Devices and Diagnostics for OIRD

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OIRD (opioid-induced respiratory depression) remains a significant public health concern due to clinically indicated and illicit opioid use. Respiratory depression is the sine qua non of opioid toxicity, and early detection is critical for reversal using pharmacologic and non-pharmacologic interventions.

Keywords: opioids ; OIRD ; diagnostics ; sensor

1. Introduction

The prevalence of opioid-induced respiratory depression (OIRD) remains a public health concern due to both clinically indicated and illicit opioid use. The number of drug overdose deaths almost tripled between 1999 and 2015, primarily due to opioid overdose. The death toll from opioid overdoses in the United States is approximately 115 per day [1]. Compounds that bind to opioid receptors are referred to as opioids. Typically, the term opioid refers to natural alkaloid derivatives of opium poppies such as morphine and codeine. Moreover, semi-synthetic opioids have also been synthesized from natural opioids, including oxycodone from thebaine and heroin from morphine. Methadone, fentanyl, and propoxyphene are synthetic opioids. While opioids have known risks, they remain one of the most common types of treatment for postoperative pain as well as for certain chronic pain conditions. According to a recent, hospital-acquired OIRD ranges from 0.1% to 37% after controlled opioid administration, with improper monitoring accounting for almost one-third of cases [2]. The rate of overdose deaths in outpatient settings for patients receiving opioids for non-cancer chronic pain has been observed to range from 0.2–1.8% yearly [3]. Furthermore, those people who use drugs (PWUD) account for a significantly higher proportion of opioid overdose deaths compared to those treated for pain with medically indicated chronic opioids [4]. Opioid toxicity is characterized by respiratory depression and its early identification and diagnosis are crucial for administering effective treatment. Opioids reduce respiratory function by binding opioid receptors in brainstem respiratory centers and other sites along the central and peripheral nervous systems. Under normal circumstances, hypoxia and hypercarbia increase respiratory effort and rate. However, opioids dull both of these physiological responses. As a result, there is a pressing need for low-barrier technologies that can detect opioid excess in vivo, identify its downstream effects (such as OIRD), and enable rapid interventions to prevent harm from opioid toxicity.

2. Established Devices Used for Detection of OIRD: Requiring Modification to Impact the Public Health

While new technologies are being developed and miniaturized to detect opioids in vivo, there remains a need to detect the downstream effects of opioid excess, such as opioid-induced respiratory depression. Although there is some variability in definitions of respiratory depression (based on studies), at its most basic level, respiratory depression is the result of decreased minute ventilation, a combination of tidal volume and respiratory rate. Diagnostics of OIRD present a unique set of challenges. The respiratory status of patients in non-continuously monitored environments is often assessed using infrequent vital signs such as respiratory rate and oxygen saturation. Despite their value, these measurements serve only as surrogate indicators of an individual's respiratory health. A marked decrease in ventilation leads to hypercarbic respiratory failure, the sine qua non of severe opioid toxicity [5]. In many clinical settings, respiratory rate and oxygen saturation are often used to assess respiratory status, with sedation assessment and capnography also playing a role, particularly in inpatient settings. As a result, technologies used to detect OIRD, particularly those that can be scaled and conceivably used for out-of-hospital public health interventions, commonly measure one aspect of decreased ventilation (often respiratory rate) or a surrogate measure (e.g., decreased oxygen saturation). In the absence of low-cost, scalable modalities to measure minute ventilation, surrogate measurements, balancing their sensitivities and specificities, may be needed from a public health perspective. Early detection and intervention with naloxone or supportive respiratory care are highly reliable ways to reverse OIRD and prevent irreversible morbidity or mortality. It is important to modify existing technologies and develop new, innovative detection modalities to detect respiratory depression faster to quickly identify OIRD and connect victims to therapies.

2.1. Pulse Oximeter

Pulse oximeters are used for non-invasive, inexpensive measurements of oxygen saturation, heart rate, as well as respiratory rate (only in advanced models). By measuring the variation in absorption of light in oxygenated and deoxygenated blood, and extrapolating SpO_2 based on a reference standard, oxygenation can be calculated. Although with advancement in technology the pulse oximeter performance has been improved to function under adverse conditions like excessive motion and low perfusion, yet the issue of false alarms remains elusive due to a variety of factors and can contribute to provider fatigue [6]. Primarily pulse oximetry is a measure of oxygenation, not ventilation. Hence, decreased ventilation can be present for a longer time before being detected by a pulse oximeter, and the use of supplemental oxygen can further delay this response. In cases of acute opioid overdose, it could be asserted that desaturation being a late sign of the toxicity event, could further taper the chances of therapeutic intervention for an already emergent condition. However, from a public health perspective, in the existing opioid overdose epidemic, the reliability, low cost, high clinical sensitivity for overdose in opioid use contexts, pulse oximetry is a compelling technology. OIRD leading to hypoventilation or decrease in oxygen saturation level causes a rapid drop in oxygen at opioid overdose. The rise of hypoventilation upon overdose increases the sensitivity of pulse oximeter in terms of SpO_2 [7]. For pulse oximetry to have a scalable public health intervention impact, it is imperative to couple them with devices capable of summoning help (e.g., friends, family, bystanders, EMS personnel) upon detection of a sustained critical desaturation event. The drive to incorporate pulse oximetry on a variety of mobile phone-connected wearables (e.g., watches and bracelets), permits monitoring outside of hospital environments, making the barrier to use and decreased chance for stigma favorable.

2.2. Capnography

Capnography, although is less commonly used than pulse oximetry, is more sensitive in detecting OIRD as it is capable of indirectly measuring ventilation from exhaled CO_2 using an infrared sensor. When plotted as a function of time, these values provide a more accurate measure of ventilation and can detect OIRD earlier than a pulse oximeter. OIRD can be detected using capnography on basis of the observed decline in end-tidal CO_2 ($ETCO_2$) peek detection (indicating reduced respiratory rate) and/or a higher concentration of CO_2 (indicating retention). Respiratory rates that fall below predetermined “normal” values or $ETCO_2$ levels above programmed alarm cutoffs would trigger a notification. These alarm set values may need to be adjusted as per an individual’s normal physiology due to several factors such as medical comorbidities. Capnography also suffers from some disadvantages such as $ETCO_2$ does not always readily correlate to CO_2 levels in the blood. These values are differentiated by a gradient that is a surrogate to physiologic dead space and can be variable [8]. Further, capnography requires the use of specialized equipment to quantify exhaled breath and requires the patient to wear a sampling line (e.g., nasal cannula) appropriately, which can be challenging and uncomfortable [9]. Finally, from a public health point of view, the cost involved in using a capnography system prevents it from being used as a technology that could scale and be deployed to mitigate risk from opioid overdose in the community. Hence, there must be a low-cost, less invasive variation of capnography, connecting victims to help in the cases of hypercarbic respiratory failure.

3. Novel, Contactless Sensing Modalities: Sonar, Radar, Computer Vision

Contactless monitoring systems provide a fascinating method of monitoring for OIRD as they do not require the user to instrument themselves or wear anything, and the technologies to transmit and receive these signals are in some cases ubiquitous. One family of systems involves using active sonar with commodity devices such as smartphones and smart speakers [10]. These systems leverage the internal hardware of these devices (e.g., speaker, microphones, processor) and thus can be done with the software only. These systems use frequency-modulated continuous waveform (FMCW) and convert the device’s speaker and microphone into a short-range active sonar system. At specific moments of high risk (e.g., before opioid self-injection or during sleep) the devices transmit custom, inaudible, FMCW where the transmitted frequency increases linearly with time between 18 and 22 kHz (wavelength 1.7–1.9 cm) within a duration of 10 ms [11][12]. The custom acoustic signals reflect off a surface (in this case, a moving chest during respiration), and the echo arrives back to the device’s microphones after a time delay. The echo is captured by the microphones, distance from the reflector is processed, and a respiratory rate is generated [11]. Experimental systems using these techniques developed by researchers have shown high accuracy for measuring respiratory rate and good sensitivity for identifying breathing patterns associated with opioid toxicity (>87% for RR < 8 breaths/minute) including prolonged apnea (>95%) [11]. These systems could be useful from a harm reduction standpoint, whereby a person who uses drugs could monitor their breathing when engaging in a high-risk opioid use event (e.g., self-injection), where there is a circumscribed window of elevated risk. For people using chronic opioid therapy to manage a pain condition, nocturnal monitoring could be done as this represents a higher risk environment, particularly if the patient is prescribed other central nervous system depressants (e.g., benzodiazepines), has obstructive breathing or consumes alcohol. The generally low cost and ubiquity of smartphones and smart speakers make active sonar a novel and compelling OIRD solution from a public health standpoint, as does the fact that these devices have built-in connectivity to summon help should an emergency arise.

Radar-based systems are also examples of contactless systems. Radar-based systems transmit electromagnetic waves into the environment, while reflected waves from the thoracic cavity are captured at the transceiver and used to determine a patient's respiratory rate. This method of monitoring has its challenges. Due to radar's sensitivity to the environment and its high travel speed, it can be difficult to distinguish the intended target (a patient's variably shaped thoracic wall) from other potential sources of movement. In addition to their high sensitivity in detecting the millimeter movements involved in respiration, radar-based systems are also highly sensitive to noise introduced by non-respiratory body movements. Since these devices use electromagnetic waves, a variety of factors (for example physical movements, metal jewelry, and radio-frequency interference) need to be considered, which may affect the practical applicability at the point of need (PON) [13].

Contactless respiration measurement is also possible through computer vision with remote system settings [14]. The respiratory rate of an individual is calculated (based on movement or pixel intensity variation) by extracting thoracoabdominal pixel changes and tracking them from sequential video frames. One system by Chaterjee et al. using a consumer-grade camera observed high correlation (r = 0.88) with ground truth and 93% of measurements within 3 breaths/minute [15]. A computer vision-based system can utilize existing commercially available cameras, which are inexpensive and require little additional technical knowledge on the part of the user. Photoplethysmography, another computer vision-based technique, can be combined with this contactless monitoring technique to measure heart rate based on subtle changes in coloration in the face (depending on variations in blood flow) that are imperceptible to the human eye. Vital sign information combined with respiratory data could be useful for identifying individuals who may be experiencing an opioid overdose. McDuff and colleagues have demonstrated that using commodity hardware computer vision techniques, heart rate can be identified to within four beats/minute [16]. Computer-vision-based systems have several limitations in addition to privacy concerns, such as their sensitivity to low light levels, increased interference with magnified images, and errors caused by camera movement. A drawback of contactless systems, such as other devices, includes the need for subjects to be relatively stationary when measurements are taken, otherwise gross motor movements can overpower the signal associated with tidal breathing.

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