Journal of Clinical Monitoring and Computing (2024) 38:407–414
https://doi.org/10.1007/s10877-023-01075-5

REVIEW

Electrocardiogram alterations in non-traumatic brain injury: a systematic review

Yaroslava Longhitano[1] · Maria Bottinelli[2] · Federico Pappalardo[3] · Giulia Maj[3] · Andrea Audo[4] · Una Srejic[5] · Frank Anthony Rasulo[6] · Christian Zanza[7]

Received: 1 March 2023 / Accepted: 30 August 2023 / Published online: 22 September 2023

Abstract

The presence of abnormal electrocardiograms in individuals without known organic heart disease is one of the most common manifestations of cardiac dysfunction occurring during acute non traumatic brain injury. The primary goal of the present review is to provide an overview of the available data and literature regarding the presence of new-onset electrocardiographic (ECG) alterations in acute non traumatic brain injury. The secondary aim is to identify the incidence of ECG alterations and consider the prognostic significance of new-onset ECG changes in this setting. To do so, English language articles from January 2000 to January 2022 were included from PubMed using the following keywords: "electrocardiogram and subarachnoid hemorrhage", "electrocardiogram and intracranial hemorrhage", "Q-T interval and subarachnoid hemorrhage ", "Q-T interval and intracranial bleeding ", "Q-T interval and intracranial hemorrhage", and "brain and heart- interaction in stroke". Of 3162 papers, 27 original trials looking at electrocardiogram alterations in acute brain injury were included following the PRISMA guideline. ECG abnormalities associated with acute brain injury could potentially predict poor patient outcomes. They could even herald the future development of neurogenic pulmonary edema (NPE), delayed cerebral ischemia (DCI), and even in-hospital death. In particular, patients with SAH are at increased risk of having severe ventricular dysrhythmias. These may contribute to a high mortality rate and to poor functional outcome at 3 months. The current data on ECG QT dispersion and mortality appear less clearly associated. While some patients demonstrated poor outcomes, others showed no relationship with poor outcomes or increased in-hospital mortality. Observing ECG alterations carefully after cerebral damage is important in the critical care of these patients as it can expose preexisting myocardial disease and change prognosis.

Keywords Electrocardiogram · Subarachnoid hemorrhage · Intracranial hemorrhage · Q-T interval · Q-T dispersion · Intracranial bleeding · Brain–heart interaction · Stroke

Yaroslava Longhitano and Maria Bottinelli have contributed equally to this work.

✉ Christian Zanza
christian.zanza@live.it

[1] Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh, Pittsburgh, PA, USA

[2] Department of Anesthesiology and Intensive Care, "Maggiore Della Carità" University Hospital, Corso Mazzini18, 28100 Novara, Italy

[3] Department of Cardiac Anesthesiology, AON SS. Antonio E Biagio E Cesare Arrigo H, Alessandria, Italy

[4] Department of Cardiac Surgery, AON SS. Antonio E Biagio E Cesare Arrigo H, Alessandria, Italy

[5] Department of Anesthesiology, Pain Medicine, and Critical Care, University of California, San Diego, USA

[6] Department of Anesthesiology, Pain Medicine, and Critical Care, Spedali Civili, University of Brescia, Brescia, Italy

[7] Italian Society of Pre-Hospital Emergency Medicine (SIS-118), Consultant in Anesthesia and Critical Care and Consultant in Internal and Emergency Medicine, Taranto, EU, Italy

1 Introduction

At the beginning of the 20th Century, Dr. Cushing described how intracranial pressure affected blood pressure following intracranial hemorrhage. In doing so, he was the first to suggest a physiologic connection between the central nervous system (CNS) and cardiac function [1].

Abnormal electrocardiographic (ECG) findings, in the absence of known organic heart disease, are among the most common manifestations of cardiac dysfunction observed in patients with central nervous system (CNS) disorders [2–4]. ECG changes [5, 6], dysrhythmias [7], and myocardial damage [8, 9] are some of the manifestations of cardiac dysfunction that can occur as a result of acute brain injury. The etiology of these ECG changes is not completely understood, but they are believed to be related to autonomic changes in the brain, particularly the hypothalamus, which frequently occur in patients with acute cerebrovascular disease [8, 9]. After a stroke or subarachnoid hemorrhage (SAH), insults to the anatomical structure of the central autonomic network in the hypothalamus can result in an accelerated sympathetic discharge [10–12]. Sudden increases in intracranial pressure [10] can cause hypothalamic dysfunction [13], which subsequently leads to cardiac nerve stimulation, accompanied by severe sympathetic activity, resulting in structural damage to the myocardium.

Neurocardiology is an emerging field that studies these brain–heart relationships. [14]. The exact mechanisms underlying the development of cardiac dysrhythmias and electrocardiographic alterations following stroke and subarachnoid hemorrhage are still unclear, and their prognostic significance remains unknown [15, 16]. It is important to consider that ECG alterations could be an early indicator of non-traumatic brain injury, and understanding these patterns could aid in early diagnosis.

Many studies have analyzed the presence and role of ECG alteration in acute non traumatic brain injury and a systematic review of the data could help clarifying the incidence of ECG alterations in non-traumatic brain injury and whether these alterations are related to poor outcome. The primary aim of the present review is to provide an overview of the available data and literature regarding the ECG alterations in acute non traumatic brain injury (SAH and Stroke) and their underlying incidence. The secondary aim is to investigate the prognostic significance of new-onset electrocardiographic changes in SAH and Stroke.

2 Materials and methods

2.1 Data sources and search strategy

We followed the recommendation of the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-analysis protocols), encoding the review on PROPSERO with serial number 364178. (17).

A systematic review of the literature was performed collecting the articles present in PubMed and Scopus with the following keywords: “electrocardiogram and subarachnoid hemorrhage”, “electrocardiogram and intracranial hemorrhage”, “Q-T interval and subarachnoid hemorrhage ”, “Q-T interval and intracranial bleeding”, “Q-T interval and intracranial hemorrhage”, and “brain and heart- interaction and stroke”. We included all articles published from January 2000 to January 2022 that disclosed ECG abnormalities following acute brain injury in humans. (Fig. 1) The studies were independently screened by two authors (MB and YL) and the disagreements between the two authors were solved by a third reviewer (CZ). After identification of all the articles, we then removed: all duplicates, all articles not written in English, and all records ineligible by automatic tools. The relevance of the screened articles was decided upon following review of the titles and abstracts. (Supplemental File) Articles excluded from consideration included: (a) all the articles containing data from traumatic brain injury (avoiding the bias that the trauma could have caused on cardiac injury) (b) all the articles seeking a brain–heart correlation based on serum levels of catecholamines or cardiac enzymes (c) all the articles whose primary endpoint was different from the primary endpoint of the review (d) all case reports, narrative review, editorials, commentaries, letters to the editor, opinion articles, meeting abstracts, and original articles lacking an abstract and e) all articles not available on PubMed. (Supplemental file).

2.2 Quality assessment

The level of evidence (LOE) of each study was assessed according to the *Grading of Recommendations, Assessment, Development and Evaluations* (GRADE) evidence system [17]. We selected relevant risk of bias indicators, and we evaluated risk of bias with regards to population selection, outcome assessment and treatment. For each criterion, studies were classified as high or low risk of bias. The included trials were judged as “low risk of bias” when all domains were judged as low risk of bias. Conversely, trials were judged as “high risk of bias” when unclear or high risk of bias was judged in one or more domains. LOE

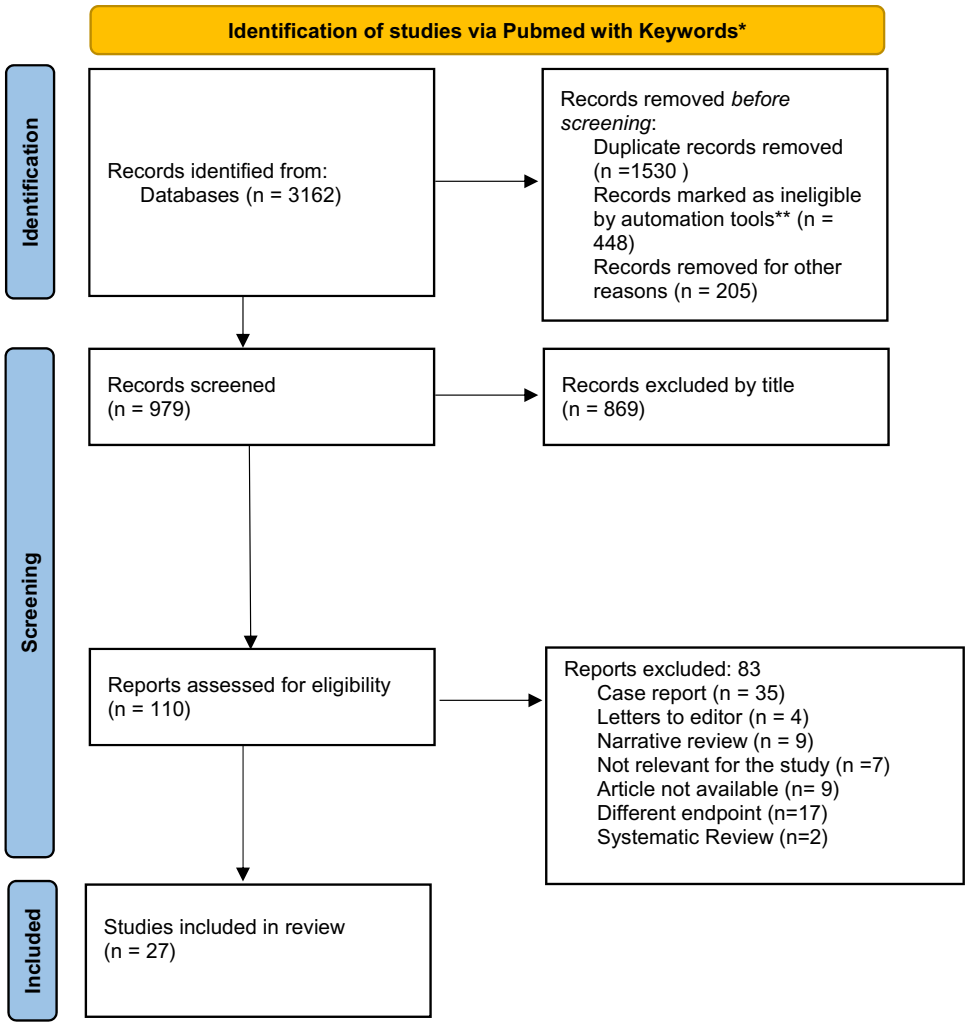

Fig. 1 Flowchart of screened papers *Keywords: "electrocardiogram and subarachnoid hemorrhage", "electrocardiogram and intracranial hemorrhage", "Q-T interval and subarachnoid hemorrhage ", "Q-T interval and intracranial bleeding " "Q-T interval and intracranial hemorrhage" "brain and heart- interaction and stroke **Automation tools used: containing in the title the keywords "Genome, RNA, gene, genetics, dementia, platelets, RM, angiography, troponin, mioglobin, aspirin, colchicin, hypertension, inflammation, TGF, Covid, hearth failure, coronary spasm, malformation, mice, fibrillation, coagulant, stress, donor transplant, lipid-like, traumatic, Takotsubo,

was further analyzed by two experts (MB and YL). Disagreement was resolved by consensus (Supplemental file). We used a standardized electronic spreadsheet (Microsoft Excel, version 14.4.1; Microsoft, Redmond, Washington, USA) to extract the data from all the included studies and recorded trial characteristics.

2.3 Endpoints

To assess the incidence of ECG alteration and cardiac dysrhythmias in acute non-traumatic brain injury. To evaluate whether ECG abnormalities could predict adverse events and worsening of outcome.

3 Results

As shown in TAB-Prisma, 3162 articles were identified. 110 articles met initial eligibility criteria and 27 were included for the final analysis (Supplemental File). The excluded articles consisted of 35 case reports, 4 letters to editor, 9 narrative reviews, 7 articles not relevant for the study, 9 full articles not available, 17 studies with different end points, and 2 systematic reviews (Supplemental file). The studies that relate ECG aberrations with acute nontraumatic brain injuries are shown in the Supplemental file. A population of approximately 3.000 patients was reviewed. 21 studies investigated the presence of ECG abnormalities in SAH. A heterogenous group of ECG abnormalities was noted in these studies. They focused on the analysis of three groups of ECG changes: Dysrhythmias, ECG morphological alterations and QTc prolongation.

The ECG abnormalities studied were ST segment depression, ST segment elevation, peaked T waves, T wave inversion, prolonged QTc, U wave abnormalities, non-specific ST changes (NSSTC), and P wave abnormalities.

QTc prolongation has been long studied and several studies noted a correlation between a prolonged QTc in the ECG of patients with subarachnoid hemorrhages [18, 19]. Indeed, the QT interval on the ECG has been found to vary

amongst the 12 leads [20] and this variability is now thought to reflect the regional myocardial electrical recovery of a patient post SAH [85–88]. This "QT dispersion" is defined as the difference between the longest and shortest QT in the 12-lead ECG and is considered to reflect arrhythmogenicity [21]. The greater the QT dispersion is, the greater seems to be the underlying regional inhomogeneity of ventricular repolarization and the higher the risk of dysrhythmias [22]. In all the selected articles, the QT interval was measured from the first deflection of the QRS onset to the end of the T wave as it merged with the isoelectric TP baseline. Bazett's formula was used to correct the QT for the heart rate, and dispersions were calculated as the difference between the maximal and minimal precordial values. Kawasaki looking for a correlation between ECG alterations and in-hospital death retrospectively analyzed 122 cases of SAH following ruptured aneurysm [10]. The population was divided into survivors and non survivors, a prolonged QTc interval was more common non-survivors than in survivors (536.0 ± 50.0 vs 462.0 ± 59.0, $p < 0.0001$) and an abnormal Q wave, ST segment depression and T wave inversion were more frequently present in non-survivors [10]. A case control study reported that 21 of 38 patients with SAH (55%) had a prolonged QTc (> 500 ms) compared to a QTc prolonged in 5 of 30 control patients [21]. They also proved that QTc was prolonged in SAH and that this correlated with the Hunt Hess grade of the patient [21]. The incidence of ECG repolarization abnormalities in patients with subarachnoid hemorrhage (SAH) varied between studies, with one retrospective cohort study reporting approximately 65% of abnormalities in 834 patients [23], and another retrospective study finding that 66.7% of 159 patients with acute SAH had abnormal ECG findings [16]. Schuiling et al. published a paper designed to study the prognostic value of these ECG changes and noted that only 20.7% of patients had no repolarization abnormalities on the ECG [24]. Among 450 patients with stroke, 338 (75%) showed new ECG abnormalities, including ventricular repolarization abnormalities, cardiac dysrhythmias, and other abnormalities, compared to a baseline ECG taken before the cerebrovascular accident [25]. A population of 361 patients with acute cerebral events was divided in two groups by Togha et al.: (1) those with previous cardio-vascular disease (CVD) and (2) without CVD. In the latter group of 228 patients, the ECG alterations were as follows: (1) QTc prolongation in 30.7% and (2) pathologic Q wave in 14.5%. Other ischemic ECG changes observed in Togha's group without CVD included: (1) ST-segment depression in 7%, (2) ST-segment elevation in 9.6%, (3) T-wave abnormalities in 28.9%, and (4) abnormal U-waves in 11.8%. Among these alterations, the U wave abnormality was the only abnormality present mainly in patients without previous CV comorbidities [24]. While studying the incidence of dysrhythmias in SAH, Togha et al. found them to occur 16.2% of the time in patients without any previous CV disease [26]. Among the population of 450 patients with stroke in Ornella's study, cardiac dysrhythmias such as atrial fibrillation, ventricular tachycardia, SVEB and VEB were found in 97 cases (28.7%) [15]. Additionally, several studies evaluated whether the heart rate (either tachycardia or bradycardia) was related to prognosis [27, 28]. In Y.S. Jeong's pool of patients, 50% had clinically significant dysrhythmias [29].

4 Discussion

This systematic review of the literature highlights the observation that the brain and heart can suffer together during acute non-traumatic head injury. Overall, the main ECG alterations found in the studies were ischemic-like changes and prolonged QTc intervals. The next question may be: " What is the clinical relevance of these findings?" Liming Zhang et al. studied whether ECG abnormalities could predict poor outcomes by evaluating the incidence of neurogenic pulmonary edema (NPE), delayed cerebral ischemia (DCI), and in-hospital death [23]. They concluded that ECG abnormalities are independently associated with adverse clinical outcomes. In particular, QTc prolongation in patients with acute non-traumatic head injury was independently associated with an increased risk of NPE and DCI while ST depression was associated with an increased risk of in-hospital death [23]. Christensen et al. and Stead el al noted some independent risk factors for poor outcomes at 3 months after acute ischemic stroke were ECG alterations such: atrial fibrillation, A-V block, ST-depression, ST-elevation, inverted T-wave, and QTc prolongation [30, 31]. Moreover, Sakr et al. indicated that only ST depression seems to be a significant predictor of the neurological outcome status [16]. A similar observation in a multivariate logistic regression run by Kuroiwa et al. identified abnormal ST-segments as an independent variable predicting poor in-hospital outcome [32]. In a clinical trial Schuiling et al. observed that ischemic-like ECG abnormalities and ST- depression are independent predictors of poor outcomes, and these appeared to be associated with the occurrence of DCI [24]. Finally, in a logistic regression model, after correcting for ICH severity and prior cardiac history, the presence of inverted T waves was independently associated with increased mortality [27].

Besides localized minor ECG abnormalities, dysrhythmias could have a role in predicting adverse events and worsened outcomes. As highlighted from the literature, patients with SAH are at risk of having severe ventricular dysrhythmias and the clinical significance of these dysrhythmias was evaluated by several publications. Di Pasquale et al. used Holter detection for cardiac dysrhythmias in patients with SAH which showed not only that ECG alterations

are frequent in SAH patients but also that life-threatening tachyarrhythmia and bradyarrhythmia occurred in the early stages of subarachnoid hemorrhage [33]. In line with this, Frontera confirmed this data, finding that dysrhythmias following SAH can be life-threatening [34]. Atrial fibrillation/flutter as well as ventricular tachycardia are associated with an increased risk of cardiovascular comorbidities, and a high rate of mortality in addition to poor functional outcomes at 3 months [34].

Kawasaki ran a univariate analysis and a regression analysis for risk stratification and poor outcomes in SAH and the ECG score (based on ECG abnormalities) [10]. ECG score was the most powerful risk factor and was correlated with an association between in-hospital death and the neurological status estimated by Hunt and Hess grade. Y. S. Jeong found that clinically significant dysrhythmias were, after correction for many parameters, still independently predictive of death and poor outcome [29]. According to these results, Park and Schimdt proved that Heart Rate Variability (HRV) correlated with occurrence of clinical events and HRV analysis would be able to predict clinically relevant events via a model that could predict complications such as infection and DCI [25, 35].

Other studies have found that ECG alterations caused by acute non-traumatic brain injury are risk factors for the development of complications and poor outcomes. Prolongation of the QTc interval is often observed in the acute phase of SAH. On the subject of QTc intervals, Frangiskakis found that prolonged QTc and decreased heart rate (HR) are independent risk factors for the development of ventricular dysrhythmias after subarachnoid hemorrhage and are associated with reduced post-bleed survival at 3 months [36]. Lazar, Hanci and Fan Xin found that an increased QT dispersion is an independent prognostic factor for negative outcomes in acute brain injury [37–39]. In the systematic review of Lederman that analyzed the current data on QT dispersion and stroke, he confirmed an association between QTc prolongation and non-surviving stroke patients [5].

The ability to use ECG aberrations to allow early prediction of serious clinical events such as: vasospasm, neurogenic pulmonary edema, and cardiomyopathy in acute brain injury patients would be of great clinical value. The potential to use the detection of QT dispersion, ECG changes score, and heart rate variability to correlate to future clinical complications has been demonstrated by many publications [40–42]. Macmillan found a correlation between QTcd and neurogenic pulmonary edema and myocardial dysfunction [40]. In a logistic regression model by W.L. Chen, Q wave abnormalities and NSSTTC were identified as independent variables associated with the development of NPE [41]. Furthermore, L. Zhang's study demonstrated that QTc prolongation and NSSTTCs are independent predictors of adverse clinical outcomes in SAH [23]. QTc prolongation is independently associated with an increased risk of NPE and DCI, while NSSTTCs are independently associated with an increased risk of NPE, DCI, and in-hospital death. Komatsuzaki's work proved a positive correlation between ECG parameters (QTd dispersion, QTc, Tp-Te interval, Tp-Te/QT ratio, and Tp-Te/QTc ratio) and Hunt and Hess grade [43]. Similar findings were reported by Ichinomiya and Stead Danese, where Qtc prolongation was observed in patients with an unfavorable outcome [42]. Additionally, the studies of Loggini and Rahar linked increased QTc dispersion to high mortality, severe clinical disease, and poor functional outcomes at hospital discharge [27, 44].

Although many publications support the relationship between ECG aberrations and the prediction of poorer outcomes in acute non-traumatic brain injury, other publications refute this [4, 45–48]. Sommargegren concluded that a prolonged QTc interval can predict myocardial injury that is not necessarily related to overall poor patient outcomes [49]. Similarly, Quin Liu and Ziabara did not find a relationship between ECG changes and overall patient outcome [45, 46]. Despite this, it is believed that close monitoring of ECG changes and evaluation of QT dispersion could be of great importance in identifying patients at risk for both myocardial and neurological deterioration in the critical care setting of acute non-traumatic brain injury."

5 Conclusion

Despite the uncertainty that lingers on the prognostic values of ECG aberrations, we believe that ECG abnormalities assessed after SAH using a standard 12-lead ECG are independently associated with an increased risk of adverse clinical outcomes in patients with non-traumatic SAH. Continuous ECG monitoring could be very useful during the acute phases of this disease. Observing ECG alterations carefully after cerebral damage could help to identify underlying undetected myocardial disease which could impair recovery. Early identification of these characteristic ECG alterations could help predict complications. The strengths of our study are the systematic approach to literature review and analysis of clinically relevant outcomes. Limitations of our study include: (1) the relatively small sample size of included studies, (2) the heterogeneity of data, (3) the lack of randomized controlled trials and (4) the lack of analysis of retrospective studies. The potential pathological features reflected in ECG changes in non-traumatic brain injury are numerous. Several studies have analyzed these alterations in tandem without focusing on just one ECG abnormality. Currently, we did not see a reproducible consensus of studies that correlated one specific ECG abnormality to a predictable poor outcome. Future studies might investigate which exact electrocardiographic aberration or collection

of aberrations correllate to a known cardiac dysfunction. If identified, clinicians could anticipate lethal dysrhythmias and plan accordingly to decrease patient mortality rates.

6 Highlights

-Certain ECG aberrations related to non-traumatic brain injury are associated with worse neurological outcome, higher risk of in-hospital death and longer hospital length of stay.

-QTc prolongation in patients with acute nontraumatic head injury was independently associated with an increased risk of neurogenic pulmonary edema and delayed cerebral ischemia.

-ST depression was associated with an increased risk of in-hospital death and poor outcome.

-This population of critical care patients can have increased risk of life-threatening tachyarrhythmias and bradyarrhythmias that could progress to heart failure leading to poor functional outcome and increased mortality.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10877-023-01075-5.

Author contributions Conceptualization: YL; Methodology: MB; Investigation: FP; Data Curation: GM, AA; Writing—Review & Editing: US; Writing—Original Draft: CZ and FAR.

Declarations

Conflict of interest The authors declare no conflict of interest and this research received no external funding.

References

1. Longhitano Y, Iannuzzi F, Bonatti G, Zanza C, Messina A, Godoy D, Dabrowski W, Xiuyun L, Czosnyka M, Pelosi P, Badenes R, Robba C. Cerebral autoregulation in non-brain injured patients: a systematic review. Front Neurol. 2021;12:732176. https://doi.org/10.3389/fneur.2021.732176.
2. Zanza C, Piccolella F, Racca F, Romenskaya T, Longhitano Y, Franceschi F, Savioli G, Bertozzi G, De Simone S, Cipolloni L, La Russa R. Ketamine in acute brain injury: current opinion following cerebral circulation and electrical activity. Healthcare (Basel). 2022;10(3):566. https://doi.org/10.3390/healthcare10030566.PMID:35327044;PMCID:PMC8949520.
3. Byer E, Ashman R, Toth LA. Electrocardiograms with large, upright T waves and long Q-T intervals. Am Heart J. 1947;33(6):796–806. https://doi.org/10.1016/0002-8703(47)90025-2.
4. Goldstein DS. The electrocardiogram in stroke: relationship to pathophysiological type and comparison with prior tracings. Stroke. 1979;10(3):253–9. https://doi.org/10.1161/01.str.10.3.253.
5. Macmillan CS, Andrews PJ, Struthers AD. QTc dispersion as a marker for medical complications after severe subarachnoid haemorrhage. Eur J Anaesthesiol. 2003;20(7):537–42. https://doi.org/10.1017/s0265021503000851.
6. Brouwers PJ, Wijdicks EF, Hasan D, Vermeulen M, Wever EF, Frericks H, van Gijn J. Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage. Stroke. 1989;20(9):1162–7. https://doi.org/10.1161/01.str.20.9.1162.
7. Mo J, Huang L, Peng J, Ocak U, Zhang J, Zhang JH. Autonomic disturbances in acute cerebrovascular disease. Neurosci Bull. 2019;35(1):133–44. https://doi.org/10.1007/s12264-018-0299-2.
8. Xiong L, Tian G, Leung H, Soo YOY, Chen X, Ip VHL, Mok VCT, Chu WCW, Wong KS, Leung TWH. Autonomic dysfunction predicts clinical outcomes after acute ischemic stroke: a prospective observational study. Stroke. 2018;49(1):215–8. https://doi.org/10.1161/STROKEAHA.117.019312.
9. Katsanos AH, Korantzopoulos P, Tsivgoulis G, Kyritsis AP, Kosmidou M, Giannopoulos S. Electrocardiographic abnormalities and cardiac arrhythmias in structural brain lesions. Int J Cardiol. 2013;167(2):328–34. https://doi.org/10.1016/j.ijcard.2012.06.107.
10. Huang CC, Huang CH, Kuo HY, Chan CM, Chen JH, Chen WL. The 12-lead electrocardiogram in patients with subarachnoid hemorrhage: early risk prognostication. Am J Emerg Med. 2012;30(5):732–6. https://doi.org/10.1016/j.ajem.2011.05.003.
11. Póvoa R, Cavichio L, de Almeida AL, Viotti D, Ferreira C, Galvão L, Pimenta J. Electrocardiographic abnormalities in neurological diseases. Arq Bras Cardiol. 2003;80(4):351–8. https://doi.org/10.1590/s0066-782x2003000400001.
12. Kawasaki T, Azuma A, Sawada T, Sugihara H, Kuribayashi T, Satoh M, Shimizu Y, Nakagawa M. Electrocardiographic score as a predictor of mortality after subarachnoid hemorrhage. Circ J. 2002;66(6):567–70. https://doi.org/10.1253/circj.66.567.
13. Samuels MA. The brain-heart connection. Circulation. 2007;116(1):77–84. https://doi.org/10.1161/CIRCULATIONAHA.106.678995.
14. Daniele O, Caravaglios G, Fierro B, Natalè E. Stroke and cardiac arrhythmias. J Stroke Cerebrovasc Dis. 2002;11(1):28–33. https://doi.org/10.1053/jscd.2002.123972.
15. Sakr YL, Lim N, Amaral AC, Ghosn I, Carvalho FB, Renard M, Vincent JL. Relation of ECG changes to neurological outcome in patients with aneurysmal subarachnoid hemorrhage. Int J Cardiol. 2004;96(3):369–73. https://doi.org/10.1016/j.ijcard.2003.07.027.
16. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. https://doi.org/10.1136/bmj.n160.
17. Fukui S, Katoh H, Tsuzuki N, Ishihara S, Otani N, Ooigawa H, Toyooka T, Ohnuki A, Miyazawa T, Nawashiro H, Shima K. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. Crit Care. 2003;7(3):R7–12. https://doi.org/10.1186/cc2160.
18. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J. 1990;63(6):342–4. https://doi.org/10.1136/hrt.63.6.342.PMID:2375895;PMCID:PMC1024518.
19. Colkesen AY, Sen O, Giray S, Acil T, Ozin B, Muderrisoglu H. Correlation between QTc interval and clinical severity of subarachnoid hemorrhage depends on the QTc formula used. Pacing Clin Electrophysiol. 2007;30(12):1482–6. https://doi.org/10.1111/j.1540-8159.2007.00895.x.
20. Sato K, Kato M, Yoshimoto T. QT intervals and QT dispersion in patients with subarachnoid hemorrhage. J Anesth. 2001;15(2):74–7. https://doi.org/10.1007/s005400170030.
21. Lee KW, Okin PM, Kligfield P, Stein KM, Lerman BB. Precordial QT dispersion and inducible ventricular tachycardia. Am

Heart J. 1997;134(6):1005–13. https://doi.org/10.1016/s0002-8703(97)70019-x.
22. Zhang L, Qi S. Electrocardiographic abnormalities predict adverse clinical outcomes in patients with subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2016;25(11):2653–9. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.07.011.
23. Schuiling WJ, Algra A, de Weerd AW, Leemans P, Rinkel GJ. ECG abnormalities in predicting secondary cerebral ischemia after subarachnoid haemorrhage. Acta Neurochir (Wien). 2006;148(8):853–8. https://doi.org/10.1007/s00701-006-0808-3.
24. Schmidt JM, Sow D, Crimmins M, Albers D, Agarwal S, Claassen J, Connolly ES, Elkind MS, Hripcsak G, Mayer SA. Heart rate variability for preclinical detection of secondary complications after subarachnoid hemorrhage. Neurocrit Care. 2014;20(3):382–9. https://doi.org/10.1007/s12028-014-9966-y. PMID:24610353;PMCID:PMC4436968.
25. Togha M, Sharifpour A, Ashraf H, Moghadam M, Sahraian MA. Electrocardiographic abnormalities in acute cerebrovascular events in patients with/without cardiovascular disease. Ann Indian Acad Neurol. 2013;16(1):66–71. https://doi.org/10.4103/0972-2327.107710.PMID:23661966;PMCID:PMC3644785.
26. Loggini A, Mansour A, El Ammar F, Tangonan R, Kramer CL, Goldenberg FD, Lazaridis C. Inversion of T waves on admission is associated with mortality in spontaneous intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2021;30(6):105776. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105776.
27. Ibrahim GM, Macdonald RL. Electrocardiographic changes predict angiographic vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2012;43(8):2102–7. https://doi.org/10.1161/STROKEAHA.112.658153.
28. Jeong YS, Kim HD. Clinically significant cardiac arrhythmia in patients with aneurysmal subarachnoid hemorrhage. J Cerebrovasc Endovasc Neurosurg. 2012;14(2):90–4. https://doi.org/10.7461/jcen.2012.14.2.90.
29. Christensen H, Fogh Christensen A, Boysen G. Abnormalities on ECG and telemetry predict stroke outcome at 3 months. J Neurol Sci. 2005;234(1–2):99–103. https://doi.org/10.1016/j.jns.2005.03.039.
30. Stead LG, Gilmore RM, Bellolio MF, Vaidyanathan L, Weaver AL, Decker WW, Brown RD. Prolonged QTc as a predictor of mortality in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2009;18(6):469–74. https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.02.006.
31. Kuroiwa T, Morita H, Tanabe H, Ohta T. Significance of ST segment elevation in electrocardiograms in patients with ruptured cerebral aneurysms. Acta Neurochir (Wien). 1995;133(3–4):141–6. https://doi.org/10.1007/BF01420064.
32. Di Pasquale G, Pinelli G, Andreoli A, Manini G, Grazi P, Tognetti F. Holter detection of cardiac arrhythmias in intracranial subarachnoid hemorrhage. Am J Cardiol. 1987;59(6):596–600. https://doi.org/10.1016/0002-9149(87)91176-3.
33. Frontera JA, Parra A, Shimbo D, Fernandez A, Schmidt JM, Peter P, Claassen J, Wartenberg KE, Rincon F, Badjatia N, Naidech A, Connolly ES, Mayer SA. Cardiac arrhythmias after subarachnoid hemorrhage: risk factors and impact on outcome. Cerebrovasc Dis. 2008;26(1):71–8. https://doi.org/10.1159/000135711.
34. Park S, Kaffashi F, Loparo KA, Jacono FJ. The use of heart rate variability for the early detection of treatable complications after aneurysmal subarachnoid hemorrhage. J Clin Monit Comput. 2013;27(4):385–93. https://doi.org/10.1007/s10877-013-9467-0.
35. Frangiskakis JM, Hravnak M, Crago EA, Tanabe M, Kip KE, Gorcsan J 3rd, Horowitz MB, Kassam AB, London B. Ventricular arrhythmia risk after subarachnoid hemorrhage. Neurocrit Care. 2009;10(3):287–94. https://doi.org/10.1007/s12028-009-9188-x.
36. Lazar JM, Salciccioli L. Prognostic value of QT dispersion in acute stroke. Int J Cardiol. 2008;129(1):1–2. https://doi.org/10.1016/j.ijcard.2008.04.003.
37. Hanci V, Gül S, Dogan SM, Turan IO, Kalayci M, Açikgöz B. Evaluation of P wave and corrected QT dispersion in subarachnoid haemorrhage. Anaesth Intensive Care. 2010;38(1):128–32. https://doi.org/10.1177/0310057X1003800121.
38. Fan X, Feng-He DU, Tian JP. The electrocardiographic changes in acute brain injury patients. Chin Med J (Engl). 2012;125(19):3430–3.
39. Lederman YS, Balucani C, Lazar J, Steinberg L, Gugger J, Levine SR. Relationship between QT interval dispersion in acute stroke and stroke prognosis: a systematic review. J Stroke Cerebrovasc Dis. 2014;23(10):2467–78. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.06.004.
40. Chen WL, Huang CH, Chen JH, Tai HC, Chang SH, Wang YC. ECG abnormalities predict neurogenic pulmonary edema in patients with subarachnoid hemorrhage. Am J Emerg Med. 2016;34(1):79–82. https://doi.org/10.1016/j.ajem.2015.09.032.
41. Ichinomiya T, Terao Y, Miura K, Higashijima U, Tanise T, Fukusaki M, Sumikawa K. QTc interval and neurological outcomes in aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2010;13(3):347–54. https://doi.org/10.1007/s12028-010-9411-9.
42. Komatsuzaki M, Takasusuki T, Kimura Y, Yamaguchi S. Assessment of the ECG T-Wave in patients With subarachnoid hemorrhage. J Neurosurg Anesthesiol. 2021;33(1):58–64. https://doi.org/10.1097/ANA.0000000000000624.
43. Rahar KK, Pahadiya HR, Barupal KG, Mathur CP, Lakhotia M. The QT dispersion and QTc dispersion in patients presenting with acute neurological events and its impact on early prognosis. J Neurosci Rural Pract. 2016;7(1):61–6. https://doi.org/10.4103/0976-3147.172173.
44. Sommargren CE, Zaroff JG, Banki N, Drew BJ. Electrocardiographic repolarization abnormalities in subarachnoid hemorrhage. J Electrocardiol. 2002;35(Suppl):257–62. https://doi.org/10.1054/jelc.2002.37187.
45. Ziabari SMZ, Akhundzadeh N, Shakiba M, Keshavarz P. The Relationship between QT interval and intra-hospital mortality in patients with spontaneous intracranial hemorrhage. Adv J Emerg Med. 2019;4(2):e25. https://doi.org/10.22114/ajem.v0i0.190.
46. van der Bilt I, Hasan D, van den Brink R, Cramer MJ, van der Jagt M, van Kooten F, Meertens J, van den Berg M, Groen R, Ten Cate F, Kamp O, Götte M, Horn J, Groeneveld J, Vandertop P, Algra A, Visser F, Wilde A, Rinkel G, SEASAH (Serial Echocardiography After Subarachnoid Hemorrhage) Investigators. Cardiac dysfunction after aneurysmal subarachnoid hemorrhage: relationship with outcome. Neurology. 2014;82(4):351–8. https://doi.org/10.1212/WNL.0000000000000057.
47. Hjalmarsson C, Bergfeldt L, Bokemark L, Manhem K, Andersson B. Electrocardiographic abnormalities and elevated cTNT at admission for intracerebral hemorrhage: predictors for survival? Ann Noninvasive Electrocardiol. 2013;18(5):441–9. https://doi.org/10.1111/anec.12056.
48. von Rennenberg R, Krause T, Herm J, Hellwig S, Scheitz JF, Endres M, Haeusler KG, Nolte CH. Heart rate variability and recurrent stroke and myocardial infarction in patients with acute mild to moderate stroke. Front Neurol. 2021;12:772674. https://doi.org/10.3389/fneur.2021.772674.
49. Liu Q, Ding YH, Zhang JH, Lei H. ECG change of acute subarachnoid hemorrhagic patients. Acta Neurochir Suppl. 2011;111:357–9. https://doi.org/10.1007/978-3-7091-0693-8_60.
50. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White

IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;28(366):l4898. https://doi.org/10.1136/bmj.l4898.