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FULL-LENGTH ORIGINAL RESEARCH

# Photoplethysmographic evaluation of generalized tonic-clonic seizures

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## Abstract

**Objective:** Photoplethysmography (PPG) is an optical technique measuring variations of blood perfusion in peripheral tissues. We evaluated alterations in PPG signals in relationship to the occurrence of generalized tonic-clonic seizures (GTCSs) in patients with epilepsy to evaluate the feasibility of seizure detection.

**Methods:** During electroencephalographic (EEG) long-term monitoring, patients wore portable wristband sensor(s) on their wrists or ankles recording PPG signals. We analyzed PPG signals during three time periods, which were defined with respect to seizures detected on EEG: (1) baseline (>30 minutes prior to seizure), (2) preseizure period, and (3) postseizure period. Furthermore, we selected five random control segments during seizure-free periods. PPG features, including frequency, amplitude, duration, slope, smoothness, and area under the curve, were automatically calculated. We used a linear mixed-effect model to evaluate changes in PPG features between different time periods in an attempt to identify signal changes that detect seizures.

**Results:** We prospectively enrolled 174 patients from the epilepsy monitoring unit at Boston Children's Hospital. Twenty-five GTCSs were recorded from 13 patients. Data from the first recorded GTCS of each patient were included in the analysis. We observed an increase in PPG frequency during pre- and postseizure periods that was higher than the changes during seizure-free periods (frequency increase: preseizure = 0.22 Hz, postseizure = 0.58 Hz vs changes during seizure-free period = 0.05 Hz). The PPG slope decreased significantly by 56.71 nW/s during preseizure periods compared to seizure-free periods. Additionally, the smoothness increased significantly by 0.22 nW/s during the postseizure period compared to seizure-free periods.

**Significance:** Monitoring of PPG signals may assist in the detection of GTCSs in patients with epilepsy. PPG may serve as a promising biomarker for future seizure detection systems and may contribute to future seizure prediction systems.

Fatemeh Mohammadpour Touserkani and Eleonora Tamilia contributed equally to this work.

**KEYWORDS**
autonomic, biosensor, epilepsy, GTCS, PPG, seizure

## 1 | INTRODUCTION

Photoplethysmography (PPG) detects alterations in blood volume as blood circulates through microvasculature structures. PPG can be measured noninvasively by means of a sensor that consists of a light source that radiates light into the underlying tissue, and a photodetector detecting reflected light from the tissue. As blood volume increases in the related vessels, signal amplitude decreases because the amount of absorbed light increases, and thereby the photodetector receives less reflected light from the underlying tissue and vice versa. PPG signals are comprised of an "AC" (alternating current) component and a baseline "DC" (direct current) component. The AC component detects changes in the tissue blood volume during each systole and reflects changes in the microvascular perfusion relative to each heartbeat. The DC component is less variable and reflects the average blood volume in the tissue, and its changes are attributable to respiration, vasomotor activity, and thermoregulation.[1]

Increase in heart rate at seizure onset,[2] stroke volume, and blood pressure, as well as change in vascular tone due to autonomic nervous system (ANS) activation may result in changes in PPG signals, which may help in the detection of seizures.

Several types of noninvasive techniques have been used in patients with epilepsy for seizure detection: ambulatory electroencephalographic (EEG) monitoring, surface electromyography (sEMG), electrodermal activity (EDA) measurements, accelerometry (ACC), mattress sensors, seizure-alert dogs, cerebral oxygen saturation sensors, skin temperature and respiratory monitoring devices, as well as video and sound monitors, among others.[3] Other devices with multimodal sensors have also been used with different combinations of modalities, for example combinations of EDA and ACC, sEMG and ACC, magnetometer and ACC, and EEG and electrocardiogram (EKG).[3] Whereas other researchers have examined heart rate variability (HRV) previously, the changes in PPG signals during seizures and their potential role in seizure detection are not well described. Our aim is to detect changes in the PPG signal characteristics from patients with epileptic seizures and to evaluate whether these changes are related to the generalized tonic-clonic seizure (GTCS) and whether PPG can be identified as an additional biomarker for GTCS detection.

**Key Points**

- PPG is an optical technique measuring variations of blood perfusion in peripheral tissues
- We analyzed PPG signals during three time periods relative to seizure occurrence: (1) baseline, (2) preseizure, and (3) postseizure
- PPG features, including frequency, amplitude, duration, slope, smoothness, and area under the curve, were extracted using MATLAB
- We observed an increase in PPG frequency during pre- and postseizure periods that was higher than the changes during seizure-free periods; the PPG slope decreased during preseizure periods, and the smoothness increased during the postseizure period compared to seizure-free periods

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

We recruited patients admitted to the epilepsy monitoring unit at Boston Children's Hospital for continuous video and audio-EEG monitoring. We asked participants to wear portable wristband sensors (E4, Empatica), which monitor PPG signals, on their wrists or ankles on both sides of their bodies. The study received approval from the institutional review board at Boston Children's Hospital, and we obtained written informed consent from all our patients or their caregivers. We only included patients who experienced at least one GTCS (with either primary generalized onset or focal onset with secondary generalization) while wearing PPG sensors. We excluded patients whose PPG recordings were affected by continuous motion artifacts.

### 2.2 | Seizure identification

Patients underwent continuous video-EEG monitoring (Natus Medical) using conventional scalp EEG montages according to the 10-20 electrode system. If a patient had multiple GTCSs during their monitoring, we only included the first GTCS episode in the analysis. Generalized tonic-clonic

semiology was confirmed by at least two board-certified pediatric epileptologists. The seizure onset and offset times were defined based on EEG findings.

## 2.3 | PPG signal selection

PPG recordings may be affected by motion. The data acquired by simultaneous three-axis accelerometer, embedded in the E4 sensor, were visually reviewed to detect motion. We preserved segments of the recordings free of motion artifact and excluded portions that were significantly affected.

For each patient, we analyzed PPG signals that were recorded (1) before and after the occurrence of seizure, to evaluate peri-ictal changes; and (2) during a seizure-free period, to evaluate intrapatient changes unrelated to the seizure occurrence.

For peri-ictal signals, we specifically defined three time periods related to seizure progression:

- Baseline period: From 5 hours to 30 minutes before the EEG seizure onset;
- Preseizure period: Five-minute period immediately preceding EEG seizure onset; and
- Postseizure period: The first hour after seizure termination on EEG.[4]

For each of the above periods, we selected 60-second segments. For intrapatient control signals, we probed the entire length of recording and marked the portions that met the criteria for control segments and were free of motion artifacts. Criteria for control segments consisted of any period that was >6 hours from the closest seizure onset. For each patient, we prepared a list of control portions. These portions were selected manually by excluding segments that were affected by motion artifact. Seizure-free signals were used to distinguish normal changes in PPG signals from changes that are triggered by seizure occurrence. For each patient, we extracted five control segments of variable duration (durations were up to 60 seconds) using a random number generator (https://www.google.com/search?q=random%20number%20generator). Patients with the diagnosis of electrical status epilepticus in sleep (ESES) were not included in the analysis of control signals because of the potential confounding impact of continuous epileptiform activities on the wristband signals. Selected segments were separated by at least 4 minutes.

## 2.4 | PPG feature extraction

We used software developed in MATLAB (MathWorks) for the preprocessing, segmentation, and feature extraction of PPG signals. A band-pass filter between 0.1 and 8 Hz was used to remove the DC component and high-frequency noise (zero-phase first-order Butterworth filter). Then, the PPG signal was segmented to identify the PPG pulses; an automatic threshold-based detection[5] was used to identify the local maxima, or peaks, within the signal. Figure 1 shows an example of three PPG pulses detected by our software from one of our patients. Minima identify the starting and end points of each PPG pulse. The following set of features were extracted from each PPG pulse, as described in previous studies on pulsatile signals for different applications.[5,6]

1. Frequency (in Hz); the inverse of the time interval between two consecutive PPG pulse peaks (in Hz);
2. Peak amplitude (in nW) with respect to the starting point;
3. Duration (in seconds); the time interval between start and end of each PPG pulse;
4. Increasing slope (in nW/s); the slope of the increasing phase of the PPG pulse (between starting and peak points), calculated as the ratio between amplitude and the phase duration;
5. Decreasing slope (in nW/s); the slope of the decreasing phase of the PPG pulse (between peak and end points);
6. Smoothness of the pulse (nW/s), calculated using the spectral arc-length metric,[5,7] defined as the arc length of the Fourier magnitude spectrum of the PPG speed profile; and
7. Area under the curve (in nW*s), calculated between the starting and end points using the trapezoidal rule.

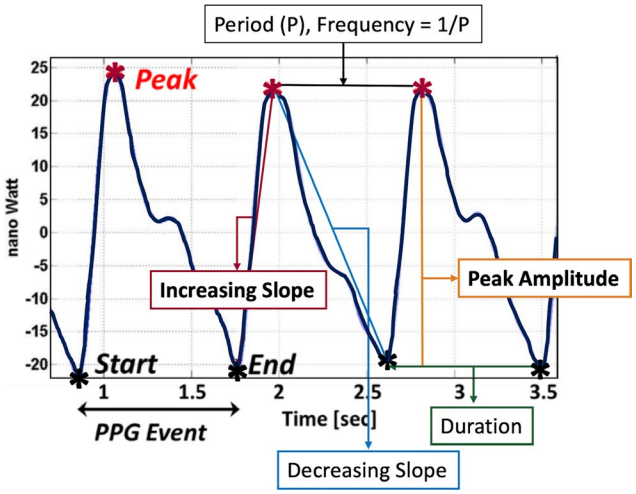


**FIGURE 1** This figure shows selected extracted features of a portion of photoplethysmography (PPG) signal from one patient. Three PPG pulses (red asterisks) detected in the PPG signal recorded from a patient with generalized tonic-clonic seizures are depicted. The local minima (black asterisks) mark the start and end points of each PPG pulse. Frequency is calculated as the inverse proportion of the period (distance between two adjacent peaks). Evaluation of peak amplitude, duration, increasing slope, and decreasing slope are also shown

### 2.5 | Statistical analysis

We used SAS, version 9.4 PROC MIXED (SAS Institute) for statistical analyses. All analyses for individual PPG signal features were carried out using a linear mixed-effect (LME) model with random-intercept to account for correlation within subjects, and for variability between subjects under the missing at random assumption. For each 60-second period, the estimate of the mean along with its standard error was obtained using this LME model. Contrasts were constructed to compare the pairwise differences among the various periods. The final model selection was performed using the Akaike information criterion. We also applied the Benjamini-Hochberg false discovery rate procedure to control for multiple comparisons across all features and periods.

This analysis allowed us to identify any pre- and postseizure changes in the PPG features, that is, changes during preseizure or postseizure periods compared to baseline, as well as any seizure-free change, that is, changes observed between seizure-free periods. Then, to identify which changes were associated with seizure occurrence, we compared pre- and postseizure and seizure-free changes. We estimated the magnitude and direction of these changes (increase vs decrease) and identified the pre- and postseizure changes that were consistently higher than the changes observed during seizure-free periods, and reported changes between two compared conditions as the mean value of their difference: a positive change represents an increase respective to the baseline or control signals, whereas a negative change suggests a decrease.

## 3 | RESULTS

### 3.1 | Patients

We prospectively enrolled 174 patients admitted to the epilepsy monitoring unit at Boston Children's Hospital between February 2015 and June 2017 (Figure 2). A total of 251 nights of data were recorded (120 patients were enrolled for one night, 34 patients were enrolled for two nights, 17 patients were enrolled for three nights, and three patients were enrolled for four nights). Sixty-five patients experienced a

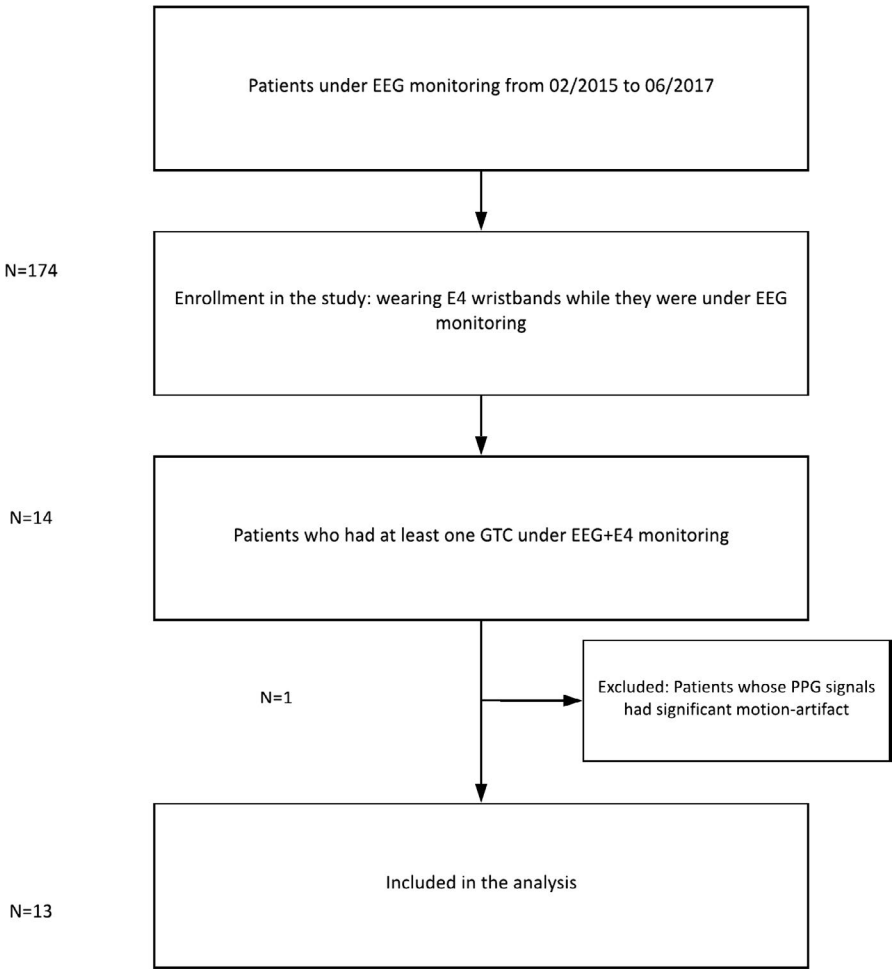


**FIGURE 2** Inclusion flow diagram of our patients with the total number of enrolled patients, number of patients who had a generalized tonic-clonic seizure (GTCS) during their monitoring, and number of patients included in the final analysis of photoplethysmography (PPG) signals. EEG, electroencephalography

seizure during EEG monitoring while wearing the wristbands. Twenty-seven GTCS (primary or secondary generalized) episodes were captured from 14 patients. Of 14 patients who had a GTCS captured during recording, only one patient was excluded due to motion artifact (7%). Thirteen patients were included, and the data from their first recorded GTCS were analyzed. Four patients (Patients 5, 6, 7, and 12) were excluded from preictal period analysis (30%) and one patient (Patient 4) was excluded from postictal analysis (7%) due to motion artifacts in those portions. In the analysis of control signals, four patients (of 13) were not included because of motion artifacts (Patients 4, 9, and 11) or ESES diagnosis (Patient 10). Demographic characteristics, age at epilepsy onset, epilepsy type, EEG findings, and magnetic resonance imaging features for these 13 patients are depicted in Table 1. The device deficiency time (the duration of recording affected by motion artifacts) for three randomly selected patients was calculated. From their entire recording, 78.6% was affected by motion artifacts. For control portions, we screened time frames that were at least 6 hours from other seizures and found that from all patients, nearly 73% of daytime and 63% of nighttime portions seem to be affected by motion artifacts.

## 3.2 | PPG changes during pre- and postseizure periods compared to baseline

We found a change in frequency, amplitude, increasing slope, decreasing slope, smoothness, and area under the curve during the pre- and postseizure periods compared to baseline (Table 2). For duration, we used the log transformation prior to analysis due to skewness.

## 3.3 | PPG changes during seizure-free periods

There were also feature changes during different seizure-free periods (see Figure 3), that is, even without a seizure trigger.

**TABLE 1** Clinical information from 13 patients with generalized tonic-clonic seizures

| Patient No. | Age, y | Age at seizure onset/gender | Epilepsy diagnosis | Ictal EEG findings | State of wakefulness before seizure onset | MRI findings |
|---|---|---|---|---|---|---|
| 1 | 14 | 7 y/female | Focal epilepsy | Rt central onset FBG | Asleep | Rt hemisphere infarct |
| 2 | 11 | 9 y/female | Focal epilepsy | Rt frontal onset FBG | Asleep | Rt hemisphere infarct |
| 3 | 12 | 14 mo/female | Focal epilepsy | Lt frontal onset FBG | Asleep | Lt frontal cortical malformation |
| 4 | 12 | 9 y/male | Focal epilepsy | Rt lateral temporal onset FBG | Asleep | Nl MRI (no etiology for epilepsy) |
| 5 | 15 | 13 y/male | Focal epilepsy | Rt central onset FBG | Awake | Malformation of cortical development |
| 6 | 14 | 6 y/female | Focal epilepsy | Lt central onset FBG | Awake | No etiology for epilepsy (Chiari I malformation) |
| 7 | 17 | 15 y/male | Focal epilepsy | Lt parietotemporal onset FBG | Awake | Lt temporal lobe tumor s/p resection |
| 8 | 16 | 15 y/female | Focal epilepsy | Lt temporal onset FBG | Awake | Nl MRI (no etiology for epilepsy) |
| 9 | 22 | 10 y/female | Focal epilepsy | Lt centroparietal onset FBG | Asleep | Lt hemisphere infarct |
| 10 | 9 | 7 y/male | Focal epilepsy | Rt frontocentral onset FBG | Asleep | Lt cortical malformation |
| 11 | 27 | 14 y/female | Generalized epilepsy | Generalized onset | Awake | Nl MRI (no etiology for epilepsy) |
| 12 | 11.5 | 10 y/female | Focal epilepsy | Left frontocentral onset FBG | Asleep | Lt hemisphere tumor |
| 13 | 17 | 14 mo/female | Generalized epilepsy | Right centrotemporal onset then spread to right frontal FBG | Awake | Rt cortical malformation |

Abbreviations: EEG, electroencephalographic; FBG, followed by generalization; Lt, left; MRI, magnetic resonance imaging; mo, month old; Nl, normal; Rt, right; s/p, status post; y, years old.

**TABLE 2** Results of comparing signal features in baseline versus pre- and postseizure phases

| Feature | Phase | Estimate | 95% CI | *P* |
|---|---|---|---|---|
| Frequency | Baseline vs preseizure | 0.02266 | 0.002319 to 0.043 | .029[a] |
| | Baseline vs postseizure | 0.382 | 0.3644 to 0.3996 | <.0001[a] |
| Peak amplitude | Baseline vs preseizure | 14.4797 | 10.1776 to 18.7819 | <.0001[a] |
| | Baseline vs postseizure | −2.1902 | −5.9168 to 1.5365 | .2493 |
| Duration(log)[a] | Baseline vs preseizure | −0.00882 | −0.02395 to 0.00631 | .2531 |
| | Baseline vs postseizure | −0.2687 | −0.2818 to −0.2555 | <.0001[a] |
| Increasing slope | Baseline vs preseizure | 78.9695 | 56.8421 to 101.1 | <.0001[a] |
| | Baseline vs postseizure | 19.5644 | 0.3977 to 38.731 | .0454[a] |
| Decreasing slope | Baseline vs preseizure | 13.7698 | 3.6558 to 23.8837 | .0076[a] |
| | Baseline vs postseizure | 60.0707 | 51.3096 to 68.8318 | <.0001[a] |
| Smoothness | Baseline vs preseizure | 0.09572 | 0.06711 to 0.1243 | <.0001[a] |
| | Baseline vs postseizure | 0.3065 | 0.2817 to 0.3313 | <.0001[a] |
| Area under the curve | Baseline vs preseizure | 6.7513 | 4.652 to 8.8506 | <.0001[a] |
| | Baseline vs postseizure | −10.7673 | −12.5857 to −8.9489 | <.0001[a] |

Abbreviation: CI, confidence interval.

[a]Statistically significant.

[b]Duration(log): log transformation of duration was performed prior to analysis.

### 3.4 | Consistency and magnitude of PPG pre- and postseizure changes versus seizure-free changes

We found a consistent pre- and postseizure increase in frequency that was higher than the seizure-free changes (preseizure = 0.22 Hz, 95% confidence interval [CI] = 0.18-0.26 and postseizure = 0.58 Hz, 95% CI = 0.54-0.62 vs seizure-free = 0.05 Hz, 95% CI = 0.03-0.07; Figure 3). During the postseizure period, we furthermore observed an increase in smoothness that was higher than the seizure-free changes (postseizure = 0.22, 95% CI = 0.17-0.27 vs seizure-free = 0.06, 95% CI = 0.03-0.08; Figure 3). Finally, during preseizure periods, we found a consistent decrease in the decreasing slope, which was higher than the seizure-free changes (preseizure = 56.71 nW/s, 95% CI = 47.21-66.22 vs seizure-free = 17.38 nW/s, 95% CI = −29.81 to 64.58; Figure 3). All other changes observed during pre- or postseizure periods were not systematically different from the changes observed during the seizure-free segments (Figure 3). Figure 3 shows the estimated mean values of all PPG features for each period and the relative changes of the features compared between different periods.

## 4 | DISCUSSION

Our study shows an increase in PPG frequency during pre- and postseizure periods that was higher than the changes during seizure-free periods. Additionally, the PPG slope decreased from preseizure periods compared to seizure-free periods, and smoothness increased during the postseizure period as compared to seizure-free periods. These results suggest that PPG analysis may offer additional information when monitoring patients with epilepsy, beyond EKG monitoring, allowing monitoring at a peripheral body site. In this study, we analyzed changes in the PPG signal from the pre- and postseizure periods as well as seizure-free periods of patients with GTCSs.

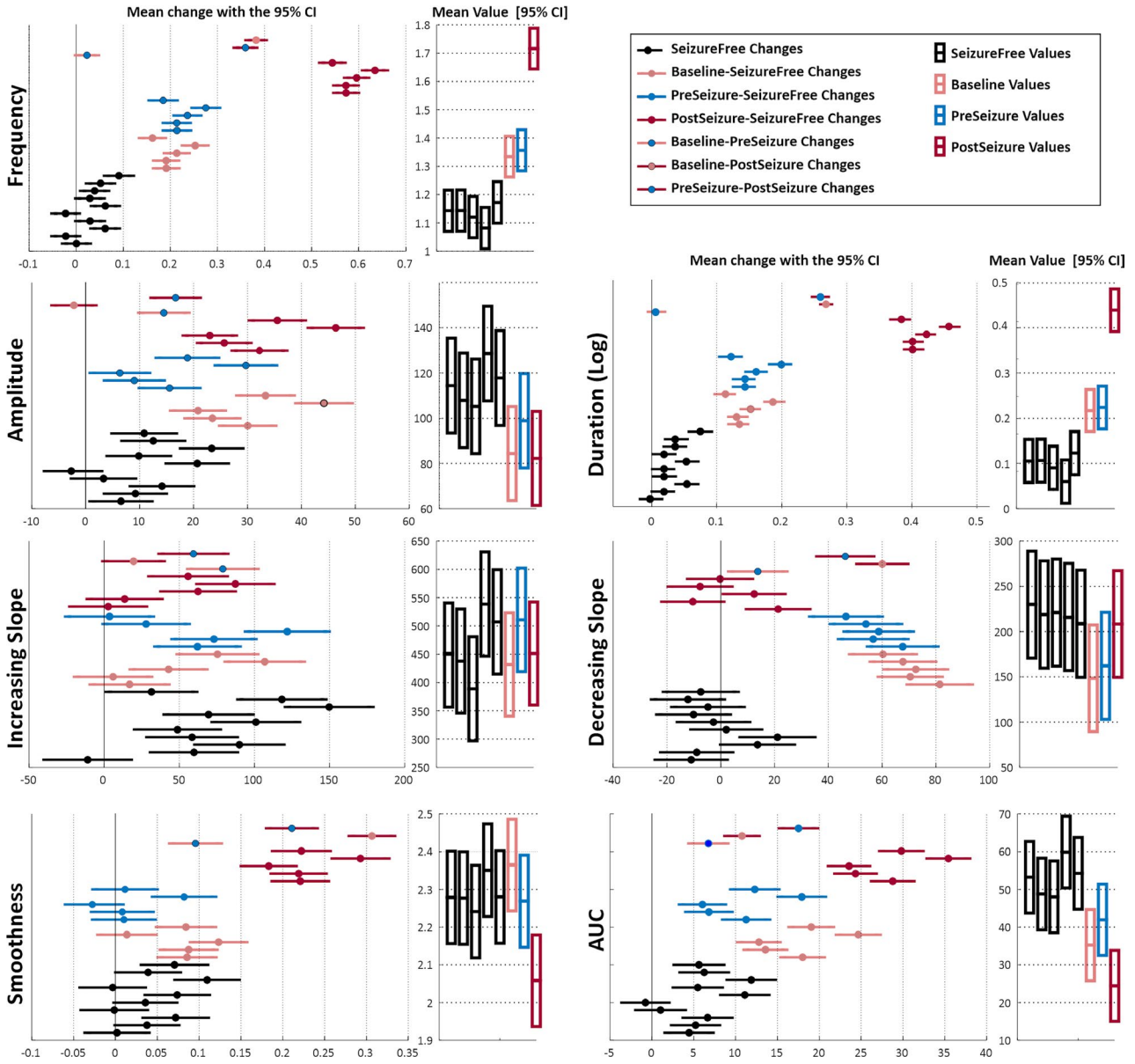


**FIGURE 3** Relative changes of each feature compared between different periods, including seizure-free, baseline, preseizure, and postseizure periods, and the estimated mean of features during each of these time periods. The units for features are as follows: frequency (in Hz), amplitude (in nW), duration(log in seconds), increasing and decreasing slope (in nW/s), smoothness (in nW/s), area under the curve (AUC; nW*s). CI, confidence interval

## 4.1 | PPG changes are more prominent before and after seizures

We found that PPG signals changed immediately before and after GTCS occurrence in patients with epilepsy. Although these changes were also present during seizure-free periods, the magnitude of changes was remarkably higher during the pre- and postseizure periods, and this difference was evident in different features of the PPG signal, including frequency, smoothness, and decreasing slope. Specifically, frequency, and smoothness changes were more prominent during the postseizure period and for decreasing slope changes were more remarkable during the preseizure period. These findings suggest that using noninvasive biosensors to monitor the PPG signals may enable seizure detection and documentation prior to or early after seizure onset in our cohort.

## 4.2 | ANS changes during peri-ictal period

PPG signals reflect the microperfusion of blood in the underlying tissue, and therefore factors that can change the perfusion may also change PPG signals. Some of these factors are known, such as heart rate, blood pressure, and vascular tone, and some have not been not well understood up to this point. Change in PPG signals before and

after seizures, as shown in this study, suggests the role of seizures in triggering these changes, and the underlying mechanism can be the change in ANS function. Frequency and duration of the PPG signals are directly affected by heart rate, and thereby their changes may also reflect heart rate alterations. Hence, not only the heart rate–dependent variables (frequency), but also other features of the PPG signal including smoothness and slope vary relative to seizure timing. The association of smoothness and slope of PPG signals with other physiologic variables that contribute to the blood flow in the underlying tissues has not been studied. Studies show that features of PPG signals may represent a variety of cardiovascular indices such as heart rate, blood pressure, and stroke volume. Although these changes might not be pathognomonic for seizures, they do indicate an autonomic change and may provide some information about a possible impending seizure.[8] Changes may suggest the use of PPG signals as an indicator of ANS activity in patients with epilepsy and as a marker for detection of GTCS episodes.

Seizures can originate from or spread to central areas that control ANS in the brain. These areas include amygdala, anterior insula, anterior cingulate cortex, posterior orbitofrontal cortex, hypothalamus, periaqueductal gray, parabrachial region in the pons, solitary tract nucleus, and ventrolateral medulla.[9] Activation of these areas during a seizure can change the ANS function during the preictal, ictal, and postictal phases of a seizure. The ANS controls blood pressure and cardiac output, which are major determining factors for vascular tone and blood flow. Given that PPG signal indicates blood volume and flow in the underlying vessels, this study suggests that changes in PPG signals may reflect ictal changes in ANS function.

## 4.3 | Comparison with prior studies using cardiac and vascular parameters

Prior studies attempted to quantify PPG pulse amplitude.[10–12] Of note, the AC component changes synchronously with each heartbeat; therefore, the signal frequency may also indirectly represent heart rate.[8] Several studies have evaluated the peri-ictal changes as a function of the ANS as well as peri-ictal changes in the heart rate.[2,13–15] The results are variable depending on type of seizure and type of epilepsy as well as patients' age group. The most prominent finding that has been shown is ictal tachycardia. Some of these studies have also shown preictal tachycardia in their participants.[2,16,17] These findings may at least in part explain the underlying mechanism of increasing frequency and decreasing duration (inverse relation with frequency) of PPG signals before seizure onset in our patients. As compared to prior studies on PPG signals in epilepsy patients,[15,18,19] we evaluated the raw PPG signals during the pre- and postseizure periods, which have not been studied before. One investigative team[18] evaluated the PPG signals in heart rate monitoring of patients with epilepsy and showed that heart rate monitoring with portable devices provides recordings similar to EKG monitoring except during episodes of seizure or wakefulness, when EKG signals are affected by motion artifact. Another study[15] also used heart rate derived from PPG signals in combination with ACC signals for seizure detection. The results of this study show good sensitivity of this multimodal approach for detection of nocturnal seizures, especially tonic-clonic seizures. An additional study[19] used PPG signals to evaluate seizure detection in patients with temporal lobe epilepsy. This study used PPG signals to derive pulse rate variability (PRV), and then used PRV for seizure detection. They also used a portable EKG sensor for HRV detection and compared the performance of these two wearable devices with hospital-based EKG in detection of seizures. Although an EKG sensor was shown to be sensitive for seizure detection, utilization of PPG signals was found to be not as helpful for seizure detection as other EKG-based signals. These studies, however, did not use the raw PPG signals for analysis, and analyzed derivatives of PPG signals, including heart rate and pulse rate variability. Based on our analysis, raw PPG signals may provide additional information regarding usability of these signals for seizure detection and prediction. Although PPG alterations with heart rate changes are known, the results of the current study also suggest that PPG signals change during pre- and postseizure periods as heart rate changes. Heart rate is only one of several potentially contributing factors shaping PPG signals; other factors include vascular tone and intravascular volume, and ultimately ANS changes. Interestingly, it is not solely frequency that changes, but also other aspects of PPG signals, such as slope and smoothness of the waves. Association between these features and other physiologic variables are not yet well established, but our data suggest that they may provide additional information beyond heart rate during the peri-ictal period as compared to baseline.

## 4.4 | PPG is variable

In our cohort of patients, PPG signals showed variability even without a seizure trigger, which is also evident in previous studies. In one study,[17] authors reported 20%-30% relative fluctuations in signal amplitude during a 5- to 10-minute test period. They also showed that, in their cohort of 10 participants, baseline value and duration of PPG pulse signals showed low- and high-frequency fluctuations during the test period, respectively.[20] Nevertheless, in the current study, pre- and postseizure changes were more

prominent than baseline variation, hence carrying potential for seizure warning.

## 4.5 | Cardiac interictal changes in epilepsy patients

In patients with epilepsy, even during a seizure-free period, the interictal state can be characterized by atypical changes in ANS function when compared to a nonepileptic control individual. Patients with refractory temporal lobe epilepsy, for example, have lower heart rate variation during normal physiologic conditions, such as breathing, or tests, such as the tilt table test, when compared to a control group.[21] Spectral analysis of HRV demonstrated decreased low-frequency band power and lower low-frequency/high-frequency power ratio in patients with temporal lobe epilepsy compared to the control group,[22] which indicates an impaired balance of ANS function in these patients. Another systematic review showed that in patients with epilepsy, analysis of HRV resulted in lower high-frequency power values than controls, which implicates vagal nerve dysfunction and is associated with increased risk for arrhythmias.[23,24] Additionally, patients who received antiepileptic treatment had higher low-frequency values, which indicates lower sympathetic activity compared to patients without treatment.

## 4.6 | Challenges

Results need to be interpreted in the setting of data acquisition. Selection and information bias cannot be excluded, although we did our best to prevent these by sampling multiple signal sections and by randomizing selection. Specifically, the body placement location was not the same for all the patients in our analysis. For some patients, the data from the right side of the body were used, whereas for other patients, the data from the left side were included in the analysis. This difference in placement location may affect the data and should be considered in future studies with larger sample sizes. Furthermore, we cannot rule out that artifact and signal processing affected results, as current PPG sensors in wrist- or ankle-worn devices may lose contact with the skin and lead to motion artifacts. PPG signals are often affected by motion artifacts, which may limit their applicability in seizure detection, at least with the current recording settings. Our patients were usually enrolled for 1-3 days in our study, and although this study included only GTCSs, some patients had other seizure types during the enrollment period, which limited the availability of control segments. This was in addition to difficulties related to motion artifacts. Device deficiency time for three randomly selected patients was 78.6% of their entire recording, and for all patients, 73% of daytime control portions and 63% of nighttime control portions had motion artifacts. Furthermore, we were unable to analyze the ictal phase, given the robust motor components of GTCSs, including disconnection between the sensor and the skin, which introduces motion artifact into the signals. Control portions were selected from periods 6 hours away from any seizure, and mostly from sleep (n = 26, 94%). Therefore, selection of control signals mainly during sleep is another limitation due to possible confounding effects of sleep or wake status of patients on their PPG signals. Overall, current difficulties with obtaining high-quality recordings limit this modality for seizure detection. Nevertheless, PPG offered additional information prior to and after seizures. A newer generation of sensors with improved contact with the skin is required to reduce motion artifacts in the future.

The preictal and postictal portions were selected within the defined range for each period (preictal: from 5 minutes before to seizure onset; postictal: from seizure offset to 1 hour after); however, within this range, there are intersubject variations. Namely, the time point of these portions relative to seizure varies between subjects, and autonomic changes may vary accordingly, and this may limit the interpretation of our results. Another limitation was related to the identification of motion artifact in our signals, as we relied on visual inspection of the signals instead of automated detection, which may imply some bias in our data. Lastly, sample selection was limited to a certain extent by data availability, and by data that were not obscured by artifact. Although we enrolled 174 patients in an attempt to capture seizures, GTCS capture rate was relatively low, not permitting confounder adjustment, and future longitudinal studies with larger numbers will be required to address modulating factors. Nevertheless, we provide an innovative account of PPG feature analysis in GTCSs, potentially highlighting overall feasibility of a novel seizure-monitoring modality on the wrist.

## 4.7 | Outlook

Most portable wrist-worn sensors and wearables now include PPG sensors. Progressively widespread application of PPG sensors in wearable biosensors increases the applicability of PPG signals as a potential biomarker for seizures in patients with epilepsy. Recently, developers introduced new features for wearable sensors that can measure respiratory rate based on the PPG signals, which may also call additional attention to the potential use of PPG signals as a biomarker in patients with epilepsy.[25] Future devices may be able to further decrease signal noise and increase signal quality, and hence PPG signals may contribute to components of biomarker analysis in the realm of seizure detection and, potentially, prediction. Prospective validation of findings and tentative cutoff values will be a next step toward clinical implementation.

## 5 | CONCLUSIONS

PPG signals show changes around the occurrence of a GTCS in patients with epilepsy, which can be detected through non-invasive methods. Monitoring PPG signal changes may assist in seizure detection. Future studies integrating PPG signals with other biomarkers in a multimodal monitoring system with larger sample sizes may assist in further validating this biomarker.

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## CONFLICT OF INTEREST

T.L. has served on the Council of the American Clinical Neurophysiology Society, as founder and consortium principal investigator of the Pediatric Status Epilepticus Research Group, as an Associate Editor for *Wyllie's Treatment of Epilepsy* 6th and 7th editions, and as a member of the New onset refractory status epilepticus (NORSE) Institute and Critical Care EEG Monitoring Research Consortium. He has served as Associate Editor of *Seizure* (Elsevier), on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, and on the American Board of Clinical Neurophysiology in the past. He is part of patent applications to detect and predict clinical outcomes, and to detect, manage, diagnose, and treat neurological conditions, epilepsy, and seizures. T.L. is coinventor of the TriVox Health technology; T.L. and Boston Children's Hospital might receive financial benefit from this technology in the form of compensation in the future. He has received research support from the Epilepsy Research Fund, National Institutes of Health, Center for Integration of Medicine & Innovative Technology/Department of Defense, Patient Centered Outcomes Research Institute, Epilepsy Foundation of America, American Epilepsy Society, Epilepsy Therapy Project, Pediatric Epilepsy Research Foundation, Danny Did Foundation, Cure, and HHV6 Foundation, and has received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt, Sunovion, Sage, Empatica, Acorda, and Pfizer, and past device donations from various companies, including Empatica, SmartWatch, and Neuroelectrics. In the past, he has served as a consultant for Eisai, Lundbeck, UCB, Amzell, Sunovion, Upsher-Smith, and Zogenix. He performs video-electroencephalographic long-term and intensive care unit (ICU) monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures, and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums/grand round travel support from national/international societies and national/international academic centers. Some of T.L.'s trainees received salary support from international foundations/societies and academic centers while working in his laboratory. His wife, Dr Karen Stannard, is a pediatric neurologist; she performs video-electroencephalographic long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## AUTHOR CONTRIBUTIONS

F.M.T. and T.L. contributed to study conception, study design, data collection, data analysis, manuscript writing, and preparing manuscript revisions. E.T. contributed to study design, data analysis, manuscript writing, and preparing manuscript revisions. F.C., S.H., R.E.A., M.J., M.B.-J., B.K., J.C., and S.M. contributed to study design, data collection, and preparing manuscript revisions. C.P. and K.K. contributed to study design, data analysis, and preparing manuscript revisions.

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