

Computed Tomography Perfusion Maps Reveal Blood Flow Dynamics in Postictal Patients: A Novel Diagnostic Tool

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ABSTRACT: **Background:** Computed tomography (CT) brain perfusion is a relatively new imaging method that can be used to differentiate patients following epileptic seizures in the setting of acute neurological deficits (e.g., hemiparesis, hemiplegia, hemianopsia, aphasia) who arrive at the emergency room with a suspected stroke.

Objectives: To evaluate brain perfusion changes in patients who had an epileptic seizure.

Methods: We retrospectively identified 721 patients who presented at our stroke center between 2012 and 2015 with a suspected acute stroke and underwent examination through a stroke protocol, including cerebral CT perfusion (CTP) and CT angiography (CTA) within 8 hours from the onset of symptoms.

Results: Out of 721 patients, 25 presented with ictal electroencephalography (EEG) findings within 24–72 hours from symptom onset without evidence of vascular occlusion on CTA. While 15 patients had to be excluded from the study due to concomitant brain pathology, we found a specific reduction in cerebral blood volume and cerebral blood flow occurring at the ictal zone, which was identified by a post hoc EEG investigation.

Conclusions: Our study shows that CTP is an easily accessible tool in emergency department setting for the detection of changes in blood flow dynamics among postictal patients. Thus, we propose the use of CTP in emergency settings to discriminate between postictal changes and acute vascular events.

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KEY WORDS: computed tomography (CT) perfusion maps, cerebral blood flow, epilepsy, postictal state, Todd's paralysis

Patients presenting to the emergency department with stroke-like symptoms or “stroke mimics” pose a diagnostic challenge. Incorrect management of such cases may lead to erroneous treatments, consume resources, and increase the cost and length of hospitalization [1]. Among the possible etiologies, acute seizures with consequent postictal Todd's paralysis are a major alternative cause to consider [2,3].

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Currently, non-contrast computed tomography (CT) and CT perfusion (CTP) play a growing role in the preliminary assessment of patients with acute neurological deficits. Besides being reliable techniques, they are readily available in emergency settings for patients presenting with a suspicion of brain ischemia. Particularly, CTP helps in the diagnosis and assessment of tissue viability prior to reperfusion therapy during the management of acute stroke [4,5].

Cerebral perfusion changes following seizure have been well documented with single-photon emission computed tomography (SPECT) and perfusion-weighted magnetic resonance imaging (MRI) [6,7]; however, their clinical utility in acute settings is limited due to the lack of these modalities in emergency departments [8]. Changes in cerebral perfusion in the context of seizures have also been reported using CTP. After the resolution of seizures, an increase in cerebral perfusion is detected in the ictal zone and its connected regions followed by a rapid, transient drop occurring a few minutes after (“postictal switch”) [6,9]. Interestingly, however, parallel to a dramatic reduction in cerebral blood flow and blood volume, other perfusion parameters in postictal patients, such as mean transient time (MTT) and time to peak (TTP) were in the normal range.

To better characterize the abnormalities in CTP following seizures, we retrospectively identified 10 individuals among a cohort of patients who underwent CTP imaging for suspicion of acute ischemic stroke from 2012–2015. In this group, abnormalities in blood perfusion detected by CTP correlated well with the location of ictal foci detected by electroencephalograms (EEG) performed on the following day.

Altogether, our data further support the evidence showing that CTP may detect early brain metabolic changes secondary to seizures and hint at its possible use in emergency settings for a better differentiation among causes of acute neurological deficit.

PATIENTS AND METHODS

PATIENTS

The study protocol was approved by the Committee on Human Research at the Sheba Medical Center. CTP is part of the standard neuroimaging protocol at our center for adult patients presenting with suspected acute stroke. The patients reported in

this study were retrospectively identified among those admitted from January 2012 to June 2015 who underwent a multimodal CT imaging study due to a suspect of acute stroke.

Inclusion criteria for the present study were:

- CTP done no more than 8 hours from symptom onset
- No active reperfusion therapy (i.e., thrombolytic and/or endovascular treatment) performed
- Presence of either interictal or ictal activity at the EEG in the next 24–72 hours
- No vascular occlusion seen on brain CT angiography performed immediately after the perfusion study
- All neurological signs and symptoms subsided during hospitalization

The clinical manifestations included weakness or plegia of one limb, aphasia, sensory deficits, or loss of consciousness. Exclusion criteria included presence of new focal structural brain abnormalities at the time of presentation in the emergency department (assessed by CT and CT angiography scans) and CTP scan of poor quality.

IMAGING ACQUISITION PROTOCOL

CTP was performed using a multidetector row scanner (Brilliance 64; Philips Healthcare, Best, Netherlands) as a 57.9

second biphasic cine series beginning 5 seconds after a power injection of 50 ml of contrast at 4 ml/s. The scan was performed in jog mode with two slabs of 4 cm for a total coverage of 8 cm. The scan consisted of 15 cycles with an inter-cycle delay of 4 seconds. Imaging parameters included 80 kVp, 125 mAs and 0.5 second rotation time.

IMAGING ANALYSIS

CTP data were post-processed with the Brain Perfusion application of the Intellispace Portal (Philips Healthcare, Best, Netherlands) [10], as previously described. MTT was measured in seconds and defined as the average amount of time it took the blood to transit through the given volume of brain maps. MTT maps were obtained by a mathematical description of time density curves for each voxel as a measure of the time between the arterial inflow and the venous outflow. TTP maps were measured by the time the contrast agent reached a maximal intensity. CBV was measured in units of milliliters of blood per 100 g of brain and defined as the volume of flowing blood for a given volume of brain. CBF was measured in units of milliliters of blood per 100 g of brain tissue per minute and defined as the volume of flowing blood moving through a given volume of brain in a specific amount of time. CBV maps were computed from the area under the time attenuation curves as an indication of blood volume available per unit of brain tissue, milliliters per 100 g of blood. Relative map values for each perfusion parameter were obtained by a normalization per-voxel to the contralateral hemisphere. All CTP and perfusion maps were reviewed by both board-certified neuroradiologists and neurologists for qualitative and quantitative analysis. Statistics were performed using a two-tailed *t* test for differences between means and a value of $P < 0.05$ was considered significant.

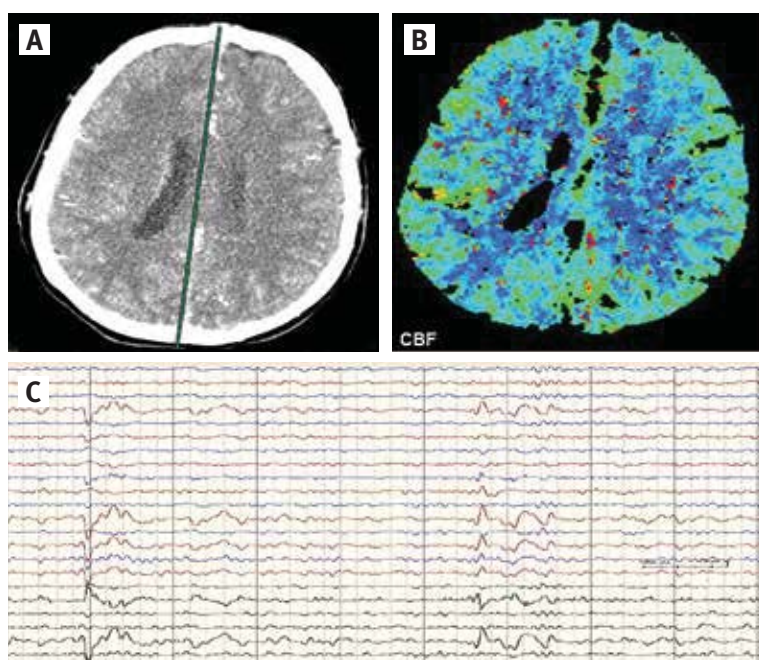
ELECTROENCEPHALOGRAMS

An EEG using 21 electrodes placed according to the International 10–20 system was performed by a certified EEG technician within 24–72 hours of the patient's admission to the hospital and the records were interpreted by board-certified neurologists.

RESULTS

Of the 721 patients who were admitted between January 2012 and June 2015 to our hospital for a suspected acute stroke and who underwent multimodal CTP within 8 hours of symptom onset, only 10 individuals complied with the inclusion criteria of this study. In this group, CTP maps were retrospectively reviewed upon performance of an EEG showing either ictal or interictal activity [Figure 1]. Based on the EEG, an epileptic focus was identified at the frontal lobe either in the right or left hemisphere. For analysis purposes, these areas were labeled

Figure 1. CTP maps reveal metabolic changes which correlate with EEG findings. **[A]** CT and **[B]** CTP findings point toward hypoperfusion of the left frontal lobe in absence of structural pathology. **[C]** EEG shows interictal activity composed of spike and wave activity localized at the left frontal hemisphere



CT = computed tomography, CTP = CT perfusion, EEG = electroencephalography

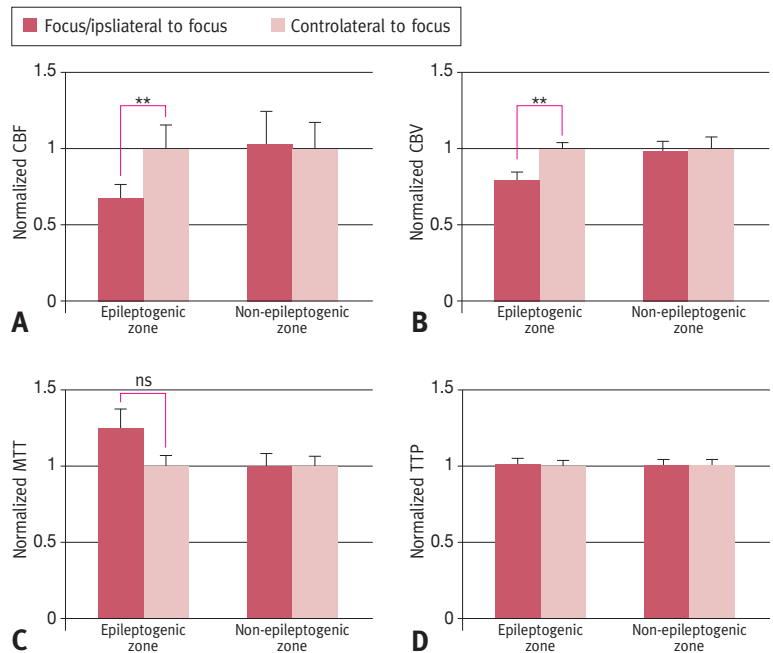
as “epileptogenic zone” and CTP map values at this level were normalized to their contralateral side. To evaluate the specificity of the detected changes, we similarly analyzed CTP maps at the cerebellum (“non-epileptogenic zone”) both ipsilateral and contralateral to the “epileptogenic zone”. Among others, this brain area was chosen as it does not share common vasculature or is thought to participate in the ictogenic processes of the “epileptogenic zone.”

Our analysis detected a decreased CBV (0.78 ± 0.056) and CBF (0.68 ± 0.090) at the focus of the “epileptogenic zone” compared to its contralateral side (1.12 ± 0.038 , $P < 0.001$ and 1 ± 0.16 , $P < 0.001$ for CBV and CBF respectively) [Figure 2A, 2B]. Interestingly, no differences in CBV and CBF were detected at the “non epileptogenic zone” that were both ipsilateral and contralateral to the epileptic focus. This finding indicates that changes of CBV and CBF specifically occur at the epileptic focus. Remarkably, however, no change could be detected in MTT and TTP both in the “epileptogenic zone” and “non-epileptogenic zone” at the focus or ipsilateral to it and at the contralateral side [Figure 2C, Figure 2D]. Altogether, these data show that CTP may specifically detect metabolic changes at the epileptic focus.

DISCUSSION

In this study, we evaluated patients who arrived to our emergency department presenting with acute stroke-like symptoms. Out of a potential of 25 participants, 10 met our selection criteria and had no brain pathology that could have altered perfusion parameters. Of these ten, clinical presentation of six patients showed hemiparesis, two displayed signs of aphasia, one experienced loss of consciousness and one patient presented headache and arm weakness. All patients had abnormal EEG following the episode without evidence of vascular occlusion seen on brain CT angiography. In addition, seven out of the ten participating subjects performed post hoc imaging (five were brain MRIs including diffusion and ADC protocols) and no evidence of a new ischemic lesion was detected. We found a specific reduction in CBV and CBF at the area of the epileptic focus occurring in the immediate postictal state when the clinical findings may simulate a stroke-like episode. Indeed, these findings differ from those detected in the infarcted tissue where areas of decreased CBF and CBV match with increased MTT and TTP due to a delay in blood flow over time in the tissue [10]. Therefore, this study supports the possibility that perfusion maps in the setting of acute neurological deficit may be used to distinguish between these two different etiologies. It is well documented that SPECT perfusion parameters have been widely used for the location of elusive epileptic foci. Indeed, using this technique, hypometabolism at the epileptic focus can be detected in patients after relatively brief complex partial seizures that may decline even more for 24–48 hours.

Figure 2. CBF and CBV are reduced at the epileptogenic focus. With seizures, CTP is able to detect a specific reduction in CBF [A] and CBV [B] at the epileptogenic focus compared to a homolateral non-epileptogenic area. No changes could be detected for MTT [C] or TTP [D] at the same areas



CBF = cerebral blood flow, CBV = cerebral blood volume, MTT = mean transient time, TTP = time to peak
 ** $P < 0.01$

This phenomenon is commonly referred to “postictal switch” and opposes the hypermetabolism detected in the same areas during the ictal state [11,12]. In contrast, little is known about changes in CT perfusion parameters following epileptic seizures. This finding represents a drawback since this imaging modality is readily available in emergency settings. Moreover, CTP may be a faster tool for assessing cerebral hemodynamics in the setting of acute neurological deficits.

This study brings up an additional, interesting speculation. While our patients presented with a transient acute focal neurological deficit, do the observed changes in CBV and CBF underlie the pathophysiological mechanisms of such a clinical phenomenon? In this respect, would a change in CBV and CBF trigger the postictal Todd’s phenomenon [7,13]? Indeed, while one theory calls for the “exhaustion phenomenon” in which neurons are hyperpolarized after electrical discharge and thus less reactive, the alternative theory is vascular related. In support of the latter, recent studies have reported a decrease in brain blood perfusion in ictal foci following seizure [14] and as such a dysregulation of neurovascular coupling [15]. Our study showed that a decreased perfusion in areas that correlated with the clinical deficit may provide further support that a deficit in neurovascular coupling may be responsible for these phenomena.

While we report interesting observations, we need to concede that our study presents some limitations. Our sample size is small and further studies on a larger population need to be performed to increase the power of analysis. In addition, our patient population was heterogeneous in terms of age and pre-morbidity, thus we may not exclude that such factors may influence the interpretations of the results. An additional argument should consider whether a clear differentiation could be found between a transient ischemic attack (TIA) or a seizure as a cause of the observed clinical symptomatology and thus the imaging data. At the time of arrival at the emergency department the patients were either unconscious or found alone without anybody who could confirm an etiology of seizures to the physician. Thus, at the moment, we cannot provide direct evidences that may differentiate between these two different etiologies. However, we must concur that neurological signs or symptoms lasting more than 24 hours are associated to brain infarction detected with the post hoc imaging [16]. In this respect, in our study, brain imaging on resolution of the symptoms was normal. In addition, CTP changes reported upon TIA differ from those reported in our present study, specifically TTP was not increased if seizures were not from an ischemic etiology [17]. Thus, considering these evidences, a suspected TIA etiology of our findings may be unlikely.

Finally, our retrospective design may not allow a better estimate of the CTP performance over other imaging modalities such as MRI perfusion.

CONCLUSIONS

In conclusion, we report that a specific reduction in CBV and CBF may be detected in the postictal phase using CTP and this may hint to a possible use of such imaging modality in emergency settings to discriminate between acute stroke and its mimics such as seizures [18,19].

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Capsule

A promising therapeutic target in HIV pathogenesis

Antiretroviral therapy (ART) effectively limits human immunodeficiency virus (HIV) replication. Nevertheless, HIV+ individuals need to be medicated for life because ART withdrawal results in rebound of persistent virus. One emerging approach to target HIV is an antibody against integrin $\alpha 4\beta 7$. Integrin $\alpha 4\beta 7$ is a receptor that facilitates homing of CD4+ T cells to the gut, a key site for HIV persistence. Guzzo

and colleagues found that integrin $\alpha 4\beta 7$ is incorporated into the HIV envelope, suggesting that antibody treatment may directly interfere with the ability of HIV to home to intestinal tissues. Their results change our perception of the role of integrin $\alpha 4\beta 7$, a promising therapeutic target in HIV pathogenesis.

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