American Heart Journal Plus: Cardiology Research and Practice 34 (2023) 100313

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Association of electrocardiographic and echocardiographic variables with neurological outcomes after ischemic Stroke

Mikhail de Jesus [a], Ankush Maheshwary [b], Manish Kumar [c], Lucas da Cunha Godoy [d], Chia-Ling Kuo [d,e], Prashant Grover [f,*]

[a] Department of Cardiology, Hartford Hospital, Hartford, CT, USA
[b] Department of Neurology, University of Connecticut School of Medicine, Farmington, CT, USA
[c] Department of Critical Care Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, NY, USA
[d] The Cato T. Laurencin Institute for Regenerative Engineering, University of Connecticut Health, Farmington, CT, USA
[e] Department of Public Health Sciences, University of Connecticut School of Medicine, Farmington, CT, USA
[f] Department of Pulmonary and Critical Care Medicine, St. Francis Hospital, Hartford, CT, USA.

ARTICLE INFO

Keywords:
Stroke
Ischemic
ECG
Echocardiogram
Echo
QT interval

ABSTRACT

Background: Cardiac dysfunction is often seen following neurological injury. Data regarding cardiac involvement after ischemic stroke is sparse. We investigated the association of electrocardiographic (ECG) and echocardiographic variables with neurological outcomes after an acute ischemic stroke.

Methods: We retrospectively collected baseline characteristics, stroke location, National Institute of Health Stroke Scale (NIHSS) at the time of admission, acute reperfusion treatment, ECG parameters, and echocardiographic data on 174 patients admitted with acute ischemic stroke. Outcomes of the stroke were based on cerebral performance category (CPC) with a CPC score of 1–2 indicating a good outcome and a CPC score of 3–5 indicating a poor outcome.

Results: Older age (75.31 ± 11.89 vs. 65.16 ± 15.87, $p < 0.001$, OR = 1.04, 95 % CI 1.01–1.07), higher heart rate (80.63 ± 18.69 vs. 74.45 ± 17.17 bpm, $p = 0.024$, OR = 1.02, 95 % CI 1.00–1.05) longer QTc interval (461.69 ± 39.94 vs. 450.75 ± 35.24, p = 0.024, OR = 1.01, 95 % CI 0.99–1.02), NIHSS score (60.9 % vs. 17.8 %, $p < 0.001$, OR = 14.90, 95 % CI 3.83–69.5), and thrombolysis (15 % vs. 5 %, $p = 0.049$, OR = 0.55, 95 % CI 0.10–2.55) were associated with poor neurological outcomes. However, when adjusted for age and NIHSS, heart rate and QTc were no longer statistically significant. None of the other ECG and echocardiographic variables were associated neurological outcomes.

Conclusions: Elevated heart rate and longer QTc intervals may potentially predict poor neurological outcomes. Further studies are needed for validation and possible integration of these variables in outcome predicting models.

1. Background

Ischemic stroke is an acute neurological dysfunction of the brain, spinal cord or retina caused by cerebral hypoperfusion. About 85 % of strokes are ischemic, caused by interruption of blood supply to a certain area of the brain. The rest of the strokes are hemorrhagic and comprise of intracerebral and subarachnoid hemorrhage [1]. Stroke is the fifth most common cause of mortality in the United States and is a leading cause of disability as the majority of the patients suffer long-term poor functional, psychological, and cognitive outcomes [2,3]. Cardiac dysfunction after a neurological injury is common [4,5] and has been extensively described in associations with traumatic brain injury, and intracranial hemorrhage [6]. Cardiac complications are the second most common cause of death in patients with cerebrovascular accident (CVA) [7]. Cardiac dysfunction frequently manifests as electrocardiographic (ECG) changes, arrhythmia, elevated cardiac biomarkers, myocardial dysfunction such as transient neurogenic stunned myocardium [5,6]. Most common ECG changes seen are T-wave inversion or peaking, ST segment changes and prolongation of QT interval [5]. Other changes include sinus tachycardia [8], sinus bradycardia, atrial fibrillation [5],

* Corresponding author at: Department of Pulmonary and Critical Care Medicine, St. Francis Hospital, 114 Woodland Street, Hartford, CT 06105, USA.
E-mail address: PGrover@TrinityHealthOfNE.org (P. Grover).

https://doi.org/10.1016/j.ahjo.2023.100313
Received 1 August 2023; Accepted 6 August 2023
Available online 11 August 2023

and premature ventricular contractions [5].

These changes have been attributed to massive catecholamine release mediated by the central neuro-endocrine axis and neuro-inflammatory response to brain injury [9,10]. The extent of sympathetic augmentation is linked to disinhibition of the insular cortex and is seen more commonly with the involvement of the right insular cortex [9,11]. This sympathetic activation causes direct myocardial damage and contributes to ECG changes and myocardial dysfunction [5]. However, little is known about the extent of cardiac involvement with cerebral infarction. In this study, we sought to examine the association between various ECG and echocardiographic variables and neurological outcomes following acute ischemic stroke.

2. Methods

This retrospective analysis included 174 patients admitted to Saint Francis Hospital from August to December in 2021. Acute stroke was defined as focal neurological symptoms with imaging evidence of cerebral infarction by computed tomography or magnetic resonance imaging of the brain. We collected baseline demographics and comorbidity variables including age, gender, race, ethnicity, coronary artery disease, lung disease, hypertension, hyperlipidemia, diabetes, body mass index, and renal disease. The characteristics of the stroke included were the location, National Institute of Health Stroke Scale (NIHSS) at the time of admission, and treatment modality. Outcomes of the stroke were based on cerebral performance category (CPC) at discharge, with a CPC score of 1–2 indicating a good outcome and a CPC score of 3–5 indicating a poor outcome.

We analyzed the first ECG at the time of presentation for presenting rhythm, PR interval length, QTc interval length, ST-segment and T-wave changes, and the presence of conduction abnormalities. PR interval prolongation was defined as a PR interval $>$ 200 ms as determined by the ECG machine. QTc interval prolongation was defined as a QTc interval $>$ 440 ms as determined by the ECG machine. ST segment changes, T-wave changes, rhythm, and left bundle branch block were determined based on the reading cardiologist's interpretation of the ECG. These findings were compared with previous ECGs available in the patient's chart to determine any change from baseline.

Echocardiograms were performed within days of presentation to the hospital. Echocardiographic data included markers of myocardial relaxation (LV lateral and septal tissue velocity), left ventricular ejection fraction (LVEF), and regional wall motion abnormalities. Impaired myocardial relaxation was defined as LV septal velocity $<$ 7 cm/s, and LV lateral velocity $<$ 10 cm/s. These variables as well as the determination of regional wall motion abnormalities were obtained from the echocardiogram report read by a cardiologist.

A descriptive analysis was conducted to summarize demographic and cardiovascular risk factors overall and by the status of neurological outcome using mean, standard deviation, as well as minimum and maximum for continuous variables and frequencies and percentages for categorical variables. The good and poor neurological outcome groups were compared for the factors using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests instead for categorical variables. Those significant at 5 % level were jointly modeled using a multivariable logistic regression model. *P*-values smaller than 5 % were considered statistically significant. All the statistical analyses were performed in R version 4.1.2.

3. Results

We included 174 patients in the analysis. Table 1 outlines the baseline characteristics of the study population. The average age of subjects was 70.87 ± 14.63 years. Majority of the patients were males 98 (56.3 %) and were non-Hispanic or Latino 158 (90.8 %). In the entire cohort, traditional risk factors were prevalent. The most common risk factors were hypertension 130 (74.7 %), dyslipidemia 90 (51.7 %), diabetes 66 (37.9 %), obesity (BMI $\geq$ 30 kg/m^2) 60 (34.9 %), renal dysfunction 37 (21.3 %) and atrial fibrillation 26 (16 %). The majority of patients had large vessel stroke 138 (79.8 %), 9 (41.8 %) patients had moderate to severe stroke symptoms (NIHSS $>$ 5). 19 (10.9 %) patients received thrombolysis and 14 (8 %) underwent mechanical thrombectomy. 98 (56.3 %) patients had poor neurological outcomes as defined by CPC scores of 3–5.

Table 1
Patient characteristics included in the study.

Patient characteristics (n = 174)	
Age (Mean ± SD (Min; Max))	70.87 ± 14.63 (23; 96)
Sex	
Female	76 (43.7 %)
Male	98 (56.3 %)
Race	
Asian	5 (2.9 %)
Black or African American	42 (24.1 %)
Native Hawaiin or Pacific Islander	2 (1.1 %)
Other	18 (10.3 %)
White or Caucasian	107 (61.5 %)
Ethnicity	
Hispanic or Latino	16 (9.2 %)
Not Hispanic or Latino	158 (90.8 %)
BMI $>$ 30 kg/m^2	60 (34.9 %)
History of Lung Disease	26 (14.9 %)
History of Hypertension	130 (74.7 %)
History of Diabetes	66 (37.9 %)
History of Dyslipidema	90 (51.7 %)
History of Renal Disease	38 (21.8 %)
History of Coronary Artery Disease	34 (19.5 %)

Patients who had poor neurological outcomes were older (75.31 ± 11.89 vs. 65.16 ± 15.87, $p < 0.001$, OR = 1.04, 95 % CI 1.01–1.07), had higher heart rates at the time of presentation (80.63 ± 18.69 vs. 74.45 ± 17.17 beats per minute, $p = 0.024$, OR = 1.02, 95 % CI 1.00–1.05), longer QTc intervals (461.69 ± 39.94 vs. 450.75 ± 35.24, p = 0.024, OR = 1.01, 95 % CI 0.99–1.02), higher prevalence of moderate or severe stroke (60.9 % vs. 17.8 %, $p < 0.001$, OR = 14.90, 95 % CI 3.83–69.5), and more likely to have received thrombolysis (15 % vs. 5 %, $p = 0.049$, OR = 0.55, 95 % CI 0.10–2.55) as compared to patients with good neurological outcomes (Table 2). In individuals with bad neurological outcomes, the QTc increased by 10.37 ± 34.26 as compared to −1.17 ± 29.47 in patients with good neurological outcomes; however, the mean difference was not statistically significant ($p = 0.071$). When adjusted for other covariates including age and NIHSS score, these ECG variables were no longer associated with neurological outcomes (Table 3). Laterality of stroke location, other ECG and echocardiographic variables that were evaluated were not significantly associated with neurological outcomes (Supplementary Table). As expected, age (Odds Ratio [OR] = 1.05, 95 % CI 1.02 to 1.08, $p = 0.002$) and severity of stroke (>mild)

Table 2
Complete Summary of investigated variables and association neurological outcomes.

Variable	Poor	Good	P-value
Age	75.31 ± 11.89 (45; 94)	65.16 ± 15.87 (23; 96)	<0.001
No stroke symptoms	6 (6.5 %)	18 (24.7 %)	<0.001
Minor stroke	30 (32.6 %)	42 (57.5 %)	
Moderate and severe stroke	56 (60.9 %)	13 (17.8 %)	
Ecg Rate Bpm	80.63 ± 18.69 (51; 143)	74.45 ± 17.17 (52; 136)	0.024
Ecg Q Tc Interval	461.69 ± 39.94 (352; 665)	450.75 ± 35.24 (378; 547)	0.026
Q Tc Interval Change From Baseline	10.37 ± 34.26 (−55; 102)	−1.17 ± 29.47 (−68; 107)	0.071
Thrombolysis	–	–	–
N	83 (85 %)	72 (95 %)	0.049
Y	15 (15 %)	4 (5 %)	

Table 3
Summary of variables significantly associated with neurological outcomes.

	OR	95 % CI	P-value
Age	1.05	[1.02, 1.08]	0.002
NIHSS	NA		<0.001
No stroke symptoms	Ref	Ref	Ref
Minor stroke	2.56	[0.78, 9.81]	0.141
Moderate and severe stroke	15.65	[4.38, 66.34]	<0.001
Ecg rate Bpm	1.02	[1.00, 1.05]	0.061
Ecg Q Tc interval	1.00	[0.99, 1.02]	0.432
Thrombolysis	0.52	[0.09, 2.24]	0.404

were associated with a risk of poor neurological outcome compared to no stroke symptoms.

4. Discussion

In this study, we investigated the correlation of ECG and echocardiographic variables with neurological outcomes after ischemic stroke. The results of our study demonstrated that none of the ECG and echocardiographic variables were associated with neurological outcomes. As expected, older age and higher NIHSS scores were strongly associated with poor neurological outcomes. Patients who had poor neurological outcomes showed a non-statistically significant increase in QTc interval from baseline as compared to a decrease in patients with good neurological outcomes. To the best of our knowledge, this is the first study evaluating the association of comprehensive ECG and echocardiographic parameters with neurological outcomes in patients with ischemic stroke.

Although our results are negative when adjusted for other covariates, the correlation of heart rate and change in QTc interval with neurological outcomes is noteworthy. Heart rate and QTc interval change have been linked with neurological outcomes in previous studies. We believe that our results may have been negative due to the small sample size of our study population. One study from 2016 found that patients who had heart rates >86 bpm following acute ischemic stroke were at increased risk for all-cause mortality, decompensated heart failure, and worse modified Rankin Scale after 90 days [12]. A recent study investigating the effect of heart rate on 1-year outcomes for patients with acute ischemic stroke found that patients with a mean and maximum heart rate of >81 bpm and > 100 bpm respectively had higher risk of recurrent stroke, myocardial infarction, or death [13]. Similarly, prolongation of the QT interval after neurologic injury such as intracranial hemorrhage is well-documented [5,7,8]. A previous analysis showed a positive correlation between QTc interval prolongation with severity of neurological damage and subsequent poor neurological outcomes in patients undergoing targeted temperature management following cardiac arrest [14]. This increase in QTc interval following stroke, is also associated with higher long term mortality [15–18]. The reasons for elevated heart rate, increase in QTc interval and poor neurological outcomes are not entirely clear; however, predominant sympathetic activation has been implicated as one of the possible pathophysiologic mechanism [14,17,19]. Right insular cortex disinhibition due to right sided stroke has been hypothesized to cause sympathetic augmentation [11], though in our study, we did not find any interaction of laterality with heart rate. Moreover, the concept of laterality in the control of autonomic nervous system has been under recent debate [20,21]. Hypertension, a risk factor for stroke, is known to be associated with autonomic dysfunction and sympathetic hyperactivity [19]. It is possible that hypertensive patients suffering from stroke may have had a higher level of sympathetic stimulation further increasing cardiovascular risk.

There are several limitations to our study. Firstly, this is a retrospective study and has inherent biases associated with retrospective analysis. Secondly, our sample size was small and may have resulted in inadequate power to detect small differences in association of change in heart rate or QTc interval or LVEF with neurological outcomes. Thirdly, our population was predominantly male limiting the generalizability of our findings. Fourthly, we used machine calculated QTc intervals instead of manual calculation in our study, which are not necessarily accurate [22]. Additionally, we did not record home medications that could have affected patient heart rates and QTc interval. We also did not record electrolytes at the time of presentation, which could have affected the QTc interval.

Despite these limitations, the findings of this study are clinically relevant. Our results suggest that heart rate and change in QTc interval following stroke, may predict neurological outcomes in large scale studies. The heart rates of >81 bpm predicting neurological outcomes, fall in the normal heart rate range of 60 to 100 bpm and may be considered inconsequential. However, our results along with previous analysis raise questions if heart rate over 80 bpm following acute stroke should be considered abnormal. More large-scale studies are needed for validation prior to widespread clinical use and to understand mechanism as well as possible therapeutic modalities that may impact neurological outcomes favorably.

5. Conclusion

None of ECG and echocardiographic variables studied were associated with neurological outcomes following ischemic stroke. Increased heart rate and increase in QTc interval, may reflect severity of neurological injury and may be used as potential prognostic markers along with age and NIHSS. More studies are needed to understand the mechanism, and validation prior to routine clinical use.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100313.

Authors' contributions

MDJ, AM, MK, and PG made substantial contribution to the article design and conception of the work. MDJ, AM, and MK contributed to the acquisition of data and drafting of the manuscript. LDCG and CLK analyzed data and assisted with result interpretation. MDJ, MK, and PG made major contributions to interpretation and editing of the manuscript. MDJ, MK, and PG made critical revisions. All authors contributed to the article and approved the submitted version.

Ethical statement

Hereby, I Prashant Grover, MD, consciously assure that for the manuscript Association of Electrocardiographic and Echocardiographic Variables with Neurological Outcomes After Ischemic Stroke the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation).
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

The violation of the Ethical Statement rules may result in severe consequences.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] P. Tadi, F. Lui, Acute Stroke, StatPearls Publishing, 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK535369/.

[2] Anon, Stroke 101: fast facts on stroke, Available at: https://drbreatheeasyfinance.com/cashflow-quadrant-book-summary/?fbclid=IwAR0eX0TWSuRphudFv97nFFlT8GWYma0kwtdiDQUEhR8pUOQXHU3vzQQyVeA.

[3] B. Carvalho-Pinto, C. Faria, Health, function and disability in stroke patients in the community, Braz. J. Phys. Ther. 20 (2016) 355–366.

[4] M. Samuels, The brain-heart connection, Circulation 116 (2007) 77–84.

[5] A. Grunsfeld, J. Fletcher, B. Nathan, Cardiopulmonary complications of brain injury, Curr. Neurol. Neurosci. Rep. 5 (2005) 488–493.

[6] I. van der Bilt, D. Hasan, W. Vandertop, A. Wilde, A. Algra, F. Visser, G. Rinkel, Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis, Neurology 72 (2009) 635–642.

[7] S. Yoshimura, K. Toyoda, T. Ohara, H. Nagasawa, N. Ohtani, T. Kuwashiro, H. Naritomi, K. Minematsu, Takotsubo cardiomyopathy in acute ischemic stroke, Ann. Neurol. 64 (2008) 547–554.

[8] X. Fan, F. Du, J. Tian, The electrocardiographic changes in acute brain injury patients, Chin. Med. J. 125 (2012) 3430–3433.

[9] H. Lim, M. Smith, Systemic complications after head injury: a clinical review, Anaesthesia 62 (2007) 474–482.

[10] H. Nguyen, J. Zaroff, Neurogenic stunned myocardium, Curr. Neurol. Neurosci. Rep. 9 (2009) 486–491.

[11] H. Ay, W. Koroshetz, T. Benner, M. Vangel, C. Melinosky, E. Arsava, C. Ayata, M. Zhu, L. Schwamm, A. Sorensen, Neuroanatomic correlates of stroke-related myocardial injury, Neurology 66 (2006) 1325–1329.

[12] C.H. Nolte, H. Erdur, U. Grittner, A. Schneider, S.K. Piper, J.F. Scheitz, I. Wellwood, P.M.W. Bath, H.C. Diener, K.R. Lees, M. Endres, Impact of heart rate on admission on mortality and morbidity in acute ischaemic stroke patients – results from VISTA, Eur. J. Neurol. 23 (2016) 1750–1756.

[13] K. Lee, B. Kim, M. Han, J. Kim, K. Choi, D. Shin, J. Cha, D. Kim, D. Kim, W. Ryu, J. Park, K. Kang, S. Lee, J. Kim, M. Oh, K. Yu, B. Lee, K. Hong, Y. Cho, J. Choi, T. Park, S. Park, K. Lee, J. Kwon, W. Kim, S. Sohn, J. Hong, J. Lee, J. Lee, J. Lee, P. Gorelick, H. Bae, Effect of heart rate on 1-year outcome for patients with acute ischemic stroke, J. Am. Heart Assoc. 11 (2022), e025861.

[14] M. Kumar, W. Perucki, B. Hiendlmayr, S. Mazigh, D.M. O'Sullivan, A.B. Fernandez, The Association of Serum Magnesium Levels and QT interval with neurological outcomes after targeted temperature management, Ther. Hypothermia Temp. Manag. 12 (2022) 210–214.

[15] S. Ahn, J. Lee, Y. Kim, M. Yun, J. Han, S. Kim, M. Park, K. Park, D. Kang, J. Kim, S. Kwon, Prognostic significance of prolonged corrected QT interval in acute ischemic stroke, Front. Neurol. 12 (2021), 759822.

[16] C. Hjalmarsson, L. Bokemark, S. Fredriksson, J. Antonsson, A. Shadman, B. Andersson, Can prolonged QTc and cTNT level predict the acute and long-term prognosis of stroke? Int. J. Cardiol. 155 (2012) 414–417.

[17] O.S.M. Amin, A.S. Sheikhbzeni, A.N. Siddiq, Relationship of QTc interval prolongation with acute ischemic stroke, Med. Arch. 74 (2020) 195–198.

[18] M. Hromadka, J. Seidlerova, V. Rohan, J. Baxa, J. Sedivy, D. Rajdl, I. Ulc, P. Sevcik, J. Polivka, R. Rokyta, Prolonged corrected QT interval as a predictor of clinical outcome in acute ischemic stroke, J. Stroke Cerebrovasc. Dis. 25 (2016) 2911–2917.

[19] G. Mancia, G. Grassi, The autonomic nervous system and hypertension, Circ. Res. 114 (2014) 1804–1814.

[20] C.F. Chen, H.F. Lin, R.T. Lin, Y.H. Yang, C.L. Lai, Relationship between ischemic stroke location and autonomic cardiac function, J. Clin. Neurosci. 20 (2013) 406–409.

[21] M. Zhao, L. Guan, J.P. Collet, Y. Wang, Relationship between ischemic stroke locations, etiology subtypes, neurological outcomes, and autonomic cardiac function, Neurol. Res. 42 (2020) 630–639.

[22] I. Goldenberg, A.J. Moss, W. Zareba, QT interval: how to measure it and what is "normal.", J. Cardiovasc. Electrophysiol. 17 (2006) 333–336.