RESEARCH PROTOCOL - Utility of a Smart Phone Application in Assessing Radial Artery Patency - the CAPITAL iRADIAL Study

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Appendix to: Di Santo P, Harnett DT, Simard T, et al. Photoplethysmography using a smartphone application for assessment of ulnar artery patency: a randomized clinical trial. *CMAJ* 2018. doi: 10.1503/cmaj.170432.

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1. LIST OF ABBREVIATIONS

AE: Adverse events
DUS: Doppler ultrasound
MAT: modified Allen's test
SAE: Serious adverse events

2. INTRODUCTION

2.1 Lay Summary

Accessing the arteries of the heart through the blood vessels of the wrist is becoming increasingly popular. By obtaining access via the artery in the arm as opposed to the groin, there is less risk of complications and improved patient satisfaction. However, using the wrist can cause blockage of the artery after the procedure. If there is too little blood flow from a second artery that supplies the hand, this could result in significant injury. Therefore, it is important to test these blood vessels in the wrist prior to having this procedure. The best way to evaluate these arteries involves the use of ultrasounds but this takes a long time and is expensive. Therefore, the artery is usually evaluated with a clinical test known as the modified Allen's test, which relies on the doctor watching the flushing of the hand during compression of the artery. Currently smart phones with cameras are able to assess blood flow by passing light through the skin and watching differences in brightness. This may be a better way to assess the arteries in the hand as it is less subjective than simply watching the flushing of the hand. This study aims to assess the ability of an iPhone application in determining whether there is sufficient blood flow through the arteries of the wrist and comparing it to both the clinical test and the ultrasound.

2.2 Rationale & Study Aim

Over the past decade, the transradial approach to cardiac catheterization has emerged as the preferred method of angiography and intervention. There have been several observational and randomized controlled trials which have shown an association between transradial access and reduced risk of bleeding and other vascular complications, increased cost-effectiveness, improved patient satisfaction, and a mortality benefit in high-risk patient populations. However, this technique does carry risks of complications including radial artery injury (i.e. occlusion, non-occlusive injury, spasm, hand ischemia, pseudoaneurysm, perforation), nerve damage, arteriovenous fistulisation, and bleeding. Radial artery occlusion is the most common adverse outcome. In individuals with intact collateral palmar circulation from the ulnar artery, they are usually asymptomatic and do not require further intervention. However, if an individual lacks adequate collateral circulation, they are at risk of hand ischemia and loss of tissue or function necessitating surgical intervention or, ultimately, amputation. Thus, it is important to assess competency of the collateral palmar circulation prior to transradial cardiac catheterization to mitigate the risks associated with this approach.

The gold standard evaluation of collateral circulation involves the use of colour Doppler ultrasound imaging of radial and ulnar arteries which allows for direct, objective assessment of arterial patency and competency through direct visualization of blood flow. The use of pre-procedural ultrasound remains both labour and resource intensive and hence is not feasible for practical use, therefore we must rely on clinical assessment of collateral circulation. This has been traditionally evaluated through use of the modified Allen's test (MAT), a technique performed at the bedside as part of the pre-procedural physical examination. More recently, the introduction of plethysmography and pulse oximetry (i.e. the Barbeau test) have been utilized to theoretically provide a more objective measure of assessing collateral circulation, though these too are limited by the available resources.

Given the ever increasing prevalence of smart phones, this study aims to address the utility and feasibility of an iPhone application in determining adequacy of collateral palmar circulation. Should this iPhone application provide diagnostic accuracy, it could quickly become an alternative method of providing an objective measure of collateral palmar circulation rather than relying on the subjective MAT.

3. METHODS

3.1 Study design and methodology

For this study, we will be recruiting a total of approximately 450 patients over one year, beginning in March 2015. Patients will be randomized in a 1:1 fashion to the MAT or iPhone-based assessment using concealed envelopes prepared using a computer random sequence generator by the principal investigator. All subjects will also undergo plethysmography (Barbeau and reverse Barbeau) and Doppler ultrasound studies of the radial and ulnar artery.

Modified Allen's test

- The investigator will apply pressure to the participant's wrist to compress both the radial and ulnar arteries
- Participant will be asked to make a fist several times
- Participant will then be asked to keep their hand open while the investigator releases the pressure over one of the arteries
- This will then be repeated once more on the same arm by releasing the opposite artery, as well as on the radial and ulnar arteries on the opposite arm

iPhone plethysmography application

- The investigator will apply the camera lens of an iPhone to the participant's thumb
- The investigator will then apply pressure to the participant's wrist to compress either the radial or ulnar artery in isolation for up to two minutes
- This will then be repeated once more on the same arm by releasing the opposite artery, as well as on the radial and ulnar arteries on the opposite arm

Conventional plethysmography (i.e. Barbeau test)

- The investigator will apply a standard clamp sensor on the participant's thumb
- The investigator will then apply pressure to the participant's wrist to compress either the radial or ulnar artery in isolation for up to two minutes
- This will then be repeated once more on the same arm by releasing the opposite artery, as well as on the radial and ulnar arteries on the opposite arm

Doppler Ultrasound imaging

- The investigator will apply a small amount of ultrasound gel and an ultrasound probe to the participant's wrist at 1cm proximal to the radial head

3.2 Participant Identification and Recruitment

Prospective research participants will be patients planned to undergo coronary angiography or who have undergone angiography in the Coronary Care Unit (CCU) and reference center, day unit, cardiology clinic, as well as the H3, H4 and H5 inpatient wards at the University of Ottawa Heart Institute will be recruited.

3.3 Inclusion Criteria

All persons who are patients who are greater than 18 years of age at the University of Ottawa Heart Institute and are candidates for coronary angiography.

3.4 Exclusion Criteria
Exclusion criteria include hemodynamic instability, need for emergent angiography (active chest pain or STEMI), inability or unwillingness to provide informed consent and known surgical removal of the radial or ulnar artery. If the patient had undergone transradial access in the preceding week, the assessment and ultrasound were performed on the contralateral limb and the accessed limb was excluded to avoid discomfort.

3.5 Consent
Only patients who have signed their consent to have their records reviewed for research will be approached. It will be the responsibility of the health care team to approach the patient for consent to review their record. A co-investigator or study staff member will review the consent process with the patients and obtain informed consent. This will be performed by ensuring the patient is able to understand and appreciate the implications of participating in the study as well as the risks and benefits of their involvement. The written informed consent form will be provided and once reviewed, questions will be answered.

3.6 Outcomes
The primary outcome of this study is the overall diagnostic accuracy of the iPhone application or MAT in assessing the competency of collateral blood supply to the hand compared with DUS. Though both left and right radial vascular access sites will be assessed when available in all patients, in clinical practice the right radial artery (RRA) is preferentially used. The RRA will therefore be defined as the potential primary access site except in patients who have no palpable right radial pulse, previous RRA graft harvests, recent or ongoing arterial access in that artery (e.g. invasive hemodynamic monitoring or arterial stab for blood gas analysis), or an arteriovenous fistula in the right upper extremity in which cases the left radial artery (LRA) will be selected.

The secondary endpoint is the diagnostic accuracy of the iPhone application for radial or ulnar artery patency using results from both right and left arteries (irrespective of expected primary access site). Prespecified variables (i.e. age, sex, BMI, and presence of a palpable pulse) will be used to determine predictors of poor diagnostic performance. Additionally, the diagnostic accuracy of the HRMA will be compared to that of conventional plethysmography.

3.7 Withdrawal from Study/Early Termination
Participants may withdraw from the study at any time without penalty or prejudice. Participants may be withdrawn from the study if:

- The participant fails to comply with the requirements of the study.
- The study doctor feels it is in the best interest of the participant.
- Participant needs additional treatment that would interfere with the study.

4. STUDY RISKS
Participants may experience very mild discomfort with compression of the radial and ulnar arteries while performing the tests.

5. SAFETY REPORTING
Adverse events (AE) and Serious Adverse Events (SAE) will be defined and reported according to ICH GCP and Regulatory standards. AEs and SAEs will be reported from the signing of the consent and followed until resolution.

6. DATA CAPTURE, SAMPLE SIZE AND STATISTICAL ANALYSIS

6.1 Data Capture

The patient's medical record will be reviewed to obtain information regarding demographic information (e.g. gender, age, height, weight, body mass index, ethnicity), cardiac risk factors (e.g. hypertension, diabetes, smoking, family history of heart disease, hyperlipidemia, previous myocardial infarction, previous cardiac intervention, previous strokes), past medical history, and current medications. The results of the four

6.2 Sample Size

Assuming a diagnostic accuracy of 80% using the MAT, in order to achieve an 80% power to detect a 10% difference in diagnostic accuracy using the iPhone application, a sample size of 438 participants was calculated.

6.3 Statistical Analysis

All continuous variables will be reported as mean ± standard deviation. Categorical variables will be described as number (%). Comparisons between diagnostic arms will be performed using chi-square or Fisher's exact tests. Within arm comparisons will be performed using McNemar's tests when comparing proportions for paired data. Artery level data will be analysed using generalized estimating equations. Logistic regression will be used to generate the model for predictors of false positive assessment. All calculations will be performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

7. ETHICAL CONSIDERATIONS

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the patient. It is the responsibility of the investigator, or a person designated by the investigator to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee will also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary.

The protocol, informed consent and any accompanying material provided to the patient will be submitted by the investigator to an IRB for review. An approval letter or certificate (specifying the protocol number and title) from the IRB must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol. Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IRB approval must also be submitted by the investigator in accordance with local procedures and regulatory requirements.

8. CONFLICT(S) OF INTEREST

None to declare.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator and the study centre will accept responsibility of monitoring and auditing as well as inspections by the Ottawa Health Science Network Research Ethics Board and the University of Ottawa Heart Institute. They will also provide all study-related records, as well as source documents to these instances when they are requested to. The confidentiality of the participant's identity shall be well protected and consistent with local and national regulations when the source documents are subject to direct access.

10. DATA HANDLING AND RECORD KEEPING

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: [1] Investigator's Study File and [2] patient clinical source documents. The Investigator's Study File will contain the protocol/amendments, CRF/DCS and schedule of assessments, Independent Ethics Committee/Institutional Review Board approval with correspondence, sample informed consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Patient clinical source documents will include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, special assessment reports, signed informed consent forms. All personal health information collected will be kept confidential unless release is required by law. For audit purposes only, the Ottawa Health Science Network Research Ethics Board and the University of Ottawa Heart Institute may review the patients' medical records under the supervision of Dr. Benjamin Hibbert and his staff. The Master list containing the patients' personal health information will be kept separate from the patient screening and enrollment logs. The Master List which links the patient with the independent study number will only be accessible by Dr. Benjamin Hibbert and his staff. The master link and study files will be stored separately and securely.

All paper records will be stored in a locked filing cabinet and /or office. All electronic records, including the Master List, will be stored on a secure internal hospital server and password protected, again only accessible by Dr. Benjamin Hibbert and his staff. No identifiable information will be stored on any mobile devices (laptops, USB keys, CDS, DVDs, etc). The Investigator must keep source documents as described above on file for 10 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, according to local regulations.

11. PUBLICATION POLICY

In accordance with standard editorial and ethical practice, the results of this study will be published or presented at congresses or scientific meetings. Patients will not be identifiable in any publications or presentations.

12. RESEARCH TEAM

13.1 Principal Investigator

Dr. Benjamin Hibbert

13.2 Co-investigators/Study Staff

Dr. Aun-Yeong Chong	Dr. Michel Le May	Dr. Altayyeb Yousef
Dr. Pietro Di Santo	Dr. Alexander Dick	Dr. Robert Moreland
Dr. David Harnett	Dr. Trevor Simard	Dr. George Wells
Dr. Derek So	Dr. F. Daniel Ramirez	Dr. Jaya Chandrashekar
Dr. Marino Labinaz	Dr. Ali Pourdjabbar	Dr. Roxana Mehran