

# Isolated Anisocoria as a Presenting Stroke Code Symptom is Unlikely to Result in Alteplase Administration

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*Background:* Acute stroke codes may be activated for anisocoria, but how often these codes lead to a final stroke diagnosis or alteplase treatment is unknown. The purpose of this study was to assess the frequency of anisocoria in stroke codes that ultimately resulted in alteplase administration. *Methods:* We retrospectively assessed consecutive alteplase-treated patients from a prospectively-collected stroke registry between February 2015 and July 2018. Based on the stroke code exam, patients were categorized as having isolated anisocoria [A+(only)], anisocoria with other findings [A+(other)], or no anisocoria [A-]. Baseline demographics, stroke severity, alteplase time metrics, and outcomes were also collected. *Results:* Ninety-six patients received alteplase during the study period. Of the 94 who met inclusion criteria, there were 0 cases of A+(only). There were 9 cases of A+(other) (9.6%). A+(other) exhibited higher baseline National Institutes of Health (NIH) Stroke Scale scores compared to A- (17 versus 7;  $P = .0003$ ), and no additional differences in demographics or alteplase time metrics. Final stroke diagnosis and other outcome measures were no different between A+(other) and A-. Of the A+ patients without pre-existing anisocoria, 5 of 6 (83%) had posterior circulation events or diffuse subarachnoid hemorrhage. *Conclusions:* In this exploratory analysis, zero patients with isolated anisocoria received alteplase treatment. Anisocoria as a part of the neurologic presentation occurred in 10% of alteplase patients, and was strongly associated with a posterior circulation event. Therefore, we conclude that anisocoria has a higher likelihood of leading to alteplase treatment when identified in the presence of other neurologic deficits.

**Key Words:** Anisocoria—alteplase—Rt-PA—stroke code—posterior circulation—healthcare delivery

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## Introduction

Anisocoria can be a significant neurologic finding, especially in acute evaluation settings such as stroke codes. Pupillary size is controlled by parasympathetic and

sympathetic multineuron inputs mediating constriction (miosis) and dilation (mydriasis). A disruption along these pathways may produce the asymmetries in pupil size greater than .4 mm defined as anisocoria. Causes range from benign entities such as physiologic anisocoria, mechanical damage, pharmacologic agent administration, or Adie's tonic pupil, to far more concerning causes such as structural compressive lesions (tumors or aneurysms) and acute stroke.<sup>1,2</sup>

Clinicians may activate acute stroke codes for anisocoria, mobilizing extensive resources for immediate alteplase evaluations. To date, the prevalence of anisocoria is not well described: estimates range from 6%-70% in acute stroke.<sup>3,4</sup> The frequency of anisocoria as a feature in acute stroke codes, as an isolated finding in acute stroke codes, or as a predictor of either final stroke diagnosis or outcome is not known. Furthermore, no study has evaluated how often acute stroke codes with anisocoria lead to

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intravenous (IV) alteplase administration. This analysis assessed the frequency with which anisocoria, either in isolation or in conjunction with other neurologic findings, found during acute stroke codes ultimately resulted in IV alteplase treatment.

## Methods

We retrospectively analyzed consecutive, IV alteplase-treated, stroke code patients from the prospectively-collected, Institutional Review Board-approved, University of California San Diego Stroke Code Registry from February 2015-June 2018. This database contains demographic, treatment time, and outcomes data on all patients for which a stroke code was activated. We assessed, via manual chart review, electronic medical records for demographics, exam findings, stroke code time metrics, and outcome. Patients were grouped into 3 categories based on the presence of anisocoria documented on the stroke code exam and temporally relevant progress notes as: (1) isolated anisocoria [A+(only)], (2) anisocoria with other findings [A+(other)], and (3) no anisocoria (A-). In order to account for incomplete documentation of pupil size and degree of anisocoria, we categorized a patient as having anisocoria if there was any mention of unequal pupils regardless of the size discrepancy (including physiologic anisocoria). Patients receiving neuro-intervention were excluded to avoid confounding of patient

outcomes (symptomatic intracranial hemorrhage, disposition, and 90-day modified Rankin score [mRS]).

We analyzed baseline characteristics of age, gender, ethnicity, race, coronary artery disease, diabetes, hypertension, atrial fibrillation, current tobacco use, current alcohol use, baseline NIH stroke scale (NIHSS) score, baseline mRS, as well as relevant stroke code evaluation, and treatment window time metrics. We compared continuous variables using analysis of variance (ANOVA) and categorical variables using Fisher's exact test. We compared groups for final diagnosis of stroke or stroke-related diagnoses including acute ischemic stroke, transient ischemic attack, intracerebral hemorrhage, silent cerebral infarction, aneurysm, subarachnoid hemorrhage, arteriovenous malformation, or subdural hematoma. Outcome measures of symptomatic intracranial bleeding rate, discharge destination, 90-day mortality, and 90-day mRS were assessed. Odds ratios were calculated using standard proportions, and adjusted for baseline NIHSS using logistic regression. Statistical significance was defined as  $P \leq .05$ .

## Results

A total of 96 patients received IV alteplase at our institution between February 2015-June 2018. Overall, 94 subjects were included in the final analysis: one patient was excluded due to incomplete data, and one was excluded

**Table 1.** Baseline patient demographics: A+(other) versus A-

Characteristic	A+(other)	A-	P value
<b>Age (years)</b>			
Mean $\pm$ SD	74 $\pm$ 18	67 $\pm$ 15	.19
<b>Gender</b>			
Male % (n)	44 (4)	65 (55)	.29
Female % (n)	56 (5)	35 (30)	
<b>Ethnicity</b>			
Not Hispanic/Latino % (n)	67 (6)	78 (66)	.31
Hispanic/Latino % (n)	22 (2)	19 (16)	
Unknown % (n)	11 (1)	2 (2)	
Not reported % (n)	0 (0)	1 (1)	
<b>Race</b>			
Black/African-American % (n)	100 (8)	78 (65)	.77
Native Hawaiian/Pacific Islander % (n)	0 (0)	15 (12)	
White % (n)	0 (0)	7 (6)	
<b>Risk factors</b>			
Coronary artery disease % (n)	11 (1)	20 (17)	1.00
Diabetes mellitus % (n)	22 (2)	15 (13)	.63
Hypertension % (n)	56 (5)	58 (49)	1.00
Atrial fibrillation % (n)	33 (3)	14 (12)	.15
Current tobacco use % (n)	0 (0)	15 (13)	.35
Current alcohol use % (n)	22 (2)	13 (11)	.61
<b>Clinical features</b>			
Baseline NIHSS $\pm$ SD	17 $\pm$ 13	7 $\pm$ 7	.0003
Baseline mRS $\pm$ SD	2 $\pm$ 2	1 $\pm$ 1	.0005

mRS, modified Rankin score; NIHSS, NIH stroke scale.

due to chart review showing that a neurointerventional procedure was performed. Three patients with known and documented pre-existing anisocoria noted in their medical history were included in the analysis. Fifteen subjects were excluded from the analysis of alteplase time metrics due to inaccurate time interval documentation.

There were no cases of A+(only) among the assessed IV alteplase patients. There were 9 (9.6%) cases of A+(other) and 85 cases of A-. Baseline characteristics are noted in Table 1. No A+(only) patients were found, therefore analyses focused on comparing A+(other) and A-. A+(other) had higher baseline NIHSS scores when compared to A- (17 versus 7;  $P = .0003$ ). There were no other differences noted in baseline characteristics or alteplase time metrics including onset to arrival ( $P = .74$ ), onset to stroke code ( $P = .10$ ), stroke code to computed tomography (CT) ( $P = .06$ ), stroke code to decision ( $P = .46$ ), and stroke code to alteplase administration ( $P = .91$ ), between the 2 groups (Table 2). Final diagnosis of stroke defined as acute ischemic stroke or stroke-related diagnoses, was not different between groups (Table 3). Of the 6 A+(other) patients without known pre-existing anisocoria documented in their record, 5 (83%) had posterior circulation events or diffuse subarachnoid hemorrhage as a final diagnosis. Adjusting for baseline NIHSS, there were no significant differences in symptomatic intracranial bleeding rate postalteplase ( $P = .99$ ), discharge to home ( $P = .33$ ), 90-day mortality ( $P = .14$ ), and 90-day mRS ( $P = .56$ ) between the 2 groups (Table 4).

## Discussion

In the current landscape of acute care, IV alteplase administration rates are low yet complex infrastructures and significant resources are deployed every time a stroke code is activated. This ranges from immediate evaluation by a stroke-trained expert to consumption of radiology, emergency department, and pharmacy resources. Our finding that isolated anisocoria did not result in IV alteplase administration is a relevant consideration in the mobilization of stroke code resources. As stroke code mimics may account for 25%-70% of stroke codes,<sup>5-7</sup> there may be an educational opportunity to recognize those neurologic deficits that are more or less likely to result in alteplase treatment, or final stroke diagnosis.

How frequently anisocoria presents as the primary cause for activating a stroke code is not well described in the literature. How often patients with anisocoria found during a stroke code, either in isolation or in conjunction with other neurologic findings, receive alteplase, is also unknown. In the present exploratory analysis, we found that 0% of alteplase-treated patients had isolated anisocoria. As such, it is unlikely that isolated anisocoria will result in alteplase treatment for acutely activated stroke codes.

Physiologic anisocoria may occur in up to 20% of the population.<sup>8</sup> In an intensive care setting, 19% of patients were found to have anisocoria on exam and 68% of these patients had a stroke diagnosis.<sup>4</sup> Another study using stroke registry data found the incidence of anisocoria in acute stroke presentation to be lower, between 5.8%-9.5%.<sup>3</sup> Our findings are more consistent with those of the latter study, although our population only included those treated with alteplase, a group which may have different baseline characteristics than all stroke code patients. Although we found no patients with isolated anisocoria that received alteplase, it would also be of interest to determine the percentage of overall stroke code activations for which anisocoria was present. Further work is now underway at our institution to conduct a manual chart review for the presence of anisocoria among all stroke codes in the same time period as the present study.

We included 3 patients with documented pre-existing anisocoria in our analysis. Given its prevalence in the overall population, the finding may have been underreported. During stroke codes, providers may not know a sign's chronicity as patients may be unaware or present as unresponsive.<sup>9</sup> The choice to include these patients therefore more accurately reflects the true circumstances in which providers must decide to trigger a stroke code.

Interestingly, 83% of patients without pre-existing anisocoria were noted to have diagnoses with potential involvement of the posterior circulation. Though speculative, this may contribute to the higher NIHSS found in A+(other), as posterior circulation strokes are often associated with poorer prognosis.<sup>10,11</sup>

The primary limitation of our study is the choice of the alteplase cohort itself, which biases the final diagnosis in favor of likely stroke. We intentionally chose this cohort to assess the likelihood of alteplase administration with a

**Table 2.** Stroke code time intervals: A+(other) versus A-

Time interval	A+(other)	A-	P value
Onset to arrival (min) $\pm$ SD	59 $\pm$ 38	423 $\pm$ 2881	.74
Onset to stroke code (min) $\pm$ SD	52 $\pm$ 36	87 $\pm$ 53	.10
Stroke code to CT (min) $\pm$ SD	25 $\pm$ 18	16 $\pm$ 11	.06
Stroke code to decision (min) $\pm$ SD	29 $\pm$ 19	36 $\pm$ 24	.46
Stroke code to alteplase (min) $\pm$ SD	53 $\pm$ 22	54 $\pm$ 23	.91

SD, Standard Deviation.

**Table 3.** Anisocoria and rate of final stroke diagnosis: A+(other) versus A–

Diagnosis	A+(other) (n)	A– (n)	Odds ratio	P value
Stroke	8	68	2	1
Stroke-related*	8	70	1.7	1

\*Includes final diagnosis of TIA, stroke, intracerebral hemorrhage, silent cerebrovascular accident, aneurysm, aneurysmal sub-arachnoid hemorrhage, arteriovenous malformation, and subdural hematoma.

**Table 4.** Anisocoria and outcome measures (adjusted for baseline NIHSS): A+(other) versus A–

Outcome	Unadjusted odds ratio (OR)	P value	Adjusted OR	P value
Intracranial bleeding	0.60	1	0	.99
Discharge destination home	2.21	.29	0.38	.33
90-day mortality (alive)	16	.15	9.82	.18
90-day modified Rankin > 2	0.28	.56	0	.99

NIHSS, NIH stroke scale.

finding of anisocoria, however our small sample size may limit our interpretation of outcomes. Additional limitations of our analysis include the retrospective study design, our reliance on the accuracy of database entry for NIHSS scoring, and the possibility that emergent stroke code evaluations may not include detailed pupillary assessments.

In this study, we show that stroke codes with isolated anisocoria are unlikely to result in alteplase treatment or final diagnosis of stroke. Stroke codes must continue to be activated for findings of anisocoria; but knowing if this finding is in isolation or in conjunction with other neurologic deficits, may help in the allocation of limited resources. Even in the case of true stroke, recent literature highlights the equipoise required when deciding to whether to treat nondisabling deficits such as isolated anisocoria.<sup>12</sup> Those with anisocoria in combination with other deficits would require further consideration of whether the cumulative deficits are sufficiently disabling to merit aggressive treatment with alteplase. Our analysis also revealed an association between anisocoria and posterior circulation disease. Future studies examining the entire stroke registry at our site are underway.

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