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Time-varying Spectral Index of Electrodermal Activity to Predict Central Nervous System Oxygen Toxicity Symptoms in Divers: Preliminary results

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***Abstract*— The most effective method to mitigate decompression sickness in divers is hyperbaric oxygen (HBO_2) pre-breathing. However, divers breathing HBO_2 are at risk for developing central nervous system oxygen toxicity (CNS-OT), which can manifest as symptoms that might impair a diver's performance, or cause more serious symptoms like seizures. In this study, we have collected electrodermal activity (EDA) signals in fifteen subjects at elevated oxygen partial pressures (2.06 ATA, 35 FSW) in the "foxtrot" chamber pool at the Duke University Hyperbaric Center, while performing a cognitive stress test for up to 120 minutes. Specifically, we have computed the time-varying spectral analysis of EDA (TVSymp) as a tool for sympathetic tone assessment and evaluated its feasibility for the prediction of symptoms of CNS-OT in divers. The preliminary results show large increase in the amplitude TVSymp values derived from EDA recordings ~2 minutes prior to expert human adjudication of symptoms related to oxygen toxicity. An early detection based on TVSymp might allow the diver to take countermeasures against the dire consequences of CNS-OT which can lead to drowning.**

***Clinical Relevance*—This study provides a sensitive analysis method which indicates a significant increase in the electrodermal activity prior to human expert adjudication of symptoms related to CNS-OT.**

I. Introduction

Prolonged, hyperbaric pressure diving leads to various physiological challenges including the risk for decompression sickness (DCS) [1]–[7]. DCS arises due to nitrogen bubble formation when there is a reduction in ambient pressure during the ascent phase of a dive. Symptoms of DCS may be mild such as muscle pain, nausea, skin itching and tingling; or serious like neurological dysfunctions, spinal cord injury, cardiopulmonary collapse and disseminated intravascular coagulation (DIC) [8]–[10]. Hyperbaric oxygen (HBO_2) pre-breathing is an effective method to mitigate DCS in certain situations [11]–[13] and breathing 100% oxygen underwater eliminates the risk of DCS; however, divers breathing HBO_2 are at risk for developing central nervous system oxygen toxicity (CNS-OT). Manifestations of CNS-OT include headache, diaphoresis, nausea, tinnitus, lip twitching, tingling of the limbs, or even more serious symptoms such as seizure or loss of consciousness [14], [15]. Even though it is generally acknowledged in the undersea and hyperbaric medical community that oxygen seizures are not harmful in the controlled, dry environment of a hyperbaric chamber, losing consciousness or convulsing under water could result in the dislodgement of the diver's air supply from his or her mouth, and likely lead to drowning [14], [16]–[18]. Therefore, developing tools to predict the onset of seizures due to CNS-OT will help reduce risk to divers.

Recent studies involving animal and human models breathing HBO_2 in a pressurized chamber have consistently shown seizure activities due to CNS-OT induced by HBO_2 [19-21]. Physiologically, highly-increased sympathetic activity is associated with augmented seizure activity [21]. Therefore, a sensitive measure of sympathetic activity should be a suitable tool for seizure detection.

An increasingly used measure of sympathetic activity is electrodermal activity (EDA) [22]. The EDA can be measured in the skin because the skin's conductance is proportional to sweat secretion [23]. One of the advantages of EDA is that sudomotor activity is known to be solely controlled by the sympathetic nervous system [22, 31, 32]. The association between seizures and sympathetic activity has been observed in humans, and EDA is linked to central sympathetic activity as demonstrated by the significant surge in EDA amplitude preceding epileptic seizures [22-24].

Traditionally, analysis of EDA has been in the time domain [31], using skin conductance level (SCL) and nonspecific skin conductance responses (NS.SCRs). SCL (usually expressed in microsiemens, μS) is a measure related to the slow modulations of EDA. The SCL is typically computed as a mean of several EDA measurements taken during a specific non-stimulation rest period. The skin conductance responses (SCRs) are the rapid transient events contained in the EDA signal. The NS.SCRs are the number of SCRs in a period of time, and are considered a tonic measure because they occur in response to an underlying stimuli. However, several studies have reported low reproducibility of these time-domain indices [26, 27, 31].

We have recently proven that EDA is significantly altered by cognitive stress under the water [25]. Moreover, we developed a time-varying method to better quantitatively

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assess EDA (TVSymp) data under various scenarios including stress during sleep deprivation [25-27]. Our quantitative method was shown to be more sensitive in determining stress-induced changes than the widely used methods in the literature [25-27].

As described above, there is evidence that EDA is reactive to seizures, and that the sensitivity of EDA to sympathetic arousal is maintained under the water. This suggests that EDA could be used to detect and/or predict the onset of CNS-OT manifestations under the water. Since the time-varying spectral index of EDA is highly sensitive and consistent, we hypothesize that it can be used as a reliable biomarker to predict the symptoms of CNS-OT.

II. Materials and Methods

A. Experiment

We have collected EDA during HBO_2 exposures in humans. In this paper, we have included preliminary results from N=15 subject exposures. All volunteers provided written informed consent to participate in the study. The experiments were carried out in the "foxtrot" chamber pool at the Duke University Hyperbaric Center. Subjects were immersed in 28±1ºC water to the shoulders, breathing 100% O_2 at 35 feet of seawater (oxygen partial pressure 2.06 ATA), while exercising on an underwater cycle ergometer at approximately 100W output, and executing NASA's Multi-Attribute Task Battery-II (MATB-II) cognitive testing software. The exposure lasted until symptoms of CNS-OT were observed, or if the maximum duration of 120 minutes was achieved. Due to safety purposes, subjects were seated in water to the shoulders, in a head-out position secured by a harness to prevent head submersion in the event of a convulsion or loss of consciousness. The protocol was approved by the Duke University Institutional Review Board.

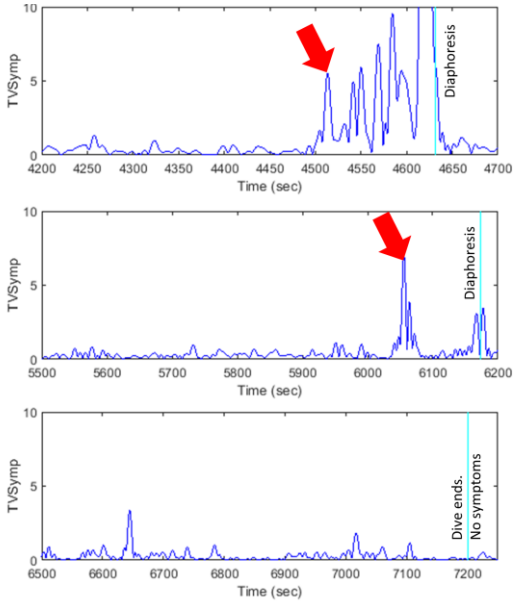

Fig 1. TVSymp of two subjects (top and middle panels) presenting symptoms of CNS-OT (diaphoresis), and one subject that did not exhibit symptoms of CNS-OT. Cyan line represents the end of the test. Red arrows mark the large increase on TVSymp before symptoms of CNS-OT were observable.

B. EDA data collection and processing

EDA signals were collected during the entire experiment. EDA was collected using a pair of stainless-steel electrodes placed in the index and ring fingers of subjects' left hand and a galvanic skin response module FE116 (ADInstruments). The sampling frequency was set to 100 Hz.

Time-invariant and time-variant spectral analyses of EDA have recently been reported as tools for sympathetic tone assessment [25]–[27] . The resulting index, TVSymp, demonstrated lower intra-subject variability compared to time-domain measures of EDA, and higher consistency and sensitivity to orthostatic and cognitive stress compared to time-domain indices as skin conductance level and the number of skin conductance responses [27].

To compute the time-varying index of EDA (TVSymp), the time-frequency representation of EDA was computed using variable frequency complex demodulation (VFCDM), a time-frequency spectral analysis technique that provides accurate amplitude estimates and one of the highest time-frequency resolutions [28]. At a sampling frequency of VFCDM decomposition of 2 Hz, the second and third components, comprising the approximate range 0.08 - 0.24 Hz, were used to compute TVSymp as defined in a previous study [26].

C. Statistics

We split the subjects into those that exhibited symptoms of CNS-OT (CNS-OT subjects, N = 11) and those who did not exhibit symptoms of CNS-OT (No CNS-OT subjects, N = 4). For each subject, we obtained the maximum value of TVSymp within a window of 5 minutes right after the subject went into high-pressure HBO_2 (Start of HBO_2) and within a window of 5 minutes right before the end of the experiment (End of test). Note that the end of the study for No CNS-OT subjects was 120 minutes (7,200 seconds) but it was variable for CNS-OT subjects as it was determined based on the observance of symptoms.

The normality of TVSymp values was tested using the one-sample Kolmogorov-Smirnov test [29]–[31]. As the values were normally distributed, we tested the significance of End of study to Start of study using the t-test. A $p < 0.05$ was considered significant.

III. Results

In Fig. 1, the three plots correspond to different subjects' dives. Subjects in the top and middle panels show symptoms of CNS-OT (diaphoresis). In both cases, a large increase in the TVSymp preceded the occurrence of symptoms of CNS-OT. There is a nearly 7-fold increase in TVSymp value, from ~0.8 to ~5.5 (the red arrows) when compared to its values prior; this increase occurred ~2 min prior to oxygen being turned off due to symptoms of CNS-OT, noted in the vertical text at the end of the recording.

Figure 2 shows box plots for CNS-OT and No CNS-OT subjects. There was a significant increase in the maximum value of TVSymp in CNS-OT subjects in the window of five minutes before symptoms compared to the windows of five minutes after the Start of HBO_2. No difference was observed in No CNS-OT subjects in the window of five minutes before

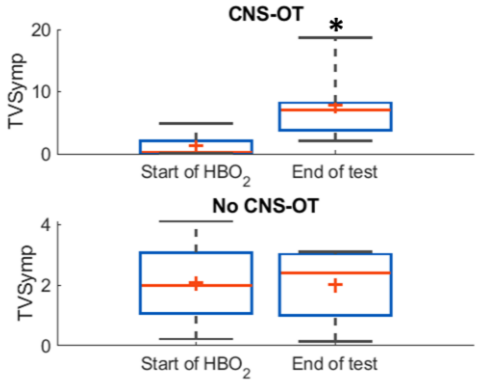

Fig 2. TVSymp values for N=11 subjects with symptoms of CNS-OT (diaphoresis), and N=4 subjects that did not exhibit symptoms of CNS-OT. * represents significance difference to Start of HBO_2.

the End of test as compared to the first five minutes after the Start of HBO_2.

IV. DISCUSSION

Although more data are needed to verify the consistency of these results, the significant elevation of TVSymp suggests that it can be a biomarker of the profound diaphoresis exhibited by the subjects as a manifestation of CNS-OT. EDA has a potentially better sensitivity to sudden diaphoresis as compared to twitching or visual disturbance, given the nature of collecting the EDA, measured from the skin's conductance which is proportional to sweat secretion [23].

Symptomatic subjects exhibited elevated dynamics in the phasic component of EDA, which are captured by TVSymp [26], before or around the time the symptoms of CNS-OT were evident. These subjects all had symptoms related to diaphoresis which is caused by the elevation of the sympathetic nervous system. Some symptomatic subjects showed a lower increase on the phasic component of EDA, possibly because their symptoms were not linked to autonomic control. With machine learning, we may be able to differentiate between autonomic and non-autonomic induced elevation of the phase component of EDA. Overall, both autonomic and non-autonomic induced elevation of EDA responses were seen 2-3 minutes prior to human expert adjudication.

We have collected and analyzed human EDA signals in both dry and water immersion conditions while subjects performed cognitive tasks at increased oxygen partial pressures and HBO_2 prebreathing in a hyperbaric chamber. We have obtained preliminary results on the feasibility of TVSymp index to detect and predict symptoms related to CNS-OT, including the onset of seizures, prior to a human expert noticing the related symptoms. Some of the results on clean EDA data showed an exciting potential to predict symptoms related to oxygen toxicity early, as we observed a several-fold increase in EDA values prior to human expert adjudication that CNS-OT had begun. Some data were not included as they were found usable due to either low signal fidelity or technical issues at the onset of our study. The former was most likely due to movement of wires and EDA electrode contact issues. The subjects were exercising and performing MATB II cognitive tests using a joystick, which led to motion artifacts in the EDA signals. Contact of the electrodes with water also degraded the EDA signal in some cases. This will be a practical challenge moving forward if these methods are to be applied to a fully submerged diver.

To automatically assess the quality of EDA data, in this study we used the simple, transparent, and flexible method recently reported [32]. Although it was able to identify several instances of data corruption, many times it was not able to properly identify data corruption clearly observed by eye. As we envision eventual automated seizure detection using a wearable EDA device, we will need to develop a more robust approach. Improving the robustness may require a sequence of algorithms to automatically and accurately determine if a data segment to be analyzed is either clean or motion corrupted. This task is crucially important to minimize sudden spikes in TVSymp values (due to abrupt motion artifacts) being falsely identified as true sympathetic responses to CNS-OT. As even in a controlled environment such as in our lab we have experienced motion artifacts in EDA data, it is highly likely that this problem will be even more prevalent when divers perform their tasks in natural environments. Hence, we need an intelligent algorithm to discern clean EDA automatically and accurately from motion- and noise-corrupted data. Note that motion artifacts in other physiological signals, including electrocardiogram and photoplethysmographic signals, are especially pronounced in data from wearable devices, thus, many methods have been developed to overcome them [33]–[37]. Both machine learning and deep learning approaches are suitable for this purpose. Deep learning has been shown to provide more accurate results than machine learning, albeit at higher computational cost.

The risk of CNS-OT occurrence is highly variable between individuals, making it hard to predict the onset of symptoms, and to determine the safety of exposure to HBO_2. Being able to establish an individual risk to develop CNS-OT would maximize the therapeutic and operational uses of HBO_2 in hyperbaric, diving, and submarine medicine (e.g. preventing DCS) [11], [13], [38], by enabling the extension of exposure time in individuals with more neurological tolerance to HBO_2.

If our ability to recognize early signs of CNS-OT holds up during further testing, we face challenges related to the practical application of the method. We will need an approach to quantify how much of an increase in TVSymp values is a true predictor of seizures. We can arbitrarily determine a threshold value for the increase in TVSymp values when CNS-OT occurs, but this value is tuned from previously collected data. Hence, when we have new subjects, this arbitrarily derived threshold value may no longer be valid. Thus, to resolve this issue, we need a machine learning approach to automatically classify (without an arbitrarily set threshold value) whether or not a given increase in TVSymp values is indeed due to increased sympathetic nervous system response to CNS-OT symptoms.

V. CONCLUSION

In summary, our results to date provide some evidence that EDA, specifically TVSymp, is reactive and has the potential to allow us to detect onset of CNS-OT and possibly predict seizures. However, further confirmation data are necessary to

observe the interplay between CNS-OT-induced seizures and TVSymp, to be able to automatically quantify the increase seen in TVSymp that is due to true response induced by CNS-OT and not motion artifacts, and to evaluate the sensitivity of EDA in an environment that recreates the extreme situations (e.g., high pressure) a diver can encounter.

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