Utility of a smartphone application in assessing palmar circulation prior to radial artery harvesting for coronary artery bypass grafting: rationale and design of the randomised CAPITAL iRADIAL-CABG trial

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ABSTRACT

Introduction There is emerging evidence supporting the use of the radial artery (RA) as a preferred secondary conduit for coronary artery bypass grafting (CABG) as it is associated with higher rates of graft patency at 5 years when compared with saphenous vein grafts (SVG). The modified Allen’s test (MAT) is traditionally regarded as the standard of care in the assessment of ulnar artery (UA) patency prior to RA harvesting. Unfortunately, due to high false-positive rates, a substantial number of pre-CABG patients are found to have an abnormal MAT despite normal UA patency, resulting in inappropriate exclusion from RA harvesting. The SVG is generally used in its place when this occurs, resulting in potentially lower rates of long-term graft patency.

Methods and analysis The CAPITAL iRADIAL-CABG trial is currently enrolling participants 18 years of age or older undergoing CABG for whom the treating physician is considering the use of an RA conduit. Eligible patients will be randomised in a 1:1 fashion to MAT or smartphone-based photoplethysmography application assessment to assess collateral palmar circulation prior to RA harvesting. The primary outcome of the trial is the use of the RA as a conduit during CABG. The primary safety outcome is postoperative palmar ischaemia as determined by clinical assessment or requirement of vascular intervention.

Secondary outcomes include vascular complications, early graft failure, need for rescue percutaneous coronary intervention during the index hospitalisation and a composite cardiovascular outcome of myocardial infarction, stroke and cardiovascular death prior to discharge from hospital. A total of 236 participants are planned to be recruited.

Ethics and dissemination The study was approved by the Ottawa Heart Science Network Research Ethics Board (approval number 20180865-01H). The study results will be disseminated via conference presentations and peer-reviewed publications.

Trial registration number NCT03810729.

Strengths and limitations of this study

► CAPITAL iRADIAL-CABG is the first randomised trial to use a smartphone application to evaluate collateral palmar circulation as part of pre-coronary artery bypass grafting (CABG) surgical assessment.

► If proven safe and efficacious, smartphone assessment might be considered as an evidence-based approach prior to radial artery (RA) harvesting in CABG.

► This could result in increased use of the RA which has been associated with improved patient outcomes.

► A potential limitation of the study is the comparison to the modified Allen’s test, which despite being the clinical standard, is a test with poor diagnostic accuracy.

INTRODUCTION

Coronary artery bypass grafting (CABG) is a common form of coronary revascularisation used to treat obstructive epicardial coronary artery disease. Traditionally, CABG is performed using the left internal thoracic artery and additional conduits include the saphenous venous graft (SVG), radial artery (RA) and/or the right internal thoracic artery. Most commonly, SVGs are used; however, SVGs frequently develop progressive atherosclerosis, leading to 50% graft failure 10 years following the initial operation.1

An increasing body of evidence has emerged supporting the use of the RA as a preferred secondary conduit as it is associated with higher graft patency rates at 5 years when compared with the SVG.2-4 Although
most randomised controlled trials assessing this have been individually underpowered to demonstrate a significant difference in outcomes. A recent large pooled meta-analysis demonstrated a significant reduction in adverse cardiac events, with a higher rate of graft patency at 5 years in RA conduits when compared with SVGs.

Prior to harvesting the RA for bypass grafting, guidelines recommend an assessment of ulnar artery (UA) patency to ensure sufficient collateral circulation in the palmar arch. The gold standard diagnostic tool for determining UA patency and collateral competency is colour Doppler ultrasound imaging, however the preoperative utilisation of this modality remains labour and resource intensive and is seldom feasible in routine clinical practice. More commonly, a bedside assessment using the modified Allen’s test (MAT) is regarded as the clinical standard. Due to low specificity with high false-positive rates, a substantial number of pre-CABG patients with normal UA patency are found to have an abnormal MAT, resulting in inappropriate exclusion from RA harvesting, which may impact longer-term outcomes.

A recent randomised controlled trial demonstrated that a point of care smartphone-based application which uses photoplethysmography was diagnostically superior to MAT in assessing UA patency prior to RA access for coronary angiography. In the proposed randomised trial, we hypothesise that the use of smartphone-based photoplethysmography application (SBPA) would result in increased RA use when compared with the clinical standard in patients undergoing CABG.

**METHODS AND ANALYSIS**

**Trial objectives and overview**

The primary objective of this study is to evaluate the efficacy and safety of SBPA in the assessment of UA patency prior to RA harvesting in CABG. The trial began participant recruitment in May 2019.

**Screening, eligibility and consent**

Patients who are scheduled to undergo CABG surgery in our institution will be screened. Eligible patients who are greater or equal to 18 years of age for whom the treating physician is considering the use of an RA conduit will be recruited. Patients with haemodynamic instability, need for emergent CABG (such as non-resolving chest pain or ST-elevation myocardial infarction) or previous surgical removal of the RA or UA will be excluded. Patients must be able and willing to provide written informed consent prior to enrolment.

**Study interventions**

Participants will be randomised in a 1:1 ratio using a computer-generated random sequence to have UA patency assessed with either the MAT or SBPA. Participant allocation will be conducted using sealed envelopes, which will be opened by the investigator performing the assessment. This will be an open-label study, and both investigators and outcome assessors will remain unblinded to the intervention arm throughout the study period.

**Modified Allen’s test**

Each participant is requested to make a fist for 30s, with the investigator applying pressure over the RA and UA to occlude blood flow. The investigator will then instruct the participant to open the fist. At this point, the participant’s hand shall appear pale. The UA is selectively released while the hand is monitored for palmar blush and the time to maximal palmar blush is recorded.

**Smartphone-based photoplethysmography**

The SBPA will be performed using the Instant Heart Rate application (V.5.282.39090; Azumio). This software was selected as it is commercially available free of charge on Apple and Android platforms and permits direct visualisation of the photoplethysmography tracing. It is also the most downloaded heart rate monitoring application worldwide. The software was originally developed for users to track their own heart rate without specialised equipment. It uses a proprietary algorithm by Azumio that was validated by comparing data collected via the application to electrocardiograms. The software uses the smartphone’s camera to emit light through the participant’s finger, resulting in colour and brightness changes. This information is then extracted by the camera lens and interpreted as changes in pulse, reflected both as a numerical value (ie, heart rate) and as a photoplethysmography tracing on the screen.

Photoplethysmography readings will be acquired by placing the smartphone camera lens over the pulp of the participant’s index finger (a video demonstration of the application can be found at https://www.cmaj.ca/content/190/13/E380/tab-figures-data). This is conducted with the participant’s hand in a supine position and resting on a firm surface. Readings before and immediately after isolated RA compression for 2min or less will be recorded. These readings will be divided into four categories as previously described by Barbeau et al1—A, no damping of pulse tracing immediately after RA compression; B, damping of pulse tracing; C, loss of pulse tracing followed by recovery of pulse tracing within 2min; D, loss of pulse tracing without recovery within 2min. Readings categorised as A or B will be used to indicate UA patency, whereas those characterised as C or D indicate inadequate UA patency.

Each participant will receive an RA conduit during CABG if the assigned test demonstrates UA patency. If the test demonstrates inadequate UA patency, the participant will receive a different conduit for CABG at the discretion of the treating surgeon with no RA harvesting.

**Outcomes**

The primary outcome of this study will be the use of the RA as a conduit in CABG surgery. The primary safety outcome is postoperative palmar ischaemia as determined...
by clinical assessment or requirement of vascular intervention. Secondary outcomes include vascular complications at the site of the RA harvest defined as minor bleeding (ie, haematoma not requiring intervention) or major bleeding (bleeding causing compartment syndrome or requiring ≥3 units of blood products, surgical intervention or need for anticoagulant reversal), early graft failure, need for rescue percutaneous coronary intervention during the index hospitalisation and a composite cardiovascular outcome of myocardial infarction, stroke and cardiovascular death prior to discharge from hospital. End-point definitions are available in online supplemental material.

Pre-specified variables such as age, sex, body mass index (BMI) and previous RA access for angiography will be used to determine predictors of poor diagnostic performance.

**Data capture and statistical analysis**

**Data capture**
The participant’s medical record will be reviewed to obtain data regarding demographic information (eg, sex, age, height, weight, BMI, ethnicity), cardiac risk factors (eg, hypertension, diabetes, smoking status, family history of heart disease, hyperlipidaemia, previous myocardial infarction, previous cardiac intervention or surgery, previous strokes), previous use of the RA as access for coronary angiography or a medical procedure, past medical and surgical history, and current medications.

In addition, information regarding indication for CABG (ie, acute coronary syndrome or elective procedure), the native vessels that are being bypassed and the degree of native vessel occlusion as determined by preoperative invasive coronary or CT angiogram will be recorded. Outcomes from the time of randomisation until the time of discharge from hospital, including bypass conduits used, post-operative complications, further cardiac interventions, cardiovascular mortality, myocardial infarction, ischaemic stroke and bleeding will also be captured. At the time of discharge from hospital the study period will be complete, and there will be no follow-up planned after this point.

Due to the fact that study investigators will need to communicate assigned test results to the treating surgeon, blinding of investigators will not be possible. Outcome assessors will also remain unblinded, as the primary outcome is dichotomous and not susceptible to subjective interpretation.

**Statistical analysis**
The formal statistical analysis plan will be finalised prior to unblinding of the study database. In brief, all continuous variables will be reported as mean (SD) for normally distributed variable or otherwise as median (IQR). Categorical variables will be described as number (percent). Comparisons between study arms will be performed using χ² or Fisher’s exact tests, as appropriate. All calculations will be performed using SAS V.9.4 (SAS Institute).

**Sample size calculation**
Based on the diagnostic accuracy of each method observed in prior studies, it was estimated that the rate of exclusion from RA harvesting using MAT and SBPA to be 20% and 10%, respectively. With 80% power and an alpha of 0.05, it was initially calculated that 200 participants were needed in each arm. A prespecified blinded sample size re-estimation was performed after 75 patients were enrolled. There were 26 (35%) patients across both groups who did not have RA harvest and therefore the sample size was re-estimated to be 118 participants in each arm, using a minimal clinically important relative risk reduction of 40% and allowing for 1% cross-over between groups.

**ETHICS AND DISSEMINATION**

**Ethics approval**
The study protocol (20180865-01H, version 2) was approved by the Ottawa Heart Science Network Research Ethics Board (approval number 20180865-01H) and will be conducted in accordance with the Good Clinical Practice standards specified in the Declaration of Helsinki. Informed written consent will be obtained from all participants prior to enrolment. Participants’ confidentiality will be strictly maintained in accordance with local and national regulations. The study results will be disseminated via conference presentations and peer-reviewed publications.

**Patient and public involvement**
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Withdrawal from study/early termination**
Participants may voluntarily withdraw from the study at any time without penalty or prejudice. Participants may be terminated from the study if they fail to comply with study requirement, need additional treatment that would interfere with the study, or if their treating physicians feels it is in the best interest for them to withdraw.

**Adverse event ascertainment**
The main adverse event of the trial is post-operative palmar ischaemia. It is determined by clinical assessment, review of the medical chart or requirement of vascular intervention.

**DISCUSSION**
The CAPITAL iRADIAL CABG study is a novel, randomised study aimed to evaluate the efficacy and safety of SBPA in assessing UA patency prior to RA harvesting in CABG surgery. One recent proof-of-concept study by Di Santo et al which compared similar SBPA to MAT demonstrated the SBPA readings had a greater diagnostic accuracy and greater specificity during assessment of UA and RA patency prior to transradial coronary angiography.
Given the higher specificity of SBPA, we hypothesise that the utilisation of this software will result in more RA harvesting in patients undergoing CABG.

We selected the MAT as our control intervention given that it is the standard-of-care method for assessing UA patency and we aim to compare SBPA to current real-world practice. Although Doppler ultrasonography has greater diagnostic accuracy, it is not commonly used in the preoperative setting as it is labour-intensive and not easily portable.

The integration of mobile digital and smartphone-based technology in the workplace and community has been far-reaching in the last decade, and has further extended its potential role in healthcare. For example, there are Food and Drug Administration-approved smartphone ECG sensors commercially available in North America, some of which include artificial intelligence-assisted calculations.12 ‘Digital biomarkers’, developed using smartphone plethysmography and artificial intelligence can now detect diabetes among our population.13 The wide-spread availability of smartphone applications, and the free availability of this application, means the current technology could immediately be implemented with near zero cost and increase utilisation for patients undergoing CABG.

Barriers to utilisation of mobile health technology among healthcare providers include concerns regarding cost, ease of use, diagnostic accuracy and difficulty in maintaining patient confidentiality.14 For instance, a recent validation study highlighted inaccuracies in assessment of blood pressure by an application sold to 148,000 users, with which approximately 80% of hypertensive individuals will be falsely reassured that their blood pressure is in the normal range.15 Although these cases may warrant concern, numerous resources and endeavours are being invested to integrate diagnostics into smartphones for a wide range of conditions (ie, ResearchStack for Android, ResearchKit for Apple).16

The primary outcome of our study is the utilisation of the RA as a conduit in CABG surgery. In the past decade, numerous studies have demonstrated that the RA conduit has a significantly higher 5-year graft patency rate compared with SVG.2,4 Based on a study done by Deb et al, among 269 participants who underwent late coronary angiography after index non-emergent CABG in 9 Canadian centres, RA conduits had a lower frequency of functional graft occlusion and complete graft occlusion when compared with SVG.3 A recent patient-level meta-analysis demonstrated a number-needed to treat of 16 with the use of RA conduits instead of SVGs to prevent one death, MI or revascularisation.17 Given the negligible cost, this cost–benefit ratio of implementing a more diagnostically accurate screening tool is extremely favourable. Moreover, the primary safety outcome is post-operative palmar ischaemia, which is expected to be non-significant due to its rare incidence as previously shown.18

Implication
To our knowledge, the CAPITAL iRADIAL CABG study is the first trial which uses smartphone-based photoplethysmography in evaluating UA patency as part of a pre-CABG surgical assessment. If proven safe and efficacious in this study, SBPA may be considered an evidence-based approach in assessing UA patency prior to RA harvesting.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


Study Endpoint Definitions

Utility of a Smart Phone Application in Assessing Palmar Circulation Prior to Radial Artery Harvesting for Coronary Artery Bypass Grafting - the CAPITAL iRADIAL CABG Study

ClinicalTrials.gov Identifier: NCT03810729

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1. Study Endpoint Definitions

1.1 Primary Clinical Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of the radial artery</td>
<td>Successful harvesting and anastomosis of the radial artery as a bypass conduit during coronary artery bypass grafting surgery.</td>
</tr>
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</table>

1.2 Primary Safety Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Post-operative palmar ischemia</td>
<td>Ischemia to the hand that was previously supplied by the harvested radial artery:</td>
</tr>
<tr>
<td>I.</td>
<td>As determined by clinical examination by the attending cardiac surgeon.</td>
</tr>
<tr>
<td>II.</td>
<td>As determined by the need for administration of vasodilators to re-establish or improve perfusion to the hand.</td>
</tr>
<tr>
<td>III.</td>
<td>As determined by the need for vascular intervention to re-establish perfusion, including open surgical repair, or endovascular repair.</td>
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</table>

1.3 Secondary Clinical Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Definition</th>
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</table>
| Bleeding complication at the site of the radial artery harvesting† | I. Minor  
Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring non-surgical medical intervention by a health care professional in order to reduce bleeding such as manual pressure, application of a pressure bandage, or utilization a radial compression device; leading to increased level of care; or requiring 1 or 2 U of whole blood or packed RBC transfusion AND otherwise not meeting criteria for major or extensive bleeding.  
II. Major  
Overt bleeding either associated with a drop in the hemoglobin of ≥3.0 g/dl (30g/L) or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet criteria for extensive bleeding.  
III. Extensive  
Overt source of bleeding with drop in hemoglobin of ≥4 g/dl (40g/L) or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or causing clinical compartment syndrome as determined by clinical evaluation by a physician or by need for surgical decompression.  |
| In-hospital graft failure or need for rescue PCI | Evidence by invasive coronary angiogram or CT coronary angiogram of either graft obstruction or failed graft anastomosis during the post-operative in-hospital period.  
I. Medical treatment of graft obstruction or failed graft anastomosis. |
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Death</td>
<td>In-hospital mortality due to a cardiovascular cause.</td>
</tr>
<tr>
<td>I. Death attributable to acute myocardial infarction</td>
<td></td>
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<tr>
<td>II. Sudden cardiac death, including unwitnessed death</td>
<td></td>
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<tr>
<td>III. Death attributable to heart failure</td>
<td></td>
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<tr>
<td>IV. Death attributable to cerebrovascular accident</td>
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<tr>
<td>V. Death attributable to cardiovascular procedure</td>
<td></td>
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<tr>
<td>VI. Death attributable to cardiovascular hemorrhage</td>
<td></td>
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<tr>
<td>VII. Death attributable to other cardiac cause</td>
<td></td>
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<tr>
<td>Stroke or transient ischemic attack</td>
<td>I. Acute episode of a focal or global neurological deficit with at least 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>A. Change in the level of consciousness</td>
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<tr>
<td></td>
<td>B. Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body</td>
</tr>
<tr>
<td></td>
<td>C. Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke</td>
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<tr>
<td></td>
<td>II. In addition, there is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist</td>
</tr>
<tr>
<td></td>
<td>The neurological event type classification:</td>
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<tr>
<td></td>
<td>I. Stroke: duration of a focal or global neurological deficit ≥24 h OR &lt;24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death</td>
</tr>
<tr>
<td></td>
<td>II. TIA: duration of a focal or global neurological deficit &lt;24 h and neuroimaging does not demonstrate a new hemorrhage or infarct</td>
</tr>
<tr>
<td></td>
<td>Stroke/TIA etiology classification:</td>
</tr>
<tr>
<td></td>
<td>I. Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue</td>
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<td></td>
<td>II. Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage</td>
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<tr>
<td></td>
<td>III. Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I. Periprocedure Myocardial Infarction related to Coronary Artery Bypass Grafting</td>
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</table>
Detection of rise and/or fall of cardiac biomarkers (preferably cTn) >10 times the 99th percentile ULN in patients with normal baseline cardiac biomarkers. In patients with elevated baseline cardiac biomarkers in whom levels are stable (≤20% variation) or falling, the post-procedure values must rise by >20%, however the post-procedure value must still reach >10 times the 99th percentile ULN, along with at least one of the following:
A. Development of new pathological Q waves
B. Angiographic evidence of new graft occlusion or new native coronary artery stenosis
C. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic cause.

II. Spontaneous MI (unrelated to coronary artery bypass surgery)
Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile upper range limit (or ULN in the absence of range limit) together with at least 1 of the following:
A. Symptoms of ischemia
B. ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads
C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

III. MI associated with sudden, unexpected cardiac death
Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood

References: