Received: 7 April 2022 | Revised: 2 July 2022 | Accepted: 5 July 2022

DOI: 10.1111/epi.17359

Epilepsia®

RESEARCH ARTICLE

Hyperperfusion Tmax mapping for nonconvulsive status epilepticus in the acute setting: A pilot case–control study

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Abstract

Objective: Nonconvulsive status epilepticus (NCSE) is misdiagnosed in >50% of cases in the emergency department. Computed tomographic perfusion (CTP) has been implemented in the hyperacute setting to detect seizure-induced hyperperfusion. However, the diagnostic value of CTP is limited by the lack of thresholds for hyperperfusion and high interrater variability. This pilot case–control study aims at identifying the diagnostic value of reverse Tmax (rTmax) in differentiating NCSE from acute ischemic stroke in the hyperacute setting.

Methods: We enrolled patients with NCSE (Salzburg criteria-based diagnosis) and stroke cases 1:1 matched for clinical features and time of presentation. CTP standard maps (mean transit time [MTT]–cerebral blood volume–cerebral blood flow [CBF]) and rTmax maps were elaborated and rated by two experts in CTP blinded to the final diagnosis. Hyperperfusion was adjudicated for standard CTP maps as an increase in CBF and a decrease in MTT, and for rTmax as the presence of a black area on 3-, 2-, and 1-s threshold maps. Cronbach alpha was used for interrater agreement; receiver operating curve analysis was run to measure accuracy with area under the curve.

Results: Overall, 34 patients were included (17 NCSE, 17 stroke; time from onset to imaging = 2 h for both groups). People with NCSE were older and more frequently had a history of epilepsy. NCSE patients had hyperperfusion on rTmax maps in 11 of 17 cases versus zero of 17 in stroke. Intra- and interrater reliability was higher for rTmax than for standard CTP maps ($\kappa = 1$ vs. $\kappa = .6$). rTmax was 82% (95%CI = 67–97%) accurate in predicting NCSE versus stroke in the hyperacute setting. Agreement between neuroimaging and electroencephalography (EEG) was limited at a hemispheric level for standard CTP maps, whereas rTMax had agreement with EEG largely reaching the sublobar level.

Michele Romoli and Elena Merli contributed equally.

Significance: rTmax mapping might represent a reliable tool to spot NCSE-induced hyperperfusion with a threshold-based reproducible approach. Further studies are needed for validation and implementation in the differential diagnosis of focal neurological deficit in the hyperacute setting.

KEYWORDS
brain perfusion, computed tomographyCT perfusionnonconvulsivestatus epilepticus

1 | INTRODUCTION

Status epilepticus represents a common neurological emergency, with an estimated incidence reaching 40 cases per 100 000 people, significantly increasing in late adulthood.[1,2] Mortality due to status epilepticus ranges 20%–30%, with early recognition and treatment being critical to limit the risk of poor prognosis.[2] Whereas the overt features of convulsive status epilepticus facilitate its treatment within an appropriate timeframe, nonconvulsive status epilepticus (NCSE) is misdiagnosed in up to 64% of cases.[3] NCSE is a frequent pattern of presentation of seizures in late adulthood and can mimic stroke in the emergency department.[4,5] Missing the diagnosis of NCSE is independently associated with longer hospital stay, higher chance of brain damage, and lower rates of good functional recovery.[3,6,7] This has a particular impact on late adults, which have both a higher chance of suffering from NCSE and lower rates of NCSE recognition and treatment.[2,3]

Despite being the gold standard test for NCSE diagnosis, electroencephalography (EEG) is not always available on a 24/7 basis. The Salzburg criteria for NCSE diagnosis have been adopted in recent years,[8] but debate carries on, particularly regarding the definition of an ictal–interictal continuum,[9] the applicability to diverse hyperacute settings, and the uncertainty of a "possible" status epilepticus diagnosis.[10,11]

To improve early recognition of NCSE, computed tomographic perfusion (CTP) has been tested in the hyperacute setting, providing potential clues to a diagnosis of NCSE.[12,13] CTP is widely available, is performed routinely in the stroke pathway, and can provide immediate insights on brain perfusion metrics in NCSE.[14,15] Brain perfusion changes represent a surrogate marker of epileptic activity, which causes a consistent and transient increase in the demand for blood supply.[13,16] Therefore, in cases of ongoing seizure activity, CTP may be able to catch a hyperperfusion pattern, with increases in cerebral blood flow (CBF) and cerebral blood volume (CBV), and faster mean transit time (MTT).[13–15] However, variability in setting and lack of standardized thresholds limit the generalizability and diagnostic value of CTP in identifying NCSE and its focus.[13] First, the area of hyperperfusion is often very broad, with CTP agreement largely stuck at a hemispheric level with EEG,[13,17] or just matching contralateral symptoms.[12] Therefore, the identification of a potential focus can be extremely difficult, especially when close to a previous ischemic lesion in poststroke epilepsy.[13,17] Second, the definition of hyperperfusion is still debated. Proposed criteria stand on asymmetry index > 10 on CBF map only,[12,15] or reduced MTT and increased CBF.[18,19] However, the correlation among standard CTP maps for hyperperfusion (MTT, CBF, CBV) is still unclear, a threshold value for hyperperfusion is lacking, and assessment in the clinical setting is still largely based on visual inspection.[12,18] This in turn leads to variability in interrater agreement and adjudication of hyperperfusion[5,20] that limit full applicability. Finally, few studies are available on the relationship between CTP findings and NCSE Salzburg criteria, highlighting the need for further studies.[15]

Key Points

- Non-convulsive status epilepticus can be difficult to recognize in the emergency setting.
- CT perfusion can identify hyperperfusion, but no thresholds for hyper-perfusion is defined on standard maps.
- Reverse Tmax (rTmax) can identify the hyperperfused tissue with clear thresholds, high reproducibility, and sublobar agreement with EEG.

Time-to-maximum (Tmax) maps were introduced in acute ischemic stroke assessment to estimate the evolution of ischemic lesions through standardized thresholds.[21] Tmax offers of a possible standardized definition of perfusion abnormalities, with progressive cutoffs to segment the area affected by changes in blood transit.[21,22] As epileptic activity propagates from the original focus, it might be hypothesized that perfusion changes have some degradation over adjacent areas. Here, we report the results of a case–control study exploring Tmax applicability to differentiate NCSE from stroke in the hyperacute

setting and the role of Tmax in providing insights into epileptic activity.

2 | MATERIALS AND METHODS

2.1 | Cohort and setting

We enrolled consecutive patients with NCSE diagnosis according to Salzburg criteria[8] undergoing brain imaging with CTP and EEG within 60 min from August 2020 to February 2022. Our hospital is a comprehensive stroke center (CSC),[23] hub of a stroke network based on a mothership paradigm, serving 1.2 million inhabitants from the province of Bologna, Emilia-Romagna Region, Italy. All people with a neurological deficit suspected for stroke are directly admitted to our CSC to undergo standardized evaluation and diagnostics, including CTP, in a fast-track pathway designed to reduce delays in reperfusion in stroke cases. Stroke mimics are managed through the same pathway, with a final diagnosis made after workup and clinical evaluation. All NCSE patients undergo the same diagnostics as stroke cases, being initially evaluated as potential stroke codes due to focal neurological signs, symptoms, or impaired consciousness. We excluded all NCSE cases not undergoing CTP, and all cases of seizures/NCSE symptomatic of an acute ischemic stroke, with consistent imaging findings. Status epilepticus was diagnosed according to the International League Against Epilepsy definition[24] and NCSE adjudicated according to Salzburg criteria.[8]

A control cohort was derived from the stroke registry of our CSC, selecting people with stroke matched in a 1:1 fashion to the NCSE cohort for (1) functional status, (2) onset-to-imaging timing, and (3) signs and symptoms at presentation. NCSE and stroke cases were managed on an identical pathway, also including blood examinations, clinical evaluation, and electrocardiography beyond brain imaging. For both groups, we collected demographic data, clinical features, timing of diagnostics, and treatment.

2.2 | EEG and NCSE diagnosis

EEGs were acquired by our neurophysiology staff soon after CTP, and in all cases before any treatment with antiseizure medications. Noncontinuous routine EEG was used in all cases. The diagnosis of NCSE was adjudicated by the neurologist managing the patient on clinical and EEG grounds and was then retrospectively independently adjudicated by two epilepsy specialists (E.M., L.M.),[8] with inconsistencies resolved by consensus. The concordance in the definition of definite and possible NCSE was optimal (κ = .96). We collected medical history data, with particular regard to previous seizures or epilepsy diagnosis, EEG patterns, timing of EEG ascertainment, treatment of NCSE, treatment effect, and mortality due to NCSE. EEG spike field, corresponding to the region thought to generate the spike, was estimated by visual inspection of scalp EEG, using all available montages, and through evaluation of the distribution of positive and negative potentials on voltage maps.[25]

2.3 | Imaging

All participants included underwent computed tomography (CT), CTP, and computed tomographic angiography (CTA) on a Revolution Evo 128, GE Healthcare CT scan. Noncontrast CT images were obtained from helical scans from the skull base to the vertex (120 kV, 400 mA, 2.5-mm section thickness with 2.5- and 5-mm reconstructions). CTP scans (80 kV, 300 mA) consisted of a continuous acquisition, with a total duration of 230 s and a scanning volume of 8 cm, starting after administration of 50 ml of iodinated contrast medium via an antecubital vein at 4.5 ml/s, followed by 50-ml saline flush (acquisition parameters: 5-mm thickness × 16i, rotation time .28 s, matrix = 512 to the convexity, collimation = 32–1.2 mm). CTA extended from the aortic arch to the frontal vertex for the arterial phase, followed by scans from C2 to the vertex for venous and delayed phases (120 kV; 320–400 mA; section thickness = .625 mm). Intravenous administration of 60–70 ml iodinated contrast medium injected at 4 ml/s and followed by 50-ml saline flush was followed by scan start with 4-s delay on bolus tracking up to threshold level (80 HU) of a region of interest placed at the level of the distal aortic arch. CTA always followed CTP to avoid potential artifacts deriving from contrast medium persistence.

2.3.1 | Definition of perfusion changes

CTP data were initially processed by two commercially available delay-insensitive deconvolution software programs (CT Perfusion 4D, GE Healthcare). Standard CTP maps, MTT, CBF, CBV, Tmax > 6, Tmax > 9.5, and Tmax > 16 were obtained, with core and penumbral volume automatically defined through the Rapid Processing of Perfusion and Diffusion software platform (iSchemaView). Tmax maps were also calculated to define hyperperfusion with different thresholds. Considering normal perfusion of 4 s for healthy brain tissue and marginal variations between gray and white matter,[26–28] we defined Tmax thresholds of 3 s or shorter as hyperperfusion. The resulting image is composed of normally colored brain parenchyma, corresponding to Tmax higher than the thresholds, and a

black area, corresponding to regions where the hyperperfusion gives very short transit timing, below the threshold proposed. Therefore, the resulting black area represents the hyperperfused region, with the remaining tissue having normal perfusion (Figure 1). We also hypothesized that the maximal hyperperfusion and fast-transit are reached at the seizure focus site, with a rather progressive normalization of perfusion changes in its surroundings. Hence, we defined via consensus Tmax thresholds at 3, 2, and 1 s as the area involved by hyperperfusion, which appears in black; we used the term reverse Tmax for these maps (rTmax3, rTmax2, rTmax1; see Figure 1).

Qualitative visual analysis was used to define hyperperfusion and hypoperfusion. Such an approach was preferred because it is directly applicable to clinical practice and because of the lack of quantitative thresholds on standard perfusion maps.[15,17,18] To this extent, our attempt was also to use rTmax mapping as a standardized method to define hyperperfusion, with clear cutoffs directly applicable to clinical practice. Visual analysis was performed by two experts in CTP (S.G., M.R.), blind to all patient details, including clinical information and final diagnosis/treatment. Hyperperfusion was adjudicated on standard maps in the case of an increase in CBF and decrease in MTT, as previously defined.[18] On rTmax maps, hyperperfusion was defined as the presence of a black area consistent on all thresholds (Figure 1). Hypoperfusion was defined as a focal decrease in regional CBF with increased MTT, or by positive Tmax6, according to the local stroke protocol. rTmax maps were elaborated and rated blind to other perfusion maps, with only noncontrast CT made available to the raters. Standard CTP maps (MTT, CBF, and CBV) were rated in separate sessions. The rating was repeated after 2 weeks to measure intrarater reliability. Disagreement was resolved by consensus for final adjudication. All maps were reconstructed using the same workstation for all groups. Agreement between EEG and CTP maps showing hyperperfusion was adjudicated as (1) hemispheric, with CTP hyperperfusion involving a large area with similar lateralization of EEG abnormalities; (2) lobar, with CTP changes in the same lobe as the EEG focus; or (3) sublobar, with CTP changes colocalizing with the EEG focus.

2.4 | Statistical analysis

Continuous variables are reported as mean and SD or median and interquartile range when nonnormally distributed, whereas categorical variables are reported as frequency and percentage. Parametric testing was used for continuous normally distributed variables, and nonparametric tests (e.g., Wilcoxon test) were used for continuous nonnormally distributed variables. Intrarater reliability is reported with Cronbach alpha, whereas the interrater agreement is reported with Cohen κ. Correlation analysis using Pearson correlation coefficient was run to define relations across CTP maps. Paired-samples t-tests were used to compare the hyperperfused volumes across maps. Receiver operating curve (ROC) analysis was run to define the predictive accuracy of hyperperfusion on CTP maps in discriminating NCSE versus acute ischemic stroke. The ROC-based area under the curve (AUC) is reported with 95% confidence intervals (CIs), whereas sensitivity and specificity are expressed as percentages. IBM SPSS Statistics software version 26.0 and R version 3.5 were used. Significance was set as $p < .05$.

3 | RESULTS

Overall, 34 patients were included (17 NCSE, 17 stroke), all with symptoms at the time of brain imaging. People with NCSE were older and more frequently had a history of epilepsy (29.4% vs. 0%), previous stroke, and diabetes (Table 1). Among those with a diagnosis of epilepsy, four had focal seizures and one had generalized seizures. Clinical features of presentation revealed balancing of speech disturbance, and sensory and motor deficit across groups, whereas impairment of consciousness was relatively more frequent among people with NCSE compared to those with stroke (Table 1). Median onset to imaging time was approximately 2 h in each group, whereas the time between CTP imaging and EEG was .5 h (Table 1).

NCSE subjects were mostly classified as focal NCSE and were symptomatic in all but one case (Table 2). Acute (35.3%) and remote (47.1%) etiology were most common, with cerebrovascular diseases adjudicated as the main determinant of NCSE (Table 2). All patients received first-line treatment with benzodiazepine, 10 required second-line treatment ($n = 4$ lacosamide, $n = 6$ levetiracetam), and one required further treatment with phenytoin. All patients had NCSE resolution after treatment, and no mortality related to NCSE was registered. No differences were found in NCSE classification, etiology, or treatment depending on CTP perfusion features (Table 2).

Hyperperfusion was found in 64.7% of people with NCSE ($n = 11$) and none of those with acute ischemic stroke, with both standard CTP maps and rTmax maps. No differences in time to CTP, time to EEG, or onset to CTP were found depending on hyperperfusion adjudication. No differences in time metrics were found depending on definite versus possible definition of NCSE according to Salzburg criteria (Table S1). Intrarater reliability was satisfactory for standard CTP maps ($\alpha = .9$) and high for rTmax maps ($\alpha = 1$). Interrater agreement was moderate with standard CTP maps (Cohen $\kappa = .6$, $p = .013$), and high for rTmax maps ($\kappa = 1$, $p < .001$).

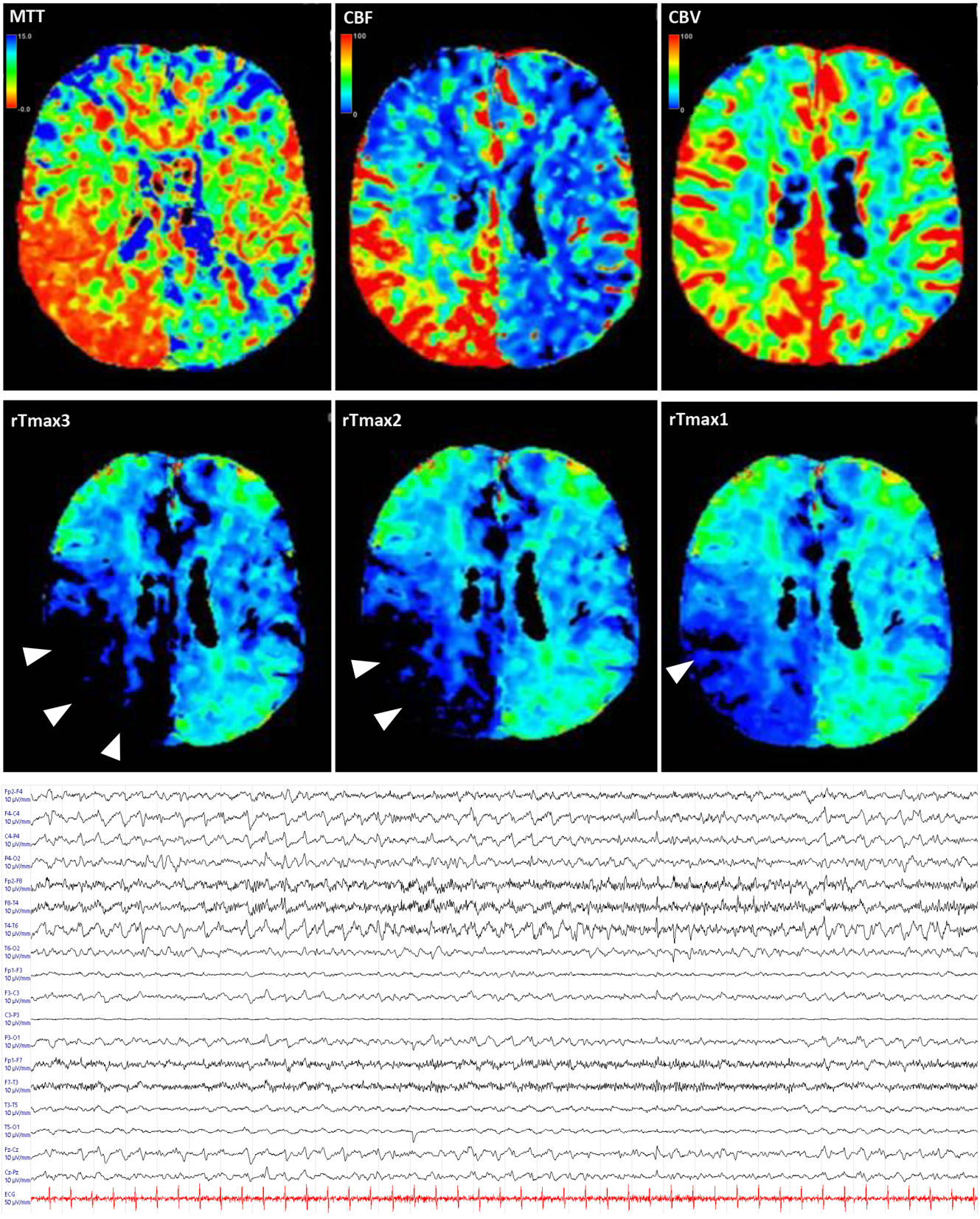

FIGURE 1 Computed tomographic perfusion standard maps (top) showing a broad area of hyperperfusion in the right hemisphere, and reverse Tmax (rTmax) maps (center) highlighting a hyperperfused black area with maximal fast transit in the right mid-superior temporal region, consistent with electroencephalogram (bottom) showing an electrographic seizure in the right temporofrontal region. CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time.

TABLE 1 Characteristics of the study cohort

Characteristic	NCSE, $n = 17$	Stroke, $n = 17$	p
Age, years, mean ± SD	79.3 ± 7.6	70.4 ± 15.8	.045[a]
Female, *n* (%)	9 (52.9%)	11 (64.7%)	.47
mRS 0–2 before admission, *n* (%)	15 (88.2%)	17 (100%)	.145
Risk factors, *n* (%)			
Hypertension	8 (47.1%)	6 (37.5%)	.078
Dyslipidemia	2 (11.8%)	2 (11.8%)	.58
Smoking	6 (35.3%)	7 (41.2%)	1
Atrial fibrillation	6 (35.3%)	7 (41.2%)	.72
Diabetes	7 (41.2%)	0 (0%)	.003[a]
Previous stroke	7 (41.2%)	1 (5.9%)	.015[a]
Epilepsy diagnosis	5 (29.4%)	0 (0%)	.015[a]
Seizure semiology, *n* (%)			
Focal	4 (23.5%)	-	
Generalized	1 (5.9%)	-	
Clinical features			
Speech disturbances, *n* (%)	15 (88.2%)	16 (94.1%)	.55
Motor deficit, *n* (%)	7 (41.2%)	8 (47.1%)	.73
Sensory deficit, *n* (%)	1 (5.9%)	1 (5.9%)	1
Impairment of consciousness, *n* (%)	6 (35.3%)	0 (0%)	.013[a]
Hemianopia, *n* (%)	6 (35.3%)	1 (7.1%)	.062
NIHSS, mean ± SD	10.2 ± 6.3	3.4 ± 1.6	<.001[a]
Neuroradiological features			
Symptom onset to imaging, h, median (IQR)	2.0 (.75)	1.8 (1.4)	.13
Symptom onset to EEG, h, median (IQR)	2.5 (1)	-	
CTP to EEG, h, median (IQR)	.5 (0)	-	
Symptoms at the time of imaging, *n* (%)	17 (100%)	17 (100%)	1
CTP hyperperfusion, *n* (%)	11 (64.7%)	0 (0%)	<.001[a]
rTmax hyperperfusion, *n* (%)	11 (64.7%)	0 (0%)	<.001[a]

Abbreviations: CTP, computed tomographic perfusion; EEG, electroencephalography; IQR, interquartile range; mRS, modified Rankin Scale; NCSE, nonconvulsive status epilepticus; NIHSS, National Institutes of Health Stroke Scale; rTmax, reverse Tmax.

[a]Statistically significant.

TABLE 2 Clinical characteristics of the NCSE group

Characteristic	Overall	Hyperperfusion, $n = 11$	Normal perfusion, $n = 6$
NCSE definition, Salzburg criteria			
Definite	14 (82.4%)	10 (71.4%)	4 (28.6%)
Possible	3 (17.6%)	1 (33.3%)	2 (66.7%)
ILAE classification, Axis 1: semiology[24]			
Aphasic SE	4 (23.5%)	2 (50%)	2 (50%)
Absence SE	1 (5.9%)	0 (0%)	1 (100%)
Focal NCSE with impaired awareness	4 (23.5%)	2 (50%)	2 (50%)
Focal NCSE without impaired awareness	8 (47.1%)	7 (87.5%)	1 (12.5%)
Etiology			
CNS lesion	2 (11.8%)	2 (100%)	0 (0%)
Infectious encephalitis	1 (5.9%)	0 (0%)	1 (100%)
Hyponatremia	1 (5.9%)	1 (100%)	0 (0%)
Limbic encephalitis	1 (5.9%)	0 (0%)	1 (100%)
Metabolic encephalopathy	1 (5.9%)	0 (0%)	1 (100%)
Subarachnoid hemorrhage	2 (11.8%)	1 (50%)	1 (50%)
Stroke	7 (41.2%)	7 (100%)	0 (0%)
Treatment			
First-line benzodiazepine	17 (100%)	11 (64.7%)	6 (35.3%)
Second-line lacosamide	4 (23.5%)	2 (50%)	2 (50%)
Second-line levetiracetam	6 (35.3%)	3 (50%)	3 (50%)
Repeated second-line phenytoin	1 (5.9%)	0 (0%)	1 (100%)

Note: Data are presented as *n* (%).

Abbreviations: CNS, central nervous system; ILAE, International League Against Epilepsy; NCSE, nonconvulsive SE; SE, status epilepticus.

Considering all patients included ($n = 34$), CTP hyperperfusion was found in NCSE subjects only. CTP hyperperfusion had a 65% sensitivity and 100% specificity in differentiating NCSE from stroke at the time of emergency department arrival, with rTmax and standard CTP maps having identical accuracy (AUC = .82, 95% CI = .67–.97; Figure S2).

Volumes of hyperperfusion were found to be consistently broader on standard CTP maps compared to rTmax maps (Figure 2). CTP standard maps showed similar volumes of hyperperfused tissue (MTT = 49.1 ± 51.6 ml vs. CBF = 49 ± 51.1 ml, $p = .79$; vs. CBV 48.3 ± 51.1 ml, $p = .27$), whereas rTmax maps showed a significant and progressive reduction of the hyperperfused volume

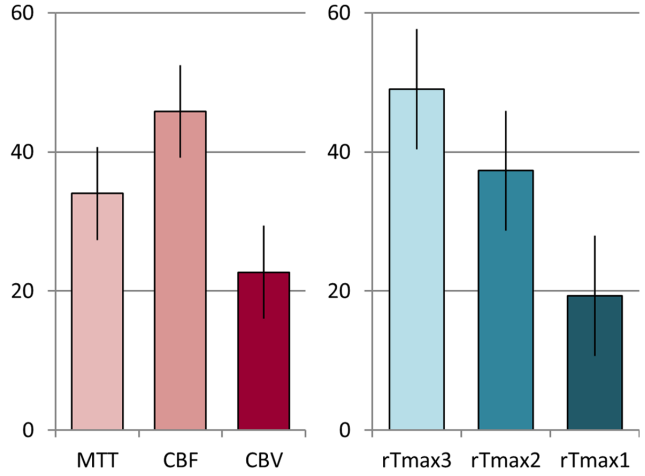

FIGURE 2 Hyperperfusion volumetric changes (ml) according to computed tomographic perfusion maps. Bars show mean volumes, and whiskers show standard errors (ml). CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; rTmax, reverse Tmax.

(rTmax3 = 52 ± 54.3 ml vs rTmax2 = 41.2 ± 45.3 ml, $p = .08$; vs rTmax1 = 19.7 ± 27.4 ml, $p = .016$; Figure 2). Final volumes of maximally hyperperfused tissue were smaller with rTmax1 versus MTT ($p = .12$) or CBF ($p = .12$). rTmax maps had high internal correlation and showed satisfactory correlation with standard CTP maps (Table S2, correlation matrix). Hyperperfusion always extended to cortical and subcortical regions, and also involved the thalamus in seven cases (35.3%, Table S3). Among those with hyperperfusion on CTP, rTmax1 maps more commonly showed sublobar agreement with EEG compared to standard CTP maps (9.1 vs. 54.5%, $p = .056$), whose agreement was limited at a hemispheric level in 36.3% of cases (Figure S1).

4 | DISCUSSION

Early identification of NCSE is critical to provide early treatment and improve prognosis.[3] EEG is often not readily available in the emergency department, contributing to rates of NCSE delayed diagnosis or misdiagnosis reaching up to two thirds of cases.[3] CTP has been implemented in the hyperacute setting to detect NCSE-related hyperperfusion, a surrogate measure of an ongoing seizurelike activity, thought to increase the blood supply to comply with metabolic demands of abnormal firing. However, hyperperfusion detection in NCSE is critically variable across studies, spanning from 30% to 80% of cases,[6,10,13,17] likely owing to differences in the time of diagnostics and duration of symptoms. This pairs with a consistent variability in interrater agreement, ranging from 70% to 90%,[13,20] which may limit the general value of CTP in diagnosing NCSE in the emergency setting. These limitations reasonably derive from the use of standard CTP maps (MTT, CBV, CBF), which have originally been designed to spot hypoperfusion in acute ischemic stroke, and lack standardized thresholds to identify hyperperfusion.[13,14]

In this pilot study, we provide data in support of an alternative elaboration of CTP maps, using rTmax to highlight hyperperfused regions with a threshold-based approach. rTmax is standardized according to time-based thresholds (3, 2, and 1 s), seems easily reproducible, has optimal interrater reliability, and identifies the hyperperfused area with a progressive delineation toward the area of the brain involved by the paroxysmal activity. Compared to CTP, rTmax has the same accuracy in predicting NCSE diagnosis versus stroke in the hyperacute setting, with 82% accuracy, 65% sensitivity, and 100% specificity. However, compared to standard CTP maps, the definition of hyperperfusion with rTmax showed optimal interrater agreement and intrarater reliability, substantially improving the performance of CTP standard maps. Because visual inspection is widely applied to adjudicate hyperperfusion with standard CTP maps,[13,18] rTmax may help in defining it in a daily setting and might provide hints on seizure focus. Specific, whereas standard CTP maps showed similar volumes of hyperperfusion across MTT, CBF, and CBV, rTmax provides a progressive reduction of the area toward the seizure focus (Figure 1). Such reduction in hyperperfused area can be seen moving from rTmax3 to rTmax2, and from the latter to rTmax1, suggesting that hyperperfusion is a dynamic phenomenon in two dimensions, time and space. This is in line with data from experimental models, where the intensity of changes in blood supply declines moving from the area involved by paroxysmal activity to the peri-ictal regions.[29,30] rTmax may then well represent slight (rTmax3), moderate (rTmax2), and maximal (rTmax1) hyperperfusion, with the latter pointing toward the seizure focus. In our pilot study, the agreement between the area of hyperperfusion on standard CTP maps and EEG seems to stay at a hemispheric or lobar level at best. This limitation reverberates in literature, with EEG-CTP concordance largely set at a hemispheric level, with little reliance on the specific identification of the seizure focus.[13,17] In our cohort, the agreement of rTmax with EEG happens at a sublobar level rather than at a hemispheric one, a finding that, paired with the shrink in overall hyperperfused volumes across rTmax maps, may help the clinician in localizing the focus responsible for the paroxysmal activity (Figure 1). This also applies to cases of NCSE in the context of poststroke epilepsy, where the discrimination of hyperperfusion in the tissue adjacent to a previous ischemic lesion might be challenging with standard CTP maps, and might be more immediate with rTmax (Figure S4). For daily practice, it

is also reassuring to see no false positives among people with acute ischemic stroke, the major time-dependent differential diagnosis. Finally, that timing of imaging, EEG assessment, and onset to hospital admission did not differ depending on hyperperfusion on rTmax seems to support the general applicability of the technique to people admitted to the emergency department for acute neurological deficits. The direct applicability of CTP may be worthy of attention also in cases in the ictal–interictal continuum,[9,31] where hyperperfusion may suggest a finding closer to NCSE than to an interictal pattern and potentially add details in favor of treatment.[31]

The results of our study need to be considered in light of several limitations. First, the study is from a single center with vast experience in CTP imaging in the emergency setting. This can extend also to EEG availability, as our tertiary hospital provides 24/7 EEG availability, with urgent requests covered overnight. Therefore, both the cohort and the setting might not be fully representative of common standards. The CTP-EEG correlation may be limited by the time elapsed between the diagnostic examinations, which, despite being very short, may still represent an issue in a process as dynamic as NCSE. Moreover, the involvement of deep structures, notably the thalami, still needs to be addressed in larger studies using standardized CTP maps. Second, this is the first report of an attempt to standardize hyperperfusion definition according to rTmax thresholds, to ease applicability and reproducibility. Such an attempt carries the need for internal validation with larger cohorts and external validation in different settings. However, it should be underlined that having similar performance in differentiating NCSE from stroke in the hyperacute setting, there seems to be room for direct applicability for larger observational studies. Third, the definition of hyperperfusion has yet to be validated, as using fewer maps to adjudicate it (e.g., MTT only) may have higher sensitivity in light of lower specificity. This has to be oriented toward the local use, as findings may acquire higher value in settings lacking 24/7 EEG service. Fourth, further studies should also focus on the differentiation of CTP patterns depending on NCSE definition (definite vs. possible), as well as on CTP patterns due to isolated seizures versus those due to NCSE, to better characterize changes in brain perfusion over time and depending on EEG abnormalities. In this study, we excluded patients presenting with postictal symptoms, therefore limiting the differentials, and the dimension of the study did not allow for specific correlation between EEG findings in the ictal–interictal continuum and CTP changes. This pilot study was directed toward the differentiation of NCSE versus stroke in the hyperacute setting. Although CTP can help in this process, the data available to date are insufficient to recommend any diagnosis of NCSE differing from EEG-based standardized criteria. Looking forward, it is reasonable to assume that CTP imaging might suggest NCSE in unclear cases, and prompt quick neurophysiological assessment and earlier treatment. Because NCSE might have features that can pass unnoticed or be misdiagnosed,[3,7,32] having a two-step approach may still be of help in the hyperacute setting, leading to early recognition and treatment of SE, potentially reducing morbidity and mortality associated with this condition.[33]

AUTHOR CONTRIBUTIONS

M.R. designed the study protocol, collected data, performed statistical analysis, and drafted the manuscript. E.M. designed the study protocol, collected data, and revised the manuscript for content. S.G. collected data and revised the manuscript for content. L.M. collected data and revised the manuscript for content. S.T., A.Za., S.C., and L.S. and P.T. revised the manuscript for intellectual content. A.Zi. revised the study protocol and results, and revised the manuscript for intellectual content.

ACKNOWLEDGMENT

Open access funding provided by BIBLIOSAN. [Correction added on 5th December 2022, after first online publication: funding statement has been added.]

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

PATIENT CONSENT

Informed consent was obtained from all patients included in the study or their close relatives, or was otherwise waived by the ethics committee.

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REFERENCES

1. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53(Suppl 4):127–38.
2. Lu M, Faure M, Bergamasco A, Spalding W, Benitez A, Moride Y, et al. Epidemiology of status epilepticus in the United States: a systematic review. Epilepsy Behav. 2020;112:107459.

3. Semmlack S, Yeginsoy D, Spiegel R, Tisljar K, Rüegg S, Marsch S, et al. Emergency response to out-of-hospital status epilepticus. Neurology. 2017;89(4):376–84.
4. Manganotti P, Furlanis G, Ajčević M, Polverino P, Caruso P, Ridolfi M, et al. CT perfusion and EEG patterns in patients with acute isolated aphasia in seizure-related stroke mimics. Seizure. 2019;71:110–5.
5. Kubiak-Balcerewicz K, Fiszer U, Nagańska E, Siemianowski C, Sobieszek A, Witak-Grzybowska A, et al. Differentiating stroke and seizure in acute setting—perfusion computed tomography? J Stroke Cerebrovasc Dis. 2017;26(6):1321–7.
6. González-Cuevas M, Coscojuela P, Santamarina E, Pareto D, Quintana M, Sueiras M, et al. Usefulness of brain perfusion CT in focal-onset status epilepticus. Epilepsia. 2019;60(7):1317–24.
7. Rossetti AO, Waterhouse E. Missed diagnosis of prehospital status epilepticus. Neurology 2017;89(4):314–5.
8. Leitinger M, Trinka E, Gardella E, Rohracher A, Kalss G, Qerama E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol. 2016;15(10):1054–62.
9. Kapinos G, Trinka E, Kaplan PW. Multimodal approach to decision to treat critically ill patients with periodic or rhythmic patterns using an ictal-interictal continuum spectral severity score. J Clin Neurophysiol. 2018;35(4):314–24.
10. Othman AS, Meletti S, Giovannini G. The EEG diagnosis of NCSE: concordance between clinical practice and Salzburg criteria for NCSE. Seizure. 2020;79:1–7.
11. Lee JW. Defining and validating the Salzburg criteria: it's complicated. Epilepsy Curr. 2017;17(1):37–9.
12. Hauf M, Slotboom J, Nirkko A, von Bredow F, Ozdoba C, Wiest R. Cortical regional hyperperfusion in nonconvulsive status epilepticus measured by dynamic brain perfusion CT. Am J Neuroradiol. 2009;30(4):693–8.
13. Gugger JJ, Llinas RH, Kaplan PW. The role of CT perfusion in the evaluation of seizures, the post-ictal state, and status epilepticus. Epilepsy Res. 2020;159:106256.
14. Meletti S, Monti G, Mirandola L, et al. Neuroimaging of status epilepticus. Epilepsia. 2018;59:113–9.
15. Giovannini G, Malagoli M, Turchi G, Miani A, Orlandi N, Vaudano AE, et al. Cortical and thalamic hyper-perfusion in non-convulsive status epilepticus. Relationship between perfusion CT patterns and Salzburg EEG criteria. Seizure 2021;92:10–7.
16. Posner JB, Plum F, Van Poznak A. Cerebral metabolism during electrically induced seizures in man. Arch Neurol 1969;20(4):388–95.
17. Van Cauwenberge MGA, Dekeyzer S, Nikoubashman O, Dafotakis M, Wiesmann M. Can perfusion CT unmask postictal stroke mimics? A case-control study of 133 patients. Neurology. 2018;91(20):E1918–27.
18. Strambo D, Rey V, Rossetti AO, Maeder P, Dunet V, Browaeys P, et al. Perfusion-CT imaging in epileptic seizures. J Neurol 2018;265(12):2972–9.
19. Mathews MS, Smith WS, Wintermark M, Dillon WP, Binder DK. Local cortical hypoperfusion imaged with CT perfusion during postictal Todd's paresis. Neuroradiology 2008;50(5): 397–401.
20. Payabvash S, Oswood MC, Truwit CL, McKinney AM. Acute CT perfusion changes in seizure patients presenting to the emergency department with stroke-like symptoms: correlation with clinical and electroencephalography findings. Clin Radiol 2015;70(10):1136–43.
21. Demeestere J, Wouters A, Christensen S, Lemmens R, Lansberg MG. Review of perfusion imaging in acute ischemic stroke: from time to tissue. Stroke 2020;51(3):1017–24.
22. Albers GW. Use of imaging to select patients for late window endovascular therapy. Stroke 2018;49(9):2256–60.
23. Zini A, Romoli M, Gentile M, Migliaccio L, Picoco C, Dell'Arciprete O, et al. The stroke mothership model survived during COVID-19 era: an observational single-center study in Emilia-Romagna. Italy Neurol Sci. 2020;41(12):3395–9.
24. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus—report of the ILAE task force on classification of status epilepticus. Epilepsia. 2015;56(10):1515–23.
25. Kane N, Acharya J, Benickzy S, Caboclo L, Finnigan S, Kaplan PW, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. Clin Neurophysiol Pract. 2017;2:170–85.
26. Olivot JM, Mlynash M, Zaharchuk G, Straka M, Bammer R, Schwartz N, et al. Perfusion MRI (Tmax and MTT) correlation with xenon CT cerebral blood flow in stroke patients. Neurology. 2009;72(13):1140–5.
27. Calamante F, Christensen S, Desmond PM, Østergaard L, Davis SM, Connelly A. The physiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. Stroke. 2010;41(6):1169–74.
28. Mihara F, Kuwabara Y, Tanaka A, Yoshiura T, Sasaki M, Yoshida T, et al. Reliability of mean transit time obtained using perfusion-weighted MR imaging; comparison with positron emission tomography. Magn Reson Imaging. 2003;21(1):33–9.
29. Engelhorn T, Doerfler A, Weise J, Baehr M, Forsting M, Hufnagel A. Cerebral perfusion alterations during the acute phase of experimental generalized status epilepticus: prediction of survival by using perfusion-weighted MR imaging and histopathology. Am J Neuroradiol. 2005;26(6):1563–70.
30. André V, Henry D, Nehlig A. Dynamic variations of local cerebral blood flow in maximal electroshock seizures in the rat. Epilepsia. 2002;43(10):1120–8.
31. Venkatraman A, Khawaja A, Bag AK, Mirza M, Szaflarski JP, Pati SBB. Perfusion MRI can impact treatment decision in ictal-interictal continuum. J Clin Neurophysiol. 2017;34(4):e15–8.
32. Vu LC, Piccenna L, Kwan P, O'Brien TJ. New-onset epilepsy in the elderly. Br J Clin Pharmacol. 2018;84(10):2208–17.
33. Gaínza-Lein M, Fernández IS, Ulate-Campos A, Loddenkemper T, Ostendorf AP. Timing in the treatment of status epilepticus: from basics to the clinic. Seizure. 2019;68:22–30.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Romoli M, Merli E, Galluzzo S, Muccioli L, Testoni S, Zaniboni A, Hyperperfusion Tmax mapping for nonconvulsive status epilepticus in the acute setting: A pilot case–control study. Epilepsia. 2022;63:2534–2542. https://doi.org/10.1111/epi.17359