Investigation of Morphological Variations of Photoplethysmography Signal in Human Epilepsy

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***Abstract*— The purpose of this study is to analyse the ictal variations in peripheral blood flow using photoplethysmogram (PPG) and single lead Electrocardiogram (ECG) signals. 11 subjects with 56 partial seizures were recorded with the PPG sensor worn on their left ankles. 6 different features from PPG pulse morphology related to hemodynamics were derived. The seizures were divided into two groups based on the side of the seizure activity. The investigation of ictal variations in features did not show any significant difference between the seizures' lateralizations. The analysis of latencies of ictal changes in the PPG features revealed the PPG pulse amplitude precede the variations in other PPG features including ictal heart rate variability. In addition, analysis of the effect of seizure lengths on ictal variations showed the seizures' lengths have no significant effect on the feature variation rates.**

***Clinical relevance*— Analysis of the extracted PPG features and their timing suggest an increase in vascular resistance due to increase in sympathetic tone which occurs prior to the ictal tachycardia. These variations is independent of the seizures' lengths and lateralizations.**

I. INTRODUCTION

More than 50 million people are suffering from Epilepsy worldwide. During a seizure, the patient might experience temporary confusion, loss of consciousness, muscular jerking, and gastrointestinal and cardiovascular dysfunction [1]. Among all these comorbidities, the cardiac abnormalities is of great research interest, since the mechanism of Sudden Unexpected Death in Epilepsy (SUDEP) is still unclear.

The variations in cardiovascular imbalance happens as a result of autonomic dysfunction. Tachycardia is the most frequent ictal comorbid happening due to an increase in sympathetic tone [2]. Despite numerous studies on ictal tachycardia, the ictal variations in vascular function has never been investigated before. In fact, the excess release of catecholamines such as norepinephrine working as anticonvulsant will affect the hemodynamics including cardiac output, blood pressure, and blood distribution in limbs. Norepinephrine calls off the blood flow from the limbs, reducing the blood volume in peripheral vessels [3]. A study on 27 mice showed a sudden drop in cardiac output after the seizure onset as well as a rise in peripheral resistance due to vasoconstriction [4].

This work analyzes the ictal variations in human peripheral vascular function using Photoplethysmogram (PPG) and one-lead Electrocardiogram (ECG) signals. PPG has conventionally been used to measure oxygen saturation level and heart rate. However, it is known that the morphology of the PPG pulse has information about the vascular function including blood pressure, cardiac output, and vascular compliance [5]. 6 different PPG features related to vascular function were derived. The normalized pulse transmit time (NPTT), the normalized crest time t_{NCT}, the normalized maximum velocity time t_{NMV}, the pulse amplitude (PA), the principle coefficient of the second derivative of the PPG pulse shape (PCA1), and heart rate were extracted from 11 subjects with focal epilepsy. The increase in the t_{NMV} and t_{NCT} and the decrease in pulse amplitude in ictal phase suggest an increase in the venous resistance on the subjects limbs (left ankle) during seizure. It was observed the drop in pulse amplitude precedes all the rest of the features including the rise in the heart rate. In addition, the effect of seizure length on the feature variations were investigated showing no association between the ictal variation rates and the seizure lengths. In order to observe the latencies of variations for each feature, the ictal variation rates with respect to baseline were calculated at three snapshots in time. The variation rates at 50 seconds before the seizure onset, right at the seizure onset, and 50 seconds after the seizure onset were compared to identify early changes in PPG features.

II. METHODS

A. Dataset

This study is approved by Institutional review Board, University of California Irvine. 11 subjects (7 males, 4 females; age 34±13.3) consented to take part in the study among the candidates undergoing long-term surface EEG monitoring in UC Irvine Medical Center. The subjects had no history of cardiovascular diseases. The 20 channel surface EEG and one-lead ECG signals were recorded at 500 Hz of sampling frequency (Nihon Kohden JE 921, paired with the QI-123-A LAN converter). The PPG signal was recorded from the left ankle of the subjects using Empatica E4 wristband [6], [7].

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TABLE I: Subjects' Clinical Characteristics

Patient	Sex	Age	Lateralization	Number of seizures	Length of recording (hour:min)
1	Male	27	Left	1	2:0'
2	Male	27	Left	17	19:0'
3	Male	23	Right	7	23:21'
4	Male	58	Left	1	5:0'
5	Female	50	Right	12	16:0'
6	Male	25	Right	5	10:41'
7	Female	33	Left	1	4:0'
8	Male	27	Right	1	4:0'
9	Male	25	Left	1	4:0'
10	Male	59	Left	9	21:0'
11	Female	21	Left	1	2:0'

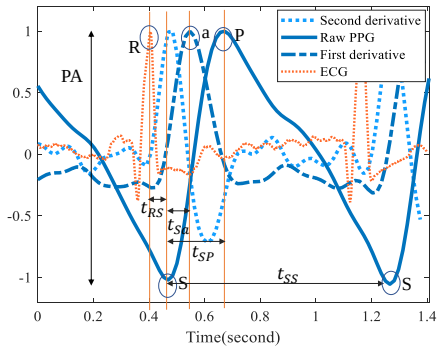

Fig. 1: The PPG pulse shape and the extracted PPG morphological features

An apparatus with a blinking LED and a port to connect to Nihon Kohden DC input box was designed and implemented to synchronize the PPG recording with EEG/ECG recording as described in [8]. Table I shows the clinical characteristics of the subjects as well as the recording duration. The seizure onset and offset times were marked by a clinician based on the EEG signal.

B. PPG features

The PPG pulse shape is the superposition of pressure from the forward propagating blood flow and its reflected wave. The PPG pulse has a stereotypical shape as shown in Fig. 1. The extracted PPG morphological features are as follows:

- **Heart Rate (HR)**: The HR is defined as the reciprocal of the time between two troughs of the PPG wave as denoted by S in Fig. 1 and is defined as:

$$HR = \frac{1}{t_{SS}}, \tag{1}$$

  where t_{SS} is the PPG pulse width.
- **The Pulse Amplitude (PA)**: The pulse amplitude is the height of the PPG pulse as denoted by PA in Fig. 1 and is dependent on many physical and physiological factors. It is mostly affected by the volume of reflected blood wave as well as venous resistance [9]. According to [10], in a cold press the veins experience vasoconstriction due to increased sympathetic tone. The vasoconstriction in veins increases venous resistance and reduces the PA. According to [11], the PA is modulated by the sympathetic activity of the skin area where the PPG signal is being recorded.
- **The Normalized Crest Time** (t_{NCT}): The crest time is the time between the diastolic trough up to the systolic peak of the next pulse. It is known that the crest time increases in case of increase in vascular resistance [9]. To eliminate the effect of heart rate in our analysis, the crest time is normalized to the pulse width as

$$t_{NCT} = \frac{t_{SP}}{t_{SS}}. \tag{2}$$

- **Normalized Maximum Velocity Time** (t_{NMV}): The PPG pulse shape is an indicative of the blood flow in vessels. The first derivative of the PPG pulse shape has information regarding the velocity of the blood flow. The maximum velocity time is the time between the diastolic trough up to the maximum slope point denoted by t_{Sa} in fig. 1. The normalized maximum velocity time is related to arterial pressure, blood viscosity, and vascular resistance and is defined as

$$t_{NMV} = \frac{t_{Sa}}{t_{SS}}. \tag{3}$$

- **The First Principle Component of the Second Derivative (PCA1)**: The second derivative of the PPG pulse shape is indicative of acceleration of blood flow and has information regarding arterial stiffness and compliance.
- **The Normalized Pulse Transmit Time (NPTT)**: the pulse transmit time is the time it takes the blood to travel from the left ventricle to the limbs and is measured by the time between the R-peak in ECG signal and the next diastolic trough in PPG signal as denoted by t_{RS} in Fig. 1. An increase in pulse transmit time is associated with pulse wave velocity and arterial stiffness. The pulse transmit time decreases in case of an increase in blood pressure [11]. The NPTT is the pulse transmit time divided by the pulse width to eliminated the heart rate variation effect,

$$NPTT = \frac{t_{RS}}{t_{SS}}. \tag{4}$$

C. Data Analysis

1) Ictal Variation Rate (VR): The baseline feature values were extracted from a 5-minute window which started 7 minutes before seizure onset. The feature sample points inside this interval were derived from individual PPG pulses and are considered as baseline. Let us denote the average value and the variance of baseline HR inside this 5-minutes window by $\mu^{HR}_{baseline}$ and $\sigma^{HR}_{baseline}$. In addition, the features were extracted for another 5-minute window starting from 1 minute prior to the seizure onset considered as ictal. A new metric is defined called the ictal variation rate (VR), in which the feature values inside the ictal 5-minute windows are normalized to the mean and variance of baseline as,

$$VR_{HR}[n] = \frac{HR_{ictal}[n] - \mu^{HR}_{baseline}}{\sigma^{HR}_{baseline}}, \tag{5}$$

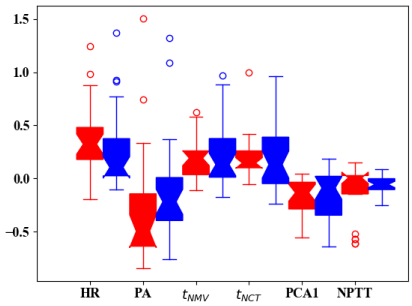

Fig. 2: The boxplot of the variations rates for seizures involving the left (blue) or right (red) hemispheres.

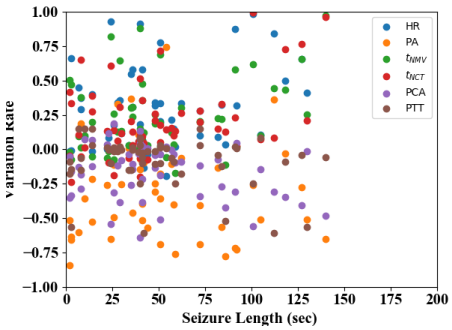

Fig. 3: The variation rates with respect to seizure length.

where $HR_{ictal}[n]$ is the n^{th} HR sample in ictal window. The ictal variation rate is derived the same way for all other PPG features.

These variation rates are compared between two categories of seizures starting in right and left hemispheres. In order to roughly estimate where the latencies of these variations start, the scatter plot of variation rates in three time instances (50 seconds before seizure, seizure onset, and 50 seconds after the seizure onset) are extracted as explained in section III.

III. Results

The ictal variation rates were extracted based on the definition in Section II for the 5-min ictal windows. According to Table I, the seizures involved only one side of the brain. To observe the effect of lateralization on ictal variation rates, Fig. 2 depicts the boxplots of the extracted variation rates for different PPG features. The blue boxes correspond to the seizures that involved the left hemisphere while the red boxes are based on the data from seizures involving the right hemisphere. According to Fig. 2, the negative values of variation rates in PA and PCA1 show these features experience a drop in ictal phase; whereas the positive values of the HR, t_{NMV}, and t_{NCT} indicate that these features experience a rise in their values in ictal phase. The increase in HR is the well known ictal tachycardia, which has been extensively studied in literature. In addition, the increase in t_{NMV}, t_{NCT}, and decrease in PA may be due to the increase in venous resistance in the area of the subjects' left ankle. This increase in vascular resistance can be justified, knowing the release of norepinephrine acting as anticonvulsant can cause vasoconstriction in limbs. Comparing the blue and the red boxes in Fig. 2 shows no significant difference in the ictal variation rates, implying these variations are independent of the seizure lateralization.

Fig. 3 represents the scatter plot variation rates right at the seizure onset with respect to seizure lengths for all 6 different PPG features. The dot points with different colors correspond to different PPG features. It can be seen the variation rates are distributed along horizontal lines, suggesting there is no relation between the variation rates and the seizure lengths.

For comparing the latencies of the ictal variations, the variation rates were estimated at three different time points (50 seconds before onset, at seizure onset, and 50 seconds after onset) using the average of two consecutive pulses. Fig. 4 shows these variation rates for all the possible pairs of the features. These rates are extracted by averaging the variation rates over two consecutive pulses, where the rates are almost the same when averaged over six consecutive pulse. According to Fig. 4(b,c,d,e), the HR variation is highly correlated with the variations in t_{NMV}, t_{NCT}, PCA1, and NPTT. The scatter plots of these pairs after the seizure onset are distrusted along the diagonal axis suggesting an increase in HR is simultaneously associated with an increase in the t_{NMV}, t_{NCT} values or a decrease in PCA1, and NPTT values. In addition a higher variation value in HR is also associated with a higher variation in these features. On the other hand, the scatter plots in Fig. 4 (a,f,g,h,i) suggest the PA starts its ictal drop even 50 seconds before the seizure onsets shown by the red dots in these figures. The early variations in PA is independent of the variations in the rest of the PPG features. Fig. 4(a) suggest the drop in PA even precedes the ictal tachycardia. In general, one can conclude 5 PPG features variations including HR, t_{NMV}, t_{NCT}, PCA1, and the NPTT are highly correlated in their ictal variations, while the PA drops independent of the rest of the features and precedes them even 50 seconds before the seizure onset.

One limitation of using PPG signal to monitor the blood flow is its sensitivity to movement artifact. The problem of PPG noise detection and rejection is not trivial. For this study, we had to manually go through the data and reject the artifactual parts.

IV. Conclusions

Norepinephrine is a type of catecholamine which is present in both central and peripheral nervous system. Conventionally, norepinephrine was considered to be released as the response of the body to the stress. In addition, the role of norepinephrine acting as anticonvulsant has been observed. The cardiovascular effects of norepinephrine include increase in heart rate and increase in peripheral vascular resistance. In this study we captured some of the ictal changes in peripheral vascular function using a PPG sensor worn on the left ankle of the subjects. The ictal drop in PA as well as the rise in t_{NCT} and t_{NMV} suggest a vasoconstriction in limbs during

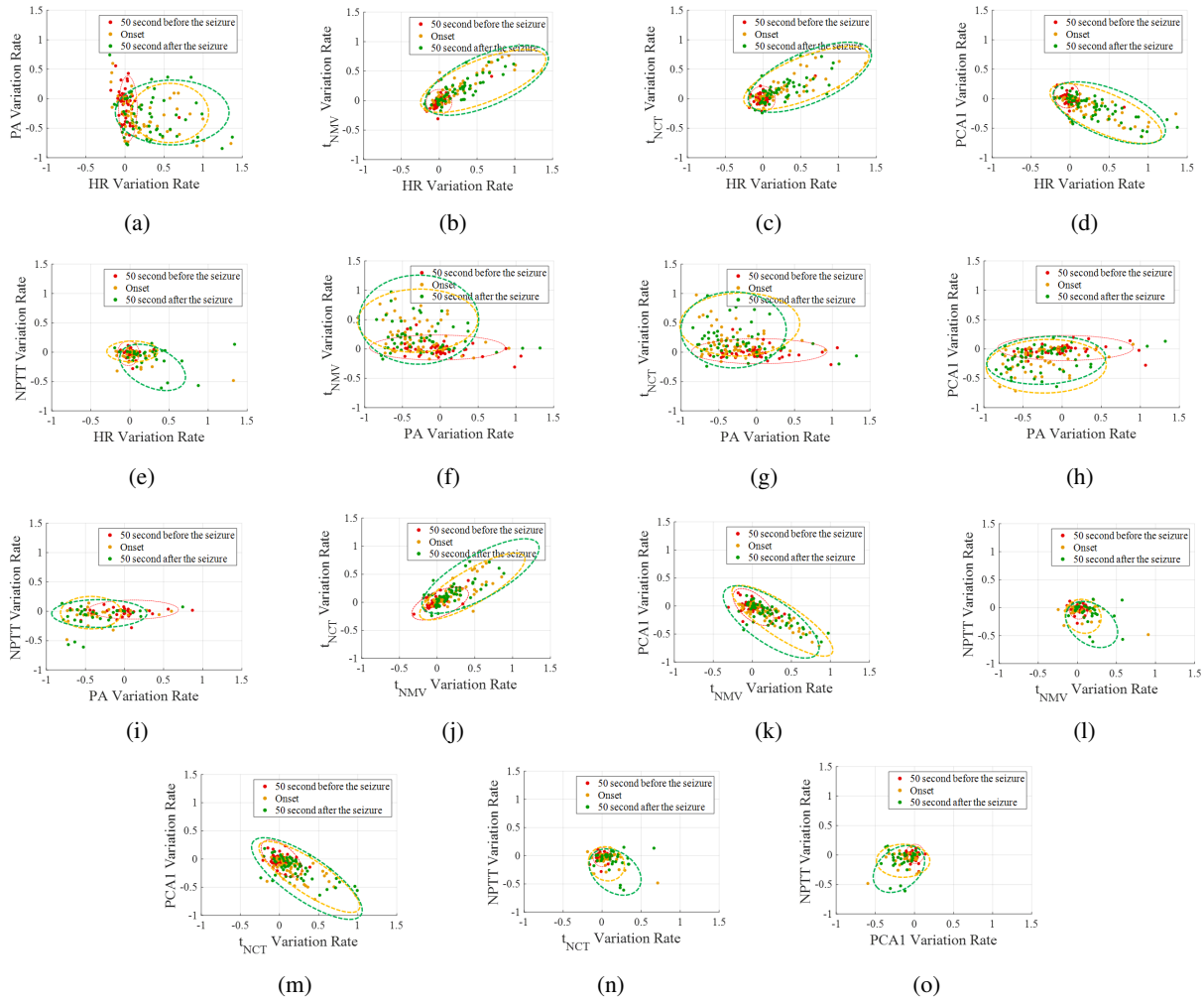

Fig. 4: The scatter plots for ictal variation rates for pairs of PPG features. Each dot corresponding to a seizure. The red, orange, and green dots correspond to variation rates for 50 seconds before, right on, and 50 seconds after the seizure onsets. Each point is derived by averaging the variation rates over two consecutive PPG pulses.

the seizure. Timing analysis of these ictal variations reveals that the changes in HR, t_{NCT}, t_{NMV}, NPTT, and PCA1 occur almost simultaneously, while the drop in PA precedes these variations and can be observed 50 seconds before the seizure onset in some cases. There were no relation between the variation rates and the seizure lengths. In addition, the seizure lateralization has no effect on the variation rates.

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