Quantifying Opioid Withdrawal through Cardio-mechanical Variability using Multi-modal Wearable Sensors*

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Abstract—**Opioid use disorder (OUD) is a significant global health issue, leading to severe physiological and psychological impacts and substantial societal costs. Current methods for assessing opioid withdrawal, primarily relying on subjective scales, suffer from limitations such as incomplete symptom capture, recall bias, and imprecision. Wearable sensor technologies offer a promising alternative for objective assessment, with previous studies demonstrating their ability to detect opioid use and measure related physiological changes. In this study we investigated the correlation between local cardio-mechanical variability quantified using dynamic time warping (DTW) distances of seismocardiogram (SCG) signals and subjective opioid withdrawal severity (SOWS) scores. In a 7-day in-patient protocol for individuals with OUD (N = 13), we found a statistically significant inverse correlation: shorter median DTW distances and reduced variance in SCG signals were associated with higher subjective withdrawal scores with statistically significant differences between the highest withdrawal bin and the two lowest bins (p=0.038 and p=0.044, respectively). Our results suggests that local cardio-mechanical variability, as captured by wearable sensors and analyzed with DTW, can serve as a valuable indicator for quantifying opioid withdrawal severity, potentially enabling more timely and effective preventive care.**

I. Introduction

Opioid use disorder (OUD) is a detrimental disease of drug abuse and addiction that greatly impacts an individual's physiological and psychological health. OUD results in immense societal costs such as increased risks for crime, harms to family cohesion, and negative impacts to employment and economy [1]. In 2016, the Global Burden of Disease estimated that 26.8 million people are living with OUD globally with the majority of those affected in the United States [2]. Those affected by OUD has continued to climb in recent years, and will result in more than 700,000 drug-related deaths in the United States by 2025 [3]. Continued opioid use leads to physical tolerance and dependence, creating a feedback loop where withdrawal, craving, and drug-liking derived from opioids intensify health risks and can even result in death [4]. While medications and alternative treatments for OUD can help lessen withdrawal symptoms and curb cravings, there are currently few methods available to accurately assess or quantify withdrawal, hindering our ability to deliver timely and effective preventive care.

Current methods for assessing opioid withdrawal primarily rely on opioid withdrawal scales, with the Clinical Institute Narcotic Assessment (CINA), Clinical Opioid Withdrawal Scale (COWS), and Subjective Opioid Withdrawal Scale (SOWS-Gossop) being the most common [5]. However, these scales have significant limitations for both clinicians and patients. Questionnaires and behavioral reports may not capture all signs and symptoms [6]. Additionally, recall bias,

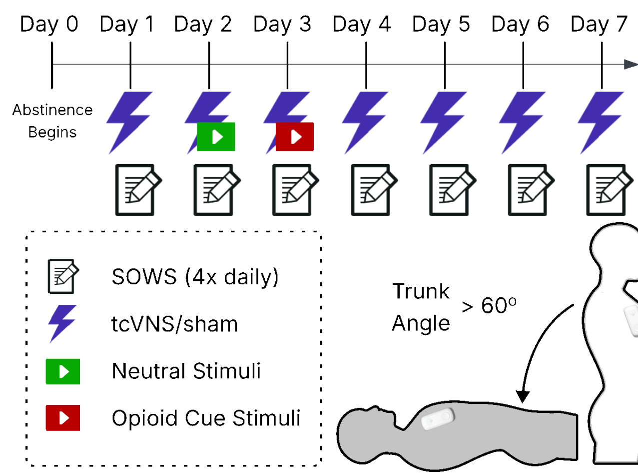

Fig. 1. Full seven-day protocol. SOWS and wearable cardiac signals (continuous ECG, SCG, and PPG) were collected over a 7-day double-blind study exploring effects of tcVNS vs. sham on patients with OUD. Signals for analysis are taken for patients in a supine position. Four times each day, tcVNS/sham stimulation and SOWS were administered. Days 2 and 3 consists of Biopac signal acquisition and blood draws during a neutral/opioid cue stimuli protocol. In this analysis we focused on the relationship between physiological and SOWS scores.

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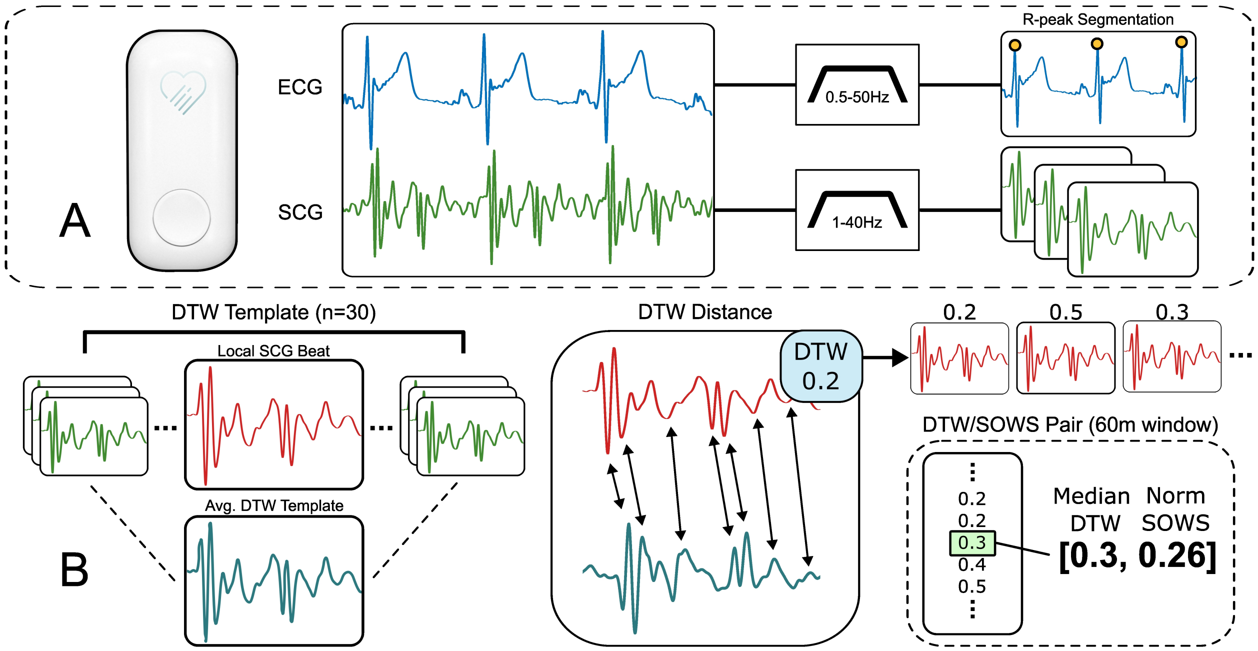

Fig. 2. Signal pre-processing pipeline. (A) The raw ECG signal is band-pass filtered between 0.5-50 Hz, while the SCG is filtered between 1-40 Hz. Key R-peaks are then identified in the ECG, which serve as fiduciary markers to segment the continuous SCG waveform into discrete, beat-by-beat cycles. (B) Pipeline for quantifying morphological changes in SCG heartbeats. First, a representative template heartbeat is created by averaging a moving window of 30 beats. The dynamic time warping (DTW) distance is then computed by measuring the similarity between this template and the local individual heartbeat. This process is repeated continuously. The final output is a feature pair associated with a SOWS, consisting of the survey's score and the median of all normalized DTW distances calculated within the 60-minute window immediately prior to the survey.

memory retrieval difficulties, fatigue, distortion, and imprecision can compromise the effectiveness and accuracy of lengthy withdrawal symptom questionnaires for both patients and caregivers [7] [8].

Leveraging wearable sensor technologies offers an alternative approach to these limitations for monitoring withdrawal symptoms while addressing the limitations of survey-based methods. Sensors have demonstrated the ability to measure symptoms like tremor, muscle aches, and anxiety, which are common in opioid withdrawal [9] [10]. For instance, one study with 30 participants used a wrist-based sensor to measure electro-dermal activity (EDA), skin temperature, and motion before and after opioid use, finding a significant increase in temperature post-consumption [11]. Another study utilized EDA, skin temperature, and accelerometer data from 30 participants to detect opioid intake with 99% accuracy in a real-time system [12]. Although these technologies appear promising for detecting opioid use, they currently have limited data quantifying the level of withdrawal symptoms and largely depend on skin temperature as their most crucial feature, which may not effectively capture crucial physiological details. Regulated by the autonomic nervous system, the heart provides crucial clinical information about sympathetic and parasympathetic drive [13]. Therefore, analyzing cardio-mechincal signals and their variability using dynamic time warping (DTW) distances may provide further insights about autonomic function and help in quantifying withdrawal symptoms for patients with OUD.

In this study, we investigated a novel method for correlating DTW distances for seismocardiogram (SCG) signals during 60-minute windows prior to measuring withdrawal severity using the SOWS. The study cohort (N = 13), comprised of patients suffering from OUD and acute withdrawal. We found that the median DTW distance, calculated for each individual SCG beat, is inversely correlated with SOWS, where shorter distances and variances equated to higher subjective withdrawal. This analysis demonstrates that cardio-mechanical variability measured using SCG can enable real-time intervention and assessment of withdrawal severity in the future.

II. Methods

A. Study Cohort and Protocol

As shown in Fig. 1, we collected data from 19 patients over a 7-day period to observe the physiological and psychological effects of transcutaneous cervical vagus nerve stimulation (tcVNS) vs. sham stimulation during acute opioid withdrawal in an in-patient clinical setting. Patients abstained from opioid use approximately 24 hours prior to hospital admission. The study protocol consisted of daily SOWS and tcVNS/sham stimulation at four time points: morning, afternoon, evening and night. A CardioTag (Cardiosense, Chicago, IL, USA) device was worn by the patient to record continuous physiological signals throughout the 7 days. Additionally, on days 2 and 3 of the study, we conducted neutral stimuli and opioid cue exposure, respectively, during which we recorded physiological signals and measured blood biomarkers. Out of the 19 patients, 9 completed the entire 7-day protocol and 10 withdrew early. From 19 patients' data, 5 were discarded due to lack of data or SOWS surveys during analysis, and 1 was excluded due to unusable data.

B. Cardiovascular Signal and SOWS Score Processing

During the entirety of the study, the CardioTag device collected raw cardio-mechanical signals (i.e., SCG, electrocardiogram (ECG), and photoplethysmogram (PPG)). For this analysis, we only focused on ECG and SCG signals. Fig. 2 (A) outlines our signal processing pipeline, where ECG (0.5-50 Hz) and SCG (1-40 Hz) were band-pass filtered prior to ECG R-peak segmentation of SCG signals [14]. Additionally, using tri-axial accelerometry data measured by the CardioTag, we estimated trunk angle using a prior algorithm from our group [15]. To address variability during movement and standing positions, we isolate supine periods and kept all portions where trunk angle exceeded 60°. SOWS scores were normalized on a 0 to 1 scale on a per-subject basis. This is to account for the intra-subject variability and ranges in withdrawal severity.

C. Dynamic Time Warping Calculations

We calculated beat-specific signal quality scores by leveraging DTW. DTW is a method of estimating the distance between two signals that are stretched or warped [16]. Useful in quantifying cardio-mechanical variability, DTW has precedence in classifying ECG segments using a reference template [17]–[19] and SCG signal quality assessments [20], [21]. As illustrated in Fig. 2 (B), a DTW template was used for each local SCG heartbeat by averaging the local beats around it with a window size of 30 beats. Rolling windows captured local signal morphology changes and periods of instability over time. Additionally, analyzing a 30-beat segment made measurements less sensitive to noise from a single anomalous beat. Using the fastdtw package in Python, we computed the DTW distance value between each local beat and the template formed by the ensemble average of the 30-beat local window.

For each SOWS measurement, the DTW distance scores from the 60 minutes immediately prior were aggregated for analysis. Only DTW distances calculated when the participant was in a supine position, as indicated by a trunk angle greater than 60°, were included in the dataset. Within each 60-minute segment, outliers were removed from the non-parametric data using the Inter-quartile Range (IQR) method. The resulting data was then grouped into five bins based on the relative SOWS score. The final feature pair used for analysis consisted of the SOWS score and the median of the DTW distances from the corresponding 60-minute windows. To assess statistical significance, a Wilcoxon rank sum test was calculated for DTW distances between each combination of SOWS bins with Bonferroni corrected p-values.

III. Results

The Fig. 3 box-plot illustrates a negative correlation between median DTW distances and binned SOWS scores, with the average median DTW distance and variance decreasing with increasing SOWS score. Table I also shows mean, standard deviation, median, and IQR of DTW distances decreasing across increasing SOWS severity. For median DTW values, a non-parametric Wilcoxon rank sum test found statistical significance when comparing the lowest SOWS score bins (0.0-0.2 and 0.2-0.4) to the highest bin (0.8-1.0), with Bonferroni corrected p-values of 0.038 and 0.044, respectively.

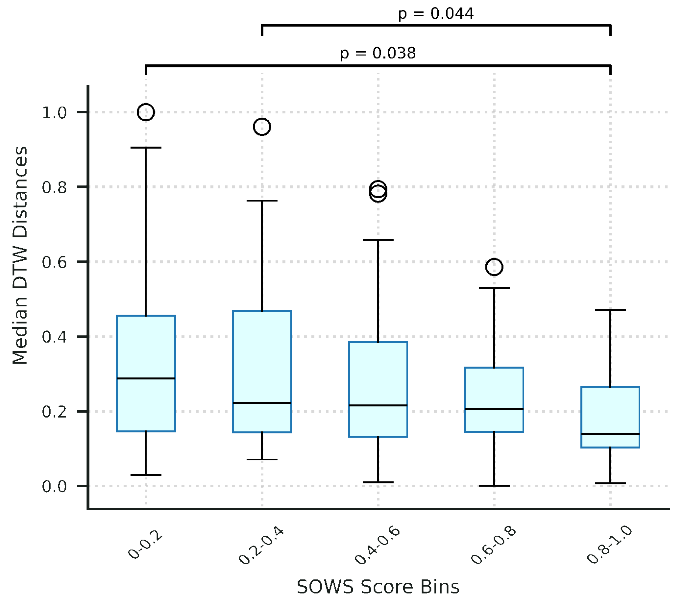

Fig. 3. Box-plot showing the average median DTW distances for 60 minutes of data prior to each normalized SOWS score across all patients. Top indicates significant Bonferroni corrected p-values (0.038, 0.044) for associated SOWS bins (0-0.2 to 0.8-1.0, 0.2-0.4 to 0.8-1.0).

IV. Discussion and Conclusion

The analysis of 13 patients with OUD found a statistically significant inverse correlation between the morphology of the SCG signal, as measured by DTW distances, and the SOWS. As withdrawal symptoms intensify, the beat-to-beat morphological variability of the SCG signal decreased. These reduced DTW distances and tighter variances at higher withdrawal scores suggest a state of diminished cardio-mechanical variability. This finding could indicate that increased stress from opioid withdrawal leads to more uniform and rigid cardiac activity.

Despite its strengths, this study is not without limitations. First, while data was collected continuously over a seven-day period, the analysis was conducted on a relatively small

TABLE I
SOWS Binned Data Summary

SOWS	Count	Mean ± Std	Median	Min	Max	IQR
0-0.2	78	0.32 ± 0.22	0.287	0.030	1.000	0.310
0.2-0.4	58	0.31 ± 0.21	0.222	0.071	0.961	0.324
0.4-0.6	60	0.27 ± 0.19	0.216	0.009	0.794	0.253
0.6-0.8	49	0.24 ± 0.14	0.207	0.000	0.586	0.172
0.8-1.0	31	0.19 ± 0.12	0.139	0.007	0.471	0.163

number of patients (N = 13). Furthermore, this analysis was limited to data collected under controlled conditions, using signals only from when patients were in a supine position within an inpatient clinical setting. Finally, the study protocol was designed with the analysis of tcVNS/sham stimulation as a primary objective. Although the current analysis appears independent, future work should investigate how this stimulation may have affected the results.

Future research can build upon this study in several key directions. As data collection is ongoing, a larger cohort can be incorporated into the analysis. To assess the method's real-world applicability, future studies should explore data from different environments and from body positions other than supine. The analysis could be expanded to incorporate other cardiac signals collected by the CardioTag device, such as the photoplethysmogram (PPG), and utilize alternative methods like spectral analysis. A more granular approach to the withdrawal scale could also be taken; instead of using the total SOWS score, future work could categorize the questions to determine which specific symptoms most impact the physiological data. Additionally, there is room for algorithm refinement, such as experimenting with different DTW templates by adjusting the 30-beat averaging window or modifying the 60-minute time period used to associate DTW values with SOWS scores. Finally, fundamental studies are needed to provide deeper insight into why cardio-mechanical variability decreases during withdrawal, which would advance the physiological understanding of the condition.

Because OUD is a time-sensitive disease, it is increasingly important to investigate how remote technologies can replace traditional withdrawal scales and surveys. When withdrawal symptoms are not monitored or addressed effectively, this can lead to relapse and increase the potential for deadly overdoses. This analysis highlights an underexplored method of quantifying withdrawal symptoms using low-cost wearable sensors, which offers the potential for timely medication adjustments and preventative care for OUD.

V. Disclosures

O. T. Inan is a co-founder and board member of Cardiosense, Inc., the company that manufactures CardioTag, and has equity ownership in that company. He also holds equity in Physiowave and Biozen.

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