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Toward Closed-Loop Transcutaneous Vagus Nerve Stimulation using Peripheral Cardiovascular Physiological Biomarkers: A Proof-of-Concept Study

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Abstract

Transcutaneous vagus nerve stimulation (t-VNS) is a promising technology for modulating brain function and possibly treating disorders of the central nervous system. While handheld devices are available for t-VNS, stimulation efficacy can only be quantified using expensive imaging or blood biomarker analyses. Additionally, the parameters and “dosage” recommendations for t-VNS are typically fixed, as there are limited biomarkers that can assess downstream effects of the stimulation outside of clinical settings. In this proof-of-concept study, we evaluated non-invasive peripheral cardiovascular measurements as physiological biomarkers of t-VNS efficacy. Specifically, we hypothesized two physiological biomarkers: (1) the pre-ejection period (PEP) of the heart – a parameter closely linked to sympathetic tone – and (2) the amplitude of peripheral photoplethysmogram (PPG) waveforms – representing changes in vasomotor tone and thus parasympathetic / sympathetic activation. A total of six healthy human subjects participated in the multi-day study, half each undergoing active or sham t-VNS stimulus. The three subjects receiving t-VNS had no decrease in PEP and an increase in PPG amplitude following t-VNS, while the subjects receiving sham stimulus had a decrease in PEP and no change in PPG amplitude. When combined with mental stress (a traumatic script being read back to the subjects), the group with t-VNS had no decrease in PEP and only a slight decrease in PPG amplitude following stimulus, while the group receiving sham stimulus had a decrease in PEP and also a slight decrease in PPG amplitude. These studies suggest that PEP and PPG amplitude measures may provide non-invasive physiological biomarkers of t-VNS efficacy, including in the presence of mental stress.
I. Introduction

The vagus nerve, the longest of the cranial nerves, has a wide distribution in the body [1], comprising both afferent (sensory) and efferent (motor) fibers. The afferent connections have direct projections to the brain areas that play a key role in neuropsychiatric disorders, emotional regulation and the autonomic nervous system (ANS) activity. The efferent connections innervate the heart, lungs, and other organs of the abdomen [2, 3].

Artificial upregulation of vagus nerve activity has been proposed as a possible means of modulating brain function to treat various disorders. Indeed, implantable devices for electrical vagus nerve stimulation (VNS) are prevalent in the treatment of various neurological [4–6] and cardiovascular disorders [7]. These studies also demonstrate that the need for surgical implantation, ongoing monitoring and care, high-cost, and the inability to provide guaranteed effects for all patients lead to unwillingness to have the VNS therapy [8, 9].

Transcutaneous VNS (t-VNS) devices provide great advantages in terms of comfort, relatively low-cost and ease of use. Additionally, multiple studies have verified that non-invasive stimulation can affect central brain regions, verified by both imaging [10–12], and physiological and/or blood biomarkers [13–15], in humans and animal models. Recently, the first high-resolution and multi-scale model of t-VNS was developed to predict vagus fiber type activation [16]. Nevertheless, the studies of the physiological effects of t-VNS on human subjects have been limited to conventional vital signs, such as heart rate or blood pressure. These vital signs have complex mechanisms regulating each of them, representing an unknown combination of sympathetic (SNS) and parasympathetic nervous system activity (PNS). Therefore, they may be unsuitable for specifically assessing the autonomic reactivity to t-VNS therapy. We hypothesize that novel physiological biomarkers that are better indicators of SNS activity and vasomotor tone will provide an improved means of specifically assessing t-VNS efficacy and, ultimately, may pave the way to enabling closed-loop adjustment of t-VNS parameters based on real-time physiological response data. Two such physiological biomarkers that we plan to investigate in this work are the pre-ejection period (PEP) and the amplitude of peripheral photoplethysmogram (PPG) signals.

The PEP, defined as the latency between the electrical depolarization of the ventricles and the opening of aortic valve, is a non-invasive measure of cardiac contractility. PEP is known to be modulated primarily by SNS activity [17], with an increase in PEP associated with a decrease in SNS activity. Due to the anticipated effects of t-VNS on ANS, measurement of PEP – which can be achieved peripherally with non-invasive sensing – can provide insights into the central effects of t-VNS. The gold standard to measure PEP non-invasively is impedance cardiography (ICG) [17]. Recently, it has also been shown that seismocardiogram (SCG) signals – capturing the vibrations of the chest wall in response to the movement of the heart and blood – can provide the timing of aortic valve opening and thereby PEP together with a simultaneously measured electrocardiogram (ECG) [18].
The PPG signal is a measurement of blood volume pulse, with an amplitude and waveform shape that is affected by both hemodynamics and arterial tone. PPG is a peripheral measure, with properties derived from vasodilation, vasoconstriction, and pulse pressure; therefore, it is generally accepted that it can provide valuable information about the cardiovascular system and potentially SNS activity [19].

In this work, as summarized in Figure 1, we quantify the peripheral effects of t-VNS from ECG, SCG, and PPG signals for two groups of subjects receiving active and sham t-VNS stimulus. This quantification provides proof-of-concept level understanding of the physiological effects of t-VNS, and begins to pave the way toward closed-loop optimization of t-VNS therapy outside of clinical settings.

II. Methods

A. Human Subjects Experiments

The study was performed under a protocol approved by the institutional review boards of Emory University, Georgia Institute of Technology, SPAWAR Systems Center Pacific, and the Department of Navy Human Research Protection Program. A total of six healthy female subjects (Ages 34.5±10.7) who experienced at least one traumatic event were recruited and written informed consent was obtained. Each subject was asked to write at least one traumatic event that she experienced; later, subject-specific voice recordings based on these scripts were prepared.

The protocol includes neutral and trauma recall scripts. Neutral scripts were designed to induce positive feelings to the subject, each lasting around 60 seconds. As a mental stressor, subjects listened to a 30-to-60 second trauma script (length comparable to usual mental stress protocols) that they had provided before the experiment. T-VNS was applied immediately after the script. The same day also included two t-VNS administrations without any mental stress intervention. To test the repeatability of the data without mental stress intervention, subjects received t-VNS two days following the trauma recall. Over the three days, each subject received t-VNS following six trauma scripts, and a total of four t-VNS without intervention were administered. Due to being more effective based on patient feedback, only the first trauma data were used in this study. For one subject, the t-VNS device did not operate properly following the first trauma script, therefore the second trauma data were used, which was already different than the first trauma script.

Both active and sham VNS were administered using handheld devices (GammaCore, Electrocore, LLC, Basking Ridge, NJ), with identical placement and operation. Subjects and the clinical staff were blinded to the devices. Active VNS devices produce an AC voltage signal consisting of five 5kHz sine pulses, repeating at a rate of 25 Hz. Sham VNS devices produce an AC biphasic voltage signal consisting of 0.2 Hz square pulses. The sham device produces a tingling sensation, due to the excitation of superficial skin nociceptors, without stimulating the fibers in the vagus nerve. During each application, the stimulation intensity was increased to the maximum the subject can tolerate, without pain. The device operation stops automatically after 120 seconds.
B. Hardware

Figure 2a shows the test setup employed for each subject. The ECG and PPG signals were measured using wireless Bionomadix RSPEC-R and PPGED-R amplifiers (Biopac Systems, Goleta, CA). For SCG measurement, a low-noise 356A32 accelerometer was used on the mid sternum (PCB Electronics, Depew, NY). Only the SCG signals in the dorsoventral direction were used in this study. Transmissive PPG measurement was taken from the index finger. All data were transmitted to the Biopac MP150 16-bit data acquisition system at a sampling rate of 2kHz. Systolic (SBP) and diastolic blood pressure (DBP) values were recorded periodically with an Omron blood pressure cuff.

C. Signal Processing and Feature Extraction

The signals were processed in MATLAB (R2016a). We extracted PEP from the ECG and SCG signals rather than the ICG, since the 25 Hz t-VNS corrupted the ICG signal, that has a bandwidth up to 30 Hz. Figure 2b summarizes the features extracted, namely heart rate (HR), R-Ao (i.e., PEP) and PPG amplitude. The ECG, SCG and PPG signals were filtered with finite impulse response (FIR) band-pass filters, with cut-off frequencies 0.6–40Hz for ECG, 0.6–30Hz for SCG, and 0.4–8 Hz for PPG, respectively.

The R-peaks in ECG signal were detected by thresholding to detect HR and for ensemble averaging the SCG and PPG into individual beats. Beat lengths of 300ms and 600ms for SCG and PPG were sufficient to detect the AO (aortic valve opening point) and systolic/diastolic points, respectively. To reduce the effects of motion artifacts on the individual, segmented SCG beats, exponential moving averaging of the successive beats were implemented [20]. Each exponentially averaged beat $\vec{e}_n$ is defined as follows:

$$
\vec{e}_n = \begin{cases} 
\vec{e}_{n,1}, & n = 1 \\
\alpha \vec{e}_{n-1} + (1-\alpha)\vec{e}_{n-1}, & n > 1.
\end{cases}
$$

where $\alpha = 2/(M + 1)$. M is termed as the ‘number of beats’ of the exponentially weighted moving average. We used M=3 since this was long enough to reduce the motion artifacts, and short enough to preserve the signal properties over time. PPG beats were not exponentially averaged and rather used directly.

After segmenting the PPG beats, systolic and diastolic points were located beat-by-beat. PPG amplitude was calculated from the amplitude difference between these two points. To investigate any relationship between blood pressure and the amplitude of PPG, the non-continuous SBP and DBP recordings have been used to calculate pulse pressure, such that $PP = SBP - DBP$. With regards to measuring PEP from SCG, the time interval from the ECG R-peaks to the second maximum of the segmented SCG beats have been extracted as the R-Ao (PEP) [18].

To interpret the changes induced by t-VNS, data from 60 seconds of rest (from the beginning of the corresponding day), first 30 seconds of trauma recall, the last 60 seconds of t-VNS, and 60 seconds from the post-VNS (100 seconds after the t-VNS stops) were used for each subject. The extracted features (HR, PEP and PPG amplitude) were normalized with
respect to the corresponding rest values, such that the normalized feature $i$ for an interval, 
$\Delta \text{Feature}_{i,\text{interval}}$, is calculated as $\text{Feature}_{i,\text{interval}}/\text{Feature}_{i,\text{rest}}$, for the intervals trauma recall, VNS, and post-VNS, to understand any deviation from the rest values. Values higher than one would mean increase, and values lower than one would mean decrease for the corresponding interval. For visualization purposes, the percent changes from the baseline values have been shown as bar-plots, such that 0% corresponds to the rest value.

## III. Results

Figures 3 and 4 show the normalized changes in HR, PEP, and PPG amplitude. Error bars show the standard error of the mean (four instances per subject, merged from all days) are (SEM). The t-VNS applications without intervention shown in Figure 3. During t-VNS, HR and PEP remain around baseline for both groups. PPG amplitude increases for the active group, and fluctuates around baseline for the sham group. During post-VNS, there is a slight increase in HR for the sham group, compared to the active group. Notably, PEP during post-VNS increases for the active group (i.e. decrease in SNS activity), and decreases for sham group (i.e. increase in SNS activity). PPG amplitude also increases for post-VNS, reaching to more than two-fold of the baseline value, versus the fluctuation around baseline for the sham group.

To understand the possible effects of blood pressure changes in the observed PPG amplitude results, changes in SBP, DBP, PP were investigated during t-VNS without trauma intervention. During VNS and post-VNS, the change in SBP, DBP and PP did not follow the PPG amplitude pattern for groups. Specifically, there was no observable difference between groups in SBP and DBP during VNS. PP of the active group showed a decrease during VNS ($-11\% \pm 3\%$, mean $\pm$ SEM), whereas the sham group fluctuated around baseline ($-4\% \pm 9\%$). For post-VNS, the active group had a slight decrease in PP ($-8\% \pm 5\%$), versus the sham group’s slight increase in PP ($+4\% \pm 9\%$).

Figure 4 summarizes the trauma recall data, with the bars representing the trauma recall, t-VNS following script and post-VNS. A notable difference is in HR during trauma recall, indicating that the sham subjects experience more HR increase during trauma recall, while the other periods for HR remain similar for both groups. PEP and PPG change similarly during trauma recall and t-VNS for both groups. A remarkable difference is PEP during post-VNS: it increases for the active, and decreases for the sham group. PPG does not show a notable difference between groups for post-VNS.

## IV. Discussion and Conclusion

In this proof-of-concept work, we quantified the cardiac (PEP) and vascular (PPG) responses to t-VNS. The most notable differences seen in the active group, as compared to the sham group were 1) Increase in PEP (i.e. decrease in SNS activity) during post-VNS periods without intervention 2) Increase in PPG amplitude (i.e. vasodilation) for both VNS and post-VNS of t-VNS without intervention. 3) Increase in PEP during the post-VNS period after mental stress. It has been previously validated by fMRI studies that the cervical vagal
afferents can be accessed by t-VNS [12]. The decrease in SNS activity observed in this work signals that t-VNS may influence the SNS through afferent signaling to the brain.

It is known that PPG amplitude can change due to both PP changes (with constant vessel stiffness), and changes in vascular stiffness (i.e. vasodilation/vasoconstriction) with constant PP [19]. From the PP recordings for the intervals without intervention, it can be said that PPG amplitude is more linked to the changes in stiffness (vasodilation/vasoconstriction), as the change in PPG amplitude does not follow the changes in SBP, DBP, or PP readings. Thus there are both cardiac contractility (PEP) changes and peripheral vascular tone (PPG amplitude) changes occurring in response to t-VNS that can be quantified compared to the sham stimulation.

The sham subject inclusion is a strength of this study, as using only an active group might cause misinterpretation of the results. Nevertheless, this study is not without limitations. Since this is an ongoing study, the results are not yet conclusive, and the dataset is small. The inclusion of more subjects and the interpretation of more physiological features are required for drawing generalizable conclusions.

The psychological effect of the sham devices is also worth mentioning: Figure 3 shows that subjects experience increased SNS activity (decrease in PEP) for sham VNS and post-sham. Based on the patient feedback, the reason for this may be the discomfort created by the sham devices.

Overall, the data suggest that t-VNS induces cardiovascular effects on subjects, that can be observed by the non-invasive sensors on the body. The measurements of these cardiovascular effects are also not corrupted by the electrical stimulation artifacts created by the t-VNS. Therefore, they may serve as continuous and convenient markers, applicable to long-term monitoring of subject-specific t-VNS therapy, outside of clinical settings. Additionally, it is known that subjects with traumatic stress show impaired extinction of conditioned fear, associated with impaired amygdala activity [21]. It is exciting that invasive VNS has been shown to enhance the extinction of conditioned fear in rats [22]. Future studies will examine whether t-VNS used in tandem with trauma recall can potentially counteract hyperarousal in response to memories of traumatic events.

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References


Figure 1.
This work includes the quantification of the downstream cardiovascular physiological changes after t-VNS therapy. The collection of physiological signals by means of a wearable patch may find use in closing the loop for non-invasive t-VNS therapy for prediction and optimization.
Figure 2.
a. Test setup for each subject. Trauma/neutral scripts were delivered with headphones. t-VNS was applied with collar electrodes on the vagus nerve on the left side of the neck. Electrode gel was applied to maintain good contact between the skin and the electrodes. An accelerometer was placed on the mid-sternum for SCG collection. PPG was measured from the index finger. ECG and PPG signals were collected with wireless modules. b. Extracted features from the collected physiological signals. After the dorsoventral (DV) SCG signals were ensemble averaged referenced by the R-peak of ECG, the Ao point of SCG beats were located and R-Ao (PEP) values were extracted. PPG amplitude was calculated as the difference between the amplitudes of systolic and diastolic points.
Figure 3.
The percent changes in physiological features for VNS without intervention both during VNS and post-VNS. All values were normalized to rest (i.e. interval/rest), for the corresponding day for each subject. Bar plots show the percent changes from the baseline rest value. Each subject received VNS four times without intervention in total. Data were merged across three days. Error bars: SEM.
Figure 4.
The percent changes in physiological features during the trauma recall (script), during VNS following the script, and post-VNS. All values were normalized to the resting data, for the corresponding day for each subject. Bar plots show the percent changes from the baseline rest value. Error bars: SEM.