

**Title:** Bitemporal seizure spread and its effect on autonomic dysfunction

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## **Abstract**

**Objective:** Autonomic dysregulation is a possible pathomechanism of sudden unexpected death in epilepsy (SUDEP). Cardiac arrhythmias and autonomic symptoms are most commonly associated with seizures arising from the temporal lobes. The aim of this study was to investigate whether simultaneous seizure activity in both temporal lobes affects the autonomic nervous system differently from seizure activity in one temporal lobe as assessed by heart rate variability (HRV).

**Methods:** Electrocardiography (ECG) and intracranial electroencephalography (iEEG) data from 13 patients with refractory temporal lobe epilepsy who had seizures that propagated electrically from one temporal lobe to the other during video-EEG-ECG monitoring were retrospectively reviewed. The time domain, frequency domain and non-linear parameters of HRV were evaluated by analysing 4-minute-long ECG epochs, sampling from baseline, preictal and postictal periods as well as epochs constituting unitemporal and bitemporal ictal activity.

**Results:** Heart rate was significantly higher during bitemporal ictal activity compared to all other time points. The time domain and non-linear parameters of HRV were significantly decreased during bitemporal activity compared to baseline and multiple components of HRV (SDNN, CV, RMSSD and SD1) were significantly lower during bitemporal activity compared to unitemporal activity. Frequency domain analysis showed no significant differences.

**Conclusion:** This study shows that bitemporal seizure activity significantly increases heart rate and decreases HRV indicating increased autonomic imbalance with a shift towards sympathetic predominance and this may increase the risk of SUDEP.

**Key words:** Sudden unexpected death in epilepsy; heart rate variability; autonomic dysfunction; bitemporal seizure

## 1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a fatal complication of epilepsy and is the most common cause of epilepsy related death, accounting for between 7.5 to 17% of all epilepsy related deaths[1] and up to 50% of all deaths in refractory epilepsy[2]. SUDEP is defined as the sudden and unexpected, non-traumatic and non-drowning death of a person with epilepsy, without a toxicological or anatomical cause of death detected during the post-mortem examination[3]. The event is typically unwitnessed which makes it difficult to determine the precise course of perimortem events. This, in addition to the fact that by definition the post-mortem does not reveal a cause of death, has made it difficult to ascertain specific risk factors and elucidate the pathophysiological mechanisms of SUDEP. Proposed theories include respiratory arrest, cerebral shutdown and cardiac arrest although these mechanisms are not necessarily mutually exclusive.

The cardiorespiratory system is tightly regulated by the autonomic nervous system and normal autonomic homeostasis is maintained by balancing parasympathetic and sympathetic activity. Autonomic disturbances are frequently reported during seizures[4-6] and in the few case reports of patients who have suffered from SUDEP and where autonomic nervous activity has been measured, there are consistent findings of autonomic imbalance[6,7]. Overall, autonomic dysfunction and an imbalance between the parasympathetic and sympathetic nervous systems are likely to play a significant role in the production of ECG abnormalities and respiratory abnormalities seen during epileptic seizures and thus may play a substantial role in SUDEP[8].

Autonomic activity and autonomic dysfunction can be measured using heart rate variability (HRV). The continuous modulation of sympathetic and parasympathetic innervations results in variations in heart rate, and HRV analysis assesses cardiac autonomic regulation through quantification of sinus rhythm variability[9]. A number of different studies have demonstrated that patients with chronic epilepsy have a reduced HRV and that seizures can further modulate

the autonomic nervous system[10,11]. However, most of these studies have been performed in the interictal state and the few peri-ictal HRV studies have largely used scalp electrodes for the EEG recordings. In this study, data was collected from patients undergoing intracranial depth electrode pre-surgical evaluation providing far greater temporal and spatial resolution in establishing the start and end of epileptiform activity compared to scalp electrodes.

The temporal lobes are important components of the central autonomic network[12] and seizures arising in the temporal lobes are most commonly associated with cardiac abnormalities[13]. Furthermore, seizures that spread bilaterally have been shown to increase the chance of a change in cardiac rhythm[14,15]. The aim of the current study was to test whether bitemporal ictal activity affects autonomic imbalance, assessed by HRV, in a way that is different from unitemporal ictal activity.

## **2. Methods**

### ***2.1. Patients***

This was a retrospective study of ECG and intracranial EEG data collected during standard clinical procedures. The medical records of epilepsy patients who had been admitted to the Telemetry Unit at the National Hospital for Neurology and Neurosurgery between February 1996 and April 2014 for intracranial depth electrode pre-surgical evaluation were reviewed. Inclusion criteria for the study were as follows: the patient must have had bitemporal depth electrode implantation and they must have experienced a partial seizure that started in either the right or left temporal lobe and subsequently spread bitemporally. As this is a retrospective study the bitemporal depth electrode implantation was not controlled and the depth electrodes were positioned based on each patient's clinical indication. To allow reliable detection of temporal lobe seizures only patients who had at least four 6 contact orthogonal depth electrodes implanted into both the right and left amygdala and hippocampus were included. The most

mesial depth electrode contacts detected epileptiform activity in the amygdala, hippocampus and parahippocampal gyrus whilst the more lateral contacts detected activity in the lateral neocortex. A table detailing the precise electrode placement protocol for each patient is shown in S1. Partial seizures with bitemporal ictal activity that subsequently developed into bilateral tonic-clonic seizures were excluded to reduce the effect of different seizure types on seizure related modulations in heart rate variability[16].

A total of 40 patients were identified as fitting the inclusion criteria however access to the data of 15 of the patients (between 2001 and 2007) was unavailable and therefore 25 patients (10 male, 15 female; mean age = 33 years, age range: 19-53 years) were selected for analysis.

## ***2.2. Video-EEG-ECG monitoring***

All patients were continuously monitored in the Telemetry unit via the use of video-EEG-ECG recording systems (Nicolet Biomedical; Viasys Healthcare, Inc, Conshohocken, PA) allowing synchronous recordings of brain activity, heart activity and clinical symptoms. There was no formal respiratory monitoring however upon video review any obvious changes in respiratory pattern or signs of respiratory distress were documented. The 25 patients were monitored for a total of 4417.5 hours (mean = 176.7 hours,  $SD = 73.9$  hours). A modified lead 1 ECG was used to generate simple ECG signals. All ECG data with a sampling rate of less than 200Hz was excluded from the HRV analysis to ensure reliable results were obtained during the HRV analysis[9]. The patients were informed to push an event button if they felt a seizure warning and clinical physiologists and specialist nurses and doctors from the epilepsy department determined the exact timings of electroclinical seizure onset and offset.

## ***2.3. Study design***

Data from February 1996 to March 2000 was reviewed using EEG review v2.1 whereas the data from between September 2008 and April 2014 was reviewed using CareFusion NicVue

v2.9.3. For each seizure, three 4 minute (240s) ECG epochs were selected at the following time points: a baseline epoch beginning three hours before seizure onset and at least three hours after a previous seizure, a preictal epoch beginning four minutes before seizure onset and a postictal epoch beginning immediately after seizure offset. The four minute epoch duration was chosen in compliance with the recommendations that for frequency domain HRV analysis the epoch duration should be approximately 10 times the wavelength of the lowest frequency band of interest which in this case was the 0.04Hz band of the low frequency component[9]. In addition, an ECG epoch constituting the full length of unitemporal seizure activity and a separate ECG epoch constituting the entire bitemporal seizure activity were also selected for HRV analysis. Seizures were excluded if either the duration of the unitemporal seizure activity or the bitemporal seizure activity was less than 30 seconds thereby providing more reliable data for HRV analysis [17,18] (mean unitemporal seizure duration = 68 seconds, SD = 35; mean bitemporal seizure duration = 79 seconds, SD = 24).

As the data used in this study was collected during standard clinical pre-surgical intracranial depth electrode evaluation, patient movement was not restricted leading to potential ECG artefacts. Therefore seizures were excluded from the analysis if there were no artefact-free ECG epochs available, if there was a discontinuation of the recording for any reason e.g. removal of electrodes during a seizure or if the R-peak amplitude was too small to make reliable R peak detection possible.

#### ***2.4. HRV analysis***

Each artefact-free ECG epoch was exported as a text file and subsequently analysed using Kubios HRV version 2.1 (Tarvainen & Niskanen, Biosignal Analysis and Medical Imaging Group (BSAMIG), Department of Applied Physics, University of Eastern Finland, Kuopio, Finland).

The HRV analysis was divided into three broad categories; *time domain, frequency domain and non-linear analysis*. For the *time domain analysis* the following parameters were calculated for all the exported ECG epochs: mean heart rate ( $\overline{HR}$ ), standard deviation of RR intervals (SDNN) and the root mean square of successive differences (RMSSD). It has been suggested that differing heart rates can affect SDNN[19] therefore in order to control for this potential bias and exclude the effect of HR on HRV the coefficient of variation (CV) was analysed, where  $CV = SDNN/RR$  and is expressed as a percent.

For the *frequency domain analysis* high frequency (HF, 0.15-0.4Hz) and low frequency (LF, 0.04-0.15Hz) band analysis was performed and a ratio of LF/HF was also calculated. The HF band is thought to be of parasympathetic origin and is closely linked to respiratory sinus arrhythmia whereas the LF band is thought to represent both sympathetic and parasympathetic activity[9]. The frequency domain analysis was only calculated for the baseline, preictal and postictal epochs due to the unreliable results that would be obtained from analysing the ECG epochs from the unitemporal and bitemporal seizure states which were unlikely to last for the necessary four minute duration.

In addition to time domain and frequency domain analysis, *non-linear analysis* of HRV was calculated and included SD1 and SD2 values which represent the short and long term variation in RR intervals respectively. Both approximate and sample entropy were also calculated to complete the non-linear measures for each ECG epoch.

## **2.5. Statistics**

Statistical analysis was performed using IBM SPSS Statistics 21 and all graphs were drawn using GraphPad Prism 7. A significance level of 0.05 was used for all effects, the confidence interval threshold was set at 95% and Holm-Bonferroni correction was applied wherever necessary.

Due to the small sample size of this study, formal normality tests such as the Shapiro-Wilk test had very little power[20] and the number of data points was not large enough to reliably determine a normal distribution of residuals. This, combined with the large interindividual variability in the data meant that non-parametric tests were preferred. The Friedman test was used to test for repeated measures in multiple groups and the Wilcoxon rank-signed test was used to test the difference between two related groups. The Kruskal-Wallis ANOVA and Mann-Whitney U tests were used to test the significance of between subject differences and linear associations were evaluated using Spearman rank correlation coefficients.

### 3. Results

A total of 13 bitemporally propagated seizures from 13 patients met the inclusion criteria, were artefact free and were consequently included in the final analysis. The clinical details of each patient are shown in Table 1.

There was no significant effect of patient age, MRI findings, laterality of seizure onset or unitemporal or bitemporal seizure duration on any of the HRV parameters being investigated.

**Table 1: Clinical background of patients**

Patient no	Age (years)	Past Medical History (in addition to Temporal Lobe Epilepsy)	Medications on admission (in addition to antiepileptic medication)	MRI findings	Laterality of seizure onset
1	38	Thalassaemia trait	Folic acid	Normal	R
2	24	nil	nil	Left hippocampal sclerosis	L
3	19	Depression	Moclobemide	Right hippocampal sclerosis	R



4	39	Cerebellar ataxia Hypercholesterolaemia	Simvastatin	Right hippocampal sclerosis Small cerebellum	R
5	40	Hypothyroid	Levothyroxine, cetirizine	Right hippocampal sclerosis	L
6	26	nil	nil	Normal	L
7	42	nil	nil	Normal	L
8	22	nil	nil	Normal	L
9	30	nil	nil	Left hippocampal sclerosis	L
10	22	nil	nil	normal	R
11	28	Anxiety	nil	Left hippocampal sclerosis	L
12	30	nil	nil	normal	L
13	39	GORD	Pantoprazole, folic acid	Left hippocampal sclerosis	L

GORD = Gastro-oesophageal reflux disease

### ***3.1. HRV analysis of the bitemporally propagated seizures***

#### *3.1.1. Time domain analysis*

Heart rate (HR) was significantly increased during bitemporal seizure activity when compared to baseline ( $p = 0.01$ ), preictal ( $p = 0.009$ ) and unitemporal ( $p = 0.02$ ) heart rate measurements. The increase in HR continued into the postictal period (Figure 1A) compared to baseline ( $p = 0.04$ ) and preictal values ( $p = 0.04$ ). In terms of the other time domain measures of HRV, the SDNN, CV and RMSSD were all significantly reduced during bitemporal activity (Figures 1B, C and D respectively) when compared to all other time points ( $p$  values for bitemporal vs baseline, preictal, unitemporal and postictal values of SDNN = 0.01, 0.009, 0.008 and 0.02

respectively; for CV = 0.02, 0.04, 0.009 and 0.02 respectively; for RMSSD = 0.01, 0.02, 0.02 and 0.01 respectively). Postictally CV was increased compared to baseline ( $p = 0.04$ ) and preictal ( $p = 0.04$ ) measurements. Descriptive statistics (median value, interquartile range, mean value and standard deviation) of each of the time domain parameters investigated are shown in S1 along with the significance level calculated using the Friedman test.

**Figure 1: Time domain parameters of HRV.** Significant changes in HR (A), RMSSD (B), SDNN (C) and CV (D) are all associated with bitemporal seizure spread. Box plot whiskers represent minimum and maximum values and the \* indicates a significant difference ( $p \leq 0.05$ ) compared to baseline, as is the case for the subsequent figure.

### 3.1.2. Non-linear analysis

In terms of the non-linear parameters of HRV, SD1 (indicating short term variability in RR intervals) was significantly reduced during bitemporal seizure activity compared to baseline ( $p = 0.01$ ), preictal ( $p = 0.02$ ), unitemporal ( $p = 0.02$ ) and postictal values ( $p = 0.01$ ). SD2 (indicating long term variability in RR intervals) was significantly raised during unitemporal seizure activity and postictally compared to baseline ( $p = 0.02$  and  $0.04$  respectively) and preictal values ( $p = 0.04$  and  $0.03$  respectively). Approximate entropy (ApEn) was significantly reduced during unitemporal and bitemporal seizure activity compared to baseline ( $p = 0.01$  and  $0.009$  respectively) and preictal measurements ( $p = 0.03$  and  $0.008$  respectively) and this decrease continued into the postictal phase when compared to baseline ( $p = 0.04$ )(Figure 2A). Sample entropy (SampEn) was also significantly reduced during bitemporal seizure activity ( $p = 0.03$ ) and postictally ( $p = 0.03$ ) compared to baseline (Figure 2B). The main descriptive statistics of the non-linear parameters of HRV are shown in S2.

**Figure 2: Changes in ApEn and SampEn.** (A) A significant main effect of epoch time on ApEn was observed with the unitemporal, bitemporal and postictal measurements significantly differing from baseline (B) Significant changes in SampEn were also observed with bitemporal and postictal SampEn values being significantly lower than baseline.

### *3.1.3. Frequency domain analysis*

Analysis of LF, HF and the LF/HF ratio at baseline, preictal and postictal epoch times were also assessed using the Friedman test. A summary of the findings is reported in S3 however no significant differences were identified.

Particularly large variances in postictal measurements were seen in the SDNN, CV, RMSSD, SD1, SD2, LF and HF measurements. Detailed examination of box plots, normal Q-Q plots and histograms of the post-ictal data identified three bitemporally propagated seizures from three different patients which were consistently different from the other results. These three seizures showed similar characteristics to each other with much larger values of postictal HRV compared to data from all the other seizures. These patients demonstrated marked postictal sinus arrhythmia, defined as a >50% increase in heart rate during inspiration compared to expiration[21], which consequently resulted in very large values of high frequency variation in HRV (an example is shown in Figure 3). No significant postictal respiratory patterns, as determined by retrospective video analysis, or postictal intracranial EEG patterns were associated with these findings. Exclusion of these data was not appropriate for the main analysis as the observed values were not due to physiological or technical artefacts. Their inclusion did not create significant associations that were absent when excluded.

**Figure 3: HRV analysis of a patient's postictal epoch:** an example of marked postictal sinus arrhythmia experienced by a patient after a bitemporally propagated seizure. It shows the ECG trace (top) and the RR intervals (bottom) during this time period. The shown ECG trace corresponds to the green highlighted area of the RR intervals. Consistent, marked sinus arrhythmia occurred in this patient approximately 1 minute 20 seconds after bitemporal seizure offset.

### *3.1.4 Individual seizure analysis*

Group analysis was performed in order to determine statistical significance and individual seizure analysis was then performed to determine the consistency of the pattern of autonomic change upon bitemporal seizure propagation. Patterns of frequency domain parameters of HRV were not analysed on an individual seizure basis as they failed to reach significance during group analysis.

The analysis showed that the 13 seizures included in the study demonstrated consistent patterns of autonomic change upon unitemporal and subsequent bitemporal ictal activity. 12/13 seizures had an increase in mean heart rate from preictal to unitemporal seizure activity (mean increase = 10.7 bpm) and then a further increase from unitemporal to bitemporal ictal activity (mean increase = 33.9 bpm). After the seizure had finished 11/13 seizures showed a drop in mean heart rate (mean reduction = 22.4 bpm). For all 13 seizures values of SDNN and CV dropped when unitemporal ictal activity became bitemporal (mean reduction = 25.3ms & 1.39% respectively) and these values increased postictally in 12/13 seizures (mean increase = 42.0ms & 3.8% respectively), similarly 12/13 seizures showed reduced RMSSD as the seizure transformed from unitemporal to bitemporal (mean reduction = 20.0ms) followed by an increase in RMSSD postictally (mean increase = 47.2ms).

For the non-linear parameters of HRV, SD1 decreased in 12/13 seizures from unitemporal to bitemporal spread (mean reduction = 14.5ms) and subsequently increased again postictally (mean increase = 33.6ms). ApEn was seen to drop upon unitemporal ictal activity in 11/13 seizures (mean reduction = 0.34) and a further reduction was observed in 9/13 upon bitemporal spread (mean reduction = 0.02). A similar pattern was seen for values of SampEn with a reduction in 10/13 seizures upon unitemporal ictal activity (mean reduction = 0.50) and then further reduction during bitemporal ictal activity (mean reduction = 0.33). No consistent patterns were found when analysing SD2.

### *3.1.5 Comparison of bitemporally propagated seizures with unitemporal seizures*

To further test whether seizure activity bitemporally affected HRV differently to unitemporal seizure activity, the 13 bitemporally propagated seizures (BtPS) were compared against 11 seizures from the same group of patients with exclusive unitemporal seizure activity (UtS).

In order to account for interindividual and interseizure variability and allow reliable comparisons of different seizure types, the time domain, frequency domain and non-linear HRV parameters for unitemporal seizure activity, bitemporal seizure activity and the preictal and postictal time period were converted to a percentage increase or decrease compared to baseline recordings ( $(\text{HRV parameter of interest} \div \text{baseline value} - 1) \times 100$ ). There were no statistically significant differences in any of the time domain, frequency domain or non-linear parameters of HRV between the two seizure types during unitemporal seizure activity, preictally or postictally as assessed by Kruskal-Willis ANOVAs with adjusted p-values for multiple comparisons. When comparing HRV parameters between ictal activity during the UtS and bitemporal ictal activity during the BtPS a significant increase in HR was observed during bitemporal seizure activity ( $p = 0.026$ ) and this is shown in figure 4. All other HRV parameters failed to reach significance.

**Figure 4:** Change in heart rate (HR) from baseline to bitemporal seizure activity in the bitemporally propagated seizures (BtPS) vs change in heart rate from baseline to unitemporal seizure activity in the exclusively unitemporal seizures (UtS). HR increase was significantly larger during bitemporal seizure activity in the BtPS than unitemporal seizure activity in the UtS ( $p = 0.026$ ).

#### 4. Discussion

This study has demonstrated a number of interesting findings. Principally, that bitemporal ictal activity during bitemporally propagating seizures (BtPS) significantly affects multiple HRV parameters (increasing HR whilst decreasing SDNN, CV, RMSSD and SD1) when compared to unitemporal activity. These parameters, in addition to decreases in ApEn and SampEn, were also found to be significantly different when comparing bitemporal ictal activity to baseline. The increase in HR and decreases in ApEn and SampEn persisted into the postictal period and postictally there was also a significant increase in CV and SD2 after bitemporal seizure activity. The results demonstrate that simultaneous epileptiform activity in both temporal lobes significantly alters HRV and autonomic dysfunction and indicates that both seizure spread and activity in the temporal lobes may be important factors in determining the extent of autonomic dysfunction and potential risk of SUDEP.

The increase in heart rate observed during seizure activity in this study is a phenomenon that is commonly seen to occur during seizures, especially when they are of temporal lobe origin[13][22]. The fact that heart rate was significantly increased during the bitemporal phase of seizure activity compared to the unitemporal phase indicates that upon bitemporal spread of epileptiform activity there is a significant change in autonomic balance with a shift towards greater sympathetic activity. An overactive sympathetic response can lead to tachyarrhythmias

and a decreased threshold for ventricular fibrillation[25]. In one study, of a case of SUDEP, and a separate study of a patient who suffered from near SUDEP during video-EEG-ECG recording both patients experienced sinus tachycardia at seizure onset before going on to develop more serious arrhythmias including ventricular tachycardia and ventricular fibrillation[7][26].

Ictal sympathetic overdrive is associated with both right and left unitemporal lobe seizures[27] particularly when of hippocampal or amygdala origin[28]. The current study confirms the aforementioned findings of sympathetic predominance in seizures of temporal lobe origin and demonstrates for the first time the significant effect that bitemporal ictal activity can have on HRV measures of autonomic activity and further increasing sympathetic predominance.

All of the time domain measures of HRV were significantly reduced during bitemporal seizure activity compared to all other time points. This is important as decreased HRV is associated with adverse outcomes in several population groups, for example decreases in the time domain parameters of HRV have been consistently shown to correlate with risk of sudden death and mortality after a myocardial infarction[29-31]. The non-linear parameters of HRV, SD1, ApEn and SampEn were all significantly reduced during bitemporal seizure activity and indicate that the ECG pattern during bitemporal seizure activity was more predictable with lower short term variability and these changes persisted into the postictal period. Reduced values of ApEn and SampEn are associated with an array of disease states including neonatal acidosis, foetal distress, postoperative ventricular dysfunction and an increased chance of sudden cardiac death in patients with congestive heart failure[32-34] and correspond to an increase in sympathetic outflow.

In terms of the frequency domain analysis, there was a large amount of variability in both the HF and LF bands and this may in part explain why no statistically significant differences

between baseline, preictal and postictal epochs were observed. It was not possible to perform frequency domain analysis of the unitemporal or bitemporal phases of ictal activity in this study as the ictal epoch durations were not long enough to perform reliable analyses[9]. Changes in HF and LF power in the preictal and postictal states have been found to be greater and more frequently observed before and after generalised seizures than partial seizures of temporal lobe origin[11]. As generalised seizures are a significant risk factor for SUDEP[7,37] it is unsurprising that they cause greater autonomic imbalance compared to other seizure types. It would have been interesting to analyse the time domain, frequency domain and non-linear HRV parameters during generalised seizures in the current study however the specific nature of the patient inclusion criteria meant that very few secondarily generalised seizures were observed during the video-EEG-ECG monitoring and those that were uniformly contained ECG artefacts during the ictal period making them uninterpretable.

It is interesting to note that ictal bradycardia and ictal asystole, although rare phenomena, are also associated with temporal lobe epilepsy particularly when there is bilateral seizure spread[38,39]. This could be explained by the fact that temporal, and particular bitemporal, seizures cause a significant increase in autonomic dysregulation and although an increase in sympathetic outflow, as seen in the current study, is more commonly observed, interindividual and interseizure variability will affect the degree and nature of the sympathetic or parasympathetic imbalance.

Subtle cardiac abnormalities are increasingly being found to occur during or immediately after ictal activity. The frequency of T-wave alternans significantly increases in the postictal phase after secondarily generalised tonic-clonic seizures[40] and prolonged and dispersed QTc intervals indicating abnormal repolarisation characteristics were found in a large proportion of pharmacoresistant focal epilepsy patients and in SUDEP patients[41]. Although not strictly a cardiac abnormality, the observation in this study that three bitemporally propagated seizures



produced marked postictal sinus arrhythmia is interesting, particularly as this was not observed during baseline or any of the other recorded epochs. In one patient the RR intervals varied from approximately 600ms to 1400ms during consecutive beats. Marked sinus arrhythmia signifies a large parasympathetic output, is thought to be benign and may have no important clinical implications. However, marked post-ictal sinus arrhythmia has been reported in four of nineteen patients with SUDEP[41]. It is possible that the presence of marked postictal sinus arrhythmia may be a risk factor of SUDEP and further studies of apparently benign arrhythmias are warranted.

To conclude, this study adds to the literature indicating that cardiac rate and rhythm are both modulated during seizure activity probably as a result of autonomic dysfunction and that these changes may be involved in the pathogenesis of SUDEP. The temporal lobes contain integral parts of the autonomic nervous system and we have shown that simultaneous ictal activity within both temporal lobes significantly alters autonomic imbalance compared to unilateral ictal activity. The bitemporal change in autonomic imbalance is represented by a shift towards sympathetic nervous system predominance and indicates that the bitemporal phase of ictal activity may increase the susceptibility to cardiac arrhythmias, and this may increase the chance of developing SUDEP.

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