Title: Opioid Overdose Detection Using Smartphones

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Abstract: Early detection and rapid intervention can prevent death from opioid overdose. At high doses, opioids (particularly fentanyl) can cause rapid cessation of breathing (apnea), hypoxemic/hypercarbic respiratory failure and death, the physiologic sequence by which people commonly succumb from unintentional opioid overdose. We present algorithms that run on smartphones and unobtrusively detect opioid overdose events and their precursors. Our proof-of-concept contactless system converts the phone into a short-range active sonar, using frequency shifts to identify respiratory depression, apnea and gross motor movements associated with acute opioid toxicity. We develop algorithms and perform testing in two environments: (1) an approved supervised injection facility (SIF), where people self-inject illicit opioids, and (2) the operating room (OR), where we simulate rapid, opioid-induced overdose events using routine induction of general anesthesia. In the SIF (n=209), our system had 96% sensitivity and 98% specificity for identifying post-injection, opioid-induced central apnea and 87% sensitivity and 89% specificity for identifying respiratory depression, both key events commonly preceding fatal opioid overdose. In the OR, our algorithm identified 19 of 20 simulated overdose events. Given the reliable reversibility of acute opioid toxicity, smartphone-enabled overdose detection, capable of alerting naloxone-equipped friends and family or Emergency Medical Services (EMS), may hold potential as a low-barrier, harm reduction intervention.

Main Text:

Introduction

Fatal opioid overdose remains a public health epidemic in the United States (*1–6*). Each day, 115 Americans die from opioid overdose and data from the Centers for Disease Control and Prevention (CDC) indicate the epidemic is worsening (*7–9*). Unlike many life-threatening medical emergencies, opioid toxicity is readily reversed with rapid identification and administration of the overdose antidote naloxone or supportive respiratory care (*10–13*). Thus, a fundamental challenge of fatal opioid overdose events is that victims die alone or among untrained or impaired bystanders, in each case with no or insufficiently timely diagnosis and treatment (*14*). To help connect potential overdose victims with widely available life-saving interventions, we developed algorithms for commodity smartphones that unobtrusively recognize opioid overdose by its physiologic precursors. Our software system, which runs as an application on smartphones, converts the phone into a short-range active sonar system, using frequency shifts to identify respiratory depression, apnea and gross motor movements associated with acute opioid toxicity. By creating overdose detection algorithms that can be deployed on devices most high-risk individuals already own (*15, 16*), we hope to provide a harm reduction system that can automatically connect with naloxone-equipped friends and family or EMS to help prevent fatal overdose events (*17, 18*).

A mobile system that can detect opioid overdose precursors and events in real-time does not currently exist due to both design and validation challenges. Existing, human-based approaches to overdose diagnosis rely on medical grade equipment or trained recognition of diagnostic signs of opioid toxicity (*19–23*). Achieving similar sensing capabilities on smartphones, without the need for medical grade equipment, is challenging since it requires tracking physiological parameters without being intrusive and violating privacy (*24,25*). In addition, validating the efficacy of any opioid toxicity system requires access to patients and data while high-risk opioid use occurs, which is difficult because this can represent a medically life-threatening situation. We overcome these challenges with an active sonar-based monitoring solution, leveraging access to two unique environments where people routinely experience overdose respiratory physiology without harm: (1) a legally sanctioned supervised injection facility (SIF), where people self-inject previously obtained illicit opioids under medical supervision and (2) the operating room (OR), during routine induction of general anesthesia.

This report describes a contactless smartphone-based system that matches the performance of an invasive respiratory impedance monitor in identifying 3 critical overdose precursors: opioid-induced respiratory depression, central apnea and simulated overdose events (*19,26,27*). The system works by placing the phone within 1 meter of the subject as it monitors them during the post-injection period, the highest risk time for a fatal overdose event and the period when a victim would most benefit from rapid identification and resuscitation.

Results

Subhead 1 : Concept and Algorithms

Our system uses frequency modulated continuous waveform (FMCW) and converts the smartphone's native speaker and microphone into a short-range active sonar system (*28–34*) that allows for portable measurement of chest motion and respiration using inaudible acoustic signals. The phone continuously transmits a custom, inaudible, FMCW where the transmitted frequency increases linearly with time between 18 kHz and 22 kHz within a duration of 10 ms (Figure 1 A,B). These custom acoustic signals reflect off a surface (in this case, a moving chest during respiration) and the echo arrives back to the smartphone's microphones after a time delay Δt corresponding to the distance of the reflector from the smartphone. The time delay Δt is given by $\frac{2d}{v_s}$, where d is the distance of the human body from the smartphone and v_s is the velocity of sound in air. When the subject's chest moves due to breathing, the distance d to the smartphone and the corresponding time delay of its echo Δt at the microphone changes. Because the frequency of the FMCW signals increases linearly over time, each of their time delays Δt translates to a unique frequency shift Δf in the reflected signals. Hence, we can measure the changing distances due to breathing motion by observing the frequency shift caused by the echo over time. The periodicity of the changes generates sinusoidal waves, the peaks of which correspond to a complete breathing cycle (Figure 1C). A peak detection algorithm then identifies the maximum amplitude of the wave, which enables determination of a subject's respiratory rate and the presence of apnea.

Our system builds on previous work using active sonar to detect sleep apnea (*28*), however the opioid use case differs from the sleep environment in several fundamental ways. First, breathing motion is diminished during opioid use, which can complicate respiratory peak detection, and subjects may use opioids multiple times over the course of a day and thus may have a diminished breathing signal at the initiation of their use event. Additionally, the sleep laboratory in prior work is a controlled environment with a lone subject who is primarily stationary. In contrast, subjects using opioids have increased motion that can affect the time delay of the echo, may engage in high-risk opioid use behaviors in the presence of others, and are generally in a much less controlled environment, which introduces other sources of potential interference (*35, 36*). Notably, the supervised injection facility where our experiments take place is a highly dynamic and stimulating environment (recording devices are prohibited within the SIF, but the environment can be observed in this public domain report (*37*)). For example, there are routinely several people around; there is talking amongst clients; staff and clients walk around; overhead music is playing and occasionally personal dogs are within the environment. In addition, there is climate control equipment, as well as a special indoor ventilation system (to remove the smoke from heroin preparation), all of which produce ambient noise. In short, there are several environmental elements in the high-risk opioid use domain that differ from the controlled setting of a sleep laboratory.

We develop algorithms that address the above challenges specific to the high-risk opioid use domain (see Materials and Methods for detailed algorithmic and experimental description). At a high level, our algorithm uses FMCW to disambiguate the reflections at different distances from the smartphone, the resolution of which is approximately 0.7 cm with a typical microphone sampling rate of 48 kHz. Thus, the algorithm can separate the subject's breathing signal from other movements in the environment that occur at a different distance (e.g., those of an opioid using companion). In addition, by tracking the distance corresponding to the subject's breathing signal, the algorithm automatically re-calibrates when a posture change occurs or when the subject or phone changes position. Figure 2 demonstrates benchmark performance across phone models (Galaxy S4, S5, S6, iPhone 5S, Google Pixel and Nexus), phone orientations, subject distance and posture, and various environmental noise and motion conditions (see Supplementary Materials and Methods for detailed experimental descriptions).

Subhead 2 : Real-world Illicit Opioid Use, Supervised Injection Facility

We first report data of our system deployment in Vancouver, British Columbia, within an approved supervised injection facility (see Figure 3). While our primary target is people who use opioids when alone (the demographic at highest risk for fatal overdose), we choose the SIF environment because it facilitates safe, real-world testing and algorithm development based on actual opioid self-injection events. Acute, life-threatening overdose events requiring medical intervention still remain relatively uncommon in this environment, occurring in less than 1% of opioid use events (approximately 500 supervised injections occur per day in the facility) (*38*). Therefore our primary outcomes of interest were post-injection central apnea (cessation of breathing for 10 seconds or more) (*27*) and opioid-induced respiratory depression (respiratory rate $\leq$7 breath/minute) (*39, 40*), both of which are necessary precursors to lethal opioid intoxication events.

We recruited participants over 209 self-injection instances (194 unique participants): 115 injection events were used as a development set and 94 were used as an evaluation set to measure algorithm performance. Results from the evaluation set are presented here. The average age was 43 ± 11.0 years; the average height and weight were 178 ± 8.3 cm and 77 ± 12.4 kg, respectively. Sixty-four participants (68%) reported using heroin; 19% reported using fentanyl; 13% reported using morphine or hydromorphone. Following injection, 47 participants (50%) experienced clinically important respiratory depression; 49 participants (52%) experienced at least one post-injection central apnea event; 8 participants (8.5%) had a manual intervention by clinical staff, of which 2 participants (2.3%) experienced an overdose event requiring clinical resuscitation (i.e., oxygen, bag-mask ventilation and/or naloxone therapy). Both overdosed participants were successfully resuscitated by the clinical staff without issue.

The system had strong performance detecting post-injection central apnea events and respiratory depression, compared to the reference standard (Figure 4 C,D). It had 95.9% (95% CI, 86.0% - 99.5%) sensitivity for identifying post-injection central apnea events (cessation of breathing for 10 seconds or longer) and specificity of 97.7% (95% CI, 88.2% - 99.9%). The system had 87.2% (95% CI, 74.2% - 95.1%) sensitivity for identifying post-injection respiratory depression (respiratory rate ≤7 breaths/minute) and 89.3% (95% CI, 76.9% - 96.4%) specificity (see Figure 4 A,B).

Figure 5A shows the distribution of the number of central apnea events per participant, as identified by our system. Forty-eight percent of the participants had no central apnea events, all of whom required no intervention. Among those who experienced a post-injection central apnea event, 71% had 1–2 central apnea events during the 5 minute post-injection monitoring period. Figure 5B is a histogram of the durations of these central apnea events. The plot shows that 66% of central apnea events were ≤20 seconds in duration. We also note that both overdosed participants had a central apnea event of at least 30 seconds prior to clinical intervention.

Subhead 3 : Simulated Overdose Detection, Operating Room

A key limitation of the SIF environment is the limited occurrences of overdose events requiring clinical resuscitation. To address this, we next report data of our system deployment in the operating room. We choose this environment because it is controlled and allows us to safely simulate the worst-case scenario of acute opioid toxicity: immediate loss of consciousness coupled with respiratory depression that would be fatal or critically morbid without intervention. Such conditions are safely reproduced during routine induction of general anesthesia (see Figure 6) when patients receive fentanyl and other anesthetic drugs.

We recruited for 35 instances of simulated overdose (34 unique participants): 15 patients were used as a development set to generate the algorithm, and 20 were used as an evaluation set to validate algorithm performance. Results from the evaluation cohort are presented here. The average participant age was 33 ± 10.8 years; the average weight was 75 ± 14.6 kg; 60% of participants were female. In the evaluation set, as expected all 20 patients experienced true overdose physiology, characterized by post-injection loss of consciousness and diminished or absent breathing. Our algorithm identified 19 of the 20 simulated overdoses as having disordered breathing. Of the 19 correctly identified patients, 18 patients experienced sustained apnea (terminated per protocol after 30 seconds); and 1 patient had severely diminished breathing that the algorithm identified as an overdose. The 1 patient who was incorrectly classified had a breathing signal just above the algorithm's threshold. In each case where the algorithm correctly identified the overdose event, it detected the onset of respiratory failure similarly to the real-time reference standard (Figure 6B). We note that specificity is not meaningful in this environment because all participants experience the simulated overdose event (i.e., all patients undergoing induction of general anesthesia lose consciousness and experience depressed breathing) (*41*).

Discussion

This report focuses on using a commodity smartphone to identify opioid overdose precursors, which are crucial indicators given the readily reversible nature of overdose events with early detection. In the setting of real-world high-risk opioid use, our results highlight the need for a multi-tier interactive alarm system on the phone that escalates or deescalates based on user feedback. Put differently, we do not envision the system alerting a third party or disturbing the user based on an isolated central apnea or respiratory depression event; rather, an alert should be sent only after a subject is unable to respond to a stimulus from the phone following a sustained central apnea or respiratory depression event, representing a potentially life threatening overdose. Evaluating such a multi- tiered system would be the next step in enabling an end-to-end overdose detection system using commodity smartphones.

Our study has the following limitations. Healthy participants recruited for the operating room experiments are likely different than the eventual intended target population. We chose this population for reasons of safety and algorithm development for the worst case scenario of acute opioid overdose. External validity is addressed in the supervised injection facility with participants who are more likely to use the application as it is eventually intended. It was beyond the scope of this study to seek and recruit subjects who use high-risk opioids alone, or to conduct our study procedures in a participant's personal environment outside of the InSite facility. In addition, development of a harm-reduction intervention does not ensure adoption and use. In order for this harm reduction intervention to be efficacious, further studies with participant feedback and human factor testing is needed to ensure the system meets the needs, values and preferences of people who use opioids, in addition to establishing the system's safety vis-a`-vis its potential to encourage moral hazard. Importantly, other harm reduction interventions such as take-home naloxone programs have been found not to increase risky behavior or lead to adverse health consequences (42–44). Further, prior data on harm reduction interventions show that people are willing to engage in behaviors to help keep themselves safe, e.g., by utilizing needle exchanges, take-home naloxone, face shields for mouth-to-mouth respiratory support and supervised injection facilities (45–47). Another potential concern is whether the system could reliably alert pre-hospital EMS providers in a time-frame that enables successful resuscitation with naloxone or supportive respiratory care. Based on historical data from Seattle, King County involving fatal overdose events and average EMS response times, we believe meaningful EMS integration is possible (for full discussion and analysis, see Supplementary Materials and Figure S1). Such a program would need to incorporate the detection algorithm's performance characteristics to leverage the operations and resources of a given EMS system. Any integrated program must also acknowledge that even with rapid connection to EMS, victims still could experience morbidity and mortality following opioid overdose (48).

In summary, we report development of a proof-of-concept system that can be implemented on commodity smartphones and can identify simulated and real-world opioid overdose events and their precursors. As a harm reduction intervention, such a system could connect people experiencing potentially fatal overdose events with known life-saving interventions (e.g., naloxone-equipped friends, family, shelter personnel, or EMS) in real time. As the number of deaths attributable to opioid overdose continues to rise, new strategies are needed to help mitigate the risk of death and disability from this public health epidemic. One key tool to reverse these events is naloxone, which is increasingly available to first responders (including police), to people through take-home naloxone programs, and is now endorsed by the US government (*49*). In addition to its use by EMS providers, the administration of naloxone by trained friends and family has been shown to be a safe and effective means of reversing overdose (*13, 50*). However, neither EMS, friends or family can intervene with naloxone or supportive respiratory care in an emergency if they are not immediately aware that an overdose is taking place. Non-invasive self-monitoring via smartphone, as we have described, could address this critical shortcoming and may represent an easily accessible strategy to help keep people safe until they are able to access long-term treatment.

Materials and Methods

Subhead 1 : Study design

We investigated the accuracy of a smartphone-based software system for identifying opioid-induced respiratory depression, central apnea and simulated overdose events. Participants served as their own controls, with ground truth measurements taken simultaneously by a respiratory impedance monitor. In both the supervised injection facility and the operating room, a development set was used to develop the algorithm and an evaluation set was used to prospectively evaluate algorithm performance. To demonstrate feasibility, we chose to stop recruitment after >200 instances of illicit opioid self-injection. These numbers were deemed clinically justified for proof-of-concept based on the confidence intervals of our primary outcomes. In the operating room, because the algorithm was highly sensitive in detecting sustained apnea following induction of general anesthesia, we did not pursue beyond 35 participants. Randomization was not applicable and investigators were not blinded. All participants provided informed consent and the studies were approved by the University of Washington Institutional Review Board, the University of British Columbia Office of Research Ethics and the Vancouver Coastal Health (VCH) Ethics Services (VCH operates the supervised injection facility, InSite).

Subhead 2 : Active sonar detection of breathing signals

Our system transmits frequency modulated continuous wave (FMCW) signals and analyses the frequency shifts resulting from human motion. The frequency shift, from which the respiratory rate is derived, was determined by performing a fast Fourier transform (FFT). We chose a FMCW chirp period of 10 ms, which gives a frequency resolution of 100 Hz. The unique challenge with opioids acting on the central nervous system is that breathing motion can be severely depressed. For our FMCW signal with a 4 kHz bandwidth this minute motion can translate to a frequency shift less than 8.33 Hz. To extract this, we perform an FFT over 15 consecutive chirps which linearly increases the frequency resolution to 6.66 Hz and thus captures even severely depressed breathing motion, down to a chest movement of 0.7 cm. By taking an

FFT over 15 chirps, any high frequency motion within this duration is averaged and hence lost. However, since the average breathing rate of human subjects is less than 20 breaths per minute, which is a relatively low frequency motion, no breathing motion is lost within the 150 ms FFT duration.

To extract the breathing signal, the algorithm first estimates the distance of the person's chest from the smartphone over time. As described previously, the breathing signal is present in a unique frequency bin corresponding to this distance. To identify this bin, we examine the FFT bins corresponding to the frequency of the custom acoustic chirp (i.e., 18-22 kHz). The algorithm starts by looking from the 18 kHz bin (corresponding to distance zero) and proceeds to 18.320 kHz (corresponding to a distance of one meter). For each bin, it examines changes in the power value over a duration of 30 seconds by performing a second FFT over it. If a peak between 0.5 to 0.7 Hz (the typical breathing frequency of a human) is observed, then that bin corresponds to the breathing signal. Therefore, the second FFT occurs until the bin that corresponds to the breathing signal is found. In the worst-case scenario, the system may iterate through 48 bins before isolating the breathing signal. Once found, the signal recurs within the same bin as long as the subject remains in place. However, when a subject moves, the bin corresponding to the distance has a motion signal instead of a breathing signal. In this scenario, the system re-initiates the search for the new bin containing the breathing signal. In particular, if the distance of the subject from the smartphone changes, we estimate the new distance by computing the bin corresponding to the breathing signal after the motion.

Subhead 3 : Detecting opioid-induced depressed breathing

Breathing motion is diminished when people use opioids~~.~~ To overcome this, we make two changes to the peak detection algorithm. First, to remove any small motion noise, we run the data through a bandpass decimating Cascaded Integrated Comb filter. The filter removes any motion noise higher than a frequency of 1 Hz and also decimates the signal by a factor of two. Second, we collect a baseline breathing signal for a duration of one minute prior to the self-injection event. From the baseline collection period, the algorithm calculates the subject's average peak amplitude, peak prominence and average peak distance. These parameters are used to identify the peaks during post-injection monitoring. For the baseline signal, the algorithm leverages the periodicity of the breathing signal and the frequency limits of the breathing signal (less than 20 breaths/min) to estimate breathing peak parameters. Specifically, only peaks that are separated by a minimum of 20 samples (corresponding to a maximum breathing rate of 20 breaths/minute) are considered. During post injection monitoring we combine this condition along with the average peak parameters that we estimated in the first step. Peaks separated by a minimum of 20 samples that have an amplitude of at least 50% of the baseline and 30% of the peak prominence are classified as breathing peaks. If the number of peaks is less than or equal to 7, the epoch is marked as a respiratory depression event. If the distance between the peaks is greater than 10 seconds, we mark a central apnea event. If the number of breaths in the epoch is at least greater than 3, we update peak amplitude, peak prominence and distance values with the combined average of new peak values. If a specific peak value is twice as great as the average peak values, the system does not use that peak value in average peak parameter computations.

Subhead 4 : Differentiating breathing from motion

Subjects using opioids may move their heads or hands, which are motions that can affect the time delay of the echo. Since subjects' faces and hands are closer to their chests and are approximately at the same distance from the smartphone, the change caused by these motions can be added to the breathing signal in its frequency bin during the primary algorithm's FFT operation. Moreover, this motion has higher amplitude compared to the more subdued breathing motion and can overpower the breathing signal, making it difficult to extract the breathing motion. While normally such motion noise would be problematic, the presence of motion provides additional information about the subject. Specifically, sustained motion indicates that the subject is active and not overdosed. Similarly, motion that is followed by breathing indicates that the subject is active and thus not overdosed. On the other hand, motion within the operational range that is followed by an absence of breathing likely indicates an overdose scenario. Hence, we modify the algorithm to differentiate between a signal corresponding to periodic, low-frequency breathing motion and one that belongs to high frequency body motion, which is aperiodic and high amplitude. We identify this by looking at the peaks in the second FFT operation of the 30- second signal corresponding to each bin. If the peaks have higher frequencies and an amplitude at least twice that of the breathing frequency peaks, then the instance is classified as a motion epoch. If the motion is absent or present only for a few seconds, the algorithm considers it to be a breathing signal and processes it to identify the respiration rate.

Subhead 5 : Distance recalibration

When we encounter a motion epoch, the distance of the subject with respect to the smartphone can change. Hence after every motion epoch we need to run the re-calibration step to detect the new frequency bin that corresponds to the new distance of the subject from the smartphone. When we encounter the first motion epoch, we set the motion bit to 1 and examine the next epochs. For subsequent epochs, we search all the nearby FFT bins until we detect the bin that has the breathing signal. We then use this new bin for the next set of epochs until we see the next motion epoch. For the first breathing epoch after the motion epoch, we update the peak parameter values to the average values of the new epoch corresponding to the new distance of the subject.

To review, we first filter the recorded signal using a high pass filter to remove audible environmental noise. We then split the data into 30-second epochs and run the distance estimation step described above on the first epoch to identify the bin that contains the breathing signal. We estimate average breathing peak amplitude, peak distance and average peak prominence for this epoch. For subsequent epochs, we check the same frequency bin in the distance estimation algorithm. If it contains the breathing signal, we use the previously estimated amplitude and prominence values to determine the breathing peaks in this epoch and subsequently update them with the new peaks of the current epoch. This continues until the bin contains a motion signal instead of breathing signal. If the subsequent epoch does not contain the breathing signal and instead contains the motion signal (high amplitudes, more peaks), we mark it as a motion epoch and run the re-calibration step for the subsequent epochs until we find the new breathing signal.

Subhead 6 : Suppressing environmental motion

High-risk opioid use is commonly done with others, which introduces another source of potential interference (*35, 36*). In this case, the interfering subject's breathing or motion may change the received echoes at the smartphone. However, since the interfering subject(s) will mostly be located at different distances with respect to the smartphone, their breathing motions (as determined by the primary FFT operation) would occur at different frequency bins than that of the subject of interest. Assuming that the smartphone is closest to the intended subject, viz., within one meter, the first frequency bin containing the breathing signal likely corresponds to the breathing motion of the intended subject. The algorithm therefore filters out any breathing detected at farther distances.

Subhead 7 : Computational complexity

In the worst case, our algorithm performs 54 FFT computations per second and one linear peak estimation algorithm. Such operations can each be computed within a few milliseconds on an off-the-shelf smartphone (*51, 52*). This delay is within the expected human response time (for visual overdose identification) of a few seconds. Finally, based on the duration of high-risk opioid self-injection events, we expect the application to run typically for less than 45 minutes per day and not more than 15 minutes per event. The algorithm's computations along with the sensor data collection consumes 6-18% of a phone's battery power for this duration. In addition, most fatal overdose events occur within a private residence, hotel or motel (*53*), which should have an available power source.

Vancouver Supervised Injection Facility

Participants

All people who inject opioids and utilize the SIF, who were over 18 years old, and had capacity to provide informed consent (as determined by InSite staff), were eligible for study inclusion. People under age 18 and impaired individuals were not eligible (per SIF protocol, severely impaired individuals are assisted and unable to use the facility). Potential participants were identified at the time they checked into the SIF for the purposes of supervised opioid self-injection, and approached by a research assistant for informed consent. Participants were approached consecutively following check-in into the facility. Participants were given a $5 coffee card for participation.

Measures

We compute the breathing rate in order to identify respiratory depression and central apnea occurrences, both of which can indicate or precede a fatal opioid overdose. We define a breathing rate of ≤ 7 breaths/min to be a respiratory depression event and the absence of breathing for 10 seconds or more to be an opioid-induced central apnea event. We chose a respiratory rate of ≤ 7 breaths per minute because the Agency for Healthcare Research and Quality (AHRQ) finds this respiratory rate sufficiently dangerous to recommend as a trigger for a hospital's Rapid Response System (*39, 40*). The Food and Drug Administration (FDA) defines an apnea event as cessation of breathing for 10 seconds or more and requires FDA-approved apnea devices to detect this threshold (*27*).

Protocol

Clients who consented obtained sterile injecting equipment per routine and were assigned to a monitored injection stall and were asked to prepare their drugs as they normally would. Monitored stalls were equipped with a dedicated off-the-shelf phone (Galaxy S4) with our pre-installed app, which was placed on the tabletop (see Figure 3). All subjects, regardless of participation, received standard clinical monitoring by the SIF clinical staff according to institutional protocols. Post-injection overdose detection by staff was defined by standard institutional triggers listed in Supplementary Table S1. Of note, routine staff monitoring relies on visual monitoring for acute clinical distress and does not involve active respiratory monitoring equipment.

Once participants had prepared their equipment and drugs, the participant was fitted with a respiratory impedance monitor for reference standard monitoring (see Figure 3B). Then the participants were asked to remain seated and breathe normally for one minute to establish a baseline respiratory rate. The smartphone, placed within one meter of the participant on the injection stall table, began respiratory monitoring at the initiation of the one minute baseline measurement (see Figure 3C). Participants then self-injected opioids and monitoring continued for five minutes. We chose five minutes because this represents the critical period when an acute overdose would occur; from a pharmacology perspective, fentanyl reaches a peak plasma concentration within 3-5 minutes and more than 80% of the injected dose leaves the plasma by five minutes (*54*). If an overdose event occurred, or a participant was in a clinical state sufficiently concerning that a trained medical staff member walked over to check on a patient, it was recorded by the research assistant and counted as an intervention event.

As we note in the main text, there were eight instances where a staff member went over to a participant post-injection out of concern for their clinical state. In the six instances (including the 2 reversed overdoses) where the respiratory impedance monitor identified disordered breathing, the algorithm identified respiratory depression or central apnea in all six. In the 2 other instances, the subjects had fallen asleep and slouched in their chairs following injection, however both had respiratory patterns that did not meet the respiratory depression or central apnea thresholds (i.e., the smartphone and respiratory impedance monitor correctly identified normal breathing while the staff misdiagnosed potential clinical distress).

Operating Room

To optimize surgical conditions, patients are routinely given fentanyl and other potent drugs immediately prior to surgery to purposefully induce apnea. In other words, the physiologic equivalent of drug overdose occurs each time a patient undergoes general anesthesia. However, patients are unharmed by this induced "overdose" because of their supra-physiologic oxygen stores and the timely ventilatory support the anesthesiologist provides. Therefore, anesthetizing a patient in the OR offers a unique way to safely simulate an otherwise lethal overdose event (characterized by unconsciousness and diminished or absent breathing) induced by fentanyl and other opioids.

Healthy patients free of cardiopulmonary disease, aged 18-55 and scheduled for elective surgery, were eligible for the operating room study and were approached on the day of surgery. Participants were given a $50 Amazon gift card for participation. Once inside the operating room, patients were fitted with standard anesthesiology cardiopulmonary monitors: pulse oximeter, blood pressure cuff, 5-lead EKG. In addition to the standard anesthesiology monitors, participants were fitted with a Vernier respiratory belt to provide reference standard respiratory monitoring. The smartphone (Galaxy S4) was placed on a surgical stand ≤1 meter away at approximately chest level (see Figure 6A). Next, the clinical team conducted their standard operating room pre-induction safety procedures (i.e., safety surgical and pre-anesthesia checklists). The ventilation mask was affixed to the patient with a strap. Operating room personnel were asked to stand away from the patient; the attending anesthesiologist was beside the patient and immediately available. Next, per standard anesthetic procedure, the participant breathed 100% oxygen for 3-5 minutes until their expired oxygen levels were greater than 85%– a level deemed safe to administer induction doses of anesthetic agents to induce apnea (*55*). This standard pre-oxygenation procedure allows the body to be safely apneic without having oxygen saturation levels fall to unsafe levels during apnea periods that may persist for as long as 7 minutes under normal conditions (*56*). The attending anesthesiologist then administered induction doses of fentanyl and propofol in doses at his/her discretion for standard induction of general anesthesia (the average fentanyl dose was 1.4 mcg/kg; the average propofol dose was 2.9 mg/kg). The attending anesthesiologist announced the moment when the patient had become apneic, at which time a timer was started. The timekeeper announced the elapsing time in 10 second intervals until 30 seconds was reached (we chose 30 seconds of apnea as a suitably safe period for a pre-oxygenated individual to be completely apneic before intervention (*56*) and termination of the protocol). At 30 seconds, the protocol was officially over, at which point the anesthesiology team assumed control of the airway (administered a neuromuscular blocking agent, if indicated) and provided manual ventilation and inserted an endotracheal tube or laryngeal mask airway. No neuromuscular blocking agents were administered during the protocol. Once the participant's airway was secured and it was deemed safe by the clinical team, the study team removed the research equipment and exited the operating room. Per the IRB protocol, the attending anesthesiologist could intervene at any moment and for any reason during the protocol should the patient require intervention. Breaking protocol was in no cases required during the study as all patients safely tolerated the procedure.

Statistical Analysis

We used standard analyses to assess the respiration rate measurements of the smartphone-based device against the reference measurements from the impedance monitor. In particular, we assessed the accuracy using scatter plots and bubble plots equipped with trend lines. To determine the accuracy of the opioid overdose precursor detection, we used standard techniques to calculate sensitivity (true positive rate) and specificity (true negative rate) and we report Clopper-Pearson confidence intervals around these estimates. For all the benchmark experiments, we compute the bias error (μ, mean of the errors), and precision error (σ, SD of the errors) to compare the respiration rate measurements of our system against the standard impedance monitor.

Supplementary materials

Materials and Methods
Fig. S1. Connecting overdose victims with EMS.

Fig. S2. Post-injection respiratory rate decrement.
Table S1. InSite institutional overdose indicators.
Table S2. Benchmark testing, individual data for Figure 2

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Author contributions. SG, JS and RN designed the experiments; RN conducted the experiments; RN and SG designed the algorithms; RN conducted the analysis with technical supervision by SG; JS, SG and RN interpreted the results and wrote the manuscript. Conceptualization: JS.

Competing Interests. All co-authors are inventors on US provisional patent application no. 62/675,560 (submitted by the University of Washington) which is related to this work. The co-authors intend to license the technology presented in this manuscript. SG is a paid consultant to Jeeva Wireless Inc.

Data and material availability. All data for interpreting the manuscript have been included. Additional information may be requested from RN, SG and JS.

Figures:

Fig. 1. Converting a smartphone into an active sonar monitoring system. (A) The smartphone's speaker transmits an inaudible, custom frequency modulated continuous wave-form (FMCW) signal, which is reflected by the subject and recorded using the smartphone's microphone. **(B)** The reflections arrive at time delays Δt_i and Δt_e during inhalation and exhalation; the changes translate to unique frequency shifts Δf_i and Δf_e. **(C)** The frequency shifts can be estimated by taking a fast Fourier transform (FFT) over 15 chirps; the breathing signal is found in a frequency bin corresponding to the subject's distance from the smartphone. Motion in

the environment from a different distance would appear at a different frequency bin and hence can be separated.

Fig. 2. Breathing rate accuracy across different scenarios. The system is evaluated across **(A)** different smartphone models, **(B)** orientations of the smartphone, **(C)** various positions of the smartphone w.r.t the subject, **(D)** in the presence of interference from another nearby moving subject, **(E)** with environmental noise from devices placed 75 cm from the subject, **(F)** as a function of distance from the smartphone and **(G)** re-calibration accuracy after the subject changes the orientation of the phone as well as slouches. In addition, **(H)** shows the fraction of time the subject's respiration and other motion was captured by the algorithm in the SIF deployment. W.r.t = with respect to.

Fig. 3. Experimental setup and sequence, supervised injection facility. (A) Supervised injection facility: Insite. Since 2003, more than 3.6 million drug use events have occurred under supervision at this facility; there have been over 6,500 overdose interventions without any deaths. There are multiple people in the environment; there is movement in the environment, talking and overhead music; there is a special ventilation system above each stall which clears smoke created from drug preparation. **(B)** Participants sit in the injection stall with experimental equipment on the tabletop. A respiratory impedance monitor is connected to the chest. **(C)** Experimental sequence.

Fig. 4. Measurement of real-world, high-risk opioid use events. (A-B) Sensitivity and specificity for respiratory depression (RD) and central apnea events (CAE). **(C)** Post-injection respiratory rate on a smartphone vs. reference standard. **(D)** Post-injection central apnea event detection on a smartphone vs. reference standard. **(E-H)** Smartphone breathing signals of 4 subjects whom InSite staff physically checked on post-injection. **(E)** OVERDOSE - subject exhibits multiple central apnea periods followed by deep breath. **(F)** OVERDOSE - subject exhibits respiratory depression with an average respiratory rate of 4 breaths/minute. **(G)** INTERVENTION - subject exhibits central apnea, is aroused by staff, becomes agitated. **(H)** INTERVENTION - subject slouches post-injection, staff physically check on patient, whose breathing does not meet respiratory depression or central apnea thresholds.

Fig. 5. Distribution of observed central apnea events in the supervised injection facility. (A) Histogram of central apnea events per participant. **(B)** Histogram of the duration of the central apnea events identified by our system.

Fig. 6. Measurement of simulated overdose events in the operating room. (A) The phone is placed within 1 meter of the patient on a surgical (Mayo) stand. A respiratory impedance monitor is fit around the patient's chest to measure the true respiratory rate and apnea status. Healthy patients wearing all standard operating room monitors have general anesthesia induced. **(B)** Comparison of time to detection of simulated overdose, based on algorithm-identified respiratory failure onset, smartphone vs. real-time detection by the reference standard.

Table 1. Demographic summary of participants in algorithm evaluation, supervised injection facility and operating room.

Safe Injection Facility (n=94)	**Age (yrs)**	43±11
	Height (cm)	178±8.3
	Weight (kg)	7±12.4
	Sex	
	Male, n (%)	80 (85)
	Female, n (%)	14 (15)
	Race	
	Caucasian, n (%)	62 (66)
	Black, n (%)	2 (2)
	First Nations, n (%)	30 (32)
	Drug injected	
	Fentanyl, n (%)	17 (18)
	Heroin, n (%)	64 (68)
	Morphine, n (%)	12 (13)
	Hydromorphone, n (%)	1 (1)
Operating Room (n=20)		
	Age (yrs)	33±10.8
	Height (cm)	174±9
	Weight (kg)	75±14.6
	Sex	
	Male, n (%)	8 (40)
	Female, n (%)	12 (60)
	Race	

	Caucasian, n (%)	16 (80)
	African American, n (%)	2 (10)
	Asian, n (%)	1 (5)
	Pacific Islander, n (%)	1 (5)