Title: Comparison of Non-invasive and Invasive Blood Pressure Monitors

NCT04506775

Investigator Study Plan/Protocol

Date: July 3, 2023

INVESTIGATOR STUDY PLAN - REQUIRED

1. TITLE
Comparison of a standalone, continuous, non-invasive blood pressure monitor (cNIBP) to radial arterial catheterization in patients undergoing surgery.

2. EXTERNAL IRB REVIEW HISTORY*
Device reviewed and accepted by Tufts IRB.

3. PRIOR APPROVALS:
Prior approvals: Departments of Anesthesiology and Perioperative Medicine and Surgery

Conflict of Interest (COI): There are no individuals involved that have a financial interest related to this research.

Clinical Engineering Department*:*
This medical device will be inspected for safety, including grounding and minimal current leakage as necessary, prior to being placed in service. The Clinical Engineering Department Electrical Safety Inspection protocol shall be used as the inspection procedure. All measurements shall meet the NFPA 99, IEC 60601 healthcare standards for electrical safety.

We will notify the Clinical Engineering Department, at 508-334-1111 directly, or through the Materials Management Department, upon delivery of said equipment. The outside manufacturers/contractors are responsible for the quality and performance of all rented, leased, contracted, or equipment on evaluation.

Biohazardous Agents:
None

Radiation:
None

4. OBJECTIVES*
The purpose of this study is to compare noninvasive and continuous radial artery blood pressure (BP) measurements over a wide range obtained by the ViTrack (a cNIBP device developed by Dynocardia) to that obtained from invasive radial artery catheterization in patients undergoing surgery or those who are being cared for in the intensive care unit (See Figures 1 and 2). As a precaution because Intensive Care Unit patients are at a higher risk for compromised skin, subjects that are admitted to the ICU will not wear this device for more than four hours while in the ICU. The BP will range from very low to very high and at a minimum will include BP ranges defined by ANSI/AAMI SP10-1992 standards: Low (SBP: 90-129 mmHg; DBP: 40-79 mmHg); Medium (SBP: 130-160 mmHg; DBP: 80-100 mmHg); and High (SBP: 161-180 mmHg; high DBP- 101-130 mm Hg).

A minimum of 30 subjects will be recruited in groups of 5. An analysis of 255 time points per patient will be used to compare ViTrack with arterial line measurements. If the bias exceeds the standards, the algorithm will be further optimized. Subsequently, an additional 5 subjects will be recruited, and the same protocol will be applied so that the correction, if required, may be validated.

5. BACKGROUND*

Currently, there is no standalone, wearable, continuous, non-invasive, accurate BP monitor (cNIBP) available that does not require calibration.[1] Consequently, accurate hypertension diagnosis and management and assessment of 24-hr BP parameters and nocturnal BP have remained elusive.

In addition, there is a need for cNIBP measurement in hospitals, where accurate, continuous BP monitoring requires invasive intra-arterial catheters that lead to complications. In intensive care units and operating rooms, intermittent BP measurements with oscillometric, automatic upper arm cuff-based devices are the only option for non-invasive monitoring.

ViTrack is a wrist device that includes a camera, LED lights, small balloon and soft silicone membrane. The soft medical grade silicone membrane is in contact with the skin. The ViTrack is placed over the radial artery at the wrist with the help of a strap.

The ViTrack will be strapped to the right or left wrist making sure it is comfortable to the subject. A one-time calibration, which takes less than 2 mins, involves gradual increase and decrease of the balloon pressure at a rate standard for conventional BP measurement (4 mmHg/s). The ViTrack balloon is less than 10 cc and sits just over the radial artery. Uniqueness of this setup is the effective isolation of the primary measurement area over the radial artery from the rest of the area under the strap and eliminates the need for a complete cuff around the limb. This unique design enables use of the device on a limb without compromising the venous and lymphatic circulation, and flow in other arteries in the limb. Other clinical studies show that subjects hardly feel the inflation and deflation of the balloon and that the ViTrack is far more comfortable when compared to standard upper arm cuff devices.

During calibration, the optical sensor captures spatiotemporal skin force change as the pressure inside a pneumatic actuator increases and decreases to gently occlude and release the blood vessel. Based on ViTracks proprietary methodology, this force information enables a direct measure of both systolic and diastolic BP (SBP, DBP). After baselining, the optical sensor continuously tracks beat –to–beat SBP and DBP in an isolated small region of skin over the radial artery with minimal contact without the need for a pressure cuff.

The proposed study is the first to compare rigorously the ViTrack to intra-arterial continuous BP monitoring.

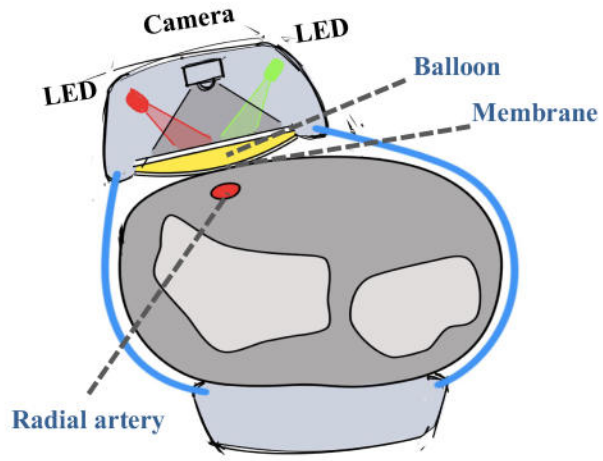

Figure 1. ViTrack components.

Figure 2: ViTrack attached to the wrist.

6. Inclusion and Exclusion Criteria*

Inclusion criteria:

a. Patients between the ages of 18 – 90 years age who are undergoing any surgery or in the intensive care unit and require intra-arterial catheterization for continuous BP measurement.
b. Patients having elective surgeries.
c. Patients having emergent surgeries, but only if research staff can have appropriate time to review study with patient and obtain signature on fact sheet prior to administration of medications that could affect coherency.
d. Patients who are able to review, verbalize understanding, and sign fact sheet and HIPAA authorization. If patient has a health care proxy (HCP) or legal guardian, study will be reviewed, and signature of HCP or legal guardian will be obtained.

Exclusion criteria:

a. Inability to obtain consent from the patient, HCP or legal guardian
b. Greater than 10% difference in BP measurements between both arms prior to surgery
c. Pregnant women
d. Prisoners
e. Inability to insert a radial artery catheter
f. Any other condition that would increase the risk of participation in the study in the opinion of the site Investigator
g. Upper extremity arteriovenous hemodialysis shunt
h. Upper extremity amputation
i. Surgical position/draping precludes access to the wrist.
j. Wrist distortion or pain from arthritis
k. Prior trauma or surgery at the radial artery monitoring site

7. STUDY-WIDE NUMBER OF SUBJECTS*

NA

8. STUDY-WIDE RECRUITMENT METHODS*

NA

9. STUDY TIMELINES*

a. The duration of an individual subject's participation in the study either in the operating room or intensive care unit will be approximately four hours.
b. The duration anticipated to enroll all study subjects is approximately 1 year.
c. The estimated date for the investigators to complete this study (complete primary analyses) is approximately 2 years.

10. STUDY ENDPOINTS*

a. The primary and secondary outcome measures: accuracy of ViTrack in measuring BP continuously as determined by use of Bland-Altman plots
b. Any primary or secondary safety endpoints: Observing for local skin irritation

11. PROCEDURES INVOLVED*

The ViTrack as outlined above will be utilized to obtain BP readings throughout the surgical procedure. This will allow us to compare BP readings between the non-invasive ViTrack device and the invasive intra-arterial catheters that are currently being used to obtain readings. The device will apply minimum force on wrist. This force will be similar to the forces applied by the fingers on the skin over the radial artery at the wrist while manually feeling the pulse.

Step by Step procedures:

1) A signed fact sheet and HIPAA authorization will be obtained prior to surgical visit.
2) Upon admission for surgical visit the patient will be prepped in the operating room.
3) A radial intra-arterial catheter will be placed on one wrist as standard of care.
4) The ViTrack BP measuring device will be placed on patient's other wrist.
5) Data will be simultaneously recorded from both the ViTrack and arterial catheter in opposite wrists.

Data collection from both the ViTrack and arterial catheter in opposite wrists will be zero-referenced to the external auditory meatus for supine patients. Both the invasive BP monitor and the ViTrack will produce an analogue output signal, the strength of which will relate to BP. When optimally calibrated the ViTrack's analog output signals should mirror that of the invasive arterial signals. To avoid discrepancies due to the internal software of the two devices, the analog signals will be sampled directly from both devices and the data will be processed through the same analog-to-digital converter and simultaneously recorded on the data-logging computer. Results and de-identified data will be securely shared with the sponsor utilizing data sharing methods below.

A member of the UMASS study team will be present to collect necessary study data; sponsor will not be present in the operating room. At the end of surgery, we will collect the device and inspect extremity on which ViTrack had been placed. We will assess environmental factors pertaining to the devices clinical use and utility as well as its comfortability, any irritations, if it caused any stress, and if the patient thinks the device could be worn for long periods of time.

Data to be collected: Age; gender; height; weight; wrist circumference of dominant arm; history of high BP, diabetes, high cholesterol and cardiovascular disease; and BP and heart rate (HR) measurements from the two devices. Once data is de-identified data will be shared with the sponsor.

12. DATA AND SPECIMEN BANKING*

NA- There is no specimen collection for this study. No data will be specifically banked for use in future studies, however fully de-identified study data will be shared among study collaborators and may be used to perform later data analysis

13. Data Analysis and Management*

A minimum of 255 data points will be selected by random computer generator from each patient's arterial line and ViTrack recordings. The analysis of 255 time points per patient will be used to compare ViTrack with arterial line measurements. For each sample data point, a "ten beat epoch average" will be calculated, i.e. four beats prior and six beats after (including the sample point itself) will be averaged. Differences in device readings will be calculated as ViTrack minus arterial line values. In addition, Bland Altman plots will be used to determine agreement between the two devices.[(2)] Our protocol will greatly exceed the AAMI guidelines by examining 255 paired measurements per patient for a minimum total of 5100 time points across 30 patients.

A sample size estimate was determined using the Bland-Altman method within MedCalc. Assuming an alpha error of 0.05, a beta error of 0.1, expected mean of differences of 5 mm Hg, expected standard deviation of 10 mm Hg, and maximum allowed differences between methods of 26 mm Hg, we calculated the minimum number of pairs to be 1570 which should be obtained with the number of subject we propose to study

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*
The ViTrack device is non-invasive and involves minimal risk to the patient. However, we will monitor skin integrity at the device placement site for skin irritation. There are no plans to form a data safety monitoring plan nor to perform an interim statistical analysis.

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*
Individual subjects may be withdrawn without their consent if while monitoring the device placement site more than minor skin irritation is noted or if surgeon or other members of the operating room team request device to be removed.

16. RISKS TO SUBJECTS*
There is a minimal risk for increased infection or skin irritation at the device placement site. There are no psychological, social, legal, or economic risks.

Infection control concerns: Existing research on laptop disinfection suggests that wiping down the laptop with a Sani-Cloth CHG 2% wipe will meet antimicrobial standards for the hospital setting and will not affect computer functionality or appearance.[3] The laptop will be cleaned with Sani-Cloth CHG 2% wipe before and after each use.

The ViTrack device consists of a white cuff which encircles the wrist and a blue plastic c-clamp that holds white cuff in place on the wrist (see Figures 1 and 2 on page 2). The white cuff is disposable. The blue plastic clamp will be cleaned with Sani-Cloth CHG 2% wipe before and after each use.

Risk of Confidentiality Breach: Efforts will be made to limit access to the subject's personal information, including research study information and medical records, to people who have a need to review this information. Dynocardia, the study sponsor, FDA, UMMS Institutional Review Board and other representatives of UMMS may need to review records of individual subjects. As a result, they may see a subject's name, but they are bound by rules of confidentiality not to reveal subject's identity to others or discuss study with others not involved with this research study. Sponsor may only see subject initials and study ID #. All other data will de-identified for review purposes.

References

1. Heard SO, Lisbon A, Toth I, Ramasubramanian R. An evaluation of a new continuous blood pressure monitoring system in critically ill patients. J Clin Anesth. 2000;12(7):509-18.
2. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.

3. Siegmund K, Hubner N, Heidecke CD, Brandenburg R, Rackow K, Benkhai H, et al. Are laptop ventilation-blowers a potential source of nosocomial infections for patients? GMS Krankenhhyg Interdiszip. 2010;5(2).

17. POTENTIAL DIRECT BENEFITS TO SUBJECTS*
Subject will not directly benefit from being in this research study.

18. VULNERABLE POPULATIONS*
NA. We will not be enrolling pregnant women, patients younger than 18 years of age or prisoners.

19. MULTI-SITE RESEARCH*
NA

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*
NA

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*
Subjects will not receive any study results.

22. SETTING
Fact sheet will be reviewed, and signature will be obtained in the pre-anesthesia clinic, hospital bed or the pre-surgical admission unit. The study itself will be performed in the operating room and/or the Intensive Care Unit. Data will be collected continuously by a laptop computer. After surgery, the password protected computer and device will be stored in the Clinical Science Wing of the Department of Anesthesiology and Perioperative Medicine in a locked cabinet in a locked office.

23. RESOURCES AVAILABLE

- Faculty and research personnel from the Department of Anesthesiology and Perioperative Medicine
- Principal investigator, co-investigators, statistician, research assistant, research coordinator and research nurse.

Principal Investigator:

This position requires advanced training in Anesthesiology and experience with research design and laboratory methods. The Principal Investigator (PI) Oversee the clinical research protocol, study staff and data analysis. PI is responsible for ensuring that all team members have current CITI training and that Good Clinical Practice is maintained throughout the study. Also ensures all study staff are appropriately trained for their respective roles, including knowledge of formed consent; and apply the ViTrack device.

Sub-Investigators:

This position requires advanced training in Anesthesiology and experience with research design and laboratory methods. Sub-Investigators may be responsible for consenting subjects, data analysis and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Statistician:

This position requires training in statistics. Statisticians may be responsible for data analysis and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Research Coordinator/Research Assistants:

Research coordinators and assistants are specialized research professionals working with and under the direction of the PI. They support, facilitate and coordinate the daily clinical trial activities and play a critical role in the conduct of the study. Other responsibilities include: maintaining records, handling IRB submissions, data management and performing any related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures

Research Nurse Coordinator:

This position requires a registered nurse with Basic Life Support certification (BLS). They are responsible for completing all Joint Commission required annual competencies to practice in the hospital. Research nurse may handle IRB submissions, oversee regulatory requirement, screen and consent subjects and perform any related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

A trained and experienced research assistant, research coordinator, research nurse or sub-investigator will perform various tasks required by the study at various time points. A trained and experienced research assistant, research coordinator, research nurse or sub-investigator will enter subject data in to the CRF, and perform regulatory functions required for the study.

Time that will be devoted to conduct and complete the research:

Adequate time has been allocated for enrollment, collection of subject data, history, demographics and data analysis. The PI, research staff and sub-investigators will work the necessary hours to complete the project.

Process to ensure that all persons assisting with the research are adequately informed about the protocol:

All research personnel that are involved in the protocol will be trained at the initiation visit. If they are unable to attend the initiation visit, the PI or a person they feel is appropriately knowledgeable will provide training including: the flow of the research study, procedures required by the protocol, the researcher's duties and functions. A signature log of all that

trained will be kept in the Regulatory Binder of the study. The binder is kept in a secure location with minimal access to unauthorized personnel (in the clinical research office). The clinical staff caring for the subject will be given information regarding the study.

Prior to commencement of the study, a meeting will be held to review the roles and responsibilities of study personnel. The study will be explained to the surgeons before the study and their assent will be obtained. In addition, other OR personnel will be briefed about the study before the patient arrives in the operating room.

24. LOCAL RECRUITMENT METHODS

Patients will be screened and recruited based on the probability of having an arterial catheter inserted for the surgery. There are more than enough patients who require arterial catheterization in one year to reach our end point.

Patients will be identified prior to the pre-operative appointment and the provider will determine if an arterial catheterization is likely. Every effort will be made to review study and obtain signature on fact sheet at the pre-operative appointment after provider has discussed study and obtained permission from patient for research staff to approach the patient. Otherwise they will be approached in the pre-anesthesia clinic, hospital room, or Surgery Admission Care Unit (SACU) prior to administration of any medications that could alter their ability to review, understand and sign fact sheet. The study will be described to them, fact sheet reviewed, questions or concerns addressed, and signature will be obtained. The patient's clinical provider will obtain permission from the patient for research staff to approach the patient.

Identifiers will not be recorded.

25. LOCAL NUMBER OF SUBJECTS

Thirty (30) patients will be recruited between the University and Memorial Campuses. We are allowing a screening failure of 50% (significant differences in BP between arms; inability to insert arterial catheter).

26. CONFIDENTIALITY

See section 11. Procedures Involved for data to be collected.

All records will be de-identified so each subject is identified by a study ID # and their name will be known only to the researchers. The study ID # will be linked to the subject's MRN via a separate ID log that contains only the MRN and Subject ID. The ID log will be stored separately on a UMMS secure drive. Background information and medical history will be stored on UMMS RedCaps secure network. RedCap is a recommended and preferred data storage site at UMMS. BP and heart rate data will be stored on the study laptop. The subject's name will not be used in any reports or publications of this study. The U.S. Food and Drug Administration (FDA), sponsor and the UMMS Institutional Review Board and/or their representatives may inspect the subject's medical records that pertain to this research study. Sponsor may only see subject initials, study ID #, and de-identified results/data. Data stored on the study laptop will be de-identified as well.

All persons accessing patient records must adhere to the following guidelines:

- The information in a patient's record cannot be disclosed without the parent/guardian's knowledge and consent; however, there are occasions when there is a legal obligation or duty to disclose information. Requests for patient information from external sources must be directed to the Medical Records Department.
- Medical records must not be left unattended where unauthorized persons might read them Access to business information, including billing information, is also granted on a need-to-know basis.
- No patient records will be left open on a computer unless actively in use.
- Patient records will be closed as soon as the necessary information has been retrieved.
- Computers with access to patient medical records will be locked unless actively attended

Who is responsible for receipt or transmission of the data or specimens locally:
The research nurses/coordinators and the investigators will be responsible. Transcription of files will take place by the primary sub-investigator, so there will be no additional transmission of files. The only identifier used throughout the transcription process will be the study ID number. These transcripts will be de-identified further (using removal of any subject's name or other PHI) and treated as non-PHI data along with automated logs, etc. They can be shared in the same manner as the other data gathered during the study.

How will data be collected and transported:
Data collected will be collected in hard copy or by electronic medical record. Each subject will be issued a study ID # that will correspond with the information listed on the Data Collection Form. If any paper records need to be transported, they will be placed in an envelope marked confidential and individual transporting records will keep record with them until it can be appropriately locked or transcribed to an electronic format. Electronic data transportation will utilize a UMMS encrypted USB drive/secure network drive.

Where and how will data be stored:
All computerized data will be stored on secured computers or network servers/drives. All paper records will be kept in a locked file cabinet in the Critical Care Research office which is secured with a lock. The electronic data is protected in a database that is password protected and encrypted.

How long will data be stored and when/how will data be securely destroyed: The study documents may be retained in the files of the responsible investigator for 5 years. However, these documents will be retained for a longer period if required by the applicable legal requirements. After that period of time the documents may be destroyed, subject to local regulations (shredded or disposed in appropriately labeled and locked "HIPAA bins").

Which staff will have access:
These data will be accessible only by approved research staff, using confidential usernames and passwords. Direct patient identifiers will be removed from study data files as soon as possible in the data processing steps. Statistical analyses will be performed using a limited dataset. All information linking identifiable data to analysis files will be kept separate from analysis files.

All data will be used only for research purposes only; published data will not contain any individual identifiers, only aggregate-level data will be reported.

Only study personnel included in IRB applications have access to project-specific data. All persons collecting or handling data are trained in human subjects' procedures, confidentiality and privacy protection. All investigators and project staff are required to receive and complete IRB and HIPAA training.

Risks to confidentiality of the data collected throughout the proposed study will be addressed as follows: Assurance and confidentiality of information will be made to all participants. Data will be handled with the same confidentiality accorded to patient's medical records. Specific procedures protecting participant confidentiality will be as follows:

- ID number, as well as full name, medical record number, and dates of service will be placed on electronic study forms or records on which data are collected and/or stored.
- Access to data files will be secured with a password-filing system (that logs entry) and is restricted to authorized staff only.
- Necessary hard-copy records containing study data of any type will be kept in locked files. Master lists linking participant information with ID number will be numbered consecutively and prepared before data collection to ensure accurate accounting. These lists will be kept locked, in duplicate, with access only by the PI and other investigators.
- All reports and publications will preserve the subjects' anonymity.
- Any breach of confidentiality will be subject to a root cause analysis and preventive measures taken as appropriate. We will report any breach of confidentiality as required. A Certificate of Confidentiality will not be sought.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Research personnel have extensive experience in conducting clinical trials. This research involves minimal to no risk to the patient. Sufficient time will be allowed for the patient to decide to participate in the study.

We are requesting a HIPAA waiver of authorization. A HIPAA waiver is necessary for screening purposes.

28. COMPENSATION FOR RESEARCH-RELATED INJURY

NA

29. ECONOMIC BURDEN TO SUBJECTS

NA

30. CONSENT PROCESS

All study personnel will have completed required CITI training prior to their addition to the study. Regular upkeep will be done to assure compliance with IRB. Fact sheet and HIPAA authorization review and signatures of the patient or their legally authorized representative (LAR) will occur either at the pre-surgical visit or in the pre-anesthesia clinic, hospital room, or

surgical admissions care unit prior to their surgery and prior to any medication administration that could affect the ability for subject to understand and sign the fact sheet. All patients will be given the necessary time to review the fact sheet and ask any questions prior to obtaining signature.

31. PROCESS TO DOCUMENT CONSENT IN WRITING

This research presents no more than minimal risk of harm to subjects, therefore we are requesting a waiver of written informed consent. We will instead use a fact sheet. All patient's will be given the necessary time to review the fact sheet and HIPAA authorization form and ask any questions prior to obtaining subject or LAR signature on the fact sheet and HIPAA authorization form.

All study staff will confirm and document that the fact sheet and HIPAA authorization was reviewed with the patient and/or LAR. The patient/LAR will be given a copy of the fact sheet and HIPAA authorization form. All study staff will follow HRP-802 INVESTIGATOR GUIDANCE: Informed Consent.

32. DRUGS OR DEVICES

When the ViTracks are not in clinical use, they will be stored in a locked room of the Clinical Science Wing of the Department of Anesthesiology and Perioperative Medicine. IND exempt due to the device being a class 2 device.

The ViTrack continuous non-invasive BP measurement (cNIBP) device is a non-significant risk device and as outlined in 21CFR812 does not need an IDE application approved by the FDA.

- It is not an implantable device and does not present a potential for serious risk to the health, safety, or welfare of a subject.
- It is not purported or represented to be used for supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject.
- It is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject.