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Pre-ictal heart rate changes: A systematic review and meta-analysis

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ABSTRACT

Purpose: To estimate the incidence of pre-ictal heart rate (HR) manifestations and to identify clinical and study-related factors modulating the estimate.
Methods: We searched articles recording concurrent pre-ictal EEG and HR in adults and children with epilepsy. Pre-ictal HR changes were classified as HR reduction (HRR) or increase (HRI). Studies reporting the total number of seizures and the number of seizures with pre-ictal HR changes were included in a random-effects meta-analysis. A random-effects meta-regression was used to identify variables affecting study heterogeneity.
Results: Thirty studies, including 1110 participants and 2957 seizures, were included. The meta-analysis showed a pooled incidence of pre-ictal HRI of 36/100 seizures (95% CI 22–50). The pre-ictal HRI incidence was 44/100 seizures (95% CI 33–55) in studies including temporal lobe epilepsy, 55/100 seizures (95% CI 41–68) in studies enrolling adults and 35/100 seizures (95% CI 16–58) when patients on antiepileptic drugs were included. The meta-regression showed that the age group, the length of the pre-ictal period, the incidence of ictal tachycardia and the time of onset of the pre-ictal HRI had a significant impact on estimates variability. The pooled incidence of pre-ictal HRR was 0/100 seizures (95% CI 0–1).
Conclusion: Review of bias evaluation and methods assessment disclosed several major limitations in the evidence-base. HR monitoring could be valuable to identify seizures prior to their apparent onset, opening the possibility to early interventions. Additional effort is necessary to delineate the target population who might benefit from its use and the mechanisms sustaining the pre-ictal cardiac changes.

1. Introduction

The alterations provoked by epileptic seizures on cardiac rate and rhythm have been recognized for more than 70 years [1,2]. Ictal cardiac changes have been attributed either to the activation of cortical structures connected to the autonomic centres, or to peripheral mechanisms regulating reflex responses, driving various cardiac manifestations [3]. Although a reduction of the heart rate (HR) can occur, the most commonly observed pattern associated with seizures is represented by an increased HR [3]. Ictal tachycardia (IT) has been reported in up to 80% of all seizures and in 82% of people with epilepsy on average [4], while ictal bradycardia (IB) is commonly considered a rare event, manifesting in less than 5% of epilepsy patients [5,6]. The possibility to detect alterations of cardiac parameters during a seizure has led to consider the HR as a potential extra-cerebral seizure biomarker [4]. In comparison to other more invasive measurements, HR assessment has the potential of providing a reliable and easily measurable signal which may be recorded continuously in a daily life environment. In addition, HR alterations have been reported to occur early during a seizure or even pre-ictally [7], demonstrating a theoretical role in seizure prediction. However, studies investigating ictal and pre-ictal HR changes have yielded controversial results and our understanding of the mechanism supporting these alterations is still limited [3]. In fact, the frequency of ictal HR manifestations in patients with epilepsy varies considerably across studies and estimates range between 38 and 100% for IT and <5 and 66.7% for IB [3,4], with higher variability when a pre-ictal onset is considered. This variance likely reflects differences in measurements along with clinical variables, including epilepsy and seizure type, age groups, use of antiepileptic drugs (AEDs), lobe of seizure onset and presence of cardiac co-morbidities. In addition, methodological issues can also be responsible for the mixed findings, including methods used to assess seizure onset and to define HR changes. Understanding the distribution of pre-ictal HR

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alterations and the temporal relation between these changes and seizure activity might represent a pivotal point to shed new light on the mechanisms shaping the ictal autonomic changes and influencing seizure spreading patterns. Moreover, this could also help to explore the utility of this measure as a seizure detection tool and to identify the target population who might benefit from its use. We aimed to perform a meta-analysis to assess the incidence of pre-ictal HR alterations and to identify clinical and study-related factors modulating this phenomenon.

2. Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Handbook guidelines [8,9].

2.1. Criteria for considering studies for this review

Retrospective and prospective studies (case-control, cohort or case series) recording concurrent pre-ictal EEG and HR in adults and children with epilepsy were considered for inclusion. Studies focusing on neonatal seizures only were excluded. Pre-ictal HR changes were classified as HR reduction (HRR) or increase (HRI) as compared to the baseline HR. Methods used to measure the HR and definitions of HR alterations were extracted and considered as separate variables assessed in the meta-regression as potential sources of between studies heterogeneity.

2.2. Search methods for identification of studies

A systematic search with no language restrictions was carried-out to identify all relevant published and unpublished studies. The search strategy included the terms “epilepsy”, “heart rate”, “ictal tachycardia” and “ictal bradycardia” and is reported in Appendix S1. The search was conducted from the first date available (1958) up to May 30, 2017 in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategies for each database were based on the strategy developed for MEDLINE, taking into account the differences in controlled vocabulary and syntax rules. In addition to the electronic searches, we hand-searched reference lists of all available review articles and primary studies and hand-searched the references quoted in the most recent congress proceedings (e.g. International Epilepsy Congress, European Congress on Epileptology).

2.3. Data collection and analysis

Two review authors (EB and AB) independently assessed the titles and abstracts of all the studies identified by the electronic searching or hand-searching. Full texts of potentially relevant studies were obtained and screened. We resolved any disagreements concerning study inclusion and exclusion by discussion. For each study included, two review authors (EB and AB) independently extracted the following data on an ad-hoc created data collection form: study design (prospective, retrospective) and setting (inpatients, outpatients); demographic and clinical data of the population (number of patients, age group, gender, type of epilepsy, drug-resistance, cardiac comorbidities, AEDs administration/withdrawal during the recording); number of seizures recorded, seizure type and focus (including focus side), definition of seizure onset (EEG, clinical, either EEG or clinical); EEG characteristics: type (scalp, intracranial), number of electrodes used (standard, non-standard), duration (continuous, intermittent, number of hours recorded), use of video recording; HR assessment methods (automatic versus manual count of R–R intervals or QRS complexes or beats) and length of ECG epoch used for HR analysis (in seconds); duration of the pre-ictal period assessed (in seconds); number of seizures presenting with ictal HR change (IT, IB and definitions adopted) and ictal HR peak/minimum reached; number of seizures with pre-ictal HR change (pre-ictal HRI and HRR) and onset time (seconds before seizure onset).

2.4. Quality assessment

The quality of included studies was evaluated using a standard assessment tool, that was slightly re-adapted (Appendix S2), and included sample representativeness, condition assessment, and statistical methods [10]. Each study was given a quality score of 0 to 8 based on fulfilment of the quality criteria. The quality score was considered as a separate variable in the meta-regression.

For studies included in the meta-analysis, two review authors (EB and AB) independently assessed the study methods and the risk of bias related to them. The following domains were considered and compared across studies: definition of HR change, definition of pre-ictal period, time interval used to calculate the HR change, assessment of onset of HR change.

2.5. Data synthesis and analysis

Studies reporting the total number of seizures recorded and the number of seizures with pre-ictal HR changes (including 0), were included in a meta-analysis.

Pre-ictal HRI and pre-ictal HRR were separately analysed. In addition, meta-analysis was separately fitted according to epilepsy type, age group and AEDs administration/withdrawal, when these variables were specified by an adequate number of studies. We used the ‘metaprop_one’ command in Stata 14.0 to estimate crude incidence rates along with their 95% confidence intervals (CI) and we expressed the estimates as the number of seizures with pre-ictal HR changes per 100 seizures. We reported the pooled, weighted estimate generated by random-effects models. To handle the studies with zero events, we used Freeman–Tukey double arcsine transformation which stabilizes the variance of the proportion restricting the 95% CI within the range of 0 and 1, even in the presence of zero events [11]. As a sensitivity analysis, the pooling process was repeated after the successive removal of incidence studies judged at high risk of bias in all the domains considered. The I^2 was used to quantify the magnitude of between-study heterogeneity and the Cochrane Q statistic was calculated to determine significance. Publication bias was investigated statistically using Begg’s and Egger’s tests. To determine the influence of the clinical variables and of the study-level factors on the observed variability, we used random-effects meta-regression. We regressed one variable at a time. Significance level was established at $p < 0.05$. All analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, U.S.A.).

3. Results

3.1. Study selection and quality assessment

The search of electronic databases yielded 1130 references (Fig. 1). One additional study was identified by hand-searching. After duplicates and non-relevant studies were removed, the titles and abstracts of the remaining studies were reviewed and the full-text of 98 articles with potentially relevant studies was assessed. Finally, 30 published studies were considered eligible for qualitative synthesis. All the included studies assessed the occurrence of pre-ictal HRI, while pre-ictal HRR was investigated in 20 studies