Wearable Biosensors to Evaluate Recurrent Opioid Toxicity After Naloxone Administration: A Hilbert Transform Approach

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Abstract

Opioid abuse is a rapidly escalating problem in the United States. Effective opioid reversal is achieved with the antidote naloxone, but often does not last as long as the offending opioid, necessitating in-hospital observation. Continuous physiologic monitoring using wearable biosensors represents a potential option to extend monitoring capability outside the clinical setting across the spectrum of opioid abuse including post- naloxone administration. The present study aims to identify the physiologic change that marks the cessation of naloxone's effect. Eleven participants were recruited in the Emergency Department after naloxone administration for an opioid overdose and continuously monitored using a wearable biosensor measuring heart rate, temperature, electrodermal activity and accelerometry. Hilbert transform was used to evaluate a 90- minute post naloxone time point. Physiologic changes were consistent with the onset of opioid drug effect across parameters, but only changes in heart rate and skin temperature research statistical significance.

1. Introduction

The United States is currently in the midst of an opioid epidemic, with over thirty thousand deaths attributed to opioids in 2015 alone [1] Unlike many other dangerous drugs, an effective antidote, naloxone, is widely available for opioid overdose. Naloxone blocks opioid receptors, to reverse the toxic effects of opioids (such as respiratory depression) when administered after an overdose [2]. Naloxone is widely available to both medical personnel and to the general public. With a duration of effect of naloxone is 30-90 minutes [2], the antidote may not last as long as the opioid that initially caused the overdose[3][4]. Consequently, patients who receive naloxone for overdose still require transport to a hospital for observation to ensure opioid toxicity will not reoccur after the antidote is no longer in effect[5]. Many individuals nonetheless refuse transport to (or observation in) a hospital after they receive naloxone, and are thus at risk for devastating consequences if opioid toxicity re-occurs in the absence of medical attention.

Wearable sensors have significant potential for use across the spectrum of opioid use disorders[6]. Using changes in continuously monitored physiologic parameters, they have already been shown to identify drug use (including opioid use) as it occurs in real time [7]-[9]. In the context of overdose and naloxone treatment, continuous biosensing may provide a way to decrease hospital observation time and possibly allow for monitoring outside of the hospital altogether. As a first step, we aim to identify the physiologic profile associated with the cessation of naloxone

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activity (which heralds a time of significant risk for recurrence of opioid toxicity). We hypothesize that as the naloxone loses effect, a participant's biometric profile will shift from one consistent with opioid withdrawal to one consistent with opioid intoxication. Since the data are collected in real time in a natural setting (as opposed to a controlled laboratory), the obtained data are highly non-stationary. Therefore, we employed a Hilbert transform approach to extract relevant features from the data.

2. Methods

This study was approved by the Institutional Review Board at the corresponding author's institution.

2.1. Hardware

The study was conducted using the E4 wrist-mounted biosensor (Empatica, Milan, Italy, Figure 1), which continuously measures skin temperature, three dimensional accelerometry, electrodermal activity (EDA) and heart rate. The accelerometer data was acquired at a sampling rate of 32Hz, heart rate at 1Hz, EDA and temperature at 4Hz. The collected data was stored on the devices' onboard memory, uploaded to a secure, HIPAA-compliant server using the Empatica Manager application, and then downloaded in *comma separated value (csv)* format using the Empatica Connect application.

Figure 1: Empatica E4 wrist mounted biosensor

2.2. Participants

Inclusion criteria for participants were as follows: 1) Emergency Department (ED) patients, 2) 18 years of age or older, 3) known or suspected diagnosis of opioid toxicity, and 4) treatment with the opioid antagonist naloxone by Emergency Medical Service (EMS) providers or by ED staff. Individuals were excluded if they: 1) use anticholinergic medications, 2) received naloxone by non-medical personnel (bystanders) only, 3) had known concomitant non-opioid ingestions at the time of presentation, 4) had an amputation of the non-dominant arm, or 5) had significant limitation of range of motion (i.e. acute orthopedic injuries).

2.3. Study Protocol

The E4 was placed on the participant's non-dominant wrist upon arrival to the ED, and continuous acquisition of biometric data occurred for the duration of study participation. Monitoring began immediately, and continued until one of the following predefined endpoints were reached: 1) discharge/transfer from the ED, 2) placement of participant on continuous naloxone infusion, or 3) decision by the participant to withdraw from the study.

Non-biometric data collected by self-report from the participant and verified by the electronic medical record (EMR) included: medical history, home medication lists, substance abuse history, social history and circumstances surrounding the current overdose event. Additional non-biometric data collected from the EMR included: demographic information, vital signs, medication administrations from the ED visit, and the timing, dose and route of naloxone administration on the day of enrollment. Clinical assessments were performed once per hour while the participant was enrolled to document presence of either opioid intoxication or opioid withdrawal.

Participant self-reported history of ingestion, as well as clinical evaluation by both the treating Emergency Physician and a Medical Toxicologist were used to classify each participant into three categories: 1) opioid toxicity without reoccurrence, 2) opioid toxicity with reoccurrence (requiring subsequent doses of naloxone), and 3) non-opioid/polysubstance intoxication. Only those in category 1 (opioid toxicity without re-occurrence) were included for this analysis.

2.4. Data Analysis

As described previously [7], to understand the rapid fluctuations and heterogeneity inherent in the measurement of locomotion at three different axes, we estimated the amplitude of the fluctuations using a Hilbert transform method[10]. We applied Hilbert

transform to the locomotion data, $d(t)$, at each of the axes, XYZ, to obtain the analytic signal

$$A(t) = d(t) + i\tilde{d}(t)$$

where i represents the complex variable and

$$\tilde{d}(t) = \frac{1}{\pi t} * d(t) \text{ with } * \text{ representing convolution.}$$

The amplitude, $a(t)$, is estimated as the absolute value of $A(t)$ and this procedure is applied to the data collected for each of the axes to obtain corresponding amplitudes. To study the fluctuations in the amplitude, we plotted the distribution of amplitudes and characterized the distribution with an appropriate distribution function. Since the obtained amplitude is from non-stationary data, we found the characterizing parameter using a running window approach with 5-minute length durations, with 4 minutes overlapping.

Naloxone has a duration of action up to 90 minutes from the time it is administered. To understand the biometric effects of this antidote, we obtained administration times and estimated the time its effects were expected to wear off (90 minutes after administration). For this analysis, 90 minutes post-naloxone administration was referred to as time N90. We calculated the characterizing parameters of the distribution 30 minutes ***before*** and 30 minutes ***after*** this time N90 using the running window approach.

We studied whether characterizing parameters of the distribution show any significant effect of naloxone ***before*** and ***after*** time N90. We also studied whether the fluctuations in other signals, such as heart rate, temperature and EDA also shows any significant difference ***before*** and ***after*** time N90.

3. Results

3.1 Demographic Data

Thirty-eight individuals were approached regarding study participation. A total of 18 were excluded due to polysubstance intoxication (N=10), bystander only/unconfirmed naloxone administration (N=5), or unwillingness to participate (N=3). Twenty participants enrolled and were monitored: 3 were classified as opioid toxicity with recurrence (requiring additional doses of naloxone) and 17 were classified as opioid toxicity with no recurrence. Eleven of the 17 non-recurrent participants were included in analysis: 1 was excluded to a device failure and 5 had insufficient volume of data for analysis. All included participants reported heroin as the opioid responsible for the overdose. Demographic data is described in Table 1.

3.2 Biometric Data

Table 1: Demographic data for all participants

	N=11
Age (mean, range)	36 (23, 50)
Race	
White	10
Other	1
Ethnicity	
Hispanic/Latino	2
Non-Hispanic/Latino	9
Gender	
Male	9
Female	2
Total dose of naloxone in mg (mean)	3.5 (2, 6)
Duration of biosensor recording in hours (mean, range)	2.6 (0.83, 6.35)

The data obtained in csv format were imported to MATLAB version R2016b, which was used for all analyses (Mathworks, Natick, MA). Figure 2 is a representative example of the accelerometer data in three of the axes, XYZ, for a single participant.

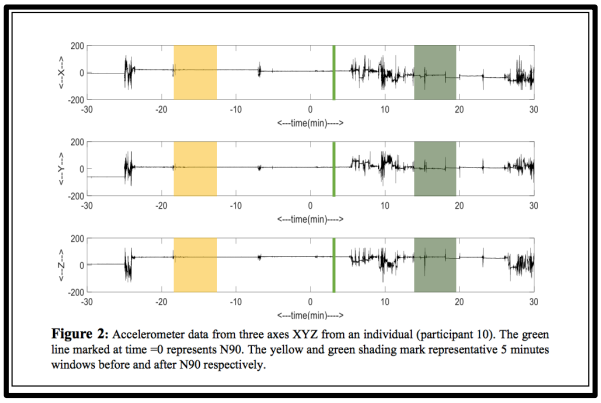

Figure 2: Accelerometer data from three axes XYZ from an individual (participant 10). The green line marked at time =0 represents N90. The yellow and green shading mark representative 5 minutes windows before and after N90 respectively.

We determined time N90 (marked as time = 0 and a green vertical line) based on documented time of naloxone administration and applied Hilbert transform to obtain the amplitude $a(t)$ for each of the axes separately. Prior to applying Hilbert transform, we subtracted the mean from the raw data. Figure 3 represents the amplitude $a(t)$ calculated for each of the axis from a 5-minute segment ***before*** (yellow

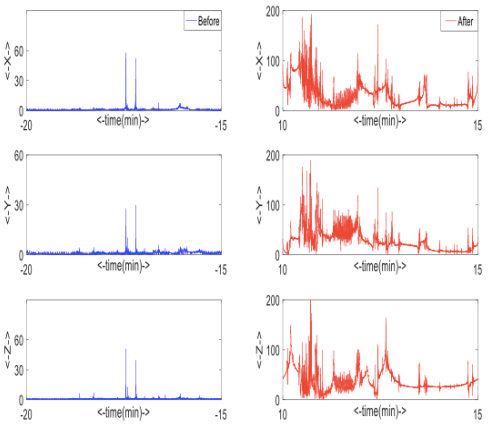

Figure 3: Amplitude estimated using Hilbert transform for the 5 minutes window (shaded regions in Figure 1) for the same participant. Left panels with blue lines represents ***before*** and right panel with red lines represents ***after***

shading on Figure 2) and ***after*** (green shading on Figure 2).

Similar to our previous work, we found that the amplitude follows a long tail distribution and we used a Gamma probability density function (pdf) to characterize the distribution. Thus, given the amplitude $a(t)$, the Gamma pdf is obtained as

$$f(a(t)|\alpha,\beta) = \frac{1}{\beta^{\alpha}\Gamma(\alpha)} a^{\alpha-1} e^{-a/\beta}$$

Where α and β represent the shape and scale parameters respectively. Since these characterizing parameters are estimated for each of the axis XYZ, we obtained a total of six measures (two measures, shape and scale, for each of the three axes). Figure 4 represents the distribution function fit of the amplitudes represented in Figure 3.

To get a comprehensive view of the changes in biometric data, we explored whether we can define a single parameter to differentiate the features in the biometric data ***before*** and ***after***. In a six dimension, hypothetical space with each of the above-mentioned measures representing the axis of this space, we defined a measure equivalent to distance as

$$D_k = \sqrt{\alpha_X^2 + \beta_X^2 + \alpha_Y^2 + \beta_Y^2 + \alpha_Z^2 + \beta_Z^2}$$

We also calculated the mean value of heart rate, EDA and temperature using the same sliding window approach.

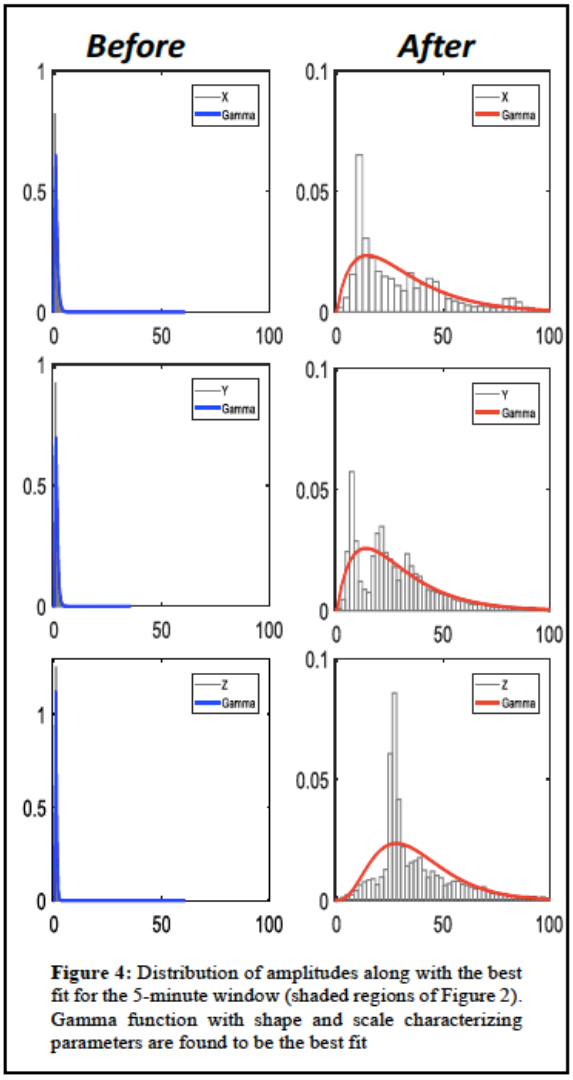

Figure 4: Distribution of amplitudes along with the best fit for the 5-minute window (shaded regions of Figure 2). Gamma function with shape and scale characterizing parameters are found to be the best fit

Figure 5 represents time evolution of D_k, heart rate, EDA and temperature calculated for each 5-minute sliding window with an overlap of 4 minutes for the participant 10.

We investigated whether the fluctuations observed in these measures are significantly different between ***before*** and ***after*** in each of the 11 participants. Table 2 shows such analysis. In seven of the participants, we found that some of the measures are significantly different between ***before*** and ***after***. However, significant differences in all of the measures were only found in three of the participants.

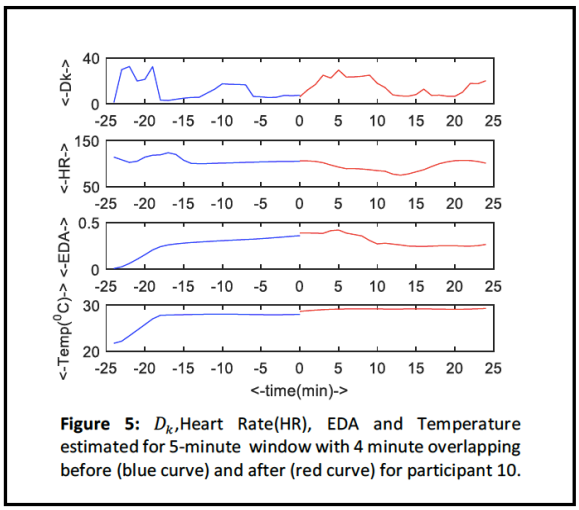

Figure 5: D_k,Heart Rate(HR), EDA and Temperature estimated for 5-minute window with 4 minute overlapping before (blue curve) and after (red curve) for participant 10.

Figure 6 represents the overall mean of D_k , heart rate, EDA and temperature along with their respective standard error. We found that in group comparison, D_k is not significant (P=0.11), heart rate is significant (P=0.007), EDA is not significant (P=0.22) and temperature is significant (P=0.01). This mixed result

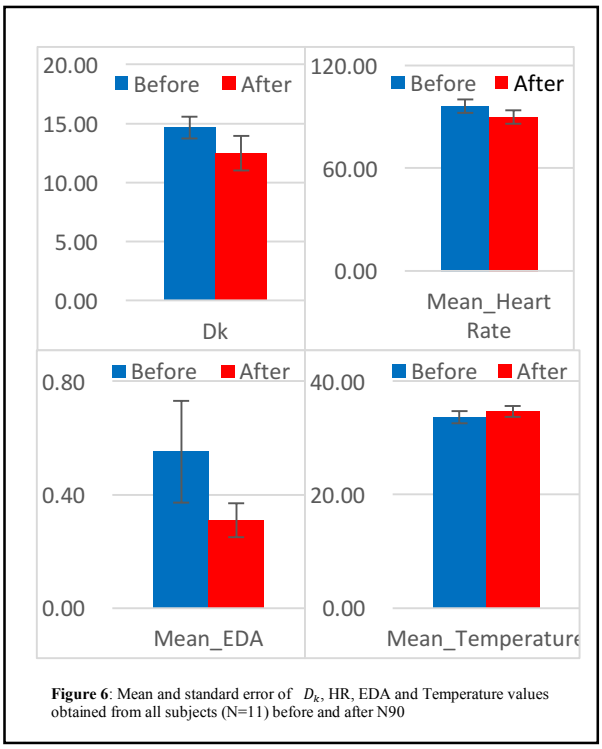

Figure 6: Mean and standard error of D_k, HR, EDA and Temperature values obtained from all subjects (N=11) before and after N90

is not surprising due to inter participant variability that is often observed in their response.

4.Discussion

Our data demonstrates a significant shift in physiology detected by a wearable biosensor as the opioid antagonist naloxone wears off. The profile change is physiologically similar to that seen with de novo opioid use in prior literature[7]. This makes sense from a physiologic standpoint since the original opioid agonist that caused the overdose in these patients would resume their physiologic effect once naloxone (the antagonist) wears off. This is clinically significant for a number of reasons. First, it can allow for remote monitoring after naloxone use, and identify risk of reoccurrence of opioid toxicity. Second, this profile should be physiologically identical to the profile for the onset of opioid use/overdose and thus

Table 2 : Mean and standard deviation (SD) for Dk, HR, EDA and skin temperature for all participants

Participant	Dk				Heart Rate			
	mean	SD	mean	SD	mean	SD	mean	SD
1	19.36	3.26	13.51*	5.37	86.2	2.38	85.48	3.13
2	13.92	7.67	11.95	2.99	116.82	4.12	108.10*	4.85
3	10.08	5.05	7.48 *	4.41	81.09	3.47	78.66*	1.4
4	12.75	2.17	14.42	6.94	80.3	2.77	79.91	8.81
5	13.71	4.64	6.04 *	3.95	92.42	19.93	77.39 *	1.49
6	12.19	4.83	8.95 *	3.09	118.51	20.61	115.05	15.31
7	16.26	5.56	10.85*	2.58	90.6	11.31	80.60 *	9.91
8	15.04	6.8	8.18 *	3.55	93.21	6.85	94.19	3.34
9	19.59	3.94	19.82	3.12	94.15	12.37	76.95 *	5.61
10	11.86	9.33	14.91	7.46	106.63	7.03	93.80 *	10.6
11	16.5	6.9	20.91 *	3.9	98.61	3.27	95.89 *	4.38
Participant	EDA				Temperature			
	mean	SD	mean	SD	mean	SD	mean	SD
1	0.17	0.03	0.23 *	0.03	36.31	0.63	36.92 *	0.33
2	0.23	0.26	0.23	0.09	35.53	0.23	35.64 *	0.2
3	0.01	0	0.01	0	32.15	0.33	33.41 *	0.62
4	0.45	0.03	0.49 *	0.02	38.93	0.14	38.98	0.46
5	0.17	0.04	0.48 *	0.15	31.32	0.44	33.20 *	0.53
6	1.05	0.45	0.18 *	0.19	33.52	0.7	32.97	0.45
7	1.73	1.67	0.19*	0.05	37.35	3.13	38.88 *	0.66
8	0.28	0.18	0.32	0.08	32.09	5.47	35.47 *	0.74
9	1.17	0.57	0.67 *	0.29	32.26	0.7	32.37	0.55
10	0.26	0.1	0.3	0.07	27.02	1.93	29.11 *	0.14
11	0.08	0.01	0.14 *	0.04	28.12	0.15	29.81 *	0.81

can be used identify de novo overdoses and trigger a warning or a call for help.

The methodology described also provides new insight toward the application of wearable sensors in opioid abuse. Using a traditional Hilbert transform method, we derived the amplitude from a highly non-stationary data. The interesting aspect of the analysis of locomotor data is the long tail distribution observed in the amplitude distribution. Such distributions represent an organization in the locomotor activity due to nonlinear interactions, and may provide clues to the detection of opioid use physiology.

5. Strengths and Limitations

Our study was conducted in a population of recreational opioid users in a natural setting; this made the data less precise than if opioids were given in a controlled laboratory setting, but this increases the generalizability of our findings to the real world.

Because participants were recruited upon arrival to the hospital, biosensor data was not available from the time of naloxone administration (in the pre-

hospital setting) to the time of hospital arrival. Transport time was variable, depending on the participants' original location, so several participants were excluded from the analysis due to insufficient volume of data. Also, as described in the recruitment setting, many participants screened out before enrollment or had to be excluded later due to concomitant ingestion of non-opioid drugs; physiologic influence from other substances would have inevitably confounded the data.

In this work, we had only a few number of participants to derive the features relevant to the effect of naloxone wearing off from the system. Although we could differentiate the effect of the antidote wearing off in the individual by observing the fluctuations of the features that we derived, as a group, we found only two features (heart rate and temperature) significantly different between ***before*** and ***after*** conditions. In this work, we employed Gamma distribution to characterize the long tail distribution, however we have not explored whether any other distribution will be a better fit than Gamma distribution.

6. Conclusions

A Hilbert transform analytic method can be applied to wearable biosensors to detect significant changes in physiology as the effect of the opioid antagonist naloxone wears off. This is a first step in the use of wearable sensors to remotely monitor patients with opioid toxicity. Potential future applications are wide, and could allow for shorter ED observation periods or possible even observation outside of the hospital after naloxone is administered for an opioid overdose. These findings also have implications beyond individuals who have received naloxone. The ability to detect opioid toxicity before it is apparent clinically could provide a means for early identification (both in and out of the hospital setting) and thus opportunities for intervention to dramatically decrease morbidity and mortality from opioid overdoses. Additional research is needed to identify other events across the spectrum of illness (opioid overdose and recurrence of toxicity), to capture naloxone administration, and to trial wearables in natural settings of opioids.

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