Original Article Development of a simple indicator that determines the distortion of pupillary size to accurately assess the autonomic nervous system

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Abstract: Pupil size variability (PSV) can be used as specific indicator of autonomic nervous system (ANS) imbalance. Pupillary size (PS) distortion by various eye movements has a vital negative influence on the reliability of PSV as an indicator of ANS imbalance. Hence, it is necessary to instruct the time and strength of distorted PS data to improve the ANS assessment. Therefore, this study proposes the minus directional indicator (-DI) as a simple directional movement indicator calculated by measured PS pixels. We used the electrooculography (EOG) for tracking the eye movements and measured PS data by pupillometer in the left eye and EOG signal in the right eye simultaneously. The PS data distortion was found when EOG was observed. The time intervals determined by -DI included the most time intervals when the obvious decrease in PS data were observed and corresponded to the time intervals when EOG signal was detected. To find the optimal threshold level of -DI, 3 threshold levels (0.2, 0.4 and 0.6) were applied. The PS distortions were significantly deleted at 0.2. In conclusion, the -DI reflected the apparent PS data distortion and very few eye movements. The 0.2 was the optimal threshold level to effectively delete the PS data distortion.

Keywords: Pupil size variability, autonomic nervous system, eye movements, electrooculography, pupillometer

Introduction

The autonomic nervous system (ANS) controls physiological conditions as well as various pathological settings [1-3]. Thus, a close connection exists between ANS balance and physiopathological conditions such as diabetic neuropathy, myocardial infarction (MI), and congestive heart failure (CHF). The imbalance of ANS owing to the increase in sympathetic activity and decreased vagal tone is associated with arrhythmogenesis and sudden cardiac death [1-3]. Specifically, ANS imbalance could lead to serious ventricular tachyarrhythmia and unexpected cardiac arrest; thus, contributing to cardiovascular mortality [2, 3]. Previous studies employed various methods including cardiovascular reflex tests [2, 3], biochemical tests, and scintigraphic tests, to assess ANS status [2]. Heart rate variability (HRV) of an electrocardiogram (ECG) is widely used as a noninvasive technique to assess ANS status.

Three vital HRV oscillatory components are considered very important: a very low frequency (VLF) component (which includes a frequency bandwidth that continues to be controversial), a low frequency (LF) component (ranging from 0.04 Hz to 0.15 Hz), and a high frequency (HF) component (ranging from 0.15 Hz to 0.4 Hz). The LF component is influenced by the baroreflex sympathetic control of blood pressure. Additionally, the HF component and parasympathetic control of heart rate are closely related [4, 5]. The LHR is calculated as the ratio of the LF component to HF component and is used to evaluate the sympathetic and parasympathetic activities of the ANS [5]. The HRV is frequently employed; however, it has several potential problems that are affected by parameters such as gender, age, drug interferences, and concomitant diseases [6, 7]. Furthermore, the HRV is significantly influenced by the activation of parasympathetic nerves and autonomic ner-



Figure 1. Electrolysis Electrode Design.

vous system dysfunction and also by obesity and poor cardio respiration fitness [8].

The measurement of pupil size variability (PSV) has emerged as a simple noninvasive method to assess the ANS such that the effects of these factors can be minimized [9-11]. Pupillary size (PS) is also regulated by two antagonistic smooth muscle systems that are influenced by the ANS. The parasympathetic innervation plays a significant role of the pupillary sphincter activity through mediation by acetylcholine as a neurotransmitter. The innervated pupillary dilator muscle in which noradrenaline acts as a neurotransmitter, assumes a role opposite to that of the pupillary sphincter. The pupillary response to light reflex is primarily influenced by increased parasympathetic activity. The resting PS in darkness and changes in PS by emotional states are mainly determined by changes in sympathetic activity [12-15]. Given these reasons, the PSV of human eyes is typically measured when a subject gazes at a fixed object in the absence of light stimulation and/ or visual accommodation.

Extant studies have examined various pupillometer technologies using infrared video pupillography and monitoring eye tracker cameras to accurately measure the PS [16-18]. However, to significantly improve the ANS assessment, it is important to resolve the PS data distortion by eye movements. The main sources of PS data distortion are attributed to eye movements combined with vertical and horizontal movements. A change in PS location could be caused by saccades or variations in gaze motion angles. Specifically, blinks cause the loss of PS data. The average blink rate varies between 12 blinks and 19 blinks per minute in a state of rest [19]. Furthermore, the blink rate is sensitive to environmental factors such as humidity, temperature, physical activity, cognitive workload, and fatigue while gazing at a certain target in a dark room [19, 20]. Therefore, it is necessary to instruct distorted PS data by eye movements. This study proposed a directional movement indicator by calculating PS pixels. The aim of this study included developing simple indicators that could determine the time as well as the strength of eye movements.

Materials and methods

EOG signal acquisition

EOG background and electrode attachment: Eye movement refers to the voluntary or involuntary movements of human eyes. There are four basic types of eye movements, namely saccades, smooth pursuit movements, vergence eye movements, and vestibulo-ocular movements. As shown in **Figure 1**, eye movements in conjunction with vertical and horizontal movements are the main cause for PS data distortion by the changes in location beyond the measurement radius. An electrooculography (EOG) signal reflects the angle variation caused by various eye movements.

The human eye can be modeled as a dipole with a positive pole at the cornea and a negative pole at the retina. The EOG signal is commonly considered as corresponding to the corneal-retinal electric potential fields that result from hyperpolarization and depolarization existing between the cornea and the retina. As shown in **Figure 2A**, a steady electrical dipole with a negative pole at the fundus and a positive pole at the cornea causes a EOG signal [19, 21].

Electric potential is provoked by the changes in dipole orientation by eye movement. Two channel EOG signals, horizontal signals, and vertical signals are commonly used to track the eye movement by analyzing the EOG signal. Each channel measurement can be detected from both eyes. Additionally, only the right eye is used to detect eye movement in the vertical direction [21]. Thus, 5 surface electrodes were placed around the eyes as shown in **Figure 2B**. Vertical channel electrodes were placed above and below the right eye (vEOG(+), vEOG(-)), and horizontal channel electrodes (hEOG(+), hEOG



Figure 2. A. Ocular dipole. B. Five electrode placement position: vertical channel (vEOG(+), vEOG(-)), horizontal channel (hEOG(+), hEOG(-)), and reference channel.

Table 1. Signa	I combinations for the basic directions	3
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Channel	Gaze Direction				
	Left	Right	Up	Down	
CH1	Positive (+)	Negative (-)	None	None	
CH2	None	None	Positive (+)	Negative (-)	

(-)) were placed on the right and left side of the outer canthi. A reference electrode was place on the forehead [19, 21, 22].

As shown in **Table 1**, there were 4 basic signal combinations that formed channel 1 and channel 2 to detect the 4 directions. A non-pattern recognition algorithm was used in 8 directions (right, left, up, down, right-up, right-down, left-up, and left-down) based on the threshold analysis and time domain features (**Figure 3**) [1, 22-24]. Hence, a non-pattern recognition algorithms was used.

EOG signal processing

The EOG signal may be corrupted with 2 noise factors. First, a baseline drift influences the

EOG signal during saccades. The baseline drift at each horizontal and vertical EOG signal component differs based on each eye movement. Several studies proposed algorithms to remove the baseline drift from repetitive signal characteristics such as electrocardiography (ECG) [18, 25]. However, the non-repetitive characteristics of the EOG signal and the algorithms to sufficiently remove the baseline drift continue to be important research topics. A previous study proposed an approach based on wavelet transform [26]. The proposed algorithms performed an approximated multilevel 1D wavelet decomposition at level 9 using Daubechies wavelets on each EOG signal component. The reconstructed decomposition coefficients provided a baseline drift

estimation. This estimation was substituted for each original signal component to yield the corrected signals with reduced drift offset.

As a second noise factor, the EOG is influenced by several different sources including residential electrical power line, measurement circuitry, electrodes, wires, and other interfering physiological sources such as electromvography (EMG) signals and electroencephalography (EEG) signals [19, 26-29]. A comparative analysis of 3 different algorithms was performed to identify optimal methods to remove these noises. This included the implementation of the following: a low-pass filter, a filter based on wavelet shrinkage denoising [29], and a median filter with a window size of 150 ms [19, 26]. The results indicated that the best performance corresponded to that of the median filter. Hence, the median filter with a window size of 150 ms was selected.

Recordings of all EOG signals were detected using Powerlab (PowerLab 8/35, ML408 (Dual



Figure 3. Classification of the EOG signal by eye movements in eight directions (right, left, up, down, right-up, right-down, left-up, and left-down).



Figure 4. The designed pupillometer.

Bio Amp/Stimulator, ADinstruments), which is a data acquisition system typically used for physiological signals. A data acquisition system including the following components was set up: an amplifier with a gain of 1 with a range of ± 2 mV and a band pass filter with a frequency range of 1 Hz to 100 Hz and a sampling rate of 1 k/s. The EOG signal processing was performed using Matlab (MATLAB 2010, Mathworks). Onset analysis with a suitable threshold level (THR on) was used to avoid background noise and involuntary EOG movements including saccades. Based on preliminary studies, values of THR corresponding to 50 µV were used. This was approximately 25% of the maximum amplitude value (200 µV) [21, 22].

Pupillometer design

The image acquiring system was designed using an infrared camera (Logitech HD Pro Webcam C910, Yeouldo-dong, Seoul-si, Korean), infrared lens, and infrared filter. The image of a pupil was captured with a self-designed user interface based on a Visual Studio 2010 C# program (Redmond, Washington, America) and a DirectShow Library as shown in **Figure 4**. After recording with a speed of 30 fps and a 640 × 480 resolution, the PS data were collected by acquiring the frames and processing each frame with the same image processing shown in **Figure 5**. Typically, a pupil is shaped like an ellipse; thus, more precise PS data were obtained by using the curvature algorithm and ellipse fitting during image processing procedures as opposed to the circle fitting method used by previous studies [11].

Subjects & experimental environment

Thirty health subjects (20 male and 10 female subjects) without a prior (over the past 5 years) ophthalmological medical history participated voluntarily in the study. The selected subjects fully understood the contents of the experiment and submitted their informed consent in writing to the experiment supervisor. The ethics committee of Yonsei University ethics approved the study. To avoid dry eyes, the wearer was strictly asked to not wear contact lenses for a time period that commenced 2 weeks prior to the study and refrain from using systemic medication for a period beginning 5 days prior to the study [30, 31]. Thirty subjects who satisfied the aforementioned conditions were recruited for the eye movement tracking algorithms feasibility experiment. All the subjects were seated in a 50 m³ room maintained at a temperature that ranged between 22°C and 23°C with a relative humidity in the range of 33-35% and an air exchange rate that was approximately 5 times per hour. The experiment was conducted in a darkroom to minimize errors caused by external light sources.

Experimental procedure

The PS was measured in a cube space with 60 cm \times 60 cm dimensions to avoid the effect of the surrounding environment. All subjects stared at the goal point that was placed 60 cm in front of the subjects. The left pupils of the subjects were measured while maintaining the heads and chins of the subjects in fixed positions. All the subjects were stabilized for 3 min to enable them to adapt to the experimental environment. This was followed by measurement of the PS for 10 min.

Minus directional indicator (-DI)

The maximal value, minimal value, and true range of PS data per 10 s was calculated. The true range was calculated using the difference between the maximal value and minimal value. The upmove and downmove values in each time interval were required to calculate the minus directional indicator (-DI). The upmove and downmove values were calculated using Equation 1. The upmove value was derived by subtracting the previous maximal value from













the present maximal value, and thus it represented an increase in PS between the previous time interval and the present time interval. The down move value was obtained by subtracting the present minimal value from the previous minimal value, and it represents a decrease of PS between the previous time interval and the present time interval. If the down move value exceeded the up move value and was greater than zero, then the decrease in the PS exceeded the increase in the PS between the previous time interval and the present time interval. The minus directional movement (-DM) reflected the value of the down move value if these conditions were satisfied. If the up move value exceeded the down move value, this indicated that the increase in PS was greater than its decrease, and therefore the minus directional movement (-DM) was equal to zero. The -DI was obtained by dividing the calculated -DM by the true range. Hence, the -DI of each time interval represented the decrease in the ratio between the previous time interval and the present time interval based on the variation amount of the present time interval. Figure 6 illustrates the flow chart of the -DI.

Equation 1. The logic for the upmove and down-move calculation

True range = the present maximal value of pupil size-the present the minimal value of pupil size

Up Move value = the present maximal value of pupil size-the previous maximal value of pupil size

Down Move value = the previous minimal value of pupil size-the present minimal value of pupil size

if DownMove value > UpMove value and DownMove value > 0,

then Minus directional movement (-DM) = DownMove value,

else Minus directional movement (-DM) = 0

Minus directional indicator (-DI) = Minus directional movement (-DM)/True range

Optimal threshold level of -DI for the rejection of the distortion of pupil size

Comparing to normal PS data, PS data by eye movement must be decreased or is not record-

ed. Accordingly, if PS data was deleted during the time interval when -DI was observed, then the mean value of the entire recording time was projected to increase, and the standard deviation was projected to decrease. The noise rejection rate of the PS distortion was influenced by the -DI threshold level. To find the optimal threshold level of -DI, the 3 threshold levels were classified as above 0.2, above 0.4, and above 0.6. The PS data at time interval determined by each threshold level of -DI was replaced as the PS data average between the time immediately prior to 10 s and immediately after 10 s.

Results

Variations in pupil size

Figure 7 illustrates the results of PS data over 600 s for all subjects. The PS data decreased as time increased. The calculated mean and standard deviation for 600 s were 2087 and \pm 871.37, respectively.

The rejection of the distortion of pupil size by -DI

Figures 8 and 9 shows the representative PS distortions by eye movements. As shown in the representative individual PS data, the PS data decreased due to various eye movements. The PS data distortion recovered to the normal PS data immediately. There was an increase in the number of PS data distortions as time increased. In representative case 1, a decrease in PS data was observed when a vEOG or hEOG signal was detected in response to eye movement. The time intervals determined by -DI included the time intervals when a sharp decrease in the PS data was observed (10-20 s, 130-140 s, 250-260 s, 310-320 s, 400-410 s, 420-430 s, 440-450 s, 550~560 s, 570-600 s). However, the time intervals instructed by -DI corresponding to 50-70 s, 170-180 s, 190-200 s, 220-230 s, 330-340 s, 350~360 s, 460-470 s, 480-490 s, and 510~520 s did not show any conspicuous PS data distortions. The time intervals instructed -DI (10-20 s, 50-70 s, 100-140 s, 170-180 s, 190-200 s, 220-230 s, 250-260 s, 270-320 s, 330-340 s, 350-360 s, 380-410 s, 420-430 s, 440-450 s, 460~470 s, 480-490 s, 510-520 s, 530-560 s, and 580~ 600 s) corresponded to instances when a vEOG signal or a hEOG signal or both signals were detected.

 Table 2. The changes in the average and standard deviations of pupil size based on the threshold level

Pupillary Size	None	-DI = 0.6	-DI = 0.4	-DI = 0.2
Mean ± STD	2087.69 ± 871.37	2118.01 ± 860.90	2127.68 ± 849.83	2131.16 ± 844.83

Similarly, the representative case 2 showed that PS data distortion was detected when an EOG signal caused by eye movement was observed. The time intervals determined by -DI included all time intervals that corresponded to a obvious decrease in PS (10-20 s, 30-40 s, 70-80 s, 110-130 s, 170-180 s, 210-220 s, 240-260 s, 270-290 s, 300-310 s, 320-330 s, 350-370 s, 400-410 s, 450-470 s, and 470-600 s). A comparative analysis between time intervals during which -DI was observed and time intervals during which PS data distortion was observed indicated that the time it is important to resolve the PS data distortion by eye movements. The time intervals instructed by -DI corresponding to 140~150 s, 190~200 s, 420~430 s, and 440~450 s did not show any (clear) PS distortions. The all time intervals determined by -DI as follows:10-40 s. 60-80 s. 100-130 s, 140-150 s, 160-180 s, 190-200 s, 210-220 s, 250-260 s, 270-280 s, 300-310 s, 320-330 s, 350-370 s, 390-410 s, 420-430 s, 440-450 s, 460-470 s, 490-500 s, 510-520 s, 530-570 s, and 580-590 s, corresponded to the times at which a vEOG signal or a hEOG signal or both signals were detected.

Figure 10 shows the the mean and standard deviation of PS data by -DI threshold levels. Before applying the -DI threshold levels, the maximal value and the minimal value of PS data were 2659.09 and 897.35, respectively. When 0.4 and 0.6 were used as -DI threshold levels, maximal and minimal values of 2662.92 and 1141.04, respectively, were calculated. The maximal value and minimal value increased by 3.83 and 243.69, respectively. When the -DI threshold level was 0.2. the maximal and minimal values calculated were 2657.73 and 1271.2, respectively. The maximal value had the very little difference as 1.36, while the minimal value increased by 373.85. As a result, the highest mean and the lowest standard deviation were observed when the -DI threshold level was set to 0.2 as shown in Table 2.

Discussion

HRV analysis is a non-invasive and sensitive tool to estimate the autonomic regulation of the heart. ANS and its main two divisions, namely

sympathetic and parasympathetic activities, are regarded as hierarchically coordinated neuronal networks that continuously control heart rate. The main advantage of ANS estimation by using the heart rate relates to the prognostic value in reducing cardiovascular risk.

The measurement time of HRV is divided into 2 methods. The first method is performed based on 24 h Halter recordings (long-term recordings) [24, 31], and the other part requires a shorter period ranging from 0.5 min to 5 min to collect data for a range extending from 200 heartbeats to 500 heartbeats (short-term recordings) [31]. Generally, 5 min of data for a range of 300 heartbeats to 400 heartbeats was recorded to estimate the sympathetic and parasympathetic activities of the ANS. The HRV was typically employed as a simple short-term tool to estimate ANS. However, it still has several potential problems. The regulation of the heart is seriously affected by parameters such as gender, age, obesity, cardio respiratory fitness, drug interferences, and concomitant diseases [6, 7]. Thus, it is not typically employed except in cases involving the estimation of prognostic value in cardiovascular risk.

PSV is widely used as an alternative tool. The primary PS distortion includes the changes in the size or shape of the pupil. Digital photographs are widely used to accurately measure PS. However, there is an increasing need for accurate measurements through photographs via small protrusions on the surface of a virtual sphere. To prevent PS distortion because of various eye movements, a video-based eye tracker used video cameras to record the eye positions of human subjects and record pupil dilation and eye movements. The eye tracker could measure gaze locations, the time length of fixations and pupil dilation, and investigate fixations, saccades, and pupil dilation responses [32]. However, the disadvantages of these methods include problems related to expensive equipment and the large amount of data processing involved.

Therefore, this study involved performing experiments to derive methods to easily determine the time and strength of the PS distortion. The

EOG signal was simultaneously measured to obtain the PS data and information related to eye movements. After gathering the PS data, the relation between the time intervals of PS distortion by the pupillometer and the observation time of the EOG signal by various eye movements was measured and compared. The results indicated that the PS distortion tended to decrease in the time interval where large and small EOG amplitudes were observed. Specifically, the PS data decreased when the eyes moved in any direction. Particularly, severe PS data distortion was observed during blinking. The results of the comparative analysis to analyze whether or not PS data distortion was observed in the time interval determined by -DI indicated that the time interval instructed by -DI included all the time intervals in which a rapid decrease in PS was observed. Furthermore, it also included the time interval with unclear PS distortion. However, EOG amplitude occurred in all the time intervals where -DI was observed. Hence, it was concluded that the -DI reflected the very small PS data distortion caused by the very few eye movements. The -DI threshold level of 0.2 was concluded as the optimal threshold level to effectively eliminate the PS data distortion. Finally, the -DI calculated only in the presence of PS data indicates the usefulness of the eye directional movement indicators. Furthermore, this indicates the usefulness of the proposed method to reflect the time and strength of distortions by eye movement. It is necessary for future studies to study a simple model of PS for PS signal restoration by estimating the previous signal pattern.

Disclosure of conflict of interest

None.

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