Evaluating wearable smart sensors for continuous measurement of vital signs in ICU patients

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1. Background and Significance

In the intensive care units (ICUs), there is continuous monitoring of vital signs and patient physiology to detect developing instability and identify need for intervention. Despite significant advances in ICU monitoring and patient care, patients are still at high risk for cardiorespiratory compromise, which is associated with both acute and long-term consequences. Thus, a major ICU focus is utilizing these hemodynamic signals to identify when such risks will arise and provide timely intervention to maintain cardiovascular function and organ perfusion to avert secondary injury. To this end, real-time, continuous physiologic measures of these hemodynamic signals are crucial in the ICU.

A current limitation of monitoring in the ICU is the lack of methods for continuous, non-invasive capture of blood pressure (BP). In critically ill patients, clinicians rely on intra-arterial BP monitoring (IA-BP), whereby a catheter is inserted into the umbilical or other central or peripheral artery to provide continuous BP measurements. However, IA-BP procedures are invasive and lead to complications, thereby escalating risks of infection, bleeding, and thrombosis, increasing discomfort, and reducing contact. Thus IA-BP is only utilized in the most critically ill patients and is typically discontinued within 1 week. In the rest of the ICU population, only periodic cuff-based BP (CB-BP) measurements are obtained. CB-BP recordings are captured periodically, can be difficult to obtain, are disruptive, especially during sleep, and are highly unreliable. The lack of real-time and continuous monitoring of hemodynamic signals impairs the clinical team's ability to detect and promptly respond to acute risks of decompensation, as well as obscuring longer-term patterns which may be sensitive markers of developing instability.

The purpose of this study is to develop biocompatible electronic devices that will allow continuous, non-invasive hemodynamic measurements in the ICU (see sample figure 1 below). Members of this research team have developed innovative, wireless devices capable of being

Figure 1: Example of wearable sensor developed by the Roger's group

comfortably and continuously worn while recording diverse physiologic measurements. These devices have already demonstrated the capability to accurately capture hemodynamic measurements in healthy adult subjects (unpublished data, see figure 2 below). We propose to 1)

optimize these devices for use in pediatric ICU patients, 2) demonstrate safety, reliability, and accuracy of these devices for continuous ICU hemodynamic signal measurements, including but not limited to BP, heart rate (HR), cerebral blood flow, temperature, and respiratory rate, and 3) demonstrate these devices are preferred by patients and parents to current measurement tools. Once validated, such sensors could fundamentally change the way patients are monitored in the ICU, eliminating risks associated with invasive monitoring, allowing continuous, real-time detection of clinically meaningful changes in ICU patients, advancing knowledge of hemodynamic signatures preceding clinically meaningful events, and ultimately offering opportunity to reduce morbidity and mortality in ICU patients.

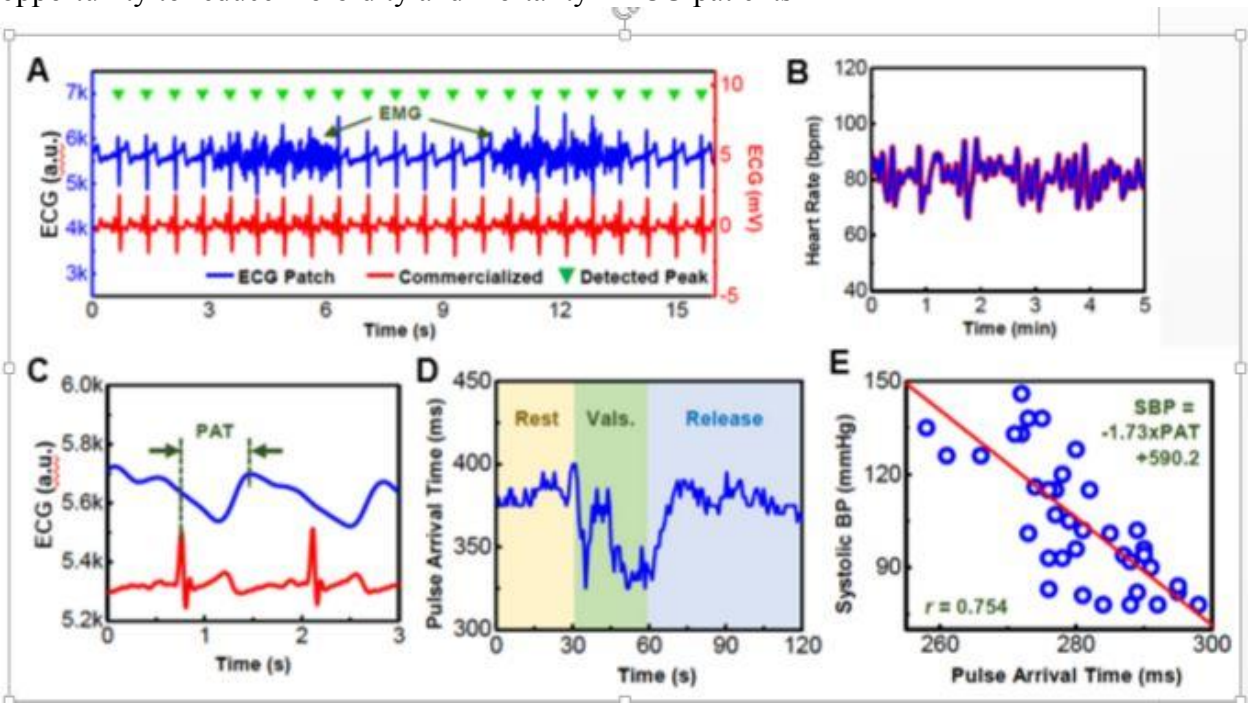

Figure 2: Example of physiology measurements using wearable sensor.(A) ECG time waveforms for commercial cardiac monitoring device(red)and wearable sensor(blue). (B) Snapshot of average heart rate vs time using conventional ECG sensor (control) and wearable sensor in newborn. (C) Snapshot of oxygen saturation vs time using wearable sensor and standard oximetry sensor (control) in newborn. (D) PPG (blue) and ECG (red) waveforms captured simultaneously and synchronized in time in healthy adult subject. Pulse arrival time (PAT) interval denoted in the waveform. (E) Pulse arrival time measurements during rest, Valsalva maneuver and release in adult subject. (F) Correlation of systolic blood pressure (measured with cuff-based BP device) and PAT measured with wearable sensor in adult subject.

2. Study Hypothesis and Outcomes

2.1. Study Hypothesis

The main hypothesis of this study is that the wearable sensors will provide accurate, reliable, safe, and continuous capture of hemodynamic and physiologic signals in children, infants, and neonates.

2.2. Outcome Measures

2.2.1. Primary Outcome

Primary outcome measures: Recorded measurements of BP as compared to the ICU standard of care monitoring, including both arterial line measurements and cuff-based measurements of the arm.

2.2.2. Secondary Outcomes

Secondary outcome measures: Recorded measurements of other physiologic signals such as HR, pain, temperature, cerebral blood flow, aEEG-like waveforms, and respiratory rate as compared to ICU standard of care monitoring. Accelerometry will be captured using these devices, and in a subset of study participants, will be compared to video recordings to validate the accuracy of these devices for detecting body position and movement (as these are known to affect BP measurement). Devices may also evaluate subjects' respiratory equipment. Questionnaire data examining parent opinions on use of wearable sensors compared to standard of care devices.

3. Study Design

3.1. Target Population

Two distinct populations will be targeted for participation in this study. The first includes patients admitted to intensive care units (ICUs) including the pediatric intensive care unit (PICU), the neonatal intensive care unit (NICU), and the cardiac intensive care unit (CCU). This includes all ICUs at the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's) and the NICU at Prentice Women's Hospital (Prentice). The first target population will contribute primarily to the collection and validation of physiologic signals including BP, HR, pain, temperature, cerebral blood flow, aEEG-like waveforms, and respiratory rate. The second target population includes any neonate, infant, or child whose parent or guardian consents to a one time visit to the Center for Autonomic Medicine in Pediatrics (CAMP) at Lurie Children's. The second population will be more physically active than the ICU population and contribute primarily to the capture and validation of these same physiologic signals in the context of increased motion, which is known to produce artifact in such recordings. The wearable sensors must be tested in a range of patients across age groups in order to validate the signals and data recorded by the devices. This requires the inclusion of patients of various ages, including neonates, infants, and children.
Up to 500 patients will be enrolled at Lurie Children's and Prentice.

3.2. Eligibility Criteria

3.2.1. Inclusion Criteria

Participants must be admitted to one of the three ICUs at Lurie Children's, admitted to the NICU at Prentice, or visiting CAMP with a parent or guardian. Anyone who satisfies one of these criteria and is under 18 years of age can participate.

3.2.2. Exclusion Criteria

Anyone with a skin abnormality that would potentially increase risk of device use will be excluded. Anyone 18 years or older will be excluded. In the ICU population, any patient or family determined by an attending physician or bedside care team to be too unstable (patient) or experiencing too much stress (family) will not be approached for recruitment.

3.3. Screening and consent

All ICU patients will be screened by the study team based on inclusion and exclusion criteria through review of electronic medical records. For screening at Prentice Women's Hospital, screening criteria will be automatically applied through the use of the electronic data warehouse, and information from infants meeting this screening criteria will be transferred to the study team through electronic data warehouse. A screening and enrollment log will be kept to track ICU patients/parents who have been approached and agreed or declined to participate in the study. The screening and enrollment log will be kept on the Northwestern University housed REDCap server. Only the study team will have access to this log. Non-ICU participants will be screened through question and answer with a parent or guardian.

3.4. Recruitment Methods

The population of ICU patients will be recruited by the study team as follows: once the study team has identified an eligible patient, the study team will obtain permission to approach the eligible patient from the nurse or attending, ensuring that the ICU care team has sufficient time to assess the condition of the patient and determine the family's approachability to discuss the study. If the family is felt to be approachable, the study staff will identify the best time to contact the family.
The population of non-ICU participants will be recruited by the study team using IRB-approved fliers distributed to affiliates of CAMP and posted in public locations in Chicago.

3.5. Informed Consent Process

All research staff will be trained on human subjects research education and good clinical practices, according to Lurie Children's IRB standards. A member of the study team will approach the prospective participant/family for consent using an IRB-approved consent form. Assent will be obtained from participants 12-17 years of age. If the prospective participant has a PCPC (Pediatric Cerebral Performance Category) score of ≥2 or has received sedative medications in the preceding 72 hours, assent will not be obtained. In the event that the participant is not capable of providing assent, a request for waiver of assent will be obtained from the IRB. If the cognitive capability of the participant changes during study participation and the participant is capable of providing assent, assent will be obtained within 48 hours.

In a private space, the study will be discussed in detail, including the rationale, the specifics of data collection, our legal and ethical obligations and procedures to ensure confidentiality, and the questionnaires. The study team will also discuss the risks of participation. The prospective participant/family will also be informed that involvement or refusal will not affect the care of their child, and will be completely optional and anonymous. The prospective participant/family will be informed that the video monitoring of body position and movement is an optional part of the study. Written material describing the nature of this study and a copy of the Informed Consent document will be provided to each family. The prospective participant/family will then be left with the consent form to review and will be given an opportunity for private discussion. They will have the opportunity to ask questions.

Once all questions are answered, the prospective participant/parents will be asked to discuss the study process in their own words before signing consent. To minimize the amount of time the study team spends in the participant's bed space, a participant's parent(s) may provide consent over the phone or a secure telecommunication platform such as Skype. The consent process as described above will not change. The family will be provided written materials describing the nature of the optional elements and given an opportunity for questions and private discussion.

Consent obtained over the phone or secure telecommunication platform will be obtained according to institutional policy. A member of the study team will explain in detail and review the informed consent document(s) with the parent(s). If the parent(s) agree to participation, they will sign a copy of the informed consent document(s) and the study team member obtaining consent will sign a copy at the same time. The parent(s) will be required to send their signed document(s) to the study team by mail, fax, or email, and the two signature pages will be combined. The parent(s) will be provided a copy of the fully executed, signed informed consent document(s) by mail, fax, or email prior to any study procedures.

For participants where a Waiver of Consent and/or HIPAA Authorization are used specifically for participants enrolled during COVID-19, the study team member approaching will review the entire consent form over the phone. In place of the signature, the study team member obtaining consent will ask the parents and/or adolescent about their interest to participate and get either a verbal consent (and/or assent) or refusal to participate.

If verbal consent and/or assent is obtained, the study team member obtaining permission will document that all the parts of the consent process were reviewed, and verbal consent was obtained on to the consent and/or assent with date and time, and sign attesting permission was obtained, and consent process was reviewed in the designated sections. A signed and completed copy of the consent and/or assent with the information stated above will be provided to the parents either via email or regular mail. The provided copy of the consent will not be returned in any form to the study team to ensure their safety.

3.6. Study Procedures

Device application: In both the ICU and non-ICU study populations, standard-of-care devices will be used in all subjects and this data will be compared to that collected using novel wearable sensors suggested in this study. After participants are consented, multiple wearable sensors (up to 5) will be placed on the participant for the duration of the study. Multiple devices are required to estimate BP. One or more devices will be placed on the chest or back, and one or more additional devices will be placed peripherally (e.g. leg, foot, arm, hand, head, or ear). One or more additional devices may be placed on the patient's respiratory support device if applicable. Placing multiple devices will allow determination of which location provides the best signals in specific populations. These devices will be placed using a medical grade skin adhesive similar to the ones used in the ICUs, which will minimize the

risk of skin irritation or allergic reaction. Alternatively, we are currently testing a "soft wrap-around device" (similar to that currently used for blood pressure monitoring in the premature babies) with a sensor. The soft wrap-around device is composed of hypoallergenic cotton. Overlying this cotton, and not touching the subject's skin, may include Coban wraps, paper tape, or a Velcro adhesion mechanism. Given the very small size of premature infant in the NICU, we may incorporate this new technology as needed in the NICU. In the ICU population, devices will be left in place for up to 72 hours, but will either be checked by the study or clinical team to ensure skin integrity and signal quality at least once every 24 hours. In the non-ICU population, devices will be left in place for up to 3 hours during a study visit to CAMP.

We have recently upgraded a new firmware version activating the ability for the sensor to continuously measure bioimpedance for respiratory rate. This function does not require any modification to the physical device itself or the adhesive. However, the bioimpedance functionality does require delivery of low amplitude sinusoidal current through the electrodes of the chest unit. The frequency of the current is 4 kHz – a frequency range used typically for human bioimpedance measurements by FDA cleared systems. The maximum current delivered is 8 μA. These parameters are below commonly used body fat percentage impedance analyzers that are widely commercially available. Furthermore, bioimpedance is standard measurements in existing NICUs / PICUs/CICUs leveraging the ECG electrodes that are then displayed on standard of care monitors. Commercially bioimpedance devices that are FDA approved inject currents that are 10x greater than our system (e.g. the CoVa Monitoring System 2 for continuous wearable sensing of thoracic impedance). Finally, the parameters in our sensor follow IEC 60601-1-2 guidelines for electromagnetic safety.

Video monitoring: In some participants, video monitoring of participant position and movement will be utilized during the study. This is an optional, additional part of the study in which families can choose to participate or not participate. If a family chooses to participate, a video camera will be utilized to capture participant movement and position for the duration of the study in the ICU or at CAMP.

Cuff-based blood pressure: While the wearable sensors are attached to participants in both the ICU and non-ICU populations, the participants will also be monitored with the normal standard of care monitoring montage. In addition, during one 3- or 4-hour period while the wearable sensors are attached to the patient, a member of the study team may take the participant's BP using the ICU standard cuff-based method every 15 minutes. Cuff-based measures typically happen every 15-60 minutes for standard clinical care, depending on the stability of the patient and physician discretion. In the ICU population, if a standard clinical cuff-based BP measure is taken during the 15-minute time epoch, the clinical measurements will be used rather than obtaining a separate research measurement. Outside of this 3- or 4-hour window and for the remainder of the study duration in the ICU cohort, cuff-based BP measures will be made only as frequently as needed for standard clinical care.

Skin temperature: While the wearable sensors are attached to the participant, skin temperatures will be taken using a standard infrared thermometer. These measurements will be made at the same interval as the above cuff-based BP, over the same 4-hour period by a member of the study team. Outside of this 4-hour window, no skin temperature measures will be made for research purposes.

Device data: Wearable sensors can stream data continuously using near field communication (NFC) or Bluetooth technology. An encrypted laptop, iPad, or similar device will be left in the patient room and used to capture the continuous data stream from the wearable sensor. Additionally, wearable sensors can include onboard memory, and physiologic streams may be recorded to this onboard memory until transfer to an encrypted laptop for analysis.
Standard of care data: In all participants where data from standard of care monitoring is captured and stored using the BedMasterEx system (all PICU and CCU beds, some NICU beds), and the Sickbay™ platform (CCU beds), this data will be used for comparison to data captured using EWP. In any participants where data are not captured and stored using the BedMasterEx system or Sickbay™ platform, video recordings will be made of the Phillips monitors using an encrypted mobile device. Within 48 hours, videos will be downloaded and transferred to a HIPAA secure server. In NICU patients without BedMasterEx data, the Somnostar system may be used to capture data for up to 4 hours of the study. All study data will be stored on an encrypted laptop and/or secure network for analysis. We will continue to follow patients for 5 years by collecting standard of care data entered into their electronic medical record.
Skin Integrity: Before and after wearable sensors are placed on the participant, the participant's skin integrity will be monitored using the ICU standard protocol, either the Braden Q scale (≥6 months of age) and/or Neonatal Skin Risk Assessment Scale (NSRAS; <6 months of age). Additionally, a validated skin integrity scale will be used to score participants' skin condition at sensor placement site before sensor placement and immediately after sensor removal. At both of these time points, photographs may be taken of the participants' skin at the site of sensor placement to document any skin changes that occur during the period of wearable sensor wear. No faces will be photographed. One or more additional skin scores and photographs may be performed/taken between 30 minutes and 48 hours after sensor removal, as deemed necessary by the study and/or clinical team. The study team will consult the ICU bedside care team or CAMP clinical team within 1 hour for any concerning changes in skin integrity.
Questionnaires: After the study period ends, the parents may be approached to complete the questionnaires. These questionnaires will take less than 10 minutes to complete and are meant to assess opinions on use of these devices in the ICUs. These questionnaires will be completed using REDCap. If preferred, the family will complete a printed version of the REDCap questionnaire and this data will then be entered by study staff into the REDCap server. All questionnaire data will be stored on the secure REDCap server housed by Northwestern University.

3.7. Study Timeline

Study recruitment, data collection, and ongoing analysis: 1-30 months
Final analysis and report preparation: 6 months

4. Study Safety

4.1. Privacy Protections

The study team will take measures to protect the privacy and confidentiality of participants. The plan to protect patient privacy includes approaching and consenting participants in a private room. Study procedures will be done in the privacy of the patient rooms in the ICU.

Study participation discussions will be limited to members of the study staff and the involved participants.
Participant data will be coded with study identifier only. All data obtained from the bedside monitors will be stored on the Azure Cloud (maintained by Data Analytics Reporting (DAR) at Lurie Children's). All data obtained using wearable sensors will be stored on an encrypted laptop and secure network for later analysis. All questionnaire responses will be collected via Research Electronic Data Capture (REDCap) hosted by Northwestern University. When preferred, parents can fill in questionnaires on paper, and these will be transferred to REDCap by study staff after collection.
To minimize the risks, only the minimum data necessary to complete the study will be collected on each study participant.
Data to be collected include:

- Demographic data (age, gender, race, sex, gestational age (in participants <1 year of age, only))
- Body mass index, height, weight, and body surface area
- Diagnosis for admission to the ICU
- Medications during the study
- All skin integrity scores (either the Braden Q scale (≥6 months of age) and/or Neonatal Skin Risk Assessment Scale (NSRAS; <6 months of age) for 24 hours before, during, and 24 hours after the sensor study
- All pain scores (Face, Legs, Activity, Cry, Consolability scale (FLACC), State Behavioral Score (SBS), Neonatal Pain, Agitation and Sedation Scale (NPASS), Neonatal Facial Coding System (NFCS)
- Alarms/clinical events during the study
- Video monitoring of patient position and movement (optional)
- Data generated by the wearable sensors and standard of care monitoring devices which will include standard physiologic measurements such as BP, HR, blood oxygenation, cerebral blood flow, pain, temperature, movement, and respiratory rate

Photographs will be labeled only by study code, and will not include subject's face. Video may include the subject's face, but all videos will be scored for position and movement within 1 month of recording, and will be deleted after scoring. All photos and videos will be stored on a password protected server accessed by a password protected computer.
Only authorized personnel listed in the IRB application will have access to study data. The screening and enrollment log used contain the code link, and this file will be stored on the REDCap server and will have access limited to the study team. The link between the participants and their study identifier will be destroyed at the conclusion of this study, so all remaining data will be fully de-identified.

Data transferred to the study team by the NU electronic data warehouse for patients meeting screening criteria in the Prentice NICU will be downloaded onto the Lurie Children's Hospital server. This data file will be used for up to one week to allow the screening process to take place, then will be deleted.
Confidentiality will be maintained with all of the medical records of this study. Subject records will be kept in a locked cabinet, under the control of the Principal Investigator. The subject will also be assigned a code in the data sheets so that the records on the computer will be kept confidential.

Potential Risks

Data risks: The risks involved with this research are minimal and include loss of privacy and confidentiality. The safeguards in place for de-identifying and storing data should mitigate this risk. To minimize this risk, access to the data is restricted to the PI and key personnel on the research team. Data will be coded, stored without identifiers. Video data, which may include identifiable images, will be stored on an encrypted device only until position and scoring analysis take place, and will then be deleted. Data collected throughout this study will remain on the hospital network and the REDCap server, and be under the same safeguards in place for clinical data. Any data stored for future studies will be further de-identified, after study conclusion. Any data transferred off of the hospital network for statistical/data analysis will be fully de-identified before transfer.
The clinical data and data from the wearable sensors will be collected and stored to the secure Lurie Children's Hospital server that is subject to security and access protections within the hospital intranet, including firewall and password access protection restricted to the PIs, Co-Is and study coordinators. Data will be tied to participant codes without patient identifiers. The participant code key will be maintained separately under physical (locked office) and electronic (additional password) access controls and accessible only by the PI and research team.
Skin discomfort/irritation risks: There is a risk of discomfort or irritation from adhesives and wearable sensors. It is possible that this additional sensor may contribute to skin irritation or discomfort or that the additional handling required in placing these sensors may be temporarily disruptive for the participants. Study staff and/or the clinical team will check on the participants in the ICU at least once every 24 hours to monitor for signs of discomfort, irritation, or allergic reaction. Sites of sensor placement will be assessed clinically before, immediately after removal, and at one or more additional time points (as deemed necessary by clinical team) between 30 minutes and 48 hours after removal for skin alteration by a trained member of the research team using a validated skin integrity scale Photographs will be taken at baseline and after study; skin changes during the period of wearable sensor use or at subsequent time points will be documented photographically. If a reaction occurs, the sensor at the site will be discontinued, and the photograph will be reviewed by a member of the NICU/PICU/CICU clinical team for decision-making about management.
Photograph risks: No faces will be photographed. There is a possibility that subjects may be able to be identified from the photographs that will be taken for the study.
Video risks: Videos will be an optional part of the study, and may contain identifiable information. Videos will be stored on an encrypted device. Videos will be scored by a member of the research team for position and movement, and video will be deleted after scoring.

Survey risks: Some questions may make parents uncomfortable or upset. Participants do not have to answer these questions if they do not want to.

4.2. Discontinuation Criteria

A participant may be discontinued if the participant is unwilling or unable to tolerate the wearable sensors. Examples may include adverse reactions to the adhesive on the wearable sensors or a patient removing the wearable sensors. The bedside clinical team or family can also request discontinuation at any time. Families participating in the video monitoring can request discontinuation of the video monitoring aspect of this study at any time during the study.

4.3. Patient Withdrawal

Any participants withdrawn from the study will have the wearable sensors removed immediately. Any data collected prior to the withdrawal will remain a part of the study, and this data will be coded.

5. Statistical Analysis

5.1. Data Management and Quality Control

Clinical data will be obtained from the electronic health records for consented participants. Data will be extracted both manually and electronically from the electronic records. Data from the bedside monitors will be retrieved from the Azure cloud at Lurie Children's. The continuous data from the wearable sensors will be directly transmitted and stored on the network-encrypted laptop. Video data will be directly transmitted and stored on the same network-encrypted laptop Continuous data measurements will be cleaned and binned by the statistical/data analyst. The cuff-based measures will be assessed by the statistical/data analyst to ensure data quality and control. Questionnaire data will be stored on the REDCap server at Northwestern University.

5.2. Statistical Plan

Measurements made through clinical standard of care will be compared to the measurements recorded by the wearable sensors. Distribution checks for normality and data accuracy will be completed for each individual and for the entire study prior to all analyses. For continuous measures of physiology, 30 second epochs will be defined for each method for comparison. For non-continuous CB-BP measures, each measure will be matched and compared to the 30-second epoch during which the measure was captured. We will further check for time lags in the relationships between methods by applying peak-picking methods to lagged regression plots for all pairs of measures.

Agreement and correlation of wearable sensor measures to standard of care measures will be assessed in two ways. First, Bland–Altman plots will be created to assess agreement between each measurement system via bias and precision, which reflect the mean or average difference between two methods and the variation in these differences, respectively. Our second method consists of individual correlations between methods assessed for each person. This correlational method will supplement additional methods, and can be directly transformed to variance shared between wearable sensor and standard of care measures, a common metric of reliability of any measure.

Formal tests of bias, precision, and correlations: While the above methods will yield useful statistics, they need to be extended to deal with the structured nature of our data. Specifically, our data are clustered, meaning that we have multiple observations within each person and multiple people in our sample, which violates standard independence assumptions inherent to many models. We propose to estimate bias and correlation/reliability using multi-level models, which yield the same statistics discussed above but account for the fact that observations taken from the same patient are more related than comparisons involving different patients.

Statistical power: The large amount of within-person data provides incredibly high statistical power for all planned and many secondary data analyses, allowing this data set to answer all proposed questions. Previous work on power in multilevel models found greater than 99% power to detect associations with the planned observations suggested here within comparable nested designs.

6. References

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