# Degree of Conjugate Gaze Deviation on CT Predicts Proximal Vessel Occlusion and May Expedite Endovascular Therapy

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*Purpose*: Recent trials have demonstrated superior outcomes with combination IV-tPA and endovascular therapy (EVT) within 6 hours of symptom onset in patients with proximal vessel occlusion (ICA, M1, or proximal M1/M2) compared to IV-tPA alone. The current standard of diagnosis for consideration of EVT is CT angiogram (CTA). Unfortunately, not all hospitals are equipped with CTA, and the decision to transfer to tertiary centers is often based on nonenhanced CT. Ipsilateral conjugate gaze deviation (CGD) is associated with worse outcomes and larger infarcts in acute ischemic stroke. We predicted that the more proximal the occlusion, the higher the degree of CGD. *Materials and Methods*: Over a period of 12 months, 182 consecutive patients with acute ischemic stroke treated at our institution were prospectively analyzed. Stroke locations were categorized based on CTA. Average degree of CGD was measured. Patient demographics, ASPECTS, collateral score, National Institutes of Health Stroke Scale, modified Rankin Scale, TICI score, length-of-stay, and mortality were collected. The median follow-up was 30 days. *Results*: Out of ninety one of 182 patients with (+) CGD, 82 (90%) patients had ICA or middle cerebral artery (MCA) territory infarcts. The median was 25.0° in those with proximal occlusion and 13.7° in those with distal MCA occlusion ($P < .001$). A higher degree of CGD is positively correlated with proximity of vessel occlusion (correlation coefficient 0.2; $P < .05$). A cut-off greater than 20.25° (area under the curve = .76) showed a sensitivity of 64.0% and specificity 84.2%. *Conclusions*: Measuring degree of CGD may help in early identification of proximal vessel occlusions and expedite transfer for clot retrieval.

**Key Words:** Acute ischemic stroke—conjugate gaze deviation—computed tomography (CT)—endovascular therapy



## Introduction

Stroke is the third highest cause of mortality worldwide and a leading cause of serious long-term morbidities. In acute ischemic stroke (AIS), each minute of delay in treatment corresponds to a loss of 1.9 million neurons.[1] Recently, landmark trials such as MR CLEAN[2] and ESCAPE[3] showed that prompt combination therapy with IV-tPA and endovascular therapy (EVT) within 6 hours of symptom onset in patients with AIS secondary to proximal vessel occlusion (ICA, M1, and M1/2) significantly improved neurological status and mortality compared to IV-tPA alone. However, triaging all suspected strokes to EVT capable sites will overwhelm their system with nonproximal strokes and stroke mimics but also negatively impact nonproximal stroke patients through additional travel time and missed intravenous thrombolysis

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opportunities. Therefore, early identification of EVT candidates is of critical importance.

In order to identify candidates for EVT, patients require CT angiography (CTA), the current gold standard in noninvasive diagnosis of proximal vessel occlusion.[4,5] Unfortunately, not all hospitals are equipped with CTA and EVT capabilities, and the initial diagnostic test consists of nonenhanced CT (NECT) alone. Although early NECT signs of ischemia (blurring of the gray-white matter junction, loss of the insular ribbon, effacement of the sulci, and hyperdense vessel) are important findings that point toward ischemic stroke, these signs are frequently not present.[4-6] Therefore, finding a simple yet objective sign on NECT head that offers clinicians diagnostic utility in identifying proximal vessel occlusions may help to expedite potential candidates for EVT treatment.

In supratentorial AIS, conjugate gaze deviation (CGD) has been shown to be almost exclusively directed toward the affected hemisphere.[1,6,7] This ipsilateral deviation is a result of dysfunction of cortical regions or subcortical fibre tracts involved in the control of voluntary eye movements. It is hypothesized that the frontal eye fields (FEF; Brodmann area), basal ganglia, parietal eye fields as well as neighbouring temporoparietal cortical regions are important areas in this context and are coincidentally regions predominantly supplied by the middle cerebral artery (MCA).[8,9] Previous studies have found that CGD correlates with worse neurological symptoms at onset, worse patient outcome and increased mortality in AIS.[4,7,8,10] Therefore, the more proximal the occlusion, the greater the vascular territory involved, and in turn, the worse the neurological impairment and patient outcome. Thus, our group hypothesizes that the higher degree of gaze deviation correlates with more proximal the vessel occlusion. In addition, by identifying the cut-off for differentiating between proximal versus nonproximal occlusion, we hope to identify patients who would potentially benefit from transfer to comprehensive stroke centers for rapid combination therapy from peripheral centers without CTA/EVT capabilities.

## Methods

### *Patient Characteristics*

During a study period of 12 months (between April 2016 and2017), 225 consecutive code stroke patients (<6 hours after symptom onset) admitted for treatment at our regional stroke center (Hamilton General Hospital) were prospectively evaluated. All patients were assessed by a stroke neurologist upon arrival and underwent NECT head and CTA carotids for confirmation of location of vessel occlusion, infarct core (ASPECTS) and collateral vessel status (good, intermediate, and poor). Out of the 225 consecutive code stroke patients admitted for treatment at our regional stroke center (Hamilton General Hospital), who were prospectively evaluated, forty-three patients were excluded from the study. We finally ended up with 182 consecutive code stroke patients in the study.

Patient demographics such as age, sex, blood pressure, clinical presentations were collected. Stroke severity is classified according to clinical parameters including National Institute of Health Stroke Scale (NIHSS) score at time of presentation ($NIHSS_{pre}$), immediate post-treatment ($NIHSS_{post}$), and 24-hour post-treatment ($NIHSS_{24h}$). TICI score was collected for patients who underwent EVT. The median follow-up was 30 days. Stroke severity at discharge from the hospital was assessed using the modified Rankin Scale, length-of-stay, in-hospital mortality, and 30-day mortality. The study was approved by the local ethics committee.

### *Assessment of Conjugate Gaze Deviation*

Patients were not given any instructions as to where to direct their gaze during the examination and no features of the layout of the CT suite were identified which would direct a patient's gaze. Both anterior circulation and posterior circulation occlusions were included. Eye deviation was determined for both globes from the initial NECT head obtained at time of initial clinical presentation with the method proposed by Coffman et al 2015. Images were reviewed and angles recorded by a radiologist (NJ) who, although not blinded to patient's data, completed all measurements before reviewing the patient chart and CTA for final diagnosis. Given that an objective and reproducible measurement for gaze deviation was used, the potential for bias was mitigated. The first line was drawn anteroposteriorly through the midline nasal structures; the second line was perpendicular to the midline; and the third line was drawn through the horizontal axis of each lens.[8] The angle of deviation was then calculated for each orbit at the intersection of the second and third lines[8] (Fig 1). The average gaze deviation for both eyes was obtained for each patient. To account for random error, only patients with average gaze deviation greater than 5° was considered for assessment of CGD. Therefore, patients with both ipsilateral gaze deviation and mean gaze deviation greater than 5° were considered as (+) CGD. Those with no eye deviation (<5°), contralateral gaze deviation, and disconjugate eye deviation were considered (−) CGD.

### *Statistical Analysis*

The study population was dichotomized into patients with proximal occlusion and those nonproximal occlusions. Baseline characteristics and outcome measures were compared between cohorts. Fisher's exact test was used for categorical variables and the Mann-Whitney *U* test as used for continuous variables. Univariate ANOVA

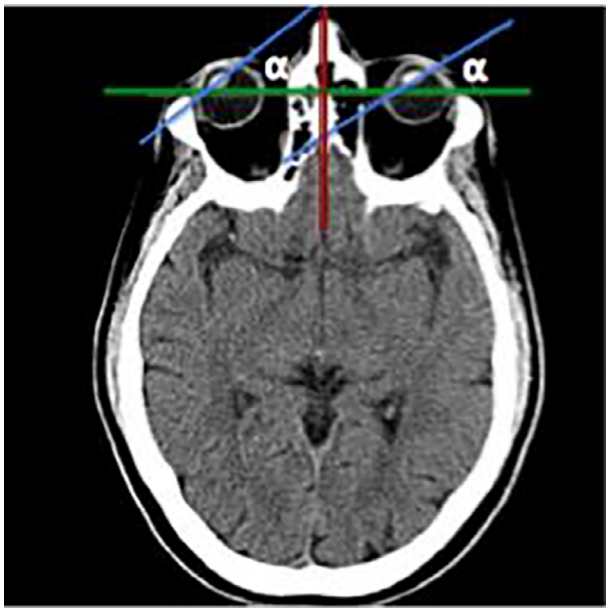


**Figure 1.** *Measuring gaze deviation (α) on noncontrast CT scan of the head in a stroke code patient presenting to the emergency department.*

was used to evaluate mean degree of CGD and patient baseline characteristics and outcome measures. Receiver operating characteristic (ROC) analysis was performed to demonstrate the sensitivity and specificity of increasing degrees of CGD in the prediction of proximal occlusion. Empirical ROC curves were plotted and area under curve (AUC) calculated with 95% confidence interval (CI) via bootstrap. Results were considered statistically significant for *P* value less than or equal to .05. The statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL).

## Results

### *Clinical Features*

In our study, there were 89 males and 93 females with a median age of 69.5 years (range 29-95), $NIHSS_{pre}$ of 14 (range 2-30) and ASPECTS score of 7 (range 4-10). In total, there were 114 (63%) patients with proximal occlusion and 64 (37%) patients without proximal occlusion. Of the 114 patients with proximal occlusion, 50 underwent combined IV-tPA and EVT, 37 underwent EVT only, and 27 underwent IV-tPA only. The degree of CGD was significantly correlated with $NIHSS_{(pre)}$ ($P = .011$). The degree of CGD was not correlated with $NIHSS_{(post)}$, $NIHSS_{(24h)}$, modified Rankin Scale, ASPECT score, collateral score, TICI score, length-of-stay, or 30-day mortality. Mortality at 30 days was 22 out of 182 patients (12%).

### *Imaging Features of Acute Arterial Occlusion*

When compared with established surrogate markers for arterial occlusion such as the hyperdense artery sign (HAS), 84 out of 114 patients (73%) with proximal vessel occlusion had HAS. Of the 30 patients without HAS, 15 patients (50%) had +CGD. In our cohort, 40 out of 114 (35%) patients had only minimal or no loss of gray white (ASPECT 9 or 10) on initial NECT. Of these, 31 patients (78%) had +CGD. Interestingly, of the 8 patients without HAS or equivocal loss of gray-white differentiation on NECT, 5 patients (63%) had +CGD.

### *Degree Conjugate Gaze Deviation and Site of Vessel Occlusion*

Vessel occlusion location is determined by CTA demonstrated 30 patients at ICA, 74 at M1, 10 at M1/2, and 30 at distal MCA branches, 3 at ACA, 1 at posterior cerebral artery (PCA), 3 at posterior inferior cerebellar artery (PICA) (1 patient had both PCA and PICA occlusions), 7 at basilar, 3 at vertebral, and 21 without visualized occlusion. The distribution of CGD varied at each location (Table 1). Of 182 patients, 90 were (+) CGD. Of the (+) CGD patients, 72 (80.0%) had proximal occlusions, 10 (11.1 %) had distal MCA occlusions, 4 (4.4%) had posterior circulation occlusions (2 patients with PICA and 2 with vertebral occlusions), and 4 (4.4%) had no visible occlusion on CTA. The presence of CGD was significantly correlated with proximal occlusion ($P < .05$).

### *Degree of Conjugate Gaze Deviation Positively Correlates Proximity of Vessel Occlusion*

The median degree of CGD in those with proximal occlusion was 25.0° (95% CI: 20.5°-26.8°) which is significantly higher than in patients with distal MCA occlusion which is 13.7° (95% CI: 2.8°-8.5°; $P < .001$; Table 2). Examination of the histogram showcasing degree of conjugate gaze deviation in the ICA and MCA territories (Fig 2) revealed a positive trend between proximity of vessel occlusion and degree of CGD (correlation coefficient was 0.2, $P < .05$).

**Table 1.** *Distribution of CGD and types of ischemic stroke in study cohort*

| | Stroke type | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gaze deviation | ICA | M1 | M1/2 | MCA distal | ACA | PCA | PICA | Basilar | Vertebral | No Stroke | Total |
| Yes | 21 | 45 | 6 | 10 | 0 | 0 | 2 | 0 | 2 | 4 | 90 |
| No | 9 | 29 | 4 | 20 | 3 | 1 | 1 | 7 | 1 | 17 | 92 |
| Total | 30 | 74 | 10 | 30 | 3 | 1 | 3 | 7 | 3 | 21 | 182 |

Abbreviations: CGD, conjugate gaze deviation; MCA, middle cerebral artery.

**Table 2.** *Degree of gaze deviation and stroke type in patients with (+) CGD*

| Stroke type | n (%total) | Median | SE | 95% Confidence interval | |
|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound |
| ICA | 21 (23.3) | 26.0 | 2.1 | 18.5 | 26.5 |
| M1 | 45 (50.0) | 25.0 | 1.3 | 20.5 | 28.0 |
| M1/M2 | 6 (6.7) | 22.0 | 5.8 | 5.0 | 37.5 |
| MCA distal | 10 (11.1) | 13.7 | 1.6 | 10.3 | 18.5 |
| PICA | 2 (2.2) | 38.5 | 3.8 | 35.0 | 42.5 |
| Vertebral | 2 (2.2) | 11.5 | 6.0 | 5.5 | 17.5 |
| No stroke | 4 (4.4) | 12.5 | 2.8 | 6.5 | 20.0 |

Abbreviation: CGD, conjugate gaze deviation.

ROC curve analysis of the sensitivity and 1-specificity of (+) CGD in the prediction of proximal occlusion produced AUC = .76 (Fig 3). The diagnostic performance of a cut-off greater than 20.25° has a sensitivity and specificity of 64.0% and 84.2%, respectively. The positive likelihood ratio was 4.04 (95% CI: 1.03-4.55) and the negative likelihood ratio was .43 (95% CI: .32 - .69).

## Discussion

To our knowledge, this is the first study to identify positive relationship between degree of CGD and proximity of vessel occlusion ($P$ <0.01). The median CGD at ICA was 26.0°, M1 was 25.0°, M1/2 was 22.0°, while distal MCA was 13.7°. From our data, gaze deviation can be found in both proximal and distal vessel occlusions. Small lesions resulting from distal occlusion affecting parts of the brain involving either spatial attention or control of eye movements, such as the basal ganglia, FEF, and parietal eye fields as well as neighbouring temporoparietal cortical regions involved in spatial attention, may be sufficient to cause CGD. Proximal occlusions involving of multiple vascular territories not only increases the likelihood for CGD, but also the degree of CGD. This reasoning may explain both the robust association between higher degrees of CGD and

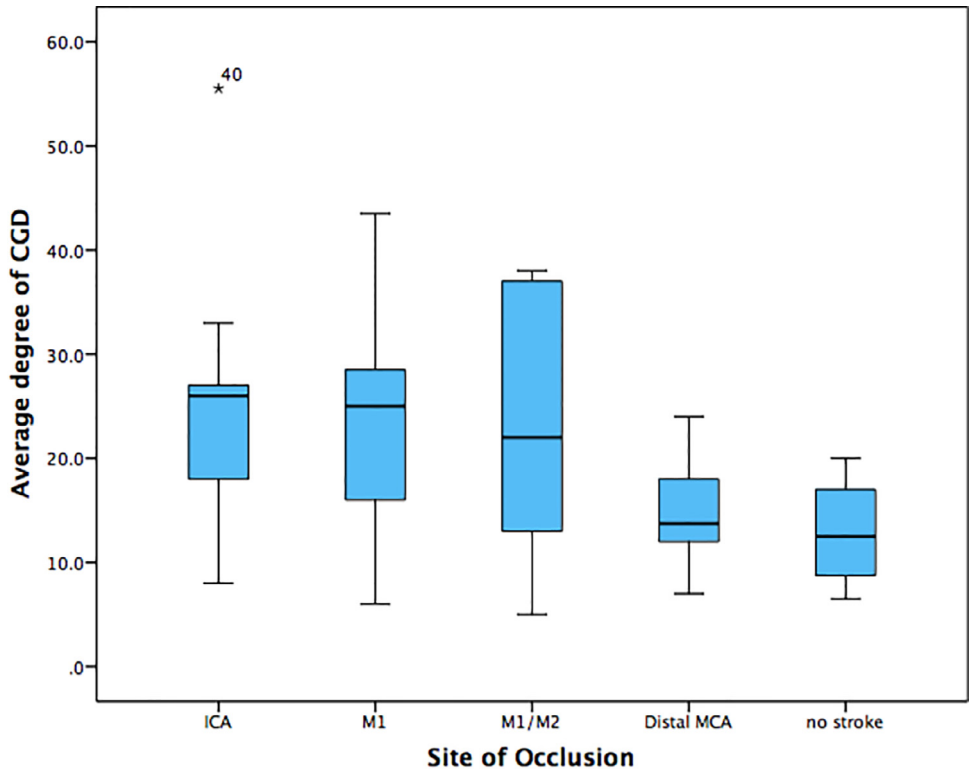


**Figure 2.** *Boxplot to show the distribution of degree of conjugate gaze deviation (+) CGD within ICA and MCA territories. Abbreviations: CGD, conjugate gaze deviation; MCA, middle cerebral artery.*

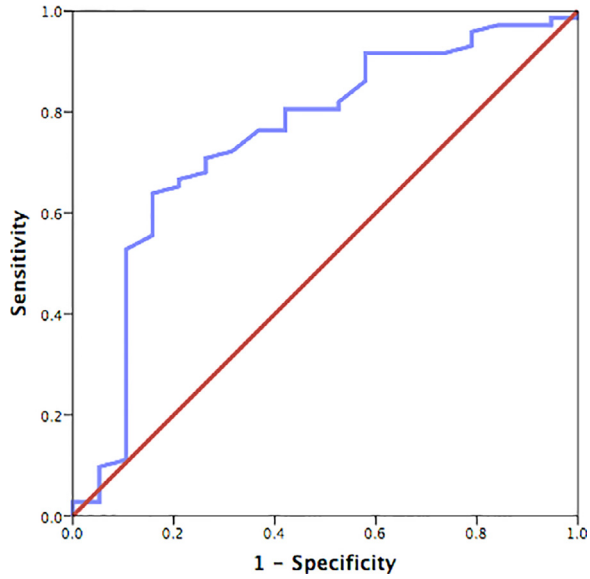


**Figure 3.** *Empirical ROC curve illustrating the sensitivity and 1-specificty of gaze deviation in predicting proximal vessel occlusion in patients with (+) CGD. Abbreviations: CGD, conjugate gaze deviation; ROC, receiver operating characteristic.*

a poor NIHSS score as well as its correlation with presence of proximal vessel occlusion.

Smaller ischemic lesions supplied by more distal MCA branches affecting the FEF can indeed cause CGD. In fact, Tanaka et al (2002) described an 82-year-old patient with isolated acute CGD resulting from single diffusion weighted imaging lesion in the caudal part of the right middle frontal gyrus. However, Tijssen et al (1991) and Ringman et al (2005) demonstrated contrarily a lack of direct involvement of the FEF in AIS patients with CGD. Thus, the mechanism leading to CGD, including common involvement of a circumscribe brain area like FEF versus "network damage" due to ischemia of a critical volume of cortical or subcortical tissue, remains incompletely understood.

In our cohort, the diagnostic performance of a cut-off greater than 20.25° demonstrated moderately strong specificity for proximal vessel occlusion. Multiple cut-offs were proposed in the past to differentiate between AIS and no AIS, ranging from 11.95° by McKean et al (2014) and 15.0° by Coffman et al (2015). The slightly higher cut-off proposed in our study may be due to our method in accounting for random error in natural gaze deviation where only patients with both eye deviation of greater than 5° were included in the (+) CGD group.

Of the 21 patients without identifiable occlusion ("no stroke"), 4 patients had (+) CGD ranging from 6.5° to 20.0°. This finding attributed to random error accounting for natural gaze deviation as patients were not instructed to ensure midline gaze or neutral position to mimic a real-life scenario. There was no significant gaze deviation in ACA, PCA, and basilar artery occlusion. Interestingly, in acute cerebellar infarcts, 2 of the 3 patients with PICA occlusions had extreme gaze deviation with a median CGD of 38.7°, which is much higher than in proximal vessel occlusion. The remaining patient had contralateral conjugate gaze deviation of 17.2°. Although a relatively rare entity, the PICA territory cohort may serve as potential mimicker of proximal occlusion on NECT. Based on our preliminary analysis, the degree of gaze deviation in PICA occlusion patients is significantly higher than proximal occlusion patients (38.7° versus 20.5°). In addition, clinical presentations specific to acute cerebellar infarcts such as limb ataxia, dysarthria, and vertigo may play crucial role in excluding this potential mimicker. On post hoc analysis with removal of the 3 patients with PICA occlusion, the sensitivity remains the same but specificity significantly improves and reaches 93.7% with AUC of .84. Thus, measuring degree of CGD in conjunction with thorough physical exam may help detect mimickers and streamline patients for the EVT pathway.

The phenomenon of CGD in infratentorial stroke has previously been described by Pierrot-Deseillingy et al (1990) and Nishimura et al (2015) in which 44% of patients with PICA territory infarcts demonstrated eye deviation on head imaging. The radiographic sign of CGD was directed contralateral to the infarcted side in 9 out of the 11 patients (81.8%), but 20% of cases demonstrated ipsilateral gaze deviation and were shown to be associated with ischemia in the posterior-inferior part of the vermis supplied by the PICA.[11,12] This may also explain the 2 vertebral stroke patients with (+) CGD, which is likely secondary PICA territory infarct given that PICA predominantly arises from the vertebral artery.

In our cohort, 73% of patients had a positive HAS, similar to results from previous studies which range from 24% to 88%.[13,14] Interestingly, 5 out of 8 patients with "normal" NECT (no HAS or definitive loss of gray-white differentiation) had +CGD, which raises the potential utility of CGD as a marker for proximal vessel occlusion on otherwise occult cases. Furthermore, assessment of CGD may also be helpful in the setting of intracranial atherosclerosis which can obscure a hyperdense vessel. In these cases, CGD as an adjuvant marker may help differentiate between acute stroke from chronic vascular disease. Due to the relatively limited number of patients, prospective studies of larger cohorts are necessary to clarify the role of CGD in imaging occult cases.

There are 4 identified limitations in our study. First, the study was a single-center prospective analysis with single reviewer design. However, the reviewer was blinded to the final diagnosis based on CTA during initial measurement of gaze deviation, and an objective and reproducible calliper method was used rather than subjective visual determination, mitigating potential bias. Second, the median follow-up time was 30 days, limiting the analysis of CGD correlation with long-term clinical outcomes. Third, this study reviewed all-comers with acute stroke symptoms, but CGD is not specific to stroke and gaze deviation may have been secondary to tumor, seizure, or

traumatic brain injury, amongst others, which may not be detected on NECT head. Finally, eye disorders (e.g., intermittent exotropia in strabismus) may also result in gaze deviation, although this is usually lone eye deviation, but was not accounted for in our study.

## Summary

This study demonstrated that measuring CGD may be a simple and objective adjunctive marker for identifying proximal vessel occlusions in those with AIS. Furthermore, measuring the degree of gaze deviation may assist in ruling out potential mimickers. These finding have important clinical and EVT pathway implications, particularly in places without access to CTA, and may be a useful clinical decision-making tool in conjunction with the full neurological examination. Since "time is brain," the early identification of patients with proximal vessel occlusion could lead to better patient outcomes by early activation of EVT team and expediting transfer to regional stroke centers. Further examination of the utility of CGD in larger prospective trials is needed to validate the results and aid in streamline the EVT pathway.

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