CT perfusion for Assessment of poor Neurological outcome in Comatose Cardiac Arrest Patients (CANCCAP): protocol for a prospective study

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ABSTRACT
Introduction Cardiac arrest remains one of the most common causes of death with the majority occurring outside of hospitals (out of hospital cardiac arrest). Despite advancements in resuscitation management, approximately 50% of comatose cardiac arrest patients (CCAP) will suffer a severe unsurvivable brain injury. To assess brain injury, a neurological examination is conducted, however, its reliability in predicting outcomes in the first days following cardiac arrest is limited. Non-contrast CT is the most employed scan to assess hypoxic changes, even though it is not sensitive to early hypoxic-ischaemic changes in the brain. CT perfusion (CTP) has shown high sensitivity and specificity in brain death patients, although its use in predicting poor neurological outcome in CCAP has not yet been explored. The purpose of this study is to validate CTP for predicting poor neurological outcome (modified Rankin scale, mRS≥4) at hospital discharge in CCAP.

Methods and analysis The CT Perfusion for Assessment of poor Neurological outcome in Comatose Cardiac Arrest Patients study is a prospective cohort study funded by the Manitoba Medical Research Foundation. Newly admitted CCAP receiving standard Temperature Management are eligible. Patients undergo a CTP at the same time as the admission standard of care head CT. Admission CTP findings will be compared with the reference standard of an accepted bedside clinical assessment at the time of admission. Deferred consent will be used. The primary outcome is a binary outcome of good neurological status, defined as mRs<4 or poor neurological status (mRs≥4) at hospital discharge. A total of 90 patients will be enrolled.

Ethics and dissemination This study has been approved by the University of Manitoba Health Research Ethics Board. The findings from our study will be disseminated through peer-reviewed journals and presentations at local rounds, national and international conferences. The public will be informed at the end of the study.

Trial registration number NCT04323020.

INTRODUCTION
In Canada, approximately 40000 cardiac arrests occur annually.1 Most cardiac arrests (~85%) occur at home and sadly it is estimated that only 10% of Canadians survive this catastrophic event.2 Resuscitated out of hospital cardiac arrest (OHCA) patients often arrive at hospital in an unresponsive coma state and consequently face a high risk of morbidity and mortality.2 Many comatose cardiac arrest patients (CCAP) have already suffered irreparable severe brain injury prior to reaching the hospital due to the severity of the initial injury. Due to the inability to accurately predict prognosis, these patients may receive treatments that are both resource intensive and futile.

Prolonged cardiac arrest has far greater consequences for the brain compared with the rest of the body.3 For every minute of oxygen deprivation during cardiac arrest, the chance of survival drops by 7%–10% and resuscitation is rarely successful beyond 10 min.1 Furthermore, in patients who are initially resuscitated, hypoxic-ischaemic brain injury is a significant cause of morbidity and mortality.4
Advancements in resuscitation management such as targeted temperature management (TTM), which is also known as hypothermic therapy, has improved survival and neurological outcomes for cardiac arrest patients.\(^7\) Even though treatment has improved, it is estimated that 50% of CCAP will suffer a severe unsurvivable brain injury.\(^8\) Despite receiving resource intensive therapies, several survivors face poor cognitive and neurological function (i.e., modified Rankin scale (mRS) \(\geq 4\)) because of the cardiac arrest.\(^8,9\)

To assess the severity of brain injury, a clinical assessment, which includes a neurological examination, is conducted. However, the reliability of this exam in predicting outcome in the first days following cardiac arrest is poor.\(^10\) In addition, sedatives and paralytic medications which are frequently used during TTM further limit the reliability of this assessment, making early assessment of neurological recovery a challenge in CCAP.\(^11\) In clinical practice, ancillary tests are used when the clinical examination is unreliable or impossible. Diagnostic imaging is the most frequently used type of ancillary test. Unfortunately, there is no single test that is uniformly used in Canada, which may lead to multiple different tests being performed. Furthermore, varying results between the different diagnostic imaging tests can cause confusion for both clinicians and families. A definitive, reliable, and validated clinical assessment for CCAP in the emergency department is warranted, to assist in the early diagnosis and prognosis of this patient population to reduce futile treatment and potentially facilitate timely organ(s) donation. CT perfusion (CTP) may fulfill this gap in clinical care.

### CTP for confirmation of poor neurological outcome

CTP is an advanced CT scan that provides both functional and anatomical information about the brain as well as information about cerebral blood flow (CBF).\(^13\)-\(^16\)

CTP is used to demonstrate whether there is persistent and adequate blood flow to all parts of the brain, including the brainstem, which is important for demonstrating brain viability. CBF is tightly regulated to meet the brain’s metabolic demands, and on average must be maintained at 50 mL/100 g/min.\(^17\)-\(^19\) A CBF drop to <20 mL/100 g/min results in ischaemic neuronal activity reduction whereby a person typically becomes clinically symptomatic from brain ischaemia. At this stage, there is potential for reversibility/recovery of neuronal function. However, CBF < 10 mL/100 g/min results in membrane failure and irreversible ischaemic neuronal damage within minutes.\(^3\)\(^,17\)\(^,20\) Based on these considerations, a test that can measure cerebral perfusion with sufficient accuracy and reliability could also be accurate and reliable in predicting neurological status at discharge, in place of a clinical assessment. To date, there has been no test capable of assessing CBF that has been shown to be useful for CCAP; therefore, we propose to study CTP in a prospective cohort study.

Since CTP is very sensitive in detecting CBF, it can detect decreased perfusion as low as 2%–3% in CBF and cerebral blood volume (CBV).\(^21\) CBF < 5 mL/100 g/min is consistent with a clinical diagnosis of brain death in nuclear scintigraphy studies.\(^22\)\(^,23\) Therefore, if CTP is unable to detect CBF, or shows markedly decreased CBF, a diagnosis of brain death can be made, given that cellular viability is not possible at such low values of CBF. We have been the first to define the features of fatal brain injury on CTP maps as ‘matched defect’ in CBF and CBV.\(^24\)-\(^26\)

We will capitalise on these unique CTP characteristics and aim to be able to better predict outcomes in CCAP at discharge.

We conducted the preliminary hypothesis testing through a prospective, single centre, pilot cohort study with 10 CCAP to establish the feasibility and safety of CTP at the time of first imaging after acute management including TTM in CCAP patients.\(^11\) To maintain blindness and reduce bias during the study, CTP procedure outcomes were not made available to clinical evaluators. On completion of patient recruitment, CTP results were compared with the poor neurological outcome (defined as a mRS \(\geq 4\)), at hospital discharge. Eight patients died in hospital. CTP correctly classified brain death in 3 of them (sensitivity of 37.5%). None of the survivors had any evidence of brain death on CTP (specificity of 100%). There were no false positives, that is, no patients with features of brain death on admission CTP survived (positive predictive value (PPV) of 100%). As mentioned, the five patients who did not show features of brain death on CTP also died resulting in a negative predictive value (NPV) of 28.6%. The low sensitivity was thought to be a factor of change in the clinical status of the CCAP after the CTP examination during their stay in the critical care setting. CTP also showed a remarkably high inter-rater reliability (kappa of 0.74–1) between the project members’ judgements of matched defect. Consequently, the need to further validate CTP as a triage tool for predicting poor neurological outcome in CCAP at discharge is warranted.

The primary objective of the CANCCAP (CT Perfusion for Assessment of poor Neurological outcome in Comatose Cardiac Arrest Patients—a prospective study) study is to validate CTP relative to the reference standard of initial clinical assessment, for predicting poor neurological outcome (mRS\(\geq 4\)) at hospital discharge in CCAP. The secondary objective is to establish the safety and inter-rater reliability of CTP in CCAP.

### METHODS AND ANALYSIS

The CANCCAP study (clinical trial Registration Number NCT04323020) is a prospective cohort study in CCAP, which builds on previous work of our team.\(^11\) The study design was conceptualised by experts in content (neuroradiology, emergency medicine, cardiology, and critical care), epidemiology and clinical trials to ensure a high-quality study. We are enrolling adult patients who are in a coma and have suffered an OHCA treated with standard
therapeutic hypothermia protocols. The CANCCAP study is under way at the Saint Boniface General Hospital, which is the provincial cardiac centre.

**Study population**

Our study population of interest are CCAP who meet the following inclusion criteria: (1) newly admitted patients who are in a coma, (2) at least 18 years old, (3) suffered an OHCA and (4) of whom the treating physician plans on instituting postcardiac arrest TTM therapies. Study exclusion criteria include: (1) no substitute decision maker available for consent, (2) known pregnancy, (3) known contraindication to CT contrast agent, for example, allergy or anaphylactic reaction and (4) known chronic kidney disease, stage 4–5 (eGFR<30 mL/min/1.73 m$^2$).

Patients were considered to be in coma at the time of hospital arrival if they are intubated and have a Glasgow Coma Score of less than 8.

**Patient and public involvement**

Survivors of cardiac arrest and their families were involved in the planning, design, recruitment and conduct of the study.

**Study intervention**

All eligible consecutive OHCA patients will be screened and enrolled by the admitting physician during the initial hospital admission. All CCAP will be admitted to the cardiac intensive care unit (CICU) and receive standard of care, which includes TTM to 36.6°C, as soon as possible after arrival to hospital. Standard of care also includes a non contrast head CT to assess for any intracranial pathology. This usually occurs just prior to ICU admission. The study CTP protocol will be performed at the same time as this standard of care head CT (figure 1). CTP images will be acquired according to a standardised stroke imaging protocol in order to ensure whole brain coverage. As previously described in Alcock et al., a total of 40 mL of CT contrast media will be injected at a rate of 5 mL/s. A set of axial images with a slice thickness of 5 mm for the perfusion analysis will be reconstructed. The CTP data will be transferred to the study imaging core lab in the Department of Radiology, University of Manitoba, Winnipeg for interpretation. The CTP results will not be available to the treating physicians and the routine care of the patient will continue as per local practice. To ensure this, the CTP will not be processed for at least 6 months after the patient’s enrolment in the study.

The CCAP will be then transferred to CICU for further standard management. Results of clinical assessment in the emergency room will be recorded as reference standard. Neurological status at discharge from hospital will be measured using the modified Rankin Score (mRS). CTP results will be validated relative to clinical assessment (reference standard) in predicting the mRs at hospital discharge.

**Retention strategies**

As previously described in Alcock et al., retention strategies are as follows. A universal requisition is used for all diagnostic imaging tests. To improve study adherence, the clinical team helps in identifying potential research participants and we maintain timely communication with our colleagues about the study. A list of enrolled patients is kept in the CT scanner. This list is then cross-referenced with the study enrolment status. Furthermore, at the end of each month, the research team sends out an email indicating the study’s enrolment status, and a brief reminder of the study and its objectives. In addition, we organise quarterly steering committee meetings to discuss the study’s progress, recruitment status/rate and ways to improve recruitment. The study design and intervention do not require significant changes to current standard clinical practice, as the addition of CTP images is the only change in practice. No issues are foreseen in data collection.

**Timeline**

The study will take approximately 2 years to complete. Study start-up procedures (clinical research documentation, institutional ethics committee approvals and training of research staff involved in the study) took approximately 3 months. Actual enrolment started on 18

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**Figure 1** Illustration of the current hospital admission standard of care (in blue) for CCAP and the intervention from our research protocol (in yellow). ER, emergency room; ICU, intensive care unit.
May 2021. Since the incidence of CCAP is low, a conservative enrolment of five patients per month is expected. Based on current enrolment rates, we should reach our target enrolment in July 2023. Another 3 months will be required to determine the adjudicated score, completing the CTP image analysis, finalisation and dissemination of the results, including abstract and manuscript preparation. A description of the study timeline can be found in Table 1.

### Data collection and management

#### Clinical data

Clinical data processes similar to those described before will be collected by a qualified data abstractor using an electronic data collection form. A case report form (see online supplemental appendix A) will be used by the qualified data abstractor to abstract clinical data from both the patient’s electronic and paper chart.

Process metrics, such as the length of stay in CICU and the total hospital length of stay, will be derived from the data collected. Clinical data cleaning and validation will be completed by a research student. The principal investigator will ensure quality assurance policies are being implemented to ensure compliance with the protocol, which includes reviewing the screening logs, monitoring of recruitment trends, reviewing the data collected on the case report forms, generating queries regarding outliers or missing data, and implementing data tracking procedures.

#### Imaging data

CTP images will be acquired at the same time as the standard of care CT scan of head. The imaging data will be transferred and stored in the secured imaging core lab in the Department of Radiology at the University of Manitoba. The imaging centre (Department of Radiology, University of Manitoba, Winnipeg) is responsible for the postprocessing of the CTP raw data, image interpretation and image analysis. CTP will be processed using a semiautomatic deconvolution algorithm on a vendor neutral software package (Oleasphere). CTP analysis will be assessed both quantitatively as well as qualitatively using a similar process described before.

Using Quantitative assessment, brain death will be defined as CBF<10mL/100g/min and CBV<2mL/100g in the brainstem. With Qualitative assessment, brain death will be defined as matched decrease of CBF and CBV in the brainstem. The perfusion maps for CBF and CBV will be assessed for binary outcome of ‘dead’ or ‘not-dead’, according to our previously published methods. The perfusion maps will be assessed by two independent neuroradiologists, who are blinded to each other’s assessment and to the clinical history of each patient. If the two neuroradiologists disagree, a consensus agreement will be achieved for the final analysis. Consensus decision reflects the real-life scenario faced in such situations. CTP parameters (CBF and CBV) will be qualitatively assessed for the presence or absence of matched decrease of CBF and CBV.

Since the prognostic value of CTP has not been established in CCAP, the outcomes of CTP will not be made available to the clinical team involved in patient care. All patients will receive standard care.

### Data analysis and power considerations

The reference standard is complete clinical assessment that includes neurological assessment, performed as per institutional protocol by a physician blinded to CTP results. Sensitivity is defined as the ability of CTP to correctly classify an individual with poor neurological outcome, while ability of CTP to correctly classify an individual as good neurological outcome is specificity. PPV is the percentage of patients showing features of poor neurological status on CTP, who clinically had poor neurological outcome. NPV is the percentage of patients with no features of poor neurological status on CTP, who did not have poor neurological outcome. The primary validity analysis will be done by calculating the sensitivity, specificity, PPV, and NPV of ‘matched defect in brainstem’ on CTP compared with the neurological status on clinical assessment, along with corresponding 95% CIs. Area under the receiver operating characteristic curve will be calculated to enable comparison of the CTP and clinical evaluation. Interobserver agreement between the two neuroradiologists will be assessed using the kappa statistic to assess the reliability of CTP.

Logistic regression will be used to build predictive models for neurological status at discharge (mRS<4/≥4) for each of CTP and clinical parameters, including demographic and any other known risk factors. Both predictive models will be used to calculate area under the receiver operating characteristic curve to enable comparison of the models. Complications associated with CTP will be reported in terms of percentage.

No imaging test has been described in the literature for a reliable and early assessment of neurological outcome of CCAP. An ideal test would minimise false positives (ie,
have a PPV of 100%). A preliminary analysis of our recent pilot study of CTP in CCAP showed 100% sensitivity, specificity, positive and NPV for absence of brainstem function on initial clinical assessment in CCAP. It also showed 100% specificity and PPV, a sensitivity of 57.5%, and a NPV of 28.6% for poor neurological outcome at hospital discharge. Based on these preliminary results, a very high specificity would be expected in this proposed study.

Based on the findings from our pilot study, we performed a sample size calculation for the primary objective of the study using Buderer’s formula. 36 It was determined that a sample size of 75 CCAPs (with a prevalence of poor clinical outcome of at least 50%) will be required in order to validate the use of CTP against the immediate clinical assessment. This number will allow us to achieve a sensitivity and specificity of 97.5%, a CI of 5% (±2.5% around the point estimate). To account for a potential drop-out rate of 20% (including technical problems with CTP acquisition, protocol violation, consent withdrawal or new contraindication for CTP), the sample size will be increased by 15. Therefore, a total of 90 CCAPs will be our target enrolment for the study.

**DISCUSSION**

CCAP continue to have a poor overall survival rate. Outcomes of the CANCCAP study will validate CTP as a relative reference standard of the initial clinical assessment for predicting poor neurological outcome (mRS=4) at hospital discharge in CCAP. Our study is the first of its kind where admission CTP will be used to assess mortality in CCAP at the time of hospital admission. If CTP is found equivalent to clinical assessment as a measure and is able to accurately characterise poor neurological outcomes in CCAP, it could become the standard ancillary test in Canada and beyond to assess the neurological status of CCAP. Assessing poor neurological outcomes, such as death or severe dependency, in CCAP will improve patient care and potentially reduce the cost burden of the healthcare system and the emotional burden on the patient’s family. Adopting the CTP protocol into routine practice to evaluate patients who suffered an OHCA and are comatose will help reduce the use of resource intensive and sometimes futile treatment to potentially dead patients post cardiac arrest. Furthermore, using CTP in this setting will improve trust and investment in organ transplantation in Canada and worldwide.

One study limitation is that our prospective study is a single-centre study; this may affect its generalisability. Our prospective study, however, has rigour in that the study intervention is controlled and the outcome measures are preselected. We expect the results to be readily generalisable to all centres with experience in CTP interpretation.

**ETHICS AND DISSEMINATION**

We have received ethics approval from the University of Manitoba Health Research Ethics Board (Ethics # HS23646 B2020:017) and the study is being conducted in compliance with Good Clinical Practices on Ethical Conduct for Research Involving Humans.

As described before, 36 deferral of consent has been approved by our institutional ethics board. Considering the altered level of the participant’s consciousness, informed consent will be obtained from a substitute legal decision-maker by deferred consent within 1 week of enrolment. Informed consent will be obtained by the site research coordinator.

All data collected for the study will remain strictly confidential. Anonymity of the study participants is addressed by using case numbers. A record of the patient’s ID and case number is being kept in a separate secure password-protected file accessible only by the study investigators and study coordinator. Data will be presented in an aggregate form only. Data collection forms will be stored for at least 10 years as per the institutional guidelines.

Knowledge translation will be enabled by several knowledge user that have been involved in the conceptualisation of this project, including, Transplant Manitoba-Gift of Life program, the Department of Radiology and the Division of Cardiology at the University of Manitoba. The knowledge users will facilitate the translation and application of study findings. The dissemination plan includes traditional dissemination vehicles (eg, presentations at local grand rounds, national and international conferences, and publications of studies in open-access peer-reviewed journals). Once proven useful, admission CTP will be incorporated in the clinical guidelines for imaging in CCAPs. This will bring the evidence-based clinical practice change to national and international levels. The knowledge translation plan will also employ other approaches that will aim to incorporate the findings into the design of future studies and clinical guidelines as well as to inform the general public. A Café Scientifique session at the end of the study will be organised to inform the general public about the results of our study and how it will influence future clinical practice. In completing the study monitoring activities, we will be conducting a type of ongoing general quality improvement in the care of patients who suffer a cardiac arrest. This will ultimately facilitate improved patient care in the CCAP population.

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Acknowledgements  We are grateful to all the patients that will participate in the study and would like to thank the SBGH Emergency Department for their involvement in subject recruitment and the CT technicians for performing the CT perfusion scans.

Contributors  JSS, AT, SRA and SAS contributed to the conception and design of the manuscript, provided input into the protocol and gave critical feedback on the manuscript. SA and SS obtained consents. SA, SS, BH and NS perform study coordinate duties and collect all clinical data. IK, EJW and KL provide study support at SBGH. JSS, SAS, EJW, IK, KL, BH, NS and SRA attend quarterly CANCAP steering meetings. SA and SS wrote the initial draft of the manuscript. All authors approved the final version of the manuscript.

Funding  This work is supported by the Manitoba Medical Research Foundation, grant number 8-2020-13. JSS receives salary research support award from Radiology consultants of Winnipeg.

Competing interests  None declared.

Patient and public involvement  Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication  Not applicable.

Provenance and peer review  Not commissioned; externally peer reviewed.

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