IRB Approved at the
Protocol Level
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Title of Project: Development of an algorithm that predicts hypoventilation due to an opioid overdose.

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Abstract

More than 64,000 Americans died from drug overdose in 2016 and drug overdose is now the most common cause of death for people under 50 years old in the United States (1). Furthermore, the number of overdose deaths is increasing with the rise of abuse of powerful synthetic opioids, such as fentanyl. In May of 2017, the National Institutes of Health (NIH) and National Institute on Drug Abuse (NIDA) directors Drs. Collins and Volkow (3) outlined how research may help reduce the death toll associated with the current opioid epidemic; one of the current critical needs is the development of new overdose-reversal interventions, including wearable technologies that can detect an (impending) overdose from physiological signals to signal for help, or trigger a coupled automated injection of naloxone. Automated detection of overdose is essential because most opioid overdoses occur when individuals are alone and unobserved by family members or first responders. Opioids cause respiration to slow and become irregular due to mu-opioid receptor mediated suppression of respiratory related regions of the brainstem and spinal cord. Importantly, there are characteristic early changes in breathing patterns that indicate a progression towards significant hypoventilation, but there is currently no method to measure these patterns non-invasively without large hospital equipment. Recently, there has been a renewed interest in respiratory monitoring using tracheal sounds (2, 4, 5). Tracheal sounds originate from the vibrations of the tracheal wall and surrounding soft tissues caused by gas pressure fluctuations in the trachea. These sounds can be collected from a microphone or a piezo-electric film transducer placed over the trachea and have been processed to monitor respiratory rate and to estimate respiratory flow. We hypothesize that individual trends in tracheal sounds detected by a machine-learning algorithm will provide an early warning sign of the onset of hypoventilation as a result of opioid overdose in humans. The aim of this study is to develop a machine-learning algorithm that detects impending hypoventilation as a result of opioid overdose from tracheal sound. This algorithm could eventually be integrated with a miniature tracheal sound sensor and could be used to detect impending respiratory depression in the outpatient setting as well as in the hospital.

A. Specific Aims

We hypothesize that advanced analysis of tracheal sound can be used to predict hypoventilation due to opioid overdose.

The specific aim of this proof of concept study is to collect tracheal sound data in 20 healthy subjects undergoing an incremental infusion of fentanyl to induce mild to moderate hypoventilation (also called permissive hypercapnia). Study subjects will receive supplemental oxygen to prevent hypoxemia. The tracheal sound data will be refined using advanced signal processing techniques and machine learning to assess whether it is possible to detect and predict the onset of hypoventilation.

The long-term objective of this project is to develop a real-time monitoring system based on tracheal sound that can be used to detect changes in minute ventilation and alarm before significant hypoventilation occurs due to an overdose of anesthetics and/or analgesics.

B. Background and Significance

RTM Vital Signs, LLC is collaborating with Thomas Jefferson University to develop a non-invasive Tracheal Sound Sensor that continuously monitors and analyzes sounds from the trachea to determine upper airway patency and the adequacy of an ambulatory person's respiratory rate (RR) and tidal volume (TV) to maintain a sufficient minute ventilation (RR X TV).

Over the last decades various mathematical methods have been developed to estimate respiratory rate and respiratory flow from tracheal sounds (2). Airflow sounds are known to occur at a frequency of 200-2000 Hz while snoring sounds occur in the 0-200 Hz band (2). There is a near-linear relationship between airflow in the trachea and respiratory sounds - increasing flow increases the amplitude of sounds. Additionally, different transformations can be applied continuously on recorded tracheal sound to extract specific information.

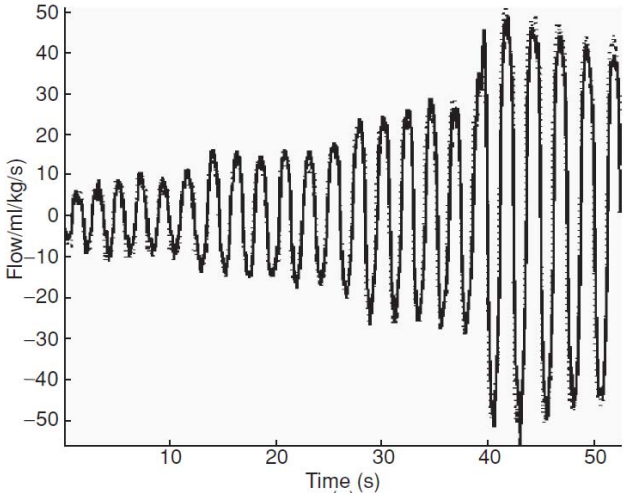


Figure 1. Actual tracheal airflow (solid line) measured with a reference pneumotachometer and estimated airflow using a microphone over the sternal notch and entropy model (dashed line). Figure modified from Yadollahi and Moussavi (2).

Previous studies have looked at the average power, envelop, spectral power, and entropy of sound signals. One of the most robust models to estimate respiratory flow from tracheal sound uses the entropy of tracheal sounds (a measure

of sound complexity) to determine tracheal airflow during inhalation and exhalation (Figure 1) (2, 4).

Using these different signal processing approaches we will generate a large set of features that will be used for subsequent machine learning analysis. Using machine-learning we will then train a risk-index algorithm that can recognize a significant change from baseline in an individual's "normal" pattern of respiratory rate and tidal volume. Thus, the hypoventilation monitoring system under development will not require previous knowledge of an individual's age, height, weight, model of the respiratory tract or external calibration.

We hypothesize that the tracheal sound algorithm will be able to accurately and reliably track, and predict, changes in arterial carbon dioxide concentration, as a marker of hypoventilation. The monitoring system will alert the patient/caregiver when the algorithm predicts impending mild hypoventilation ($PaCO_2$ >50 mm Hg) and alarm when the algorithm predicts impending moderate hypoventilation ($PaCO_2$ > 60 mm Hg); a clinical situation at increased risk for hypoxemia and death.

The long-term objective of this effort is to integrate a tracheal sound machine-learning algorithm in a miniature wearable tracheal sound sensor. This sensor can connect to a cell phone via Bluetooth and could be used in the outpatient setting to warn first responders when severe hypoventilation is predicted due to an opioid overdose. Similarly, the sensor could be used in the clinical setting to improve the safety of opioid analgesia, by alerting hospital staff if impending respiratory depression is detected/predicted in a patient.

C. Preliminary Studies/Progress Report

The Principal Investigator, Stephen E McNulty, DO and the co-investigators Jeffrey I Joseph, DO and Marc C Torjman, PhD have experience conducting invasive integrative physiology studies in humans. Dr. Stephen McNulty is a cardiac anesthesiologist with 35 years' experience managing patients with fentanyl. He will provide clinical care of the research subjects during the fentanyl infusion protocol. Jennifer Lessin, RN is an experienced research nurse coordinator who will assist with study subject recruitment and clinical care. Drs. Joseph and Torjman will record research data during the fentanyl infusion protocol. The co-investigator Dr. Michael Li is the Director of Health Data Science at TJU with 20 years of experience with advanced analytics, machine learning and their application in real-world data in healthcare.

D. Research Design and Methods

A pilot human clinical study that utilizes fentanyl to induce mild and moderate hypoventilation will be conducted in 20 healthy adults to collect the data necessary to develop a diagnostic algorithm that functions as a risk-index score that continuously predicts the onset of mild and moderate hypoventilation using signal processing and machine learning methods.

Informed Consent/Screen- Visit # 1:
Subjects will arrive at the Department of Anesthesiology's research office. Jennifer Lessin, RN will review the informed consent document and the inclusion/exclusion criteria. Subjects will complete a Drug Abuse Screening Test (DAST)(6) to determine their risk for substance abuse (Attachment 1). They will also provide a urine sample to perform a drug screen toxicology analysis. For women, we will also provide urine pregnancy testing. Dr. Stephen McNulty will also review the informed consent document, answer any of the subject's questions and obtain a signed consent form. Each subject will receive a copy of the consent form. Dr. McNulty will then perform a detailed history and physical exam and review the subject's vital sign data. Ms. Lessin will then schedule the clinical study visit # 2.

Human Clinical Study - Visit # 2:
Study subjects will be instructed to refrain from eating after 11 pm (NPO) the day prior to the study and to arrive at Thomas Jefferson University Hospital around 7 am on the morning of study visit # 2. A urine drug screen toxicology test will be repeated on all study subjects. For female subjects, we will also conduct urine pregnancy testing.

Subjects will be studied in a hospital clinical environment containing an anesthesia machine, vital sign monitors and routine emergency equipment, medications and supplies. All study subjects will be managed by Stephen McNulty, D.O. an experienced board-certified anesthesiologist with extensive experience in the respiratory effects of an IV infusion of fentanyl. Subjects will be continuously monitored using standard anesthesia vital sign monitors (ECG/upper arm cuff BP/pulse oximeter, Datex Ohmeda) and a BIS sedation monitor (Covidien) according to American Society of Anesthesiology standards. A contact microphone (BIOPAC TSD108) will be adhered to the skin over the trachea (above the sternal notch) with double-sided tape and a Tegaderm bandage. An accelerometer will be adhered to the skin close to the microphone.

A catheter will be inserted into a radial artery using ultrasound guidance, lidocaine local anesthetic and aseptic technique to acquire samples for blood gas analysis and continuously monitor the arterial blood pressure (Edwards Lifesciences Truwave). A catheter will also be inserted into a peripheral vein using aseptic technique to facilitate the infusion of fentanyl. Oxygen will be continuously delivered using a soft tight-fitting face mask connected to an anesthesia circuit (FIO2-1.0) with a side-port for continuous sampling of inspired/expired gas (sampling line to BIOPAC CO2100C gas analyzer). Respiratory rate and airflow will be continuously measured using a commercial reference pneumotachometer attached to the inlet of the face mask (BIOPAC TSD117A). All cardiovascular, respiratory, and sound monitoring will be continuously recorded through a BIOPAC MP150 data acquisition system connected to a desktop computer. Pictures may be taken after instrumentation.

Monitored study subjects will be instructed to rest comfortably in the supine position and refrain from talking. A standard IV dose of Ondansetron will be administered to minimize the risk for nausea/emesis. A standard IV dose of glycopyrrolate may be administered to minimize the risk for bradycardia. Vital signs and respiratory data will be recorded

during a 1-hour baseline period while sampling arterial blood every 15 minutes to measure pH, PaCO2, PaO2, HCO3, SaO2 and lactate concentrations (Epoc blood analysis system, Siemens, München, Germany).

After an initial bolus of 1.0 mcg/kg, a stepwise continuous intravenous infusion of fentanyl will be started at time zero (Figure 2). The infusion will start at 1.5 mcg/kg/hr and will be increased by 1.5 mcg/kg every 30 minutes. The infusion will be continued for a maximum duration of 3 hours (final infusion rate 9.0 mcg/kg/h). In a 30-year old 70 kg man, the proposed stepped infusion is projected to cause a gradual increase in fentanyl plasma concentration up to a maximum concentration of 5.8 ng/mL (Figure 3). Respiratory depression typically occurs anywhere in the 2.0 – 6.0 ng/mL fentanyl plasma concentration range (7, 8) while loss of consciousness occurs around 34 ± 7 ng/mL (7).

Vital sign monitor data, CO2 waveform data, reference pneumotach data, and tracheal sound data will be continuously recorded throughout the infusion protocol. Arterial blood gases will be measured every 10 minutes, or immediately after the decision is made to stop the infusion protocol. The fentanyl infusion will be discontinued prior to the end of the 3 hour protocol if: (1) the PaCO2 exceeds 60 mm Hg in two consecutive blood gas measurements (primary end-point), (2) the subject requires positive pressure bag/mask assisted ventilation by the anesthesiologist, or (3) the SaO2 falls below 90% on supplemental oxygen (FIO2=1.0).

The primary endpoint of the study will be the onset of moderate hypoventilation, defined as two consecutive arterial PaCO2 measurement ≥ 60 mmHg. This level of opioid induced hypoventilation is clinically significant because based upon the alveolar gas equation and the Henderson-Hasselbalch equation- breathing room air (FIO2 21%) at sea level (barometric pressure 760 mm Hg) (9), a PaCO2 of 60 mm Hg will decrease the PaO2 from 159 mm Hg to 75 mm Hg to produce an arterial partial pressure of oxygen (PaO2) ~75 mmHg. The respiratory acidosis will cause the hemoglobin oxygen dissociation curve to shift to the right and downward leading to an arterial hemoglobin oxygen saturation of ~88% SaO2.

Respiratory and vital sign data will continue to be collected for another 2 hours after discontinuation of the fentanyl infusion. Arterial blood will be sampled every 15 minutes for pH and blood gas analysis. The total volume of blood sampled will be approximately ~45 ml over a 6 hour study period (25 samples x 1.5 ml/sample = 45 ml). The narcotic antagonist Naloxone and other emergency medications will be immediately available as needed to ensure safety. After the 2 hour post infusion measurements, subjects will eat a meal and be observed for another hour or more to confirm adequate minute ventilation.

After completion of the experiment, study subjects will be given oral and written instructions similar to patients undergoing an outpatient surgical center procedure under general anesthesia. Each subject will receive a phone call around 9 pm that evening and a phone call 5-7 days later to confirm no study related adverse events.

Summary of Subject Monitoring:

1) Radial artery catheter to monitor and record the arterial blood pressure waveform.
2) Heart rate & rhythm will be monitored and recorded by an electrocardiogram.
3) Respiratory flow and tidal volume will be monitored and recorded using a pneumotach.
4) End-tidal CO2 concentration and waveform will be monitored and recorded.
5) Hemoglobin oxygen saturation (SaO2) will be measured and recorded.
6) Skin temperature will be measured and recorded.
7) Tracheal sounds will be measured and recorded using a microphone.
8) Body movement will be measured and recorded using an accelerometer.
9) Serial measurements of arterial blood pH, PaO2, PaCO2, bicarbonate, and lactate concentration.
10) Serial measurement of the Bispectral Index (BIS).

Anticipated Problems and Alternative Approaches:

The anesthesiologist has the clinical experience to produce mild and moderate hypoventilation safely using an IV infusion of fentanyl. The research team does not anticipate any major difficulties in executing this protocol. The slow intravenous fentanyl infusion will reliably induce alveolar hypoventilation in a dose dependent manor. A similar method has been safely used by research anesthesiologists in multiple clinical studies (4, 8, 10). The degree of sedation and hypoventilation is mild to moderate and the risk of hypoxemia is minimal due to the use of supplemental oxygen by face mask, continuous pulse oximetry, and frequent PaO2 measurements. Dr. Stephen McNulty is a board-certified Anesthesiologist with 35 years of expertise at TJUH managing patients with intravenous infusions of fentanyl and other anesthetics/medications that suppress minute ventilation. Dr. McNulty will closely observe and clinically manage all of the study subjects until they are awake, alert and stable.

Figure 2. Fentanyl Infusion Protocol.

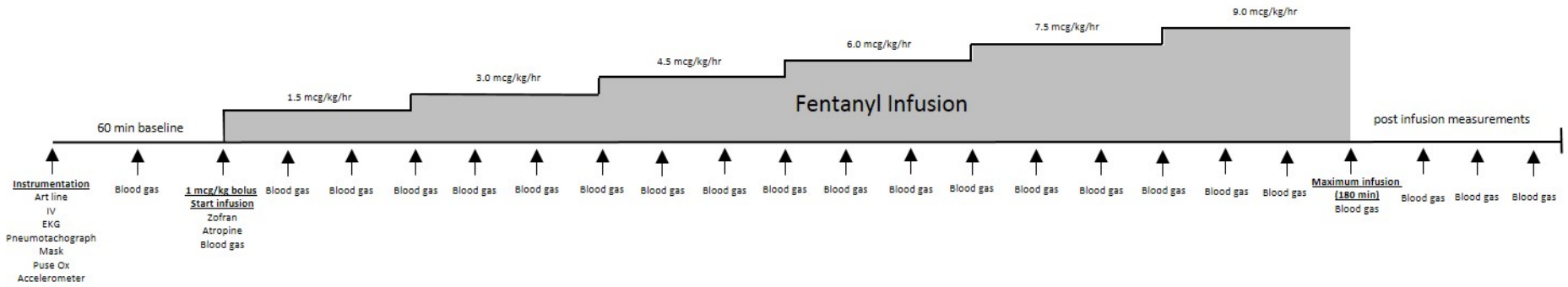
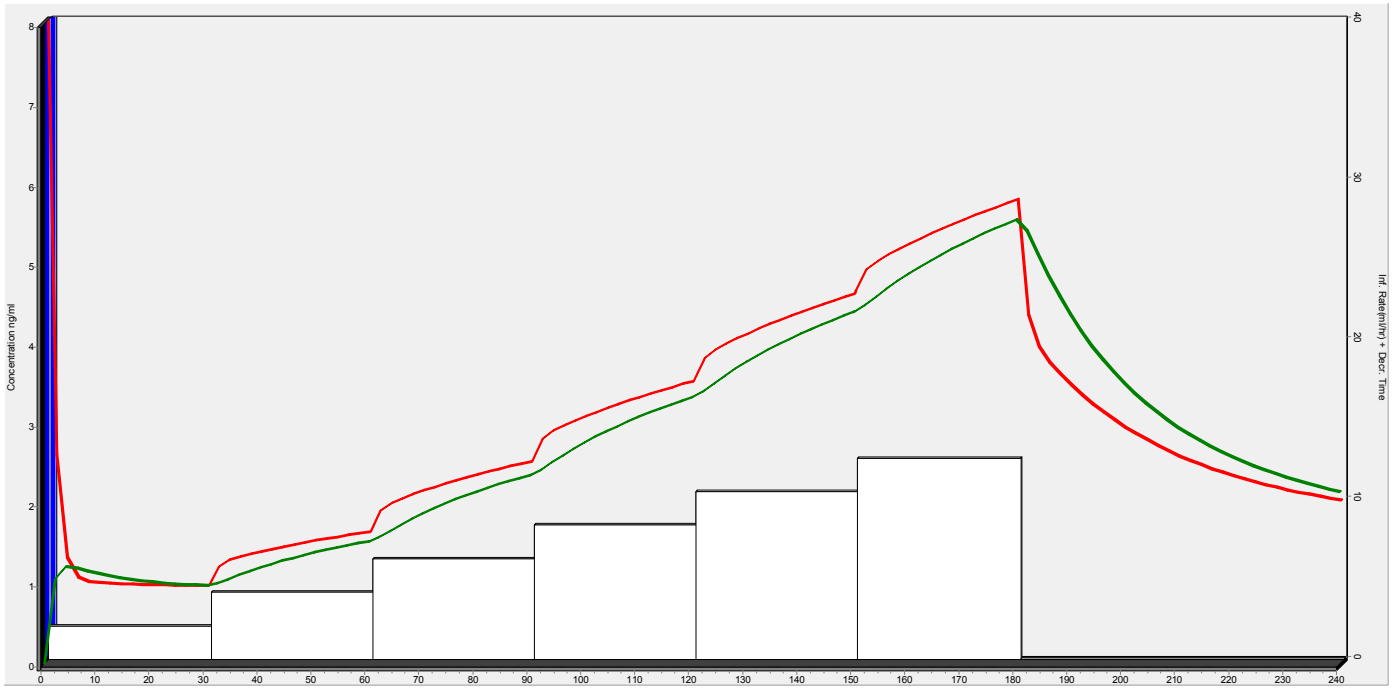


Figure 3. Projected plasma concentrations of fentanyl with the proposed stepped fentanyl infusion protocol. Using the European Society for Intravenous Anesthesia simulator (Tivatrainer, 11) we simulated the plasma concentrations of fentanyl that would be achieved with the proposed stepped fentanyl infusion protocol in a 30 year old man (70 kg, 170 cm). The specific kinetic model for fentanyl that is used by Tivatrainer has been published previously (10). The red line depicts the projected plasma concentration while the green line depicts the effect site concentration (both measured on left Y-axis, time in minutes on X-axis). The stepwise fentanyl infusion is depicted in boxes (infusion rate of 0.05 mg/mL fentanyl on right Y-axis, time in minutes on X-axis).



E. Statistical Methods

This is a pilot study and we therefore do not have prior data to conduct a power analysis. Because sound and physiological data will be collected continuously, even a relatively small number of subjects will provide a significant data set for algorithm development. If we assume a respiratory rate of 12 breaths per minute then: 12 breaths per min x 60 mins per hr = 720 breaths per hr; 720 breaths x 6 hr study time per patient = 4,320 breaths per patient; 4,320 breaths per patient x 6 subjects = 25,920 breaths for all 6 subjects. Previous studies on analysis of tracheal sound to track ventilation have used a similar n, with sometimes shorter protocols (2).

The performance of the developed prediction algorithm will be evaluated by looking at the mean absolute error in predicted PaCO2 vs. the actual PaCO2 and by comparing predicted time to hypoventilation during the fentanyl ramp vs. the observed time to hypoventilation. We plan to perform analysis on data from an initial 6 study subjects, then study up to 20 subjects to produce a more robust machine learning algorithm that detects/predicts the onset of mild and moderate hypoventilation.

F. Gender/Minority/Pediatric Inclusion for Research

Minorities will be eligible to participate in the research. Children (age < 18 years) will be excluded from participation. We aim to recruit robustly healthy young subjects for this initial proof of concept effort, because we anticipate that they will tolerate this protocol very well. We anticipate studying populations that are more varied if the proposed proof of concept study is successful.

G. Human Subjects

Inclusion criteria will be:
1. Healthy women/men between 18 and 40 years of age.
2. Negative history of drug or alcohol abuse.
3. Negative history of cigarette smoking in previous 6 months.
4. Negative history of active cardiac, vascular, pulmonary, renal, hepatic, nervous, metabolic or immune disease.
5. BMI < 30

Exclusion criteria will be:
1. Age < 18 years and > 40 years.
2. Pregnant or planning to become pregnant.
3. Positive history drug or alcohol abuse.
4. Positive drug screen for opioids, benzodiazepines, hypnotics.
5. Positive Drug Abuse Screening Test result (score of 6 or greater).
6. BMI > 30
7. History of sleep apnea.
8. History of cigarette smoking in previous 6 months.
9. History of difficult airway during anesthesia management.
10. History of allergy or skin sensitivity to tape, silicone, fentanyl, chlorhexidine.

Study Subject Recruitment & consent:
Twenty healthy volunteers will be recruited from the general population around Thomas Jefferson University using an advertising flier (Attachment 2). Potential subjects will contact the Anesthesiology

research nurse coordinator Jennifer Lessin, R.N. to review the inclusion/exclusion criteria and schedule visit # 1 (Attachment 3, phone script). Subjects will arrive at the Department of Anesthesiology's research office. Jennifer Lessin, RN will review the informed consent document and the inclusion/exclusion criteria. Subjects will complete a Drug Abuse Screening Test (DAST) (6) to determine their risk for substance abuse (Attachment 1). They will also provide a urine sample to perform a drug toxicology analysis. In female potential subjects, we will also perform a urine pregnancy test. Dr. Stephen McNulty will also review the informed consent document with subjects during visit #1, answer any of the subject's questions and obtain a signed and witnessed consent form. Each subject will receive a copy of the consent form. Dr. McNulty will then perform a detailed history and physical exam and review the subject's vital sign data. Ms. Lessin will then schedule the clinical study visit # 2 in 2 to 6 weeks.

General Approach to Minimize Risk:

We plan to study only young and healthy subjects with a good airway, at very low risk for an anesthetic complication. Clinical trials have demonstrated the safety of managing hospitalized patients with mild to moderate permissive hypercapnia, as long as hypoxemia is avoided (12). Subjects will be studied in a hospital clinical environment containing an anesthesia machine, vital sign monitors and routine emergency equipment, medication and supplies. Dr. McNulty will use TJUH standard of care operating procedures and other well-accepted safety strategies to minimize risk. Supplemental oxygen will be continuously delivered via face mask to significantly minimize the risk of hypoxemia during fentanyl induced hypoventilation.

We will use estimated maximum plasma concentrations of fentanyl up to 5.8 ng/mL. Studies on the respiratory depressive effect of fentanyl using similar incremental concentrations of fentanyl have been safely conducted (8, 10). Respiratory depression typically occurs anywhere in the 1.0 – 6.0 ng/mL (7) plasma concentration range while loss of consciousness does not occur until 34 ± 7 ng/ml (7). If respiratory depression needs to be reversed during the study, it can be rapidly reversed using one or more doses of IV naloxone.

Specific Procedures and Risks:

1. Radial artery catheterization: The radial artery will be catheterized using aseptic techniques after local anesthesia. A 5-cm 20-gauge catheter will be inserted using ultrasound guidance to minimize the potential need for multiple sticks, bleeding or hematoma. The anesthesiologist Dr. McNulty has vast experience placing catheters in a radial artery. Rare risks associated with radial artery catheter insertion and use are thrombus formation, hand ischemia, and infection. These complications are rare in healthy subjects without vascular disease who have catheters in place for only several hours (13).
2. Insertion of intravenous catheter: The insertion of an intravenous catheter for the infusion of fentanyl will be performed using local anesthesia and aseptic technique. The risks of an IV-line may include pain at the insertion site and superficial infection as well as local bruising. These risks are reduced by using local anesthesia and aseptic techniques.

3. Fentanyl infusion: Fentanyl has been used in clinical anesthesiology as an opioid analgesic for over 50 years. Possible side effects of acute fentanyl exposure include bradycardia, nausea, respiratory depression, and rarely chest wall rigidity. Before the start of the fentanyl infusion protocol subjects will be given Ondansetron to minimize the risk of nausea. Atropine or Robinol may be given to prevent/treat bradycardia. Chest wall rigidity is a rare occurrence at the fentanyl concentrations and slow infusion we are proposing, but can be reversed quickly with either naloxone or a short-acting neuromuscular blocking agent.

The aim of the present protocol is to induce mild to moderate respiratory depression up to the described endpoint of two consecutive PaCO2 measurements ≥ 60 mmHg. The fentanyl infusion will be stopped if: (1) the partial pressure of carbon dioxide exceeds 60 mm Hg in two consecutive blood gas measurements (primary end-point), (2) the subject requires positive pressure bag/mask assisted ventilation by the anesthesiologist, or (3) the hemoglobin oxygen saturation falls below 90% on supplemental oxygen (FIO2 = 1.0), (4) one blood gas of PaCO2 > 70 mmHg, and/or (5) two consecutive blood gas measurements with pH < 7.20.

Potential Benefits of Proposed Research to Human Subjects & Others- Risk/Benefit Ratio:

The risks of a slow intravenous infusion of fentanyl to induce hypoventilation managed by an experienced anesthesiologist are low. We do not anticipate any benefits of participating in this study to the human volunteer subjects. The benefit of developing an algorithm capable of detecting and preventing severe hypoventilation, hypoxemia and death due to an opioid overdose is significant. The clinical investigative team has a variety of systems and procedures in place to maximize subject safety. In the United States opioid related overdose is currently a leading cause of death in people aged <50 years (1). An accurate tool to alert first responders or family and friends in the case of an impending overdose would have significant societal impact and would potentially prevent a significant number of deaths by allowing for the timely administration of naloxone. In the hospital setting there is also a need for a continuous monitor of minute ventilation (MV = RR x TV) to improve the safety of opioid analgesia (5).

H. Data and Safety Monitoring Plan

Medical Monitor: Dr. Dietrich Gravenstein will serve as medical monitor. A medical monitor is a physician that is independent of the research team. Dr. Gravenstein has extensive educational and professional experience to serve as a subject advocate. He will monitor subject enrollment and will discuss research progress with the Principal Investigator. He is also required to review all unanticipated problems involving risk to subjects or others, serious adverse events and any subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the Principal Investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the Western IRB.

The medical monitor will also monitor any protocol deviations and/or protocol violations. He will promptly report any discrepancies or problems to the IRB. The medical monitor also has the authority

to stop the research in progress, remove individual subjects from the research, and take whatever steps are necessary to protect the safety and well-being of the subjects until the IRB can assess the monitor's report.

The Principal Investigator, Dr. Stephen McNulty, will be responsible for accuracy and confidentiality of written and electronic participant data. Accuracy of the data will be confirmed by Dr. Stephen McNulty and the monitor before the study data set is locked and before the research is published in a peer reviewed journal.

I. Literature Cited

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Attachment 1: Drug Abuse Screening Test

Attachment 2: Recruitment poster

Attachment 3: Screening script

Attachment 4: CV Stephen McNulty, DO

Attachment 5: Medical License Stephen McNulty, DO

Substance Abuse Screening Instrument (O4/05)

The Drug Abuse Screening Test (DAST) was developed in 1982 and is still an excellent screening tool. It is a 28-item self-report scale that consists of items that parallel those of the Michigan Alcoholism Screening Test (MAST). The DAST has "exhibited valid psychometric properties" and has been found to be "a sensitive screening instrument for the abuse of drugs other than alcohol.

The Drug Abuse Screening Test (DAST)

Directions: The following questions concern information about your involvement with drugs. Drug abuse refers to (1) the use of prescribed or "over-the-counter" drugs in excess of the directions, and (2) any non-medical use of drugs. Consider the past year (12 months) and carefully read each statement. Then decide whether your answer is YES or NO and check the appropriate space. Please be sure to answer every question.

		YES	NO
1.	Have you used drugs other than those required for medical reasons?	___	___
2.	Have you abused prescription drugs?	___	___
3.	Do you abuse more than one drug at a time?	___	___
4.	Can you get through the week without using drugs (other than those required for medical reasons)?	___	___
5.	Are you always able to stop using drugs when you want to?	___	___
6.	Do you abuse drugs on a continuous basis?	___	___
7.	Do you try to limit your drug use to certain situations?	___	___
8.	Have you had "blackouts" or "flashbacks" as a result of drug use?	___	___
9.	Do you ever feel bad about your drug abuse?	___	___
10.	Does your spouse (or parents) ever complain about your involvement with drugs?	___	___
11.	Do your friends or relatives know or suspect you abuse drugs?	___	___
12.	Has drug abuse ever created problems between you and your spouse?	___	___
13.	Has any family member ever sought help for problems related to your drug use?	___	___
14.	Have you ever lost friends because of your use of drugs?	___	___
15.	Have you ever neglected your family or missed work because of your use of drugs?	___	___
16.	Have you ever been in trouble at work because of drug abuse?	___	___
17.	Have you ever lost a job because of drug abuse?	___	___
18.	Have you gotten into fights when under the influence of drugs?	___	___
19.	Have you ever been arrested because of unusual behavior while under the influence of drugs?	___	___
20.	Have you ever been arrested for driving while under the influence of drugs?	___	___
21.	Have you engaged in illegal activities in order to obtain drug?	___	___
22.	Have you ever been arrested for possession of illegal drugs?	___	___
23.	Have you ever experienced withdrawal symptoms as a result of heavy drug intake?	___	___
24.	Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)?	___	___
25.	Have you ever gone to anyone for help for a drug problem?	___	___
26.	Have you ever been in a hospital for medical problems related to your drug use?	___	___
27.	Have you ever been involved in a treatment program specifically related to drug use?	___	___
28.	Have you been treated as an outpatient for problems related to drug abuse?	___	___

Scoring and interpretation: A score of "1" is given for each YES response, except for items 4,5, and 7, for which a NO response is given a score of "1." Based on data from a heterogeneous psychiatric patient population, cutoff scores of 6 through 11 are considered to be optimal for screening for substance use disorders. Using a cutoff score of 6 has been found to provide excellent sensitivity for identifying patients with substance use disorders as well as satisfactory specificity (i.e., identification of patients who do not have substance use disorders). Using a cutoff score of <11 somewhat reduces the sensitivity for identifying patients with substance use disorders, but more accurately identifies the patients who do not have a substance use disorders. Over 12 is definitely a substance abuse problem. In a heterogeneous psychiatric patient population, most items have been shown to correlate at least moderately well with the total scale scores. The items that correlate poorly with the total scale scores appear to be items 4,7,16,20, and 22.

Monitoring the breathing effects of medication

Research Study

The Thomas Jefferson University Department of Anesthesiology is looking for healthy volunteers to participate in a research study

QUALIFIED PARTICIPANTS MUST:

- Not be pregnant or planning to become pregnant
- Be between 18 -40 years
- Have never had a drug or alcohol abuse disorder
- Have not been smoking during the previous 6 months
- Have a BMI <30
- Not have any cardiovascular, pulmonary, renal, nervous system, metabolic or immune disease

QUALIFIED PARTICIPANTS RECEIVE:

- $300 compensation for time and travel
- Study-related care and exams from a board-certified physician

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TELEPHONE SCRIPT

Introduction

Thank you for calling to find out more about our research study *or*
I am returning your call to provide more information about our research study.

My name is Jennifer Lessin, and I am a research coordinator at Thomas Jefferson University. The purpose of our research study, 'Development of an algorithm that predicts hypoventilation due to an opioid overdose', is to look at a new method of monitoring breathing changes. Specifically, we want to determine whether it is possible to monitor the changes in breathing from opioid narcotics by using a small microphone that is taped to the outside of someone's windpipe.

The research study consists of two visits. During the first visit we will be asking people to complete a questionnaire to determine their risk for substance abuse. We will also collect a sample of urine to determine if they have recently used illegal drugs or if you are pregnant. We will then perform a detailed history and physical exam and review their vital signs (such as blood pressure and heart rate). If we encounter no reasons that prevent participating in this research study, a clinical study visit will be scheduled within four weeks from the initial visit.

Participants will be required to refrain from eating after 11 pm the day prior to the study. On the day of the study, participants will arrive at Thomas Jefferson University Hospital around 7 am. We will obtain another urine sample from them to determine if they have recently used any illegal drugs or if you are pregnant.

The clinical study will take place in a hospital clinical environment containing an anesthesia machine and hospital vital sign monitors. A microphone will be adhered to the skin of the neck of the participant with double-sided tape to record the sounds of breathing. An intravenous catheter will be placed in a hand or arm vein to enable the administration of the opioid medication. We will also place a similar plastic catheter into an artery of the wrist to enable continuous measurement of blood pressure throughout the study. This artery catheter will also be used to frequently draw blood samples for measuring the concentration of oxygen and carbon dioxide. Over 3 hours we will gradually increase the intravenous infusion dosage of the opioid medication fentanyl. This will cause the participant's breathing to become slower and shallower. A board-certified Anesthesiologist will closely monitor the stability of the participants health throughout the opioid infusion. The fentanyl infusion will be stopped when their breathing has become slow and shallow enough to raise the concentration of carbon dioxide in the blood a moderate degree. After stopping the infusion of fentanyl, we will monitor the stability of the participant's health until the effects of the opioid have worn off. We expect that the entire study day # 2 will take around 9 hours. Participants will need to have an adult friend/family member available to take them home after completion of the study. Research staff will call the participant around 9 pm that evening and 5 to 7 days later to ask them how they are doing.

Do you have any questions regarding the study? Now that you have a basic understanding of the study, do you think you might be interested in participating?

If No: Thank you very much for calling.[end call]

If caller is interested

But before enrolling people in this study, we need to determine if you may be eligible to participate. I would now like to ask you a series of questions about your current and past health. It will take approximately 15 minutes of your time.

There is a possibility that some of these questions may make you uncomfortable or distressed; if so, please let me know. You can skip questions you do not wish to answer.

I will keep all the information I receive from you by phone, including your name and any other identifying information confidential.

The purpose of these questions is to determine whether you may be eligible to participate in the study. Additional screening at a later time during a visit to the hospital will be necessary beyond answering these questions. Remember, your participation is voluntary; you do not have to complete these questions. Please feel free to stop me at any time if you have any questions or concerns.

Do I have your permission to ask you these questions?

Screening Questions

What is your gender?

If female, are you pregnant or planning to become pregnant?

What is your age?

How much do you weigh?

How tall are you?

Have you smoked cigarettes in the past 6 months?

Have you ever had a drug abuse problem?

Have you ever had an alcohol abuse problem?

Do you have any type of disease?

Have you ever had any type of disease?

Have you ever had surgery?

Do you take any medications?

Do you have sleep apnea?

Have you ever been told that there were difficulties with anesthesia for a surgery that you had? Or that it was difficult to maintain your breathing during anesthesia for surgery?

Do you have a skin allergy to tape?

Do you have a skin allergy to silicone?

Do you have an allergy to opioid pain medications?

Do you have an allergy to fentanyl?

Do you have an allergy to skin disinfectants?

Post Response Communication

If potentially eligible:

Based on your answers to the questions, it appears you may eligible to participate in the research study.

Would you like to schedule a time to meet with the research team to obtain more details about the research study and to assess whether you are definitely eligible to participate or not?

In addition, would you like me to send you information to review before the meeting?

Obtain the potential subject's contact information

If not eligible:

Unfortunately, based on your responses, you are not eligible to participate in the research study.

Study Team Contact Information

Thank you for taking the time to talk with me today. If you have any questions or concerns, please feel free to contact me. My name is Jennifer Lessin and I can be reached at 215 955-5804 and/or Jennifer.Lessin@jefferson.edu.