Index, 194 (6 LVO-a stroke) and 183 (5 LVO-a stroke) patients were available for analysis, respectively. The AUC of the theta/alpha ratio was 0.80 (95% CI: 0.58-1.00; Table 3; Figure 3A). At optimal cutoff, we found a sensitivity of 50% (95% CI: 19%-81%), a specificity of 83%
(95% CI: 77%-88%), a positive predictive value of 9% (95% CI: 3%-22%), and a negative predictive value of 98% (95% CI: 95%-99%; Figure 3C). Of the secondary endpoints, the pairwise derived Brain Symmetry Index in the delta frequency band had highest diagnostic accuracy for LVO-a stroke detection with an AUC of 0.91 (95% CI: 0.73-1.00), and, at optimal cutoff, a sensitivity of 80% (95% CI: 38%-96%) and specificity of 93% (95% CI: 88%-96%) (Figure 3B and 3D). The diagnostic measures of all EEG features at maximum sensitivity at a specificity of ≥70% are reported in eTable 1. The EEG feature values for patients with an LVO-a stroke and patients without an LVO-a stroke are reported in eTable 2.

This study provides Class II evidence that prehospital dry electrode scalp EEG accurately detects LVO-a stroke among patients with suspected acute stroke.
DISCUSSION

In this prehospital study, dry electrode EEG detected LVO-a stroke with a high diagnostic accuracy in a population of suspected stroke patients. However, EEG data were of insufficient quality for analysis in around one third of patients.

In ELECTRA-STROKE, an ambulatory LVO-a stroke detection device was tested by ambulance paramedics in the prehospital setting. In line with other prehospital stroke trials, we demonstrate that successful conduct of a prehospital stroke study is feasible, but has its challenges. Consistent with the MR ASAP trial, obtaining written deferred consent proved to be more challenging in a prehospital setting than in stroke trials that ran in an in-hospital setting, such as the MR CLEAN NO-IV trial. Lack of written consent led to exclusion of 17% of the patients. Still, without a deferred informed consent procedure, performing the study would have been logistically more challenging and could have resulted in substantial treatment delays.

Prehospital detection of patients with an LVO-a stroke would enable direct transport of these patients to a comprehensive stroke center while still allowing other suspected stroke patients to be transported to the closest primary stroke center. Data from nonrandomized studies suggest that this workflow can lead to shorter EVT treatment initiation times and better clinical outcomes for patients with an LVO-a stroke. In contrast, the RACECAT trial – performed in a nonurban area with relatively long initial transport times – did not find a difference in clinical outcome in suspected LVO stroke patients between a mothership and drip-and-ship model. This discrepancy between studies may be attributed to geographic differences and emphasize the need for regional solutions to optimize stroke care.

Recent in-hospital studies have demonstrated the potential of EEG for LVO-a stroke detection. In the first 100 patients enrolled in the in-hospital phase of the ELECTRA-STROKE study, the diagnostic accuracies of the frequency band powers were comparable
with the current study, with the theta/alpha ratio as the best performing EEG feature (AUC=0.83).\textsuperscript{26} The pairwise derived Brain Symmetry Index, however, did not have a good diagnostic accuracy in that study (AUC=0.38), while in the current study this EEG feature showed the best performance (AUC=0.91). This disparity may be due to a difference in EEG data quality, as the pairwise derived Brain Symmetry Index is known to be highly susceptible to artifacts and the current study included an improved, more sensitive, artifact detection algorithm than the in-hospital study. Erani et al. (2020) performed dry electrode EEG recordings in 100 suspected stroke patients and found moderately high diagnostic accuracy of EEG for LVO-a stroke detection (AUC=0.69) when using a combination of the ipsilesional relative theta and alpha power.\textsuperscript{24} We assume the diagnostic accuracy is lower compared to our study, because none of the utilized EEG features contained information on both hemispheres - as is the case for the pairwise derived Brain Symmetry Index - and the diagnostic accuracy was validated on unseen data. In our study we did not validate results in unseen data, which may have led to an overestimation of the diagnostic accuracy. Sergot et al. (2021) investigated LVO detection by means of a portable wet-electrode EEG and somatosensory-evoked potentials device.\textsuperscript{25} They used data of 109 suspected stroke patients and found a sensitivity and specificity for LVO stroke of both 80%.

The value of using prehospital stroke scales, especially the RACE, G-FAST, and ACT-FAST, for LVO-a stroke detection has recently been demonstrated.\textsuperscript{15,37} The best performing scale, the RACE, reached an AUC of 0.83 in a group of 1039 suspected stroke patients. While clinical scales have the potential to be easily implemented in the prehospital setting and can be applied to most patients, assessment remains subjective. An important aspect of progress may lie in combining EEG with clinical scales in future studies. The improvement of diagnostic accuracy for LVO-a stroke detection when combining EEG and clinical data has been shown by Erani et al. (2020).\textsuperscript{24} Unfortunately, both the RACE and G-
FAST scales are not routinely used by paramedics in the regions where ELECTRA-STROKE was performed, thus we could not study the value of combining both techniques in the current study.

Our study has several limitations. First, EEG data quality was insufficient in approximately one third of patients. The fact that ambulance paramedics had to perform the measurement in a limited timeframe and while under pressure of transporting a suspected stroke patient as quickly as possible undoubtedly contributed to this. Future innovations in EEG hard- and software should specifically address this issue, especially among groups with higher dropout rates due to insufficient EEG data quality (women, those with longer hair and those with more severe neurological deficits). Second, we only had a limited number of LVO-a stroke patients in the study, increasing the statistical uncertainty of the results. Third, we had insufficient power to determine if EEG can distinguish between LVO-a stroke and hemorrhagic stroke. This should be the focus of future studies, since hemorrhagic stroke is an important mimic of LVO-a stroke and there are data that suggest that subjecting patients with a hemorrhagic stroke to longer transportation times may negatively impact their outcome.36

In conclusion, the data from this study suggest that dry electrode EEG has potential to detect LVO-a stroke among patients with suspected stroke in the prehospital setting. Towards future implementation of EEG in prehospital stroke care, EEG data quality needs to be improved and additional validation in a larger cohort of patients is necessary.
Authors Contributions

Van Stigt and Groenendijk had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Van Stigt and Groenendijk contributed equally.

*Concept and design:* Van Meenen, Marquering, Potters, Coutinho.

*Acquisition, analysis, or interpretation of data:* Van Stigt, Groenendijk, Van Meenen, Van de Munckhof, Theunissen, Van Grondelle, Geuzebroek, Koopman, Potters, Coutinho.

*Drafting of the manuscript:* Van Stigt, Groenendijk, Potters, Coutinho.

*Critical revision of the manuscript for important intellectual content:* Van Stigt, Groenendijk, Van Meenen, Van de Munckhof, Franschman, Smeekes, Siegers, Visser, Van Schaik, Halkes, Majoie, Koopman, Marquering, Potters, Coutinho.

*Statistical analysis:* Van Stigt, Groenendijk.

*Obtained funding:* Potters, Coutinho.

*Administrative, technical, or material support:* Van Stigt, Groenendijk, Van Meenen, Van de Munckhof, Theunissen, Franschman, Smeekes, Van Grondelle, Geuzebroek, Siegers, Visser, Van Schaik, Halkes, Potters, Coutinho.

*Supervision:* Marquering, Potters, Coutinho.
REFERENCES


15. Duvekot MHC, Venema E, Rozeman AD, et al. Comparison of eight prehospital stroke


Figure 1. EEG setup as used in the ELECTRA-STROKE study. A. EEG equipment stored in a portable and lightweight bag. B. Dry electrode EEG cap (Waveguard touch, Eemagine, Berlin, Germany). C. EEG recording in the ambulance.

Figure 2. Patient flow chart. EEG = electroencephalography; LVO-a = large vessel occlusion of the anterior circulation.
Figure 3. ROC-curves for LVO-a stroke detection. A. ROC-curve of the theta/alpha ratio with, at optimal cutoff, a sensitivity of 50% and specificity of 83% for LVO-a stroke. B. ROC-curve of the pairwise derived Brain Symmetry Index in the delta frequency band with, at optimal cutoff, a sensitivity of 80% and specificity of 93% for LVO-a stroke. C. Contingency table of LVO-a stroke prediction by the theta/alpha ratio. D. Contingency table of LVO-a stroke prediction by the pairwise derived Brain Symmetry Index in the delta frequency band.
Table 1. Baseline characteristics of the patients included in and excluded from the final analysis. Reasons for exclusion were insufficient

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<tr>
<th>Table 1. Baseline characteristics of the patients included in and excluded from the final analysis. Reasons for exclusion were insufficient</th>
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<tbody>
<tr>
<td>Included (n=212)</td>
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<tr>
<td>Age – median (IQR)</td>
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<td>Sex – no. of males/total (%)</td>
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<td>Diagnosis – no./total (%)</td>
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<td>LVO-a stroke</td>
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<td>Non-LVO-a ischemic stroke</td>
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<td>Seizure</td>
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<td>Glasgow Coma Scale – no./total (%)</td>
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<td>Treatment – no./total (%)</td>
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<td>IVT</td>
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<td>EVT</td>
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<td>Symptom onset to start EEG, minutes – median (IQR)</td>
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<td>Hair length</td>
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<tr>
<td>Short</td>
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<td>Long</td>
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data quality (n=94), absence of EEG data (n=4) and a corrupted European Data Format file (n=1).

EEG = electroencephalography; EVT = endovascular thrombectomy; IQR = interquartile range; IVT = intravenous thrombolysis; LVO-a = large vessel occlusion of the anterior circulation; NIHSS = National Institutes of Health Stroke Scale; no. = number; SD = standard deviation.

Number of patients who received IVT before EVT: 7; 4.

Number of missing values: 9; 3; 10; 3; $15; 12; 32; 68.

Table 2. Baseline characteristics of all patients included in the final analysis.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=212)</th>
<th>LVO-a stroke (n=6)</th>
<th>No LVO-a stroke (n=206)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – median (IQR)</td>
<td>74 (66-81)</td>
<td>72 (69-80)</td>
<td>75 (65-81)</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex – no. of males/total (%)</td>
<td>122/212 (58%)</td>
<td>5/6 (83%)</td>
<td>117/206 (57%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>115/212 (54%)</td>
<td>6/6 (100%)</td>
<td>109/206 (53%)</td>
<td>NA</td>
</tr>
<tr>
<td>LVO-a stroke</td>
<td>6/212 (3%)</td>
<td>6/6 (100%)</td>
<td>0/206 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>M1</td>
<td>3/212 (1%)</td>
<td>3/6 (50%)</td>
<td>0/206 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Proximal M2</td>
<td>3/212 (1%)</td>
<td>3/6 (50%)</td>
<td>0/206 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>32/212 (15%)</td>
<td>0/6 (0%)</td>
<td>32/206 (16%)</td>
<td>NA</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>8/212 (4%)</td>
<td>0/6 (0%)</td>
<td>8/206 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Seizure</td>
<td>6/212 (3%)</td>
<td>0/6 (0%)</td>
<td>6/206 (3%)</td>
<td>NA</td>
</tr>
<tr>
<td>Another stroke mimic</td>
<td>51/212 (24%)</td>
<td>0/6 (0%)</td>
<td>51/206 (25%)</td>
<td>NA</td>
</tr>
<tr>
<td>Medical history – no./total (%)</td>
<td>51/212 (24%)</td>
<td>1/6 (17%)</td>
<td>50/206 (24%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4/212 (2%)</td>
<td>0/6 (0%)</td>
<td>4/206 (2%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Blood pressure – mean (±SD)</td>
<td>168 (±28)</td>
<td>154 (±27)</td>
<td>168 (±28)</td>
<td>0.22</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>91 (±17)</td>
<td>88 (±11)</td>
<td>92 (±18)</td>
<td>0.62</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>1/212 (&lt;1%)</td>
<td>0/6 (0%)</td>
<td>1/206 (&lt;1%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Glasgow Coma Scale – no./total (%)</td>
<td>211/212 (&gt;99%)</td>
<td>6/6 (100%)</td>
<td>205/206 (&gt;99%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>NIHSS – median (IQR)</td>
<td>1 (0-4)</td>
<td>14 (7-17)</td>
<td>1 (0-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment – no./total (%)</td>
<td>36/212 (17%)</td>
<td>4/6 (67%)</td>
<td>32/206 (16%)</td>
<td>0.008</td>
</tr>
<tr>
<td>EVT</td>
<td>9/212 (4%)</td>
<td>5/6 (83%)^[g]</td>
<td>4/206 (2%)^[h,i]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Symptom onset to start EEG^[j], minutes – median (IQR)</td>
<td>121 (50-449)</td>
<td>46 (32-64)</td>
<td>139 (51-476)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

EEG = electroencephalography; EVT = endovascular thrombectomy; IQR = interquartile range; IVT = intravenous thrombolysis; LVO-a = large vessel occlusion of the anterior circulation; NA = not applicable; NIHSS = National Institutes of Health Stroke Scale; no. = number; SD = standard deviation.

^[a]P-value for the difference between patients with and without an LVO-a stroke.

^[b]Of the 109 patients with a non-LVO-a ischemic stroke, 2 had an LVO stroke of the posterior circulation, located in the first segment of the posterior cerebral artery (n=1) and basilar artery (n=1). Seventy (64%) non-LVO-a ischemic strokes were located in the vascular territory of the anterior circulation.

^[c]All were intraparenchymal hemorrhages.

^[d]The patient with an LVO-a stroke who did not receive EVT had an occlusion of the extracranial internal carotid artery and proximal second segment of the middle cerebral artery (both left). The risk of EVT was deemed to great considering the minimal neurological deficit (NIHSS: 3).

^[e]The patients without an LVO-a stroke who received EVT had a distal occlusion of the second segment of the middle cerebral artery (n=3) and an occlusion of the third segment of the middle cerebral artery (n=1).

Number of patients who received IVT before EVT: 3; 5.

Number of missing values: 9; 10; 15.
Table 3. Diagnostic accuracy of EEG features for LVO-a stroke detection at optimal cutoff. The primary classifying metric, the AUC, is bolded.

<table>
<thead>
<tr>
<th>Frequency band power</th>
<th>AUC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative delta</td>
<td>0.59 (0.34-0.83)</td>
<td>0% (0%-39%)</td>
<td>100% (98%-100%)</td>
<td>NA</td>
<td>97% (93%-99%)</td>
<td>NA</td>
</tr>
<tr>
<td>Relative theta</td>
<td>0.68 (0.44-0.92)</td>
<td>33% (10%-70%)</td>
<td>80% (74%-85%)</td>
<td>5% (1%-17%)</td>
<td>97% (94%-99%)</td>
<td>1.7 (0.5-5.4)</td>
</tr>
<tr>
<td>Relative alpha</td>
<td>0.77 (0.54-0.99)</td>
<td>67% (30%-90%)</td>
<td>84% (78%-89%)</td>
<td>12% (5%-27%)</td>
<td>99% (96%-100%)</td>
<td>4.2 (2.2-8.0)</td>
</tr>
<tr>
<td>Relative beta</td>
<td>0.50 (0.26-0.73)</td>
<td>33% (10%-70%)</td>
<td>80% (74%-85%)</td>
<td>5% (1%-17%)</td>
<td>97% (94%-99%)</td>
<td>1.7 (0.5-5.4)</td>
</tr>
<tr>
<td>Delta/alpha ratio</td>
<td>0.76 (0.53-0.98)</td>
<td>50% (19%-81%)</td>
<td>86% (81%-90%)</td>
<td>10% (4%-26%)</td>
<td>98% (95%-99%)</td>
<td>3.6 (1.5-8.7)</td>
</tr>
<tr>
<td>Theta/alpha ratio</td>
<td>0.80 (0.58-1.00)</td>
<td>50% (19%-81%)</td>
<td>83% (77%-88%)</td>
<td>9% (3%-22%)</td>
<td>98% (95%-99%)</td>
<td>2.9 (1.2-6.9)</td>
</tr>
<tr>
<td>(Delta+theta)/(alpha+beta) ratio</td>
<td>0.70 (0.47-0.94)</td>
<td>33% (10%-70%)</td>
<td>86% (74%-85%)</td>
<td>5% (1%-17%)</td>
<td>97% (94%-99%)</td>
<td>1.7 (0.5-5.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency asymmetry</th>
<th>AUC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pdBSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>0.91 (0.73-1.00)</td>
<td>80% (38%-96%)</td>
<td>93% (88%-96%)</td>
<td>24% (10%-47%)</td>
<td>99% (97%-100%)</td>
<td>11.0 (5.5-21.7)</td>
</tr>
<tr>
<td>Theta</td>
<td>0.78 (0.54-1.00)</td>
<td>60% (23%-88%)</td>
<td>92% (87%-95%)</td>
<td>18% (6%-41%)</td>
<td>99% (96%-100%)</td>
<td>7.6 (3.2-18.3)</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.47 (0.22-0.73)</td>
<td>20% (4%-62%)</td>
<td>97% (93%-98%)</td>
<td>14% (3%-51%)</td>
<td>98% (94%-99%)</td>
<td>5.9 (0.9-40.5)</td>
</tr>
<tr>
<td>Beta</td>
<td>0.78 (0.53-1.00)</td>
<td>20% (4%-62%)</td>
<td>96% (92%-98%)</td>
<td>12% (2%-47%)</td>
<td>98% (94%-99%)</td>
<td>5.1 (0.8-33.9)</td>
</tr>
</tbody>
</table>

AUC = area under the receiver operating characteristic curve; CI = confidence interval; EEG = electroencephalography; LVO-a = large vessel occlusion of the anterior circulation; NA = not available; NPV = negative predictive value; pdBSI = pairwise derived Brain Symmetry Index; PLR = positive likelihood ratio; PPV = positive predictive value.

*194 patients, of whom 6 with an LVO-a stroke.

*183 patients, of whom 5 with an LVO-a stroke.

The presence of an LVO-a stroke was indicated if the EEG features were: \textgreater 0.88; \textless 0.25; \textless 0.12; \textless 0.07; \textgreater 0.64; \textless 0.26; \textgreater 0.58; \textgtrsim 0.52; \textgtrsim 0.52; \textgtrsim 0.52; \textless 0.52; \textgtrsim 0.53.
Prehospital Detection of Large Vessel Occlusion Stroke With Electroencephalography: Results of the ELECTRA-STROKE Study
Maritta N van Stigt, Eva A Groenendijk, Laura C Van Meenen, et al.
Neurology published online October 17, 2023
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