Protection of Human Subjects

Risks to Human Subjects

Human Subjects Involvement, Characteristics and Design

Under our original study (protocol number 647002) for detecting patient-ventilator asynchrony (PVA), we have collected a dataset of ventilator waveform data for 502 patients who were receiving mechanical ventilation (MV) in the intensive care unit (ICU). One of the most clinically important types of pathologic patient-ventilator interactions (PPVI) is PVA, a frequently occurring phenomenon in mechanically ventilated patients, identified in between 10 and 63.5% of patients.(81,82) PVA is a general term encompassing a number of PPVI sub-types including but not limited to ineffective patient triggering of a ventilator-delivered breath (patient attempts to breath but does not receive a breath from the ventilator), double triggering (two breaths delivered in rapid sequence without exhalation in between), flow asynchrony (ventilator delivers inspiratory flow slower than patient's flow demand), and delayed breath termination (patient attempts to exhale before the ventilator will allow exhalation).(83,84) PVA has been associated with prolonged time on mechanical ventilation, subjective dyspnea, increased work of breathing, and increased use of sedative medications. The gold standard for assessing PVA requires invasive monitoring through either an esophageal balloon measuring intrathoracic chest pressure or chest electromyography.(81) Clinically, these modalities are rarely utilized due to their invasive nature.

To explore new non-invasive modalities of detecting PVA we utilized Raspberry Pi (RPi) microcomputers attached to mechanical ventilators to perform data acquisition of ventilator waveform data (VWD). VWD was then aggregated onto a central server and used for development of PVA detection algorithms. These PVA detection algorithms focused on two types of asynchrony thought to result in volutrauma, double trigger asynchrony (DTA) and breath stacking asynchrony (BSA). With further work in the future, the development of novel data acquisition, storage, and analytic platforms optimized for patient-derived VWD will dramatically improve the scientific understanding of patient-ventilator interactions, and will ensure that patients realize only the beneficial effects of MV.

In our study, we will prospectively identify a cohort of adult subjects age >/=18 who are receiving mechanical ventilation in either the emergency department (ED) or ICU and who are expected to require mechanical ventilation for >/= 24 hours (based on the judgment of the primary physician caring for the patient). Mechanical ventilator data will be continuously collected using the usual data export capabilities of the mechanical ventilator for the duration of use of mechanical ventilation. Data exported from the ventilators will be transferred wirelessly to a secure server using a commercially available USB-based storage drive that connects to a data export terminal on the back of the ventilator designed for this purpose to allow for unobtrusive data collection. Data representing only pressure, flow, and time, are exported in the form of special characters according to the American Standard Code of Information Interchange (ASCII) and do not contain any PHI/PII. The wireless data storage drive lacks a screen or other graphical user interface and neither the acquired data nor products of analysis will be available to treating clinicians.

Sources of Materials

We collect data from mechanical ventilators by directly linking a RPi device to it. In this study we only use one mechanical ventilator, the Puritan Bennet Model 840 (PB-840) (Covidien Ltd.; Dublin, Republic of Ireland) due to its ability to return VWD to attached devices without additional licensing fees or attachment of costly equipment. The RPi's are able to link directly to ventilator using an RS-232 DB-9 to USB null modem adapter. We wrote specifically designed software in Python for capturing VWD that only requires connecting the serial port of the ventilator to the RPi's USB port using the DB-9 to USB adapter, and input of the power supply to the RPi. Once connected, our software automatically begins passive collection of VWD from the ventilator.

PB-840 VWD records air flow, pressure, and "BS" (breath start) and "BE" (breath end) tokens to describe when a breath has started and ended. Sequential files ≤ 2 hours length are stored locally on the RPi and are backed up automatically every hour to minimize data loss in the event of hardware failure.

Potential Risks

There is no additional risk involved to the patient beyond the standard risk inherent in a retrospective analysis derived from reviewing protected health information (PHI) and personally identifiable information (PII) in the electronic health record (EHR). VWD does not contain PHI/PII and cannot be used to re-identify subjects. The treating physicians and staff will have no access to the information we collect, therefore our study will not influence the care received by the patient.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Patients will be recruited after discussion with the primary team of the respective intensive care service (this would include medical, surgical, burn, cardiothoracic, neurologic intensive care units as well as the emergency room).

Informed consent will be obtained from the patient (or their surrogate) either in person or via telephone. The overwhelming majority of patients requiring mechanical ventilation are unable to give written consent due to sedation/analgesia and the manifestations of their underlying disease. For that reason, the majority of contact will be with surrogate decision makers, who are often very hard to locate as they are not reliably at the bedside and frequently do not have access to fax machines/scanners. Given our limited staff to contact surrogates in person, we are thus requesting waiver of written consent so that we can contact surrogates by phone.

We will collect non-PHI, coded waveform data and securely store it as listed above for a 72-hour period from the time of screening while obtaining consent. No PHI will be collected during this time period. In the event that he surrogate cannot be found or consent is not granted, all information will be deleted. We hypothesize the largest effect of PVA on clinical outcomes will be early after the initiation of mechanical ventilation. As it frequently requires several days to identify a suitable surrogate in the ICU environment, this 72 hour grace period is necessary to avoid systematically excluding patients from study who are early in the course of mechanical ventilation or who suffer early death. This grace period will prevent systematic bias in the study and allow generalizability of results to real world patient populations.

Subjects will be assessed on their abilities to understand and to express a reasoned choice concerning:

- the nature of the research and the information relevant to his/her participation;
- consequences of participation for the subject's own situation, especially concerning the subject's health condition; and
- consequences of the alternatives to participation

If all three criteria cannot be met, the patient will be judged as not having capacity and a surrogate will be approached.

Identification of the surrogate will be performed in accordance with the UCOP Guidance on Surrogate Consent for Research and will be consistent with the intent of the Common Rule (45 CFR 46, Subpart A) and all other federal and state laws and regulations pertaining to protecting human subjects participating in research.

Process for obtaining consent in person:
Subjects and their surrogates who are able and willing to travel to the UCDMC will be approached for consent. The subject will be given ample time to review the consent and ask questions about the study. If the subject or their surrogate are interested in enrolling, a signature will be obtained in person after a designated study staff person has reviewed the entire consent document with the subject and the subject has had all of his/her questions answered. The subject will be given a copy of the signed consent document.

Process for obtaining consent by telephone:
A study staff person will contact the surrogate (obtained via the patient demographics in the electronic medical record). The study staff person will review the entire consent with the subject over the telephone and the subject will be encouraged to ask any questions he/she may have about the trial and informed of risks and alternatives. If the subject is interested in enrolling, a study staff person will document the name, date, and decision in a telephone encounter in the electronic medical record. This note will then be printed and kept in a physical registry of all enrolled patients, which will be kept in a locked office by the primary investigator.

HIPAA Authorization for Research form will be discussed at the time of consent and documented in the aforementioned EMR telephone encounter.

Protections Against Risk

The review of subjects' medical records is for limited information. The data are derived from clinically indicated procedures. There is an extremely low probability of harm to the subjects' status, employment, or insurability. The precaution taken to limit record review to specified data and coding of the data further minimize the major risk, which is breach of confidentiality.

The clinically indicated procedures/care were already completed, or would be completed, regardless of the research. None of the results of the research would affect the clinical decisions about the individuals because the results are not factored into clinical care decisions. Subjects are not deprived of clinical care to which they would normally be entitled.

The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.

Potential Benefits of the Proposed Research to Human Subjects and Others

There is no direct benefit to the patient from enrollment in the study.

Importance of Knowledge to be Gained

While mechanical ventilators can be life-saving, they can also injure the lung and cause substantial patient distress when ventilator settings are not synchronized with patient respiratory drive, a phenomenon known as patient-ventilator asynchrony (PVA). PVA has been linked to increased work or breathing, patient discomfort, increased sedation requirements, and in a small study, increased mortality.(84,85) Like many other physiologically injurious events, immediate detection of PVA is possible via bedside examination, but rapid detection can be delayed for various reasons.(86) Automated detection of PVA would have benefit of reducing cognitive burden on providers and allow them to be automatically alerted the instant PVA occurs. This could have benefits for improving patient comfort and may even improve patient outcomes.

Using VWD we can also perform a variety of analyses that may have been impossible before. There are unanswered questions of which ventilator mode causes more asynchrony and it would be possible to also perform larger epidemiologic studies to determine if incidence of PVA leads to adverse outcomes for patients. In our current proposal we are also investigating whether VWD can be used to detect incidence of ARDS. Successful completion of this proposal will yield insight into additional diagnostic and predictive mechanisms for ARDS, which could have benefit for reducing the mortality of ARDS by diagnosing it more rapidly when it manifests, or by helping providers responsively deliver necessary treatment for ARDS before the disease worsens. This could have future benefit for reducing ARDS mortality rates by enabling more rapid ARDS diagnoses and prevention of the disease from progressing to more advanced stages.