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Preictal autonomic dynamics in psychogenic nonepileptic seizures

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ABSTRACT

Objectives: Psychogenic nonepileptic seizures (PNES) resemble seizures but are psychological in origin. The etiology of PNES remains poorly understood, yet several theories argue for the importance of autonomic dysregulation in its pathophysiology. We therefore conducted a retrospective study to investigate autonomic dynamics leading up to a seizure to inform their mechanistic relevance.
Methods: One hundred one patients with PNES and 45 patients with epileptic seizure (ES) were analyzed for preictal heart rate (HR) and respiratory rate (RR) at baseline and at minute intervals from 5 min to onset.
Results: Patients with PNES showed rising HR ($p < 0.001$, repeated-measures analysis of variance (ANOVA)) and rising RR ($p = 0.012$, repeated-measures ANOVA) from baseline to the onset of their seizures. Patients with ES did not exhibit significant preictal HR or RR increase. Patients with PNES had nonsignificantly higher preictal HR and RR than patients with ES.
Significance: Patients with PNES exhibit increasing autonomic arousal prior to seizure events unlike patients with epilepsy. This may reflect increasing levels of preictal anxiety, and future studies could study patients' subjective experiences of the preictal period, and more definitive measures of ventilation to see if this supported a model of PNES as "panic without panic".

1. Introduction

Psychogenic nonepileptic seizures (PNES) are seizures that occur without evidence of electrographic ictal discharges seen on electroencephalography (EEG) and are presumed to have a psychological cause [1]. Its etiology is uncertain, however, with biological, social, and psychological factors thought to be relevant [2–4]. One investigative approach was to examine autonomic nervous system (ANS) activity, both as a potential biomarker to distinguish PNES from epileptic seizures (ES) and because of its potential etiological importance. There is significant comorbidity of PNES with anxiety and panic disorders [3] as well as post-traumatic stress disorder (PTSD) [5], conditions that are characterized by over activity of the ANS [6], and some have argued that anxiety may be a driver of seizure production [2]. Goldstein and Mellers found that there was an increase in peri-ictal panic symptoms in PNES compared with epilepsy, but without the subjective experience of panic – so called 'panic without panic' [7]. Stone and Carson reported a PNES case series in which patients describe a rising sense of unease leading up to their seizures, with symptoms very similar to panic [8]. In a meta-analysis, we found that panic disorder and panic symptoms were moderately strongly associated with PNES, however, the temporal relationship between these was usually unclear [9].

We proposed to study evidence of autonomic changes preceding the onset of PNES, with a view to their etiological significance. Though previous investigations have noted increased heart rate (HR) before a PNES event [10,11], few have looked at its preictal changes in an acute temporal sequence, and none have looked at respiration in this way, the hallmark of most panic attacks. Anxiety and panic are generally accompanied by arousal of the ANS, and therefore, changes in autonomic parameters in the preictal period may reflect the state of anxiety of patients with PNES before seizure onset. We therefore aimed to quantify these autonomic indicators in the lead-up to a PNES event to infer the state of anxiety or panic of patients in this period, hypothesizing a rising HR and respiratory rate (RR) before seizure onset, as well as significant differences between patients with epilepsy and PNES on the same measures. We further hypothesized that this would be more evident in patients with PNES with convulsive seizure semiology, since hypermotor seizures appear to involve more hyperventilation [12] and arguably behaviourally suggest greater anxiety or panic.

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2. Methods

One hundred and twenty patients with PNES and 45 patients with epilepsy from the epilepsy services of the Austin and St. Vincent's Hospitals, two of Melbourne's statewide tertiary-referral epilepsy centers, were retrospectively analyzed for preictal HR and RR. This study sample comprised sequential patients with PNES from the Austin outpatient and St. Vincent's inpatient services and sequential inpatients with epilepsy from St. Vincent's Hospital, between 2010 and 2016. Eleven patients whose seizures were induced by hyperventilation manoeuvres were excluded from the analysis, as this would artificially increase the RR count. Eight patients who had a comorbid diagnosis of both PNES and epilepsy were also excluded. This left 101 patients with PNES and 45 patients with epilepsy for analysis. Each patient contributed only one of their seizure events to the final analysis.

Diagnoses of the condition of each patient and determination of seizure onset were made by expert consensus based on video-EGG (vEEG). Patients with PNES were subdivided into three following groups based on seizure semiology as described by Chen et al. [13] because of their simplicity of classification: 'hypermotor' in which events were characterized by violent and disorganized movements, pelvic thrusting, or postural mannerisms; 'hypomotor' for events with altered responsiveness with mild or negligible motor activity; and 'other' for anything which did not fit the other two categories, with the majority being focal motor activity with preservation of consciousness. This subtyping was conducted through observation of the seizure videos by the lead author (AMI), after establishing reliability (Cohen's kappa, 0.75). Where the video was no longer available, these patients were excluded from semiology subtyping.

Heart rate was measured from three consecutive RR beats from continuously recorded electrocardiography (ECG) traces routinely included in vEEG recordings. Heart rate was measured at baseline, 5 min, 4 min, 3 min, 2 min, and 1 min, before the seizure event occurred as well as immediately prior to onset. Respiratory rate was measured by direct observation of the video included in the vEEG patient file. It was measured by counting the number of typical trunk and abdominal breathing movements within a 30-s window and then multiplying by two to give the rate per minute. This was done at baseline, 5 min, 4 min, 3 min, 2 min, and 1 min, before the marked event. They were counted by AMI after achieving acceptable interrater reliability with nursing staff (intraclass correlation coefficient of 0.99). Only cases where the full video period was available and where RR could be counted at every interval were included, limiting this part of the analysis to 26 PNES and 14 epilepsy cases. Baseline values for heart and respiratory rates were taken at the start or the end of the recorded vEEG file, depending on which end was the furthest away from a seizure event.

As a measure of chronic hyperventilation, serum bicarbonate levels of patients recorded prior to their analyzed event were also assessed, if available; levels after the event if not.

Statistical analysis was undertaken using IBM SPSS version 23, using mean and standard deviation, and repeated-measures analysis of variance (ANOVA) to analyze differences between recorded time intervals, with post hoc paired *t*-tests using Bonferroni correction. Independent *t*-tests and chi-squared tests were performed for demographic data and serum bicarbonate level comparison.

This study was granted ethical approval by the Human Research Ethics Committee at Austin Health (reference number: LNR/17/Austin/240) and St Vincent's Health (reference number: LNR/16/SVHM/243).

3. Results

3.1. Patient demographics

There were a total of 69 female patients and 32 male patients with PNES, with ages ranging from 16 to 83 (mean: 38.17 ± 16.98). For the group with epilepsy, there were 26 female and 19 male patients, with ages ranging from 16 to 71 (mean: 37.93 ± 11.76). The groups did not differ on gender ($\chi^2 = 1.532$; $p = 0.217$) or age ($p = 0.975$; independent sample *t*-tests). Thirteen patients with PNES had no video available for subtyping; of the remainder, 32 had hypermotor PNES, 12 had hypomotor PNES, and 44 patients with 'other' PNES semiology. In the patients with PNES, there was a significant effect of hospital site on RR ($F(1,24) = 11.37$; $p = 0.003$; between-effects mixed ANOVA) but not for HR ($F(1,58) = 0.078$; $p = 0.78$; between-effects mixed ANOVA), so site was included as a between-subjects factor in the subsequent analyses.

3.2. Patients with PNES

There was a rise in HR from baseline to seizure onset which was statistically significant ($F(4.58, 265.81) = 17.31$, $p < 0.001$, repeated-measures mixed ANOVA with Greenhouse–Geisser correction; Fig. 1). There was also a significant rise in HR from 5 min to onset ($F(3.70, 218.31) = 8.14$, $p < 0.001$, repeated-measures mixed ANOVA with Greenhouse–Geisser correction), though the rise from 5 min to 1 min was not significant.

Baseline HR was significantly lower than all other time points on post hoc *t*-tests (Bonferroni corrected) versus 5 min ($p = 0.002$), 4 min ($p = 0.001$), 3 min ($p < 0.001$), 2 min ($p < 0.001$), and 1 min ($p < 0.001$), as well as preonset ($p < 0.001$). Preonset HR was significantly higher than all other time points (paired *t*-test, Bonferroni corrected) 1 min ($p = 0.005$), 2 min (0.014), 3 min ($p = 0.011$), 4 min ($p = 0.006$), and 5 min ($p < 0.001$) before onset, as well as baseline ($p < 0.001$). There were no other significant differences between the measured time points.

In the PNES subtype analysis, the hypermotor, hypomotor, and 'other' subtypes of PNES showed a similar trend to the overall patients with PNES (Fig. 2). There was no significant time vs. subtype interaction ($F(12, 100) = 0.620$; $p = 0.820$; mixed ANOVA), nor main effect of subtype ($F(2,55) = 0.506$; $p = 0.606$; mixed ANOVA), nor any significant difference between any of the time points when comparing each subtype.

Preictal RR showed a significant increase from baseline to 1 min before onset ($F(5, 120) = 3.055$; $p = 0.012$; repeated-measures mixed ANOVA; Fig. 3), though the increase from 5 min to 1 min was nonsignificant. On post hoc *t*-tests, 2 min RR was significantly higher than baseline ($p = 0.046$), otherwise there were no other significant differences between the measured time points. As with HR, there were no significant differences between the PNES subtypes.

3.3. Patients with epileptic seizure

For ES events, preictal HR had a trend towards increase from baseline to preonset ($F(2.11, 44.26) = 2.67$; $p = 0.078$; repeated-measures ANOVA with Greenhouse–Geisser correction; Fig. 4). On post hoc *t*-tests, there were no significant differences between any of the measured time points.

The RR in patients with epilepsy showed no significant change throughout the measured preictal period ($F(5, 65) = 0.92$; $p = 0.470$; repeated-measures ANOVA; Fig. 5) and no significant differences between any of the measured time points on post hoc *t*-tests.

3.4. Comparative analyses

Patients with PNES had mean preictal HR and RR that appeared higher than patients with ES (HR PNES: 82.241 vs. ES: 75.068; RR PNES: 17.628 vs. ES: 17.048), but these differences were not significant. When comparing HRs of the populations with PNES and ES, there was no significant interaction between diagnosis and time ($F(6, 75) = 0.754$; $p = 0.608$; Hotelling's trace of two factor repeated-measures ANOVA; Fig. 6) but a trend towards an effect of diagnosis on HR overall ($F(1, 80) = 3.624$; $p = 0.061$; between-effects of two factor repeated-measures ANOVA). Heart rate at 4 min before onset was higher for

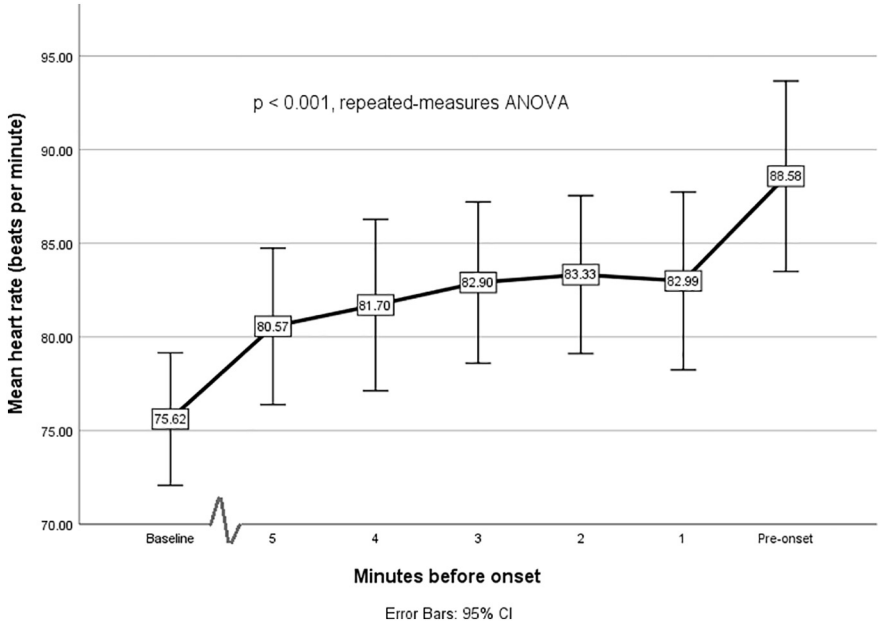

Fig. 1. Pre-ictal heart rate in PNES.

PNES than ES ($p = 0.037$; Bonferroni corrected), but there were no other significant differences in HR between the groups.

There was no significant effect of diagnosis on RR ($F(1, 38) = 0.213$; $p = 0.647$; between-effects of two factor repeated-measures ANOVA; Fig. 7) and no interaction between diagnosis and time ($F(5, 34) = 1.047$; $p = 0.407$; Hotelling's trace of two factor repeated measures ANOVA). There were no significant group differences in RR at any time point.

There was no difference between the serum bicarbonate levels measured days prior to or after the seizure events (24.6 ± 2.9 vs 23.0 ± 5.2; $p = 0.07$; independent *t*-test), which did not suggest chronic hyperventilation for either group, and did not differ between them (PNES: 24.4 ± 3.5; ES: 24.1 ± 3.8; $p = 0.691$; independent *t*-test). Furthermore, there were no significant differences in levels between the PNES subtypes ($F(2,50) = 0.789$; $p = 0.46$). The values for the groups and subgroups are shown in Table 1.

4. Discussion

Previous studies exploring the association of PNES with ANS activity have considered its use as a biomarker in distinguishing PNES from patients with epilepsy, though the results of these investigations have been mixed [14]. To our knowledge, studies that have explored the dynamics of autonomic parameters acutely prior to a PNES event have not examined changes at high temporal resolution, and therefore, our study aimed to address this gap in research. Our analyses suggested a slow rise in preictal HR and RR in patients with PNES. This implies increased preictal autonomic activity, which may be an indicator of the state of

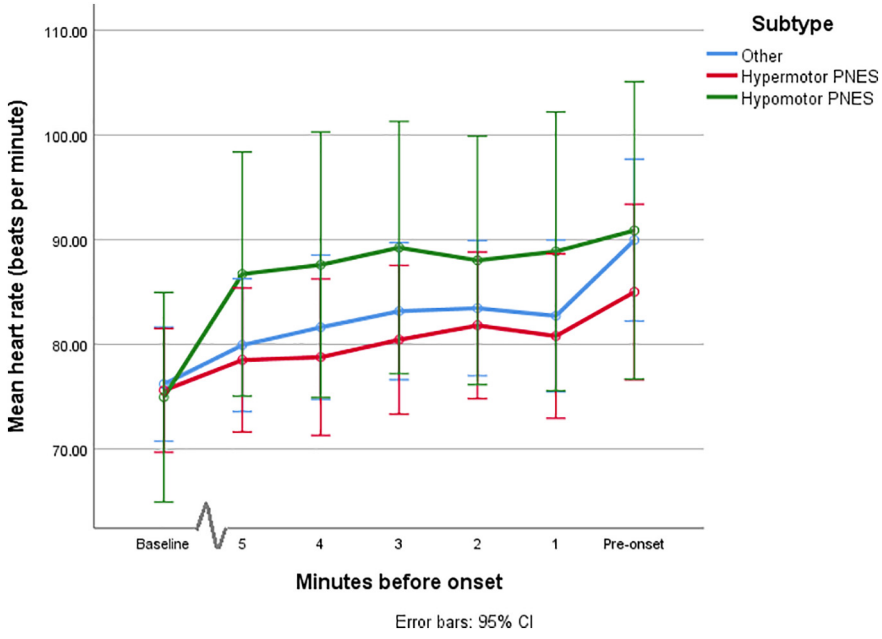

Fig. 2. Comparison of pre-ictal heart rate in PNES subtypes.

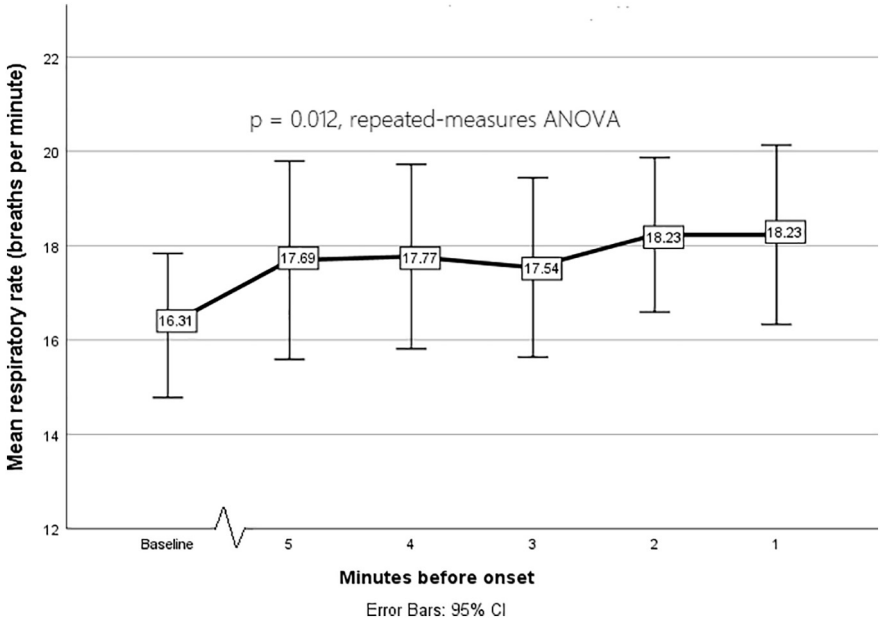

Fig. 3. Pre-ictal respiratory rate in PNES.

anxiety, as there is a broad correlation of autonomic activity with anxiety level. More specifically, there was a significant increase in HR from baseline to 5 min before seizure onset as well as sharp rise from 1 min to preonset. Therefore, it may be that patients with PNES experience anxiety or panic building up acutely before their seizure occurrence, and our results suggest that this could be within a time period of 5 min or more before the onset of a seizure. Though not dramatic, these rates and increases are consistent with those seen in the minutes preceding panic attacks [15].

The result is similar to van der Kruijs et al., who found significant increases in HR in the 10–5 min period before a PNES event and a nonsignificant rise at 5 min compared with onset [11]. From our data, the mean HR values showed a slow increase in absolute means in the period from 5 min to 1 min before onset (Fig. 1), but there was no statistically significant rising trend nor a difference in means between time points during this period. The results for our RR analysis were similar, and this limits interpretations for a 'build-up' of anxiety in this timeframe of 5 min to 1 min, and it may be that any increase in autonomic activity occurs over a longer preictal timespan, as previously described [8,11].

However, there was a significant difference, in the group with PNES, of HR from 1 min to event onset. Interestingly, our values of absolute mean HR measured around these two time points were similar to previous reports (Reinsberger – PNES: 89 ± 18 bpm; complex partial seizures (CPS): 78 ± 14 bpm at 30 s before seizure onset [10]; Opherk & Hirsch – PNES: 84 ± 14 bpm; ES: 71 ± 13 bpm during the first 10 s of the ictus [16]) and thus was not a novel finding. Two possible reasons for this rise in HR are there is an acute increase in panic or anxiety in patients with PNES right before event occurrence. Alternatively, the sharp increase in HR may be due to increased motor seizure-like movements of the patient at the onset of the event, as suggested by Oliveira et al. [17], or in anticipation of them. It is notable that a similar increase is apparent in the group with epilepsy, though not statistically significant (Fig. 4),

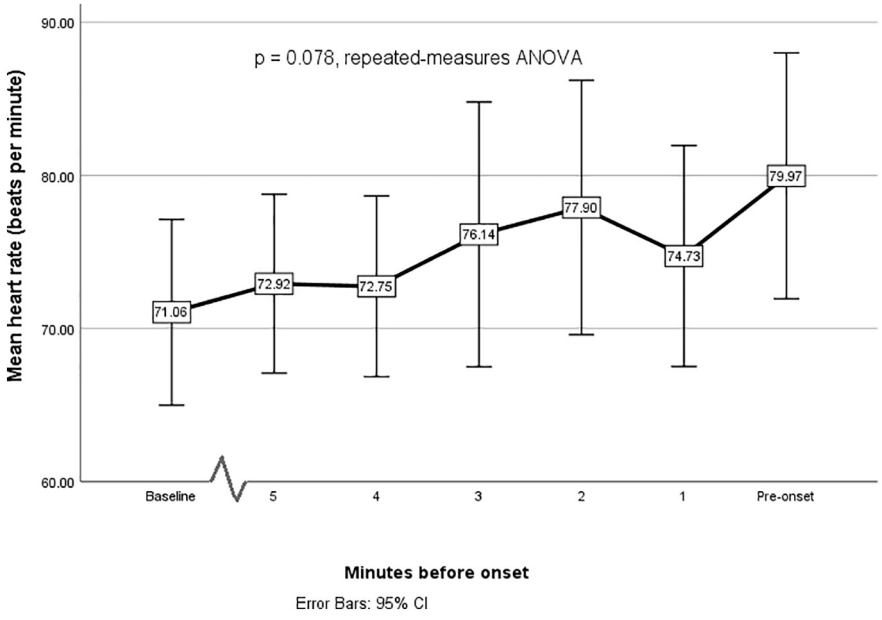

Fig. 4. Pre-ictal heart rate in epileptic seizures.

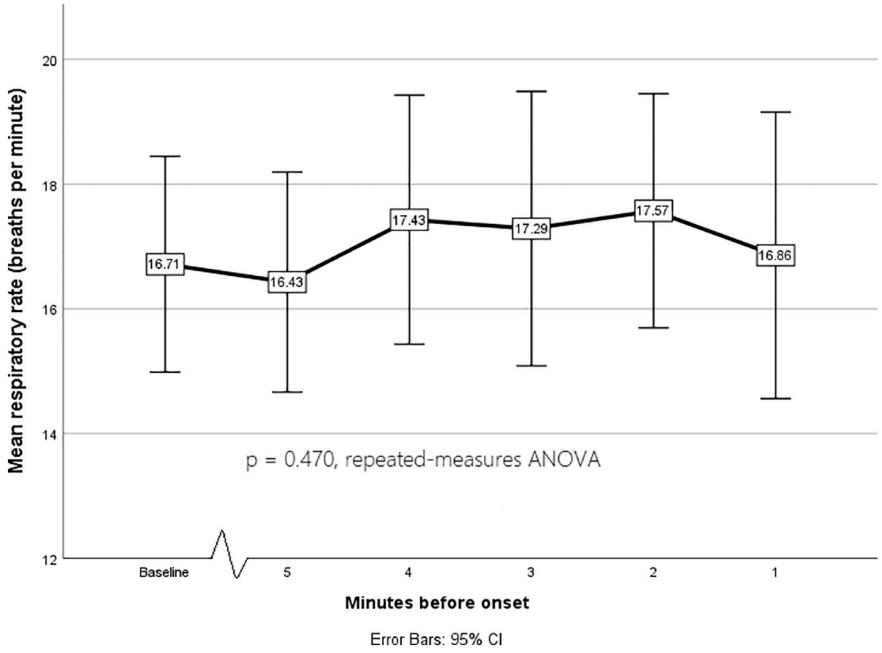

Fig. 5. Pre-ictal respiratory rate in epileptic seizures.

and perhaps suggests our definitions of seizure onset points were too late, missing some subtle early motor activity. When analyzing PNES subtypes, the mean HR in the hypomotor group with PNES appeared higher in the preceding 5 min, but with less evidence of the late rise from 1 min to onset (Fig. 2), albeit without reaching statistical significance (presumably because of the smaller sample). This increased HR in the 5 min prior may suggest higher levels of preictal anxiety or panic in the hypomotor PNES, but could also support the idea that the late rise in HR seen in the hypermotor PNES (and the group with epilepsy) reflects preparation for, or early, motor activity. However, the smaller numbers of the subtypes limit these interpretations.

While we have provided evidence for preictal autonomic changes in PNES, it is not certain how important this increase is to the etiology of PNES. There are multiple theories for PNES etiology [18], and this preictal rise is consistent with several of them. For example, in a model proposed by Brown and Reuber, preictal anxiety and dysautonomia are precursors but not determinants of a seizure [19]. Instead, seizure production is realized by cognitive factors, dependent on the triggering of a 'seizure scaffold'. Alternatively, our results may support the idea that there could be a rising sense of anxiety experienced by patients with PNES, relieved by a wilful dissociation into a seizure [8]. These feelings of panic manifested in somatic symptoms, such as palpitations and breathlessness, and were

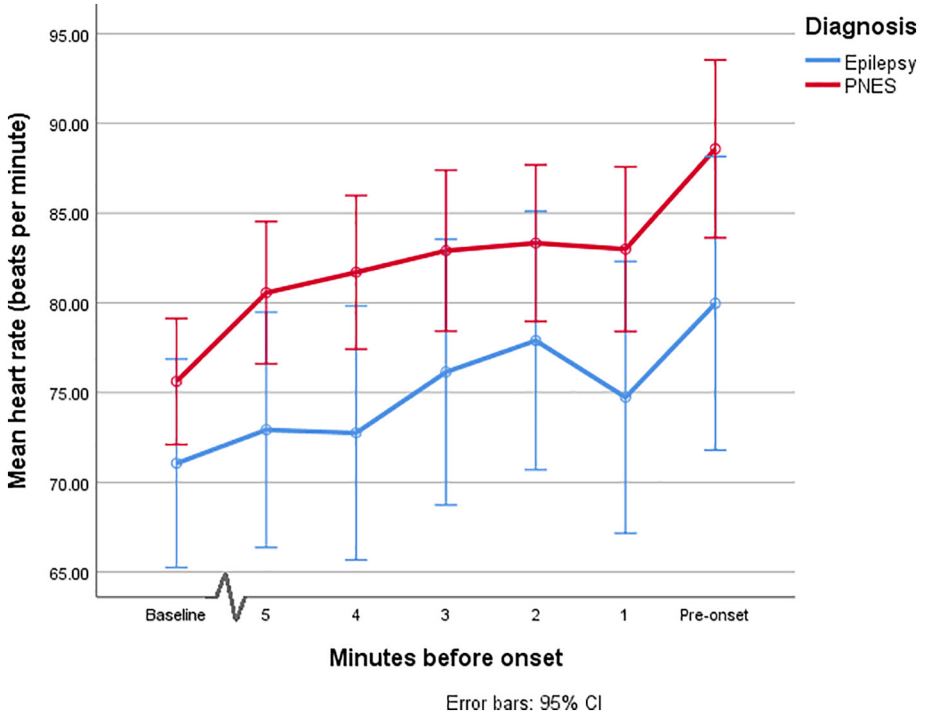

Fig. 6. Comparison of heart rate in PNES vs. ES.

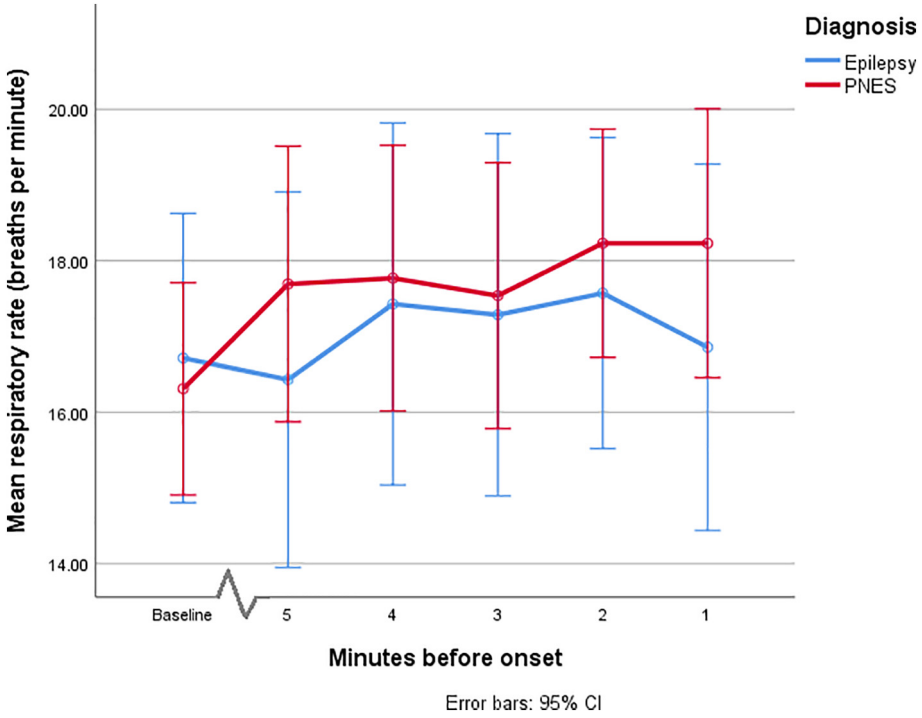

Fig. 7. Comparison of respiratory rate in PNES vs. ES.

said to arise minutes to hours before the PNES event. Our findings of a rising trend of HR and RR in the population with PNES are consistent with the accounts of these patients, though to further test this theory would require more systematic subjective investigation.

For the group with ES, our results invite discussion on the possible role of anxiety in ES events in comparison with PNES events: though not significant, the HR data are suggestive of preictal changes. There have certainly been reports of anxiety being present in ES events [20,21], postulated to be due to the activation of fear circuitry by aberrant epileptic discharges. Alternatively, any preictal changes may be a feature of, or reaction to focal epileptic activity [22].

Another implication of our results is the limited potential of these autonomic indicators as biomarkers for distinguishing PNES from ES. While the absolute means appeared different between groups, these differences were not quite significant. Previous studies have generally shown an increase in ANS parameters of patients with ES compared with PNES [14]. However, the methodological and statistical approaches, as well as the time frame in which the ANS parameters were measured, have differed greatly from the current study. For example, Ponnusamy et al. measured HR variability [23] in patients in a resting, supine state, finding lower resting vagal tone in ES and PNES compared with healthy controls [24], and higher general ANS activity in the group with ES than PNES in the ictal period [25]. Furthermore, Opherk & Hirsch found HR to be higher in ES during the ictus [16], and Jeppesen found sympathetic activity in the ictal period to be higher in patients with epilepsy [26]. However, Reinsberger argued that the time periods that best distinguishes patients with PNES and ES are the preictal and postictal periods [10] – they found a significantly higher HR 30 s before seizure onset in PNES compared with patients with ES. Our results lend some support to Reinsberger et al., in that we found a trend towards preictal differences between the two diagnoses.

There were a number of limitations to this study. The data were obtained retrospectively, and the patient group from the Austin Hospital were an outpatient population while those from St Vincent's hospital were all inpatients, introducing selection biases, particularly as the group with epilepsy were all inpatients. There was a difference between the RR of the two sites' patient groups with PNES, perhaps due to increased anxiety in the inpatient St Vincent's group. Our data were representative of an older population of patients with PNES and ES than previous studies as well [27]. The shortening and splitting of the vEEG videos for archiving purposes led to several limitations. Firstly, the baseline measurements could not be standardized to a single time epoch, which limits interpretations of baseline measurements in the two patient groups. Notably, however, our baseline was similar to that reported in previous studies (Reinsberger – PNES: 77 ± 10.0; CPS: 75 ± 10.7 [10]; Oliveira – PNES: 75 ± 1.4; CPS: 73 ± 2.5 [28]) which supports the utility of its measurement. Secondly, there was a substantial amount of missing data for RR as the video files in the vEEG were often missing or only displayed the preceding 2–3 min before an event, therefore, reducing the power of our ANOVA analysis. Thirdly, our study lacked subjective measures of preictal anxiety, as well as data on previous psychiatric history, diagnoses, and medications, as well as other demographic information that may have usefully informed the analysis or constituted significant confounds. Fourthly, our method of recording the RR, though reliable, remains subjective to a degree. Moreover, RR is only one aspect of ventilation, which would ideally include tidal volume and demand as well. Future studies could employ respiratory bands or other objective measures to capture whether hyperventilation occurs.

Table 1
Serum bicarbonate by seizure type.

Seizure type	Number of patients	Level (mean ± SD; mmol/L)
Hypermotor PNES	32	23.8 ± 3.1
Hypomotor PNES	12	24.6 ± 3.6
Other PNES	44	25.0 ± 4.2
Epilepsy	45	24.1 ± 3.8

5. Conclusion

We have provided evidence for an increase in autonomic activity as early as 5 min before seizure onset in patients with PNES, and most prominent immediately before seizure onset. Our results reinforce the notion that there is prevalence of preictal autonomic excitation in

patients with PNES, though its involvement in seizure production remains unclear. Future studies could further elucidate the dynamics of the preictal period in PNES, through larger, prospective, and more systematic patient studies of preictal psychology, and more objective studies of ventilation.

Conflicts of interest and source of funding

None of the authors has any conflicts of interest to disclose.

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Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm this report is consistent with those guidelines.

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