Computed tomography perfusion as a diagnostic tool for seizures after ischemic stroke

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Abstract

Introduction: Cerebral cortical ischemia is a risk factor for post-stroke seizures. However, the optimal imaging method is unclear. We investigated CT perfusion (CTP) in detecting cortical ischemia and its correlation with post-stroke seizures compared with non-contrast CT (NCCT).

Methods: We included patients with acute ischemic stroke admitted to the Royal Melbourne Hospital between 2009 and 2014. Post-stroke seizure information was collected. Cortical involvement was determined on acute NCCT and CTP (Tmax, cerebral blood volume [CBV], cerebral blood flow [CBF]). The association between cortical involvement detected by different imaging modalities and post-stroke seizures was examined.

Results: 352 patients were included for analysis. 59% were male, median age was 73 years (interquartile range 61-82). Follow up was available for 96%; median follow up duration was 377 days (interquartile range 91–1018 days). Thirteen patients had post-stroke seizures (3.9%). Cortical involvement was significantly associated with post-stroke seizures across all modalities. CBV had the highest hazard ratio (11.3, 95%CI 1.1 – 41.2), followed by NCCT (5.3, 95%CI 1.5 – 18.0) and CBF (4.2, 95%CI 1.1 – 15.2). Sensitivity was highest for Tmax (100%) followed by CBV and CBF (both 76.9%), and NCCT (63.6%). Specificity was highest for CBV (77.8%), then NCCT (75.6%), CBF (54.0%), and Tmax (29.1%). Receiver operating characteristics area under the curve was significantly different between imaging modalities ($p<0.001$); CBV: 0.77, NCCT 0.70, CBF 0.65, Tmax 0.65.

Conclusion: CTP may improve sensitivity and specificity of cortical involvement for post-stroke seizures compared to NCCT.

Keywords

Ischemic stroke, CT-perfusion, non-contrast CT, post-stroke epilepsy, seizures

Introduction

Stroke is the most common risk factor identified in adults with new onset epilepsy in developed countries [1]. Up to 12% of patients experience seizures after stroke [2-5]. Post-stroke seizures are associated with increased mortality, prolonged hospital stays and loss of independence [6,7]. Involvement of cerebral cortex, whether hemorrhagic or ischemic, is one of the most consistent risk factors for post-stroke seizures [8,4,3,2,5,9]. The association appears independent of infarct size [1]. The optimal method to detect cortical involvement has not been established. Studies have tended to combine findings from different modalities for analysis despite their differing sensitivities. Most studies have relied on non-contrast CT (NCCT) because of its widespread availability and its essential role as the first line of imaging in patients presenting with acute stroke [10,5]. Some studies have supplemented NCCT with MRI in selected patients using a variety of sequences, which have markedly different degrees of sensitivity in detecting acute ischemic stroke [3,4,11,12]. Although MRI with diffusion weighted imaging (DWI) is regarded as the gold standard to detect early ischemia, its use in mainstream acute stroke protocols is limited. In two separate studies of acute stroke imaging, fewer than 60% of eligible patients were able to undergo MRI protocol for reasons including incompatible devices, medical instability and scanner unavailability [13,14]. Therefore an alternative with greater sensitivity than NCCT, but fewer practical limitations than MRI, is desirable.

CT perfusion (CTP) is gaining popularity in acute stroke imaging due to its ability to visualize early infarcted tissue as well as at-risk ischemic penumbra [15]. Combined NCCT/CT angiography (CTA)/CTP has been found to have 80% sensitivity in detecting acute ischemia compared to 58% with NCCT/CTA, and 45% with NCCT alone [16]. Compared to DWI, CTP has similar sensitivity, but has the advantages of being more widely available, requires considerably less scanning time, and avoids issues with incompatible devices [16,17]. Its use has not yet been explored in relation to post-stroke seizures.

This study aimed to determine cortical involvement in ischemic stroke using NCCT and CTP, and to subsequently estimate its association with post-stroke seizures depending on imaging modality. We hypothesized that the greater sensitivity of CTP would increase the detection of cortical involvement, thereby improving the utility of cortical involvement as a diagnostic marker for post-stroke seizures.

Methods

Subjects

Subjects were identified from a prospective database of patients admitted under the acute stroke unit at the Royal Melbourne Hospital. Patients who were diagnosed with ischemic stroke and underwent CTP at admission were eligible for inclusion. We included patients from April 2009 onwards when CTP was introduced in stroke imaging in our hospital. Patients were included up to October 2014. The hospital provides services to adults over 18 years of age; no other age limit was imposed. Patients were contacted via phone survey for the occurrence of seizures before and after stroke using a questionnaire modified from Tan et al [18], supplemented by hospital records. Patients with no follow up information, history of seizures prior to stroke or previous stroke were excluded (Figure 1). Ethical approval was granted by the Melbourne Health Human Research Ethics Committee (project number QA2010089).

Data collection

Information extracted from the database included age, sex, vascular risk factors, presentation time, Oxfordshire stroke classification and use of thrombolytic treatment. Follow up information collected included time from stroke to first seizure, seizure recurrence and use of anti-epileptic medications. In accordance with guidelines from the International League Against Epilepsy [19,20], seizures within 7 days of stroke were classified as early seizures and those after 7 days as late seizures. Post stroke epilepsy was defined as recurrent late seizures, or a single seizure occurring more than one month after stroke.

Imaging protocols

CT scans were acquired with a Siemens Somatom multidetector scanner (Siemens, Erlangen, Germany). Acute NCCT scans (5 mm thick slices) within 12 hours of stroke onset were included. For CTP, 40mL of iodinated contrast was injected intravenously at 8 mL/s in the cubital fossa where possible. CTP processing at the Royal Melbourne Hospital changed during early 2012. Prior to this (n = 132), two separate slabs at the ganglionic and supraganglionic levels were obtained as 2 x 12 mm thick slices each. Images were taken every second for 40 seconds following an initial 4 second delay. Perfusion maps were acquired using Siemens software (Siemens Syngo, NeuroPCT, Siemens). More recent scans (n = 220) obtained full brain coverage with 10 x 10 mm thick slices. Following an initial 4 second delay images were taken every second for 300 seconds. Perfusion maps were acquired using RAPID software (RAPID, noncommercial research version, Stanford University). Inter-test variability was performed on those patients with perfusion maps obtained with both types of processing during the transition.

MRI with DWI was also performed for a subset of patients (n=179), at clinical discretion; where ischemic lesions were not initially detected with NCCT or CTP, or to assess reperfusion or extension post intervention. DWI images were acquired with a 1.5T scanner (Signa, GE Healthcare, Milwaukee, Wisconsin). DWI images (5mm thick slices) acquired within 7 days of stroke onset were included for analysis.

Image analysis

Acute NCCT and CTP scans were evaluated for the presence or absence of cerebral cortical involvement (Figure 2). Perfusion maps included were Tmax, cerebral blood volume (CBV) and cerebral blood flow (CBF). Areas of reduced CBV, CBF and elevated Tmax indicate infarcted tissue, while areas of elevated Tmax with preserved CBV and CBF indicate ischemic penumbra. For NCCT, criteria for cortical involvement were loss of grey-white matter differentiation and sulcal effacement. Involvement on Tmax required a value greater than 6 seconds, a previously validated threshold [17], in a cortical region. Involvement on CBV and CBF was counted where

there was unequivocal asymmetric reduction in a cortical region. For DWI images, cortical involvement was determined by increased signal intensity. In all cases changes needed to be visible in at least two adjacent slices to determine cortical involvement. Analysis was performed by a research fellow with training in advanced neuroimaging. Images were analysed out of time with seizure data collection to avoid interviewer bias. 10% of scans were randomly selected for analysis by an experienced neuroradiologist for inter-rater variability.

Statistical analysis

Continuous variables were compared using Wilcoxon Mann-Whitney U test, categorical variables were compared using Fisher's exact test. Inter-rater and inter-method agreement was estimated with Cohen's Kappa. Time-to-event analysis with Cox proportional hazards model was performed with the event of interest defined as time to the first post-stroke seizure. To investigate the utility of cortical involvement as a diagnostic marker for seizures after stroke, receiver operating characteristics (ROC) curve analysis was performed for all four imaging modalities. Areas under the ROC curve (AUC) for different modalities were compared with the Chi-squared test, using data from patients who had undergone all four types of scans. Analysis was performed with Stata statistical software (Stata 13.0, College Station, TX: Statacorp LP). A two-tailed p value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 352 patients were eligible for inclusion. Their median age was 73 (interquartile range 61 - 82), and 59% were male. The median onset to presentation time was 126 minutes (inter-quartile range 68 – 298 minutes), 45% were treated with IVtPA, and the most common stroke type was partial anterior circulation infarct (PACI).

Comparison of characteristics of those who received CTP and those who did not over the same time period are shown in table 1. There was no significant difference in age, sex or premorbid function

as measured by modified Rankin Scale (mRS). As expected, those who underwent CTP presented earlier, and a higher proportion received ivtPA. They were also more likely to have atrial fibrillation, hypertension, and an anterior circulation stroke compared to those who did not have CTP imaging.

Seizure data follow up

Follow up information was available for 341 out of 352 patients. Median follow up time after stroke was 377 days (inter-quartile range 91 to 1018 days). Four patients were excluded due to a history of pre-stroke seizures, leaving 337 for analysis. Of these 337 patients, 13 reported post-stroke seizures (3.9%); 5 (1.5%) had early seizures, and 9 (2.7%) had post stroke epilepsy (one patient had both). The median time from stroke to seizure occurrence was 76 days (IQR 5 – 167 days). Characteristics of those with post-stroke seizures and those without are shown in table 2. Those with post-stroke seizures were more likely to be female and have a total anterior circulation infarct (TACI) than those without post-stroke seizures.

Image analysis

Inter-method agreement in identifying cortical involvement between Siemens and RAPID processing software was substantial (kappa 0.65). Inter-rater agreement for cortical involvement on CTP was almost perfect: kappa for Tmax was 1.0, CBV 0.89, CBF 1.0, and on NCCT was substantial (kappa 0.79) [21].

Five patients' Tmax maps were excluded due to inadequate quality, and 27 patients did not have a NCCT within 12 hours. 80/310 patients (26%) were found to have cortical involvement on NCCT, 82/337 (24%) on CBV, 159/337 (47%) on CBF and 239/332 (72%) on Tmax. Because of the small number, all patients reporting seizures were combined for analysis. Survival analysis and ROC analysis results are shown in table 3. Across all imaging modalities, those with cortical involvement were more likely to experience a post-stroke seizure. Cortical involvement on CBV had the highest hazard ratio for post-stroke seizures at 11.3 (95% confidence interval (95%CI) 3.1 – 41.2, $p <$

0.001). The corresponding hazard ratio on CBF was 4.2 (95%CI 1.1 – 15.2, $p = 0.030$), and NCCT was 5.3 (95%CI 1.5 – 18.0, $p = 0.008$). All patients with post-stroke seizures had cortical involvement on Tmax, hence no hazard ratio was calculated. Accordingly Tmax was the modality where cortical involvement exhibited the highest sensitivity for seizures, at 100%. On both CBV and CBF, cortical involvement had 76.9% sensitivity, and on NCCT it was 63.6%. The modality with the highest specificity of cortical involvement as a diagnostic marker for post-stroke seizures was CBV at 77.8%, followed closely by NCCT at 75.6%, CBF at 54.0% and Tmax at 29.1%. Because of the low number of post-stroke seizures in this cohort, all modalities had high negative predictive values (Tmax 100%, CBV 98.8%, CBF 98.3%, NCCT 98.3%) but low positive predictive values (CBV 21.2%, NCCT 8.8%, CBF 6.3% and Tmax 5.0%). ROC AUC in descending order was CBV: 0.77 (95%CI 0.65 – 0.89), NCCT 0.70 (95%CI 0.55 – 0.85), CBF 0.65 (95%CI 0.53 – 0.78), Tmax 0.65 (95%CI 0.62 – 0.67). There was a significant overall difference in AUC between modalities ($p < 0.001$), suggesting that the utility of cortical involvement as a diagnostic marker for post-stroke seizures depends on the imaging modality.

Given the small proportion of patients with DWI, analysis was limited to a qualitative description of the findings. Of the 179 patients with DWI within 7 days of stroke onset, 118 (65.9%) had cortical involvement and 61 (34.1%) did not. Five in the former group and one in the latter group developed post-stroke seizures.

Discussion

As far as we are aware this is the first study to report the use of CTP in the investigation of post-stroke seizures. A limitation of the previous research in this field is the lack of standardization of imaging methods, employing different methods between and even within studies to detect cortical involvement. This study aimed to address this by separating analysis depending on the type of neuroimaging.

The analysis confirmed the importance of cerebral cortical involvement in epileptogenesis, as cortical involvement was associated with a significantly increased risk of post-stroke seizures regardless of the imaging modality used. The analysis also showed that the imaging modalities used in this study are not equal in their detection of cortical involvement and therefore may be of differing utility in the prediction of post-stroke seizures. Although they all displayed high degrees of sensitivity, CBV had the highest specificity (77.8%), positive predictive value (21.2%), hazard ratio (11.3) and ROC AUC (0.77), suggesting that it may be the most clinically useful of the modalities examined.

Owing to the small number of patients with post-stroke seizures, it was not feasible to perform separate subgroup analyses for early seizures, late seizures and post-stroke epilepsy. The etiology of these different types of seizures is thought to differ, however cortical involvement has been implicated in all types of post-stroke seizures [8,4,3,2,5,9]. Analyzing the subgroups of seizures separately would be of interest in future, larger studies. It would have been useful to examine follow up NCCT, which has greater sensitivity than acute NCCT in detecting ischemic infarction [22]. However in practice, follow up NCCT is not always performed. In this cohort only 217 patients (64%) received a follow up NCCT between 12 - 72 hours post stroke. This study is also limited by the relatively short duration of follow up, with the median at just over one year. However it has been shown that the majority of late onset seizures occur within the first year after stroke [23]. Further, the overall rate of post-stroke seizures in this study is consistent with the literature [2,4,3]. With these limitations in mind, the data nonetheless provide clear direction for further research focusing on the CBV parameter in selecting patients at increased risk of post-stroke seizures.

It is unknown whether CTP would be equally useful in the larger group of acute stroke patients who did not receive CTP as part of their routine investigations. Under current practice, patients who present early are more likely to undergo CTP imaging to guide thrombolysis and endovascular treatment decisions [15]. We have previously shown that ivtPA treatment does not influence the development of post-stroke seizures [18]. Those in the CTP group were more likely to have

hypertension and atrial fibrillation, although these risk factors were not associated with the development of post-stroke seizures in this study, nor in others [24,25]. There was a higher proportion of anterior circulation strokes in those receiving perfusion imaging, which has been reported as a risk factor for post-stroke seizures compared to non-anterior circulation stroke [2].

CTP has been shown recently to improve acute stroke management [15]. Findings from this study suggest that it may also inform longer-term outcome. The apparent difference between imaging modalities suggests that carefully targeted neuroimaging should be considered in future studies. For example, risk factors for post-stroke seizures have been combined in an overall risk scale, one of which is cortical involvement [11]. Ensuring the use of the most appropriate imaging modality to identify cortical involvement could be one way to improve the scale.

The findings from this study may also help to guide stratification of stroke patients for follow up. Undiagnosed and uncontrolled epilepsy can markedly impair patients' quality of life, and incurs substantial costs for health services [26,27]. It would be useful to select patients at increased risk of post-stroke seizures for more prolonged specialist follow up, ensuring timely diagnosis and treatment as this is better done under specialist care than in the community [26]. This study indicates that targeted neuroimaging can be used to help select these patients. It is possible that those with cortical involvement on CBV are suitable candidates for longer term monitoring. Finally, this study provides support for CTP to become more widely used in acute stroke imaging, as it has the potential to better inform clinicians of patients' seizure risk.

Conclusion

These findings highlight the difference in the ability of different imaging modalities as potential diagnostic tools for post-stroke seizures. They also provide support for the increasing use of CTP in clinical practice. It seems that CTP may provide a way to enhance our detection of patients at higher risk, with CBV showing particular promise.

Compliance with ethical standards

We declare that all human and animal studies have been approved by the Melbourne Health Human Research Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of Interest

We declare that we have no conflict of interest.

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Figure legends

Fig. 1. Patient Flow Diagram. Patients were excluded from the initial pool of 1636 admitted to the Royal Melbourne Hospital Stroke Unit with a first ischemic stroke during the study period due to lack of CT perfusion imaging ($n = 1284$), lack of follow up information ($n = 11$) and pre-stroke seizures ($n = 4$), leaving 337 for analysis.

Fig. 2. CT perfusion and non-contrast CT images from two patients showing examples with and without cerebral cortical involvement. Row A: Patient with right middle cerebral artery territory ischemic stroke. Cerebral cortical involvement was detected on all imaging modalities. Row B: Patient with right cerebellar stroke. No cerebral cortical involvement was detected on any imaging modalities. CBV: cerebral blood volume, CBF: cerebral blood flow, NCCT: non-contrast computed tomography.

Table 1. Baseline characteristics of patients who received CTP imaging and those who did not during the study period (April 2009 to October 2014).

	CTP performed	No CTP performed	p value*
Number	352	1284	
Age (median, IQR)	73 (61, 82)	72 (61, 82)	0.62
Sex (male)	59%	56%	0.36
Oxfordshire stroke subtype			
TACI	30.1%	18.1%	<0.001
PACI	50.0%	37.5%	<0.001
POCI	9.7%	30.3%	<0.001
LACI	8.5%	12.1%	0.07
Premorbid mRS (median, IQR)	0 (0, 2)	0 (0, 2)	0.45
Diabetes	24%	25%	0.45
Atrial Fibrillation	32%	20%	<0.001
Hypertension	59%	44%	<0.001
Hypercholesterolemia	50%	53%	0.28
Smoking	19%	21%	0.27
ivtPA received	45%	12%	<0.001
Onset to presentation, minutes (median, IQR)	126 (68, 298)	292 (103, 722)	<0.001

*Dichotomous variables were tested with Fisher's exact test; continuous variables were tested with Mann-Whitney U test.

CTP: CT-Perfusion, TACI: total anterior circulation infarct, PACI: partial anterior circulation infarct, POCI: posterior circulation infarct, LACI: lacunar infarct, mRS: modified rankin scale, IQR: inter-quartile range, ivtPA: intravenous tissue plasminogen activator.

Table 2. Characteristics of patients with and without post-stroke seizures.

	Post-stroke seizure	No seizure	p value*
Number	13	324	
Age (median, IQR)	75 (56 - 79)	73 (61 - 81)	0.70
Sex (male)	31%	60%	0.04
Oxfordshire stroke type			
TACI	53.9%	23.8%	0.02
PACI	38.5%	55.8%	0.26
POCI	7.7%	10.4%	0.61
LACI	0.0%	9.2%	0.62
Premorbid mRS (median, IQR)	0 (0, 0)	0 (0, 1)	0.04
Diabetes	39%	23%	0.19
Atrial Fibrillation	23%	38%	0.39
Hypertension	85%	59%	0.08
Hypercholesterolemia	45%	47%	0.58
Smoking	15%	21%	0.46
ivtPA received	46%	46%	0.61
Onset to presentation, min (median, IQR)	125 (61, 425)	127 (68, 296)	>0.99

*Dichotomous variables were tested with Fisher's exact test; continuous variables were tested with Mann-Whitney U test. The groups differ significantly in sex, the proportion with TACI and premorbid mRS.

TACI: total anterior circulation infarct, PACI: partial anterior circulation infarct, POCI: posterior circulation infarct, LACI: lacunar infarct, mRS: modified rankin scale, IQR: inter-quartile range, ivtPA: intravenous tissue plasminogen activator.

Table 3. Survival analysis and receiver operating characteristics analysis for the risk of post-stroke seizures with cortical involvement, by imaging modality.

	Hazard ratio (95% confidence interval)	Sensitivity	Specificity	NPV	PPV	ROC AUC (95% confidence interval)*
Tmax[†] (n=332)	-	100%	29.1%	100%	5.0%	0.65 (0.62 – 0.67)
CBV (n=337)	11.3 (3.1 – 41.2)	76.9%	77.8%	98.8%	21.2%	0.77 (0.65 – 0.89)
CBF (n=337)	4.2 (1.1 – 15.2)	76.9%	54.0%	98.3%	6.3%	0.65 (0.53 – 0.78)
NCCT[‡] (n=310)	5.3 (1.5 – 18.0)	63.6%	75.6%	98.3%	8.8%	0.70 (0.55 – 0.85)

*ROC AUC was significantly different between modalities ($p < 0.001$, Chi squared test).

[†] No hazard ratio was calculated for Tmax as it showed cortical involvement in all patients with post-stroke seizures. Five patients' Tmax maps were excluded due to inadequate quality.

[‡] Twenty-seven patients did not have NCCT.

CBV: cerebral blood volume, CBF: cerebral blood flow, NCCT: non-contrast CT, NPV: negative predictive value, PPV: positive predictive value, ROC AUC: receiver operating characteristics area under the curve.