Opportunities and Barriers for ECPR in Canada

May 4, 2016, Toronto, Ontario

Meeting Report

Canadian Blood Services
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RiM 2016
Resuscitation in Motion
A conference igniting Canadian and international synergies for future impact in resuscitation science

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The meeting was held in collaboration with Rescu and the Canadian Resuscitation Outcomes Consortium (CanROC) who facilitated the scheduling of this meeting immediately following the Resuscitation in Motion meeting and the inaugural CanROC Assembly in May 2016.

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Executive Summary

Extracorporeal cardiopulmonary resuscitation (ECPR) is an emerging therapy for patients with cardiac arrest refractory to conventional resuscitation. ECPR entails the use of extracorporeal membrane oxygenation (ECMO) to sustain perfusion in patients with cardiac arrest. Best available evidence from around the world is of low quality but observational studies have suggested that ECPR is associated with increased survival in subgroups of out-of-hospital cardiac arrest patients and provides organ donation opportunities in non-survivors. Organized by Canadian Blood Services in collaboration with the Canadian Resuscitation Outcomes Consortium, we assembled an interdisciplinary group of clinicians and researchers from across Canada, with support from international experts, to discuss opportunities and barriers for ECPR in the Canadian context. Representatives included experts from prehospital care and paramedics, emergency medicine, resuscitation, cardiac surgery, ECMO specialists, neurology and neurointensive care, critical care, organ donation, transplantation, health policy, health economics and bioethics.

There was consensus from this expert interdisciplinary group that ECPR is a potentially viable strategy to save lives in Canada. The group agreed that further investigation is warranted because the evidence supporting this practice is not definitive and equipoise remains. The clinical processes were defined and separated into 3 distinct phases: prehospital care; emergency department care and ECMO deployment; ECMO maintenance, prognosis and outcomes. The group agreed that the efficacy and cost-effectiveness of ECPR in the Canadian setting need to be determined before considering broad implementation. In addition, the group identified several other high priority questions about the implementation of ECPR:

1. What are the requirements for system preparedness, capacity, training and logistics related to an ECPR program?
2. What are best practices in ECPR to optimize neurologically favorable survival?
3. How can prognostication be accurately done for patients treated with ECPR?
4. What is the optimal approach to end-of-life issues for patients treated with ECPR?
5. What is the best strategy for optimizing organ donation opportunities for patients treated with ECPR who do not survive?

Opportunities for research and development in this field were identified with emphasis on the need for collaborative interdisciplinary research on the efficacy, effectiveness and implementation of ECPR in Canada. Future work should include the development and evolution of this working group into a national research collaborative, surveillance of the literature for data from ECPR clinical trials currently underway to guide our research agenda, the development of a minimum data set for ECPR research in Canada, and the development of pilot studies to support future clinical trial implementation.

1. Introduction

Sudden OHCA is a leading cause of death in developed countries and, despite recent improvements in enhancing successful resuscitation in the prehospital setting, outcomes after CPR remain poor(1, 2). Currently in Canada, most patients with out-of-hospital cardiac arrest (OHCA) that is refractory to conventional CPR will die. Treatment options with proven efficacy for this population are not available. The use of extracorporeal membrane oxygenation (ECMO) for patients in refractory cardiac arrest has emerged as a novel, yet unproven treatment option for this group of patients. The use of ECMO for patients in cardiac arrest is termed "extracorporeal cardiopulmonary resuscitation" or ECPR.

ECMO is a form of heart-lung bypass that oxygenates and circulates blood external to the body through cannulation of large arteries and veins. Currently, ECMO is used in some major hospital centers for a variety of indications, including respiratory failure(3), cardiac failure(4), septic shock(5) and, in some cases, refractory cardiac arrest(6). The concept behind ECPR is that vital functions of the cardiac arrest victim can be supported while underlying reversible causes are identified and treated. There is evolving experience with the application of extracorporeal cardiopulmonary resuscitation (ECPR) for adult OHCA.

Several moderately sized observational studies have demonstrated improved outcomes for patients treated with ECPR compared with those treated with conventional CPR. However, the quality of evidence from this body of literature is low because of methodological limitations and high risk of bias (7). A comprehensive systematic review of international practices of ECPR for refractory OHCA of presumed cardiac etiology (excluding accidental hypothermia, overdose and other non-cardiac causes) in adults has been conducted (8). Twenty observational studies, case series and case reports with a total of 833 patients (aged 16-75 years) were included and reviewed. Overall, 22% of patients survived to hospital discharge, including 13% who had good neurological recovery. For those studies reporting longer-term outcomes, overall survival rates were 21% at 3 months including 15% with good neurological function and 16% at 6 months including 9% with good neurological function. Initial shockable cardiac rhythms, witnessed events, and a reversible primary cause of cardiac arrest were considered favorable prognostic factors. Bundle treatments such as coronary revascularization, hemodynamic interventions and targeted temperature management neuroprotection were variable between studies. The patient populations studied were variable but generally included patients aged 10-75 years old, with a time interval from collapse to initiation of resuscitation of <5-15 minutes, a presumed cardiac etiology for their arrest, and no return of spontaneous circulation after 10-30 minutes. Studies generally excluded patients with a Do-Not-Resuscitate order, any disability with severe limitation of daily activities, a presumed non-cardiac cause of arrest (e.g. trauma, uncontrollable bleeding, drug overdose, poisoning, drowning, accidental hypothermia), or severe comorbidities.

Kim et al(9) performed a meta-analysis of data from 10 observational studies to determine whether ECPR, when compared with conventional CPR was associated with improved outcomes in adult patients. This review included patients with in- or out-of-hospital cardiac arrest. Studies which

included cases of cardiogenic shock or post cardiac surgery cardiac arrest were excluded as well as any studies with the majority of cardiac arrest events caused by trauma, avalanche, hanging and/or drowning. While ECPR did not appear to improve survival to discharge compared to conventional CPR in this group of studies, survival and good neurologic outcome tended to be superior in the ECPR group at 3-6 months after the arrest. These authors also recommended that strict indications criteria be used for implementation since ECPR showed better outcomes in studies with pre-defined criteria. Choi et al 2016(10) attempted to determine whether ECPR is associated with improved survival outcomes compared to conventional CPR at a national level in Korea. A Korean national OHCA cohort database from 2009-2013 was used to compare primary outcomes between ECPR and non-ECPR groups by a multivariate logistic regression and a propensity score matching analysis. While acknowledging several limitations of the study, in contrast to the findings of Kim et al, the authors did not observe a significant improvement in survival associated with ECPR, but called for well-designed RCTs to clarify the potential benefit of this strategy.

Reviewing comparative studies published to date demonstrates significant heterogeneity in study design specifically around the population studied. For example, some studies define the patient population as having cardiac arrest, whereas others specify cardiac arrest refractory to conventional CPR. This is a subtle yet key distinction. Many patients in a group identified as those who received conventional CPR from the outset may be salvageable with conventional approaches. Those patients identified as those refractory to conventional CPR are a very different group with near 0% survival if only conventional CPR is available. This issue can be an important source of bias, especially if the comparison groups are defined differently. For example, if patients in the ECPR group were all refractory to conventional therapy prior to the use of ECPR and comparator patients were treated with conventional CPR from the outset without fulfilling refractory criteria, selection bias is likely.

There are no randomized trials of ECPR versus conventional treatment for cardiac arrest published in the literature, however two are currently underway. The “Prague OHCA Study”(11) is a randomized controlled trial comparing a “hyperinvasive” treatment strategy with conventional therapy for out-of-hospital cardiac arrest. The “hyperinvasive” treatment strategy is a bundle of treatment including the use mechanical chest compression devices by paramedics, prehospital intra-arrest cooling and rapid transfer of patients to the regional cardiac centre for consideration of ECPR. Eligible patients will be between the age of 18 and 65, have a witnessed out-of-hospital cardiac arrest of presumed cardiac cause, have a minimum of five minutes of ACLS performed by emergency medical services without sustained return of spontaneous circulation, a Glasgow Coma Score of <8, and the ECMO team will be available. The “Emergency Cardiopulmonary Bypass for Cardiac Arrest” study(12) is a randomized control trial being conducted in Vienna. This study compares standard ACLS treatment for out-of-hospital cardiac arrest with a strategy of rapid transport to an emergency department capable of ECPR. Eligible patients will have a witnessed out-of-hospital cardiac arrest with presumed cardiac cause with immediate initiation of bystander CPR. Included patients will be those without return of spontaneous circulation after 15 minutes of advanced cardiac life support. Patients will be excluded if they suffer a cardiac arrest due to an obvious non-cardiac cause (e.g. traumatic cardiac arrest, exsanguination, strangulation, hanging, drowning, accidental hypothermia, amniotic fluid embolism, pulmonary embolism, intoxication, intracranial hemorrhage), have a non-

shockable initial cardiac rhythm, are pregnant, have a DNR order, cannot be transported with ongoing CPR, receive insufficient quality of bystander CPR at the discretion of the emergency physician or emergency medical technician, have an estimated transportation time exceeding 30 minutes, or they have significant comorbidities (psychiatric conditions, mental handicap, severe neurologic conditions, nursing home or institutionalized patients).

When employing advanced resuscitation treatments, in addition to the first and foremost priority of saving of the patient's life, consideration should also be given to the potential for deceased organ donation when resuscitative efforts fail. Because abdominal and thoracic vital organs can recover despite anoxic injury after cardiac arrest(13) patients who suffer cardiac arrest, including those treated with ECPR, may be eligible for organ donation. Traditionally, organ donation has not been reported as an outcome in the vast majority of CPR studies but the 2015 ILCOR Advanced Life Support Consensus on Science and Treatment Recommendations now includes the following strong recommendation: "We recommend that all patients who have restoration of circulation after CPR and who subsequently progress to death be evaluated for organ donation". In addition, ILCOR also includes this statement: We suggest that patients who fail to have restoration of circulation after CPR and who would otherwise have termination of CPR efforts be considered candidates for kidney or liver donation in settings where programs exist (weak recommendation, low-quality evidence). (7). In a systematic review of ECPR international practices and outcomes by Ortega et al (8), authors found that only 3/20 studies identified reported organ donation outcomes. The review authors were able to obtain data on organ donation outcomes from 5 additional studies after sending a request for this information to the primary authors. A total of 88 potential deceased donors were identified among non-survivors from these 8 studies (total n for 8 studies=160). Of these potential donors, 17 (19%) became actual donors: 15 DBD and 2 cDCD. Data on organ recipients was not available.

More research is needed to determine whether ECPR should be implemented broadly across Canada. While ECPR appears to be a promising development in resuscitation, the efficacy and cost-effectiveness of this intervention are not clear. In addition, there remain many unresolved practical issues. There are difficulties in predicting which cardiac arrest patients have reversible conditions at the time when decisions around ECPR deployment must be made. Existing clinical protocols vary in inclusion and exclusion criteria, definitions of refractory cardiac arrest, and allowable time limits for duration of CPR and time to deployment of ECMO. ECPR is highly technical, logistically challenging, and resource-intensive.

In order to consider ECPR in the Canadian context and identify knowledge gaps and opportunities for collaborative research, the Canadian ECPR Research Network was formed. An inaugural meeting was held in Toronto on May 4, 2016. This paper describes the meeting, summarizes the discussions held and identifies next steps.

2. Meeting process

This meeting brought together experts in prehospital care, emergency medicine, critical care, resuscitation science, neuroscience, cardiology, ECMO, bioethics, end-of-life care, organ donation, transplantation and health economics (*Appendix 2: List of Participants*) to examine the opportunities, barriers and downstream consequences related to the study of ECPR for OHCA in Canada.

Prior to the meeting, participants were given a selected bibliography of key reference articles. At the start of the meeting, presentations were given by invited national and international experts to provide context and background for participants. After the presentations and large group discussion, participants were separated into three smaller groups to discuss different aspects of the ECPR strategy including prehospital, emergency department and critical care unit considerations. Each group presented a summary of their discussion in a plenary session for discussion by all attendees.

Discussions focused on:

- Reviewing the clinical process of ECPR in each clinical setting,
- Identifying knowledge gaps relating to each of the steps in the clinical process
- Identifying opportunities and barriers for ECPR research in Canada,
- Identifying overarching issues that may impact on future ECPR trials in Canada (ethics, costs vs. benefits, training and education requirements, etc.).

The meeting closed with a discussion on the feasibility of a research program for ECPR in the Canadian setting and on next steps to continue working collaboratively towards addressing identified knowledge gaps.

3. Presentations

Dr. Steven Brooks (Co-Chair)

Associate Professor, Department of Emergency Medicine, Queen's University
Emergency Physician, Kingston General Hospital, Kingston, Ontario

Context of ECPR in Canada

Dr. Brooks discussed the growing interest and opportunities for using ECPR to improve outcomes for OHCA in Canada. In cases of failed conventional advanced cardiovascular life support (ACLS), good premorbid status and reversible causes of the primary cardiac arrest, ECPR is a reasonable rescue therapy for selected patients, as per the 2015 Consensus on Science and Treatment Recommendations developed by the International Liaison Committee on Resuscitation (ILCOR)(7). A high-level summary of available evidence was provided indicating that for selected patients, survival was improved when measured against conventional CPR. Some studies also reported that when patients did not survive, there was an opportunity for organ donation. Dr. Brooks noted that while the evidence available was generally of low quality (observational or case studies), there are two randomized controlled trials (RCTs) comparing conventional CPR and ECPR underway in Prague(11) and Vienna(12). These trials are expected to have results published in 2018.

Dr. Zach Shinar

Emergency Physician, Sharp Memorial Hospital, San Diego, California
(Presenting by phone)

Describing an emergency department-based ECPR program in the United States

Dr. Shinar presented information about the pioneering ECPR program implemented in the emergency department at Sharpe Memorial Hospital in San Diego. His talk outlined the implementation of the program 6 years ago and highlighted some of the challenges and successes. A cohesive team transferred intraoperative cardiopulmonary bypass experience to the emergency department (ED). Dr. Shiner discussed the clinical process, logistic organization and staff role assignments. He reviewed the inclusion criteria (age <70yrs, witnessed arrest, "no flow" time <10min, reversible cause) and processes of care (cardiac catheterization, interventional radiology for extremity perfusion cannula insertion, antidote, dialysis, warming vs. cooling) as the patient transitioned from the ED to the intensive care unit (ICU). The roles of nurses, paramedics and physicians were discussed, as was family support and involvement in decision-making. He noted that a critical factor in starting the program was obtaining support and buy-in from all affected departments including cardiology, cardiac surgery, perfusion, ICU, ED and emergency medical services (EMS). In doing so, it was important to understand the motivation of those involved, as there were people who initially did not support the program. He acknowledged that there were many areas where more data is still needed to optimize processes and outcomes. Of note, data was not collected regarding neuroprognostication, ICU outcomes, end-of-life (EOL) care decisions or conflicts with family. In spite of this, the program has seen a survival rate of approximately 20% (n=32) at the time of the presentation. His group has published their results from an earlier time in the program(14).

Dr. Brian Grunau

Emergency Physician, St. Paul's Hospital, Vancouver, British Columbia
Clinical Assistant Professor, Department of Emergency Medicine, Faculty of Medicine, University of British Columbia

ECPR for out-of-hospital cardiac arrest: The development of a structured protocol in Vancouver

Planning for the ECPR program at St. Paul's Hospital, Vancouver (provincial cardiac center) was started in 2014, with implementation in 2016. Prior to starting, Dr. Grunau's group conducted research to identify the number of potential eligible patients within the catchment area and potential benefits to those patients(15). Dr. Grunau described the process of obtaining support for the program through the development of a working committee composed of both administrators and physicians. The committee had representation from ED, cardiac surgery, perfusion, ICU, cardiac anaesthesia, interventional cardiology, ethics, and administration. The hospital was required to absorb costs, which was one of the biggest challenges. After hospital approval, the program collaborated with emergency medical services and together modified the existing regional treatment algorithm for OHCA to incorporate ECPR therapies. The goal of this coordinated system is the comprehensive identification of eligible patients with early transport to hospital after failure of initial on-scene efforts to achieve ROSC. Dr. Grunau described the inclusion/exclusion criteria and transport time targets for optimal ECPR outcomes. The components of the program include: prehospital integration with early selective patient identification and prehospital protocol activation, CPR en route to hospital with mechanical compression, a rapid response ECPR team including ED staff, cardiovascular surgery, and perfusion, availability of emergent coronary angiography, and post-ED ECPR management in a cardiovascular ICU with ECMO expertise. Dr. Grunau concluded that while ECPR was resource-intense and logistically challenging, he held the opinion that it was likely of benefit to certain patient groups and may be cost effective. The opportunity for organ donation in cases where the patient could not be saved was presented as an additional potential benefit. This program will be evaluated in terms of effectiveness and cost effectiveness(16).

Dr. Romergryko G Geocadin

Professor, Departments of Neurology, Anesthesiology/Critical Care Medicine and Neurological Surgery, Division of Neuroscience and Critical Care, Johns Hopkins University of Medicine, Baltimore, Maryland

Neuroprognostication and end-of-life decision making after cardiac arrest for the ECPR population

Dr. Geocadin provided an overview of the current literature regarding prognostication after cardiac arrest. He highlighted the fact that there is no established pre-arrest or intra-arrest factor that is a reliable predictor of neurologic functional outcome. He emphasized that exit criteria for ECPR, including neuroprognostication, EOL decision making, and the ability to diagnose brain death on ECMO need to be well defined. Dr Geocadin encouraged the group to use the term 'favourable neurologic outcome' rather than 'neurologically intact' as an outcome measure for all studies reporting survival outcomes. The process and criteria for neuroprognostication in patients after cardiac arrest, which includes clinical,

neurophysiologic and imaging criteria, were reviewed. These include well-known poor prognostic signs such as absence of pupillary response at 72 hours and motor response at 3- 5 days, absence of bilateral N20 response on somatosensory evoked potential at 72 hours and absence or poor motor response at 3 to 5 days after return of spontaneous circulation. However, these parameters have not been studied adequately in patients who have been subjected to ECPR. Further, the impact of targeted temperature management (TTM) on the optimal time to prognosticate and its potential to delay sedative/analgesia drug elimination that may mask neurologic recovery should be considered. The influence of ECMO related neurological injuries (embolic, hemorrhagic) and limitation of access to some types of neuroimaging (e.g. MRI) may also complicate the prognostic process for patients treated with ECPR.

Dr. Sam D. Shemie (Co-Chair)

Division of Critical Care, Montreal Children's Hospital, McGill University Health Centre
Medical Advisor, Deceased Donation, Canadian Blood Services
Professor of Pediatrics, McGill University, Montreal, Quebec

The intersection of ECPR and Organ Donation: Inherent conflict or natural convergence?

Dr. Shemie provided information on organ donation, including statistics and the differences between donation after neurological determination of death (NDD) and donation after circulatory determination of death (DCD). Anoxic brain injury after resuscitated cardiac arrest is becoming the most common etiology for deceased organ donation, particularly in DCD. Thus there is substantial convergence between all forms of CPR and potential opportunities for organ donation. While CPR techniques including ECPR, and outcomes, are improving, the most common outcome after resuscitated cardiac arrest is death. Although all organs undergo hypoxic-ischemic injury during CPR and ECPR, existing data shows that cardiac arrest during the clinical process from brain injury to donation does not impact on transplant outcomes(17).

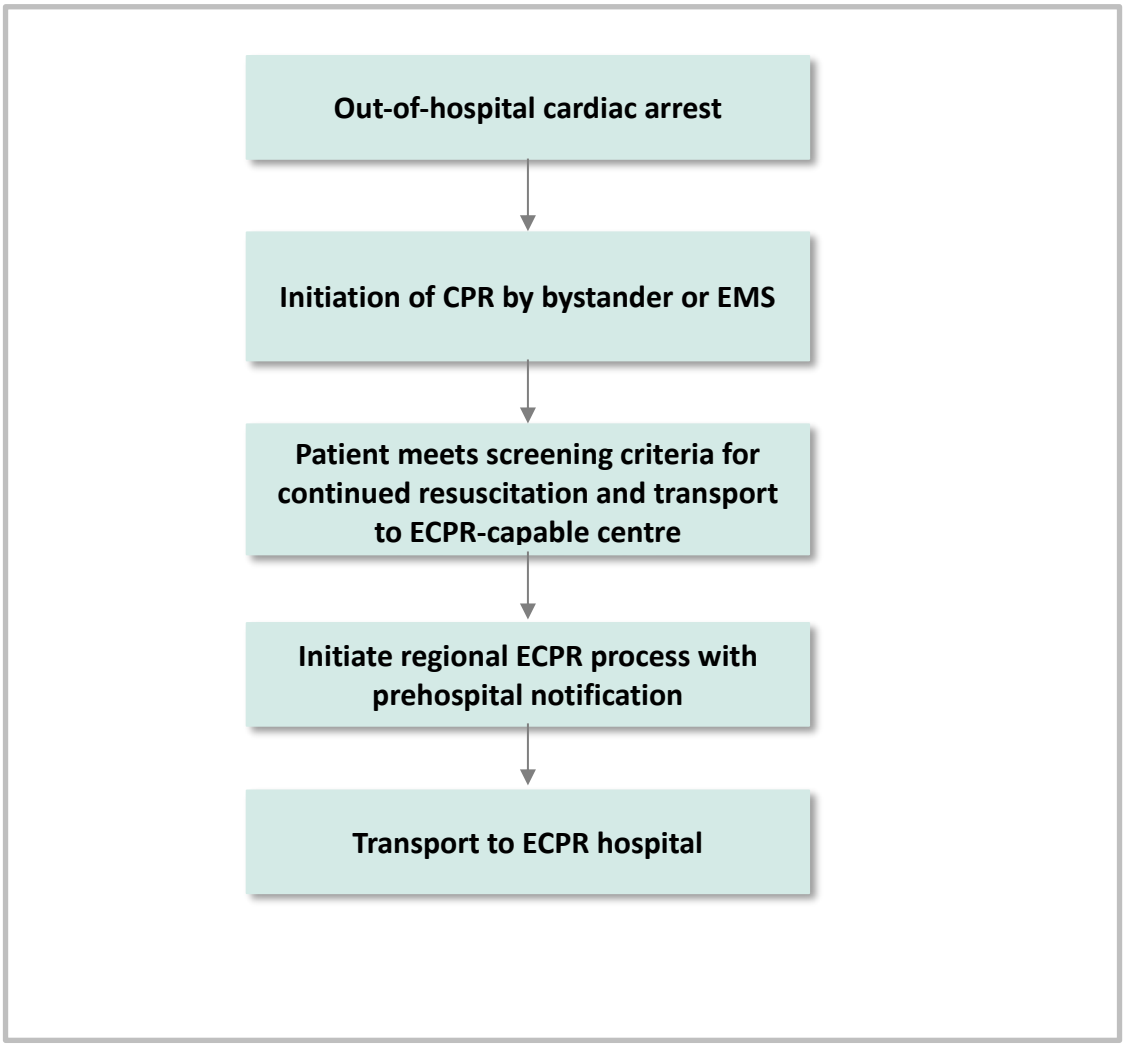
Dr Shemie reemphasized that the primary focus of any resuscitative intervention, including ECPR, is to save the patient's life. However, in cases where all reasonable, resuscitative interventions have failed, then the option of organ (and tissue) donation should be routinely provided whenever possible and appropriate. As well, any study reporting outcomes after CPR or ECPR should routinely include organ and tissue donation. Paradoxically, both CPR and organ donation save lives and are part of a continuum of outcomes after cardiac arrest. Any cost-benefit analysis of CPR interventions should include organ donation and transplantation. This is particularly important given that renal transplantation saves lives, saves costs and improves economic productivity as compared to dialysis treatment for patients with end-stage kidney failure. Dr. Shemie concluded that the intersections between CPR, ECMO and organ donation are inevitable, evolving and measurable, but will require cautious progress and collaboration between CPR, ECMO, ICU, neurosciences and organ donation communities.

4. Opportunities and challenges

Meeting attendees identified knowledge gaps and discussed practical barriers and challenges associated with each step in the clinical sequence of ECPR from patient contact to hospital discharge. Participants were also asked to identify high priority research questions related to the barriers and challenges identified. Attendees were divided into three working groups based on their area of expertise. The working groups were: 1) prehospital care, 2) emergency department care and ECMO deployment, and 3) ECMO maintenance and outcomes/prognosis. Each group was provided with a flowchart with high-level components of the clinical sequence within their domain to frame their discussion of potential barriers and challenges along the clinical sequence (Figures 1, 2, and 3). Each group had a dedicated scribe to record the discussion. In the paragraphs below we highlight aspects of the discussion in each group. Due to time constraints, participants were not able to discuss all aspects of the clinical sequence in their domain, and as a result, the following summary is not comprehensive, but focuses on the items discussed in the working groups during the time allotted.

1. OHCA and prehospital care

Figure 1. Components of the clinical sequence in the prehospital setting between recognition of out-of-hospital cardiac arrest and transportation to an ECPR-capable facility



Issues and discussion points:

❖ ***Screening OHCA patients by paramedics***

There are standardized and validated criteria for determining which OHCA patients should receive ongoing resuscitation and transportation to the hospital (18, 19). However, there are no standardized, evidence-based criteria for rapid screening of OHCA patients in the field to determine which are eligible for rapid transportation to ECPR hospitals (where decisions on which patients will be placed on ECMO will be made). Consensus on criteria would need to be established based on clinical rule methodology to identify a subgroup of OHCA patients who will benefit from ECMO. These criteria would require testing in the field to ensure that paramedics can effectively and consistently apply the criteria.

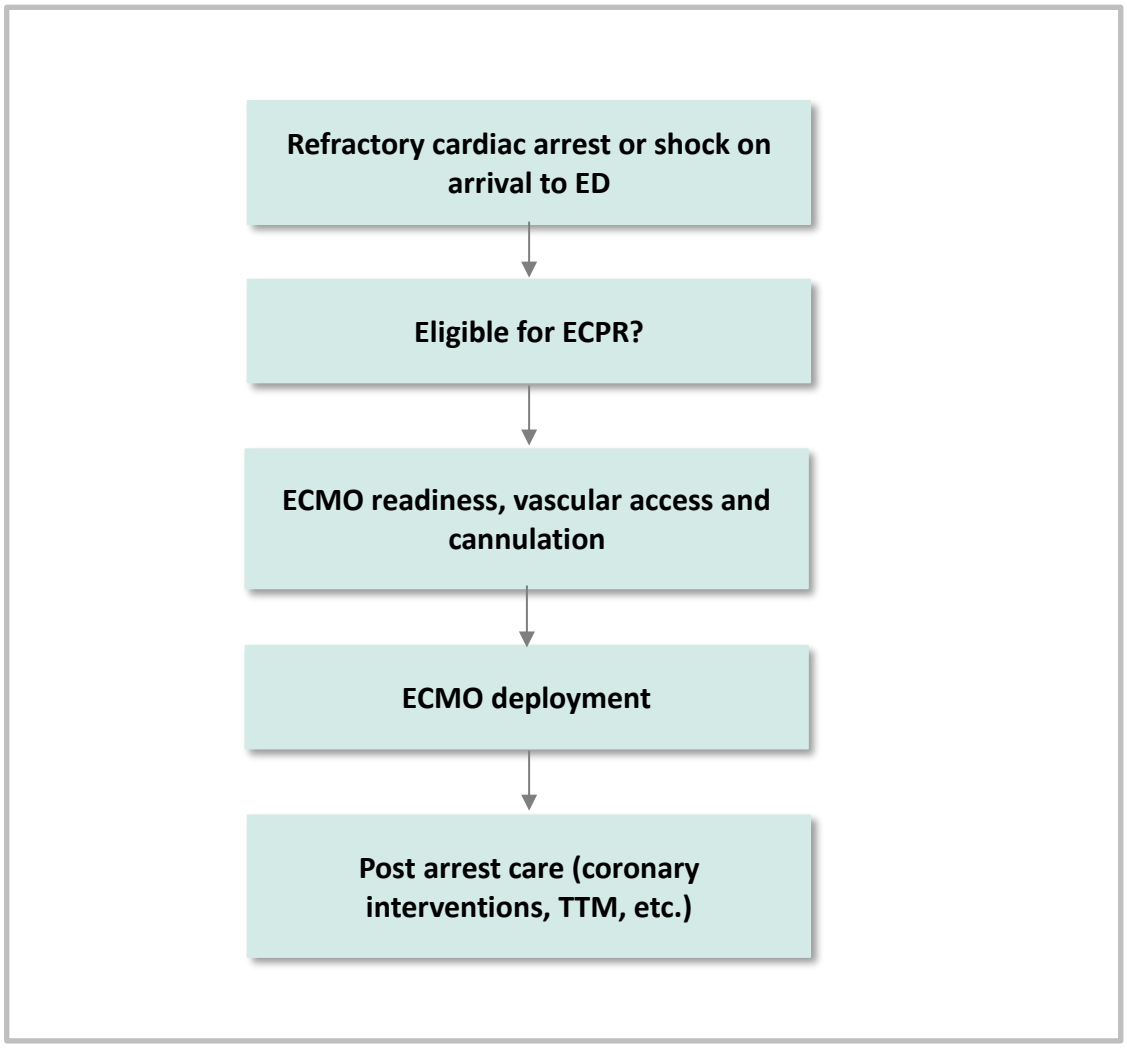
❖ ***Keeping paramedics and the public safe, and ensuring no further harm is done to patients***

ECPR requires the rapid transport of eligible patients with ongoing CPR to previously identified hospitals with requisite expertise. Participants identified several questions related to this process:

- What are the risks to paramedics and public safety with rapid transport?
- What are the pros and cons of using mechanical compression devices during transport?
- Are some patients harmed further when put in a rapid transport process? What is the risk to patients of transport to hospital, in comparison to further on-scene efforts where the focus is high-quality CPR and ACLS care processes? What is risk to the patient in bypassing hospitals that are not set up for ECPR for OHCA patients? What factors would go into this decision (Estimated time to hospital? Estimated time to cannulation?)
- Is it better for patients for longer intervention on the scene? What is the optimal time for onsite CPR prior to transport to hospital? What are the effects of deployment of a mechanical CPR device early during resuscitation?
- Should indicators of the quality of CPR delivery be routinely assessed as part of ECPR trials? What metrics of performance in conventional resuscitative techniques (e.g. chest compression fraction, proportion receiving ALS care, etc.) and systems of care (e.g. EMS response times, overall survival) should be achieved prior to consideration of adding resource-intensive ECPR programs? What measures (e.g. end-tidal CO2, cerebral oximetry) should be used to reflect the quality of CPR delivered?

2. ED care and ECMO deployment

Figure 2. Components of the clinical sequence in the emergency department setting from initial assessment of the patient with refractory cardiac arrest to implementation of post cardiac arrest care once ECMO has been deployed



Issues and discussion points:

- ***Inclusion and exclusion criteria for ECPR***

  Many of the same concerns related to eligibility that were identified in prehospital care are applicable on arrival at the hospital. There is a lack of standardized, evidence-based criteria for determining which patients will be eligible to receive ECPR treatment. Although observational studies may describe the outcomes among a certain group of patients considered "eligible" in that setting, robust data demonstrating which characteristics are the best predictors of good outcomes may require a broad application of ECPR therapies, a practise which is not likely to be feasible in most institutions. Eligibility should be similar across programs and based on predictors of recovery with good outcomes.

  Additional question and issues were raised:

  - What co-morbidities are acceptable? There is a need to exclude those patients with low chance of survival but should patients with co-morbidities that have variable severity, e.g., COPD, diabetes, be eligible for ECPR? Physicians rarely have this information at the time ECPR is being considered.
  - Are there types of patients in which conventional CPR is less effective that could benefit from a primary strategy of ECPR, e.g. morbidly obese patients?
  - Should ECPR be considered for those who suffer cardiac arrest after admission to the emergency department?
  - Post cardiac arrest shock (ROSC in field) should probably be included but because of worse outcomes in certain shock states, what additional criteria are required?
  - What is the definition of "refractory" cardiac arrest? How long should conventional CPR be continued before considering ECPR? There have been case reports of patients surviving after prolonged (i.e. 40 minutes) conventional CPR.
  - Delays of 5 – 75 minutes onto ECMO have been reported with good outcomes; however, program criteria for ECPR initiation should not be developed on the basis of outliers.

- ***Logistics issues***

  While many of the logistic issues have been worked out by the pioneering programs, e.g., Sharp Memorial Hospital in San Diego and St. Paul's Hospital in Vancouver, each program will be required to design and set up logistics according to their own unique situations.

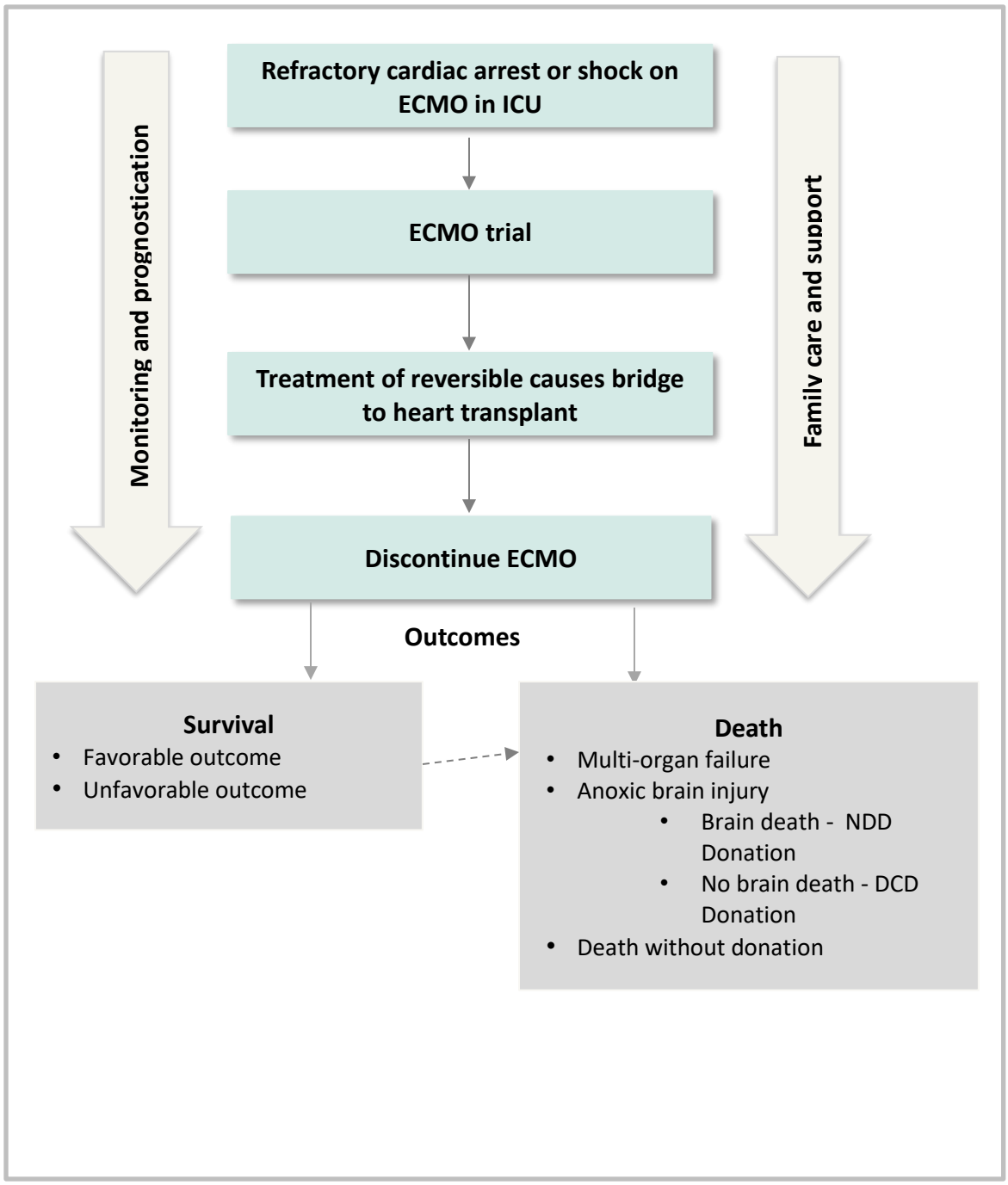
  Some of the key considerations include:

  - ***ECMO readiness:*** **Evidence indicates a correlation between arrest-to-ECPR durations and outcomes, with survival rare if > 75 minutes.** Therefore, rapid assessment for eligibility in the prehospital setting is a requirement as well as pre-activation and preparation at the hospital.
  - ***Room and equipment logistics:*** Where is the pump stored? How is the circuit kept primed? Where will cannulation be done? How is the room set up to ensure maximum efficiency and delivery of services?

- ***Personnel and training:***
    - Who is the cannulating practitioner? The processes are complicated and require skill and experience. Different programs have used different professionals including ED physicians, Intensivists, interventional radiologists, general surgeons and cardiac surgeons as the cannulating practitioner. What are the response times of these practitioners?
    - Who will be running the code?
    - Who will be managing the ECMO circuit during the initial set up and maintenance in the emergency department? What is the role of the perfusionist? Are there other professionals who could be trained to manage the ECMO machine in the emergency department before the patient can be transported to a critical care setting?
    - ECPR treatment is expected to be a relatively rare occurrence for most programs; therefore, staffing models and programs to train and maintain competency require a great deal of planning and organization. Will all staff be trained or only a sub-set? Will there be an on-call schedule or rotation? If required staff is off-site, will they be able to achieve the required arrest-to-ECPR initiation targets? What type of training will be provided so staff maintain competency?
- Can a system of care offer this service on a 24-7 basis, which would be required for an institution to partner with prehospital services in a clear pathway?

3. ECMO maintenance and prognosis / outcomes

Figure 3. Components of the clinical sequence in intensive care setting from initial assessment of the patient on ECMO arriving in the ICU to the discontinuation of ECMO



Issues and discussion points:

- ***Post-arrest care***

  There are many knowledge gaps related to care of the patient once placed on ECMO in the ICU:

  - What are the approaches to nutrition, hemodynamic support, ventilation management, anticoagulation, sedation, and left ventricle decompression, etc., for the ECMO patient?
  - What are the indications for coronary angiography among patients treated with ECPR?
  - What is the role of TTM in ECPR? What is the optimal target temperature for patients being treated with ECPR? How long should ECPR patients be treated with TTM? Does TTM during ECPR increase complication rates of ECMO (e.g. severe bleeding) or interfere with neuroprognostication?
  - What are optimal flow rates for patients treated with ECPR in the emergency department? How should flow rates be titrated?

- ***Neurological evaluation and prognostication***

  Neuroprognostication is a dynamic, iterative process. Decisions made too early can lead to patients who may otherwise have survived with favorable neurological functionality being withdrawn from ECMO and other forms of life support. Inaccurate neuroprognostication may also result in inappropriate use or continuation of ECMO in patients with no hope of meaningful neurologic recovery and a high risk for survival in a permanent vegetative state. Any anticipated increased time (ICU length of stay) required for neuroprognostication should be factored into considerations of cost-benefit and impact on ICU capacity and access.

  How does ECPR impact neuroprognostication after cardiac arrest?

  Patients treated with ECPR provide an additional challenge because it is not clear whether conventional approaches to neuroprognostication in post cardiac arrest patients are valid when a patient is on ECMO. In addition, many patients treated with ECPR are patients who have refractory cardiac arrest and may have suffered a prolonged period of cardiac arrest prior to ECPR initiation when compared with those who responded to conventional CPR. It is likely that the anoxic injury to key organs is, on average, more severe than those who respond to a shorter period of conventional CPR. The reliability of established neuroprognostication criteria in patients with prolonged, refractory cardiac arrest treated with ECPR (with potentially longer “no-flow” and CPR times) is still unknown. Also, the relationships between medications, TTM, ECMO and neuroprognostication are not known.

Other questions related to prognostication were identified:

- Should decision making for neuroprognostication be divided into phases: physiologic futility - no recovery of myocardial function versus poor or no recovery of brain function? What is the predictive value of absence of return of myocardial function after ECPR?
- What is the role of clinical evaluations, electrophysiology (EEG, SSEP) measures, neuroimaging, and brain blood flow and brain biomarkers with respect to neuroprognostication and how can confounding factors such temperature and drugs be managed?
- What is the period of observation for neuroprognostication on ECMO and what clinical and imaging criteria must be applied? How does TTM or other therapies affect the length of the period of observation?
    - Absence of pupillary response at 72h?
    - Motor responses at 3 – 5 days?
    - 72 hours after return to normothermia?
    - 72 hours after cardiac arrest if no TTM used?
    - >72 hours if confounding factors, e.g. delayed drug elimination on ECMO?
- How feasible is CT neuroimaging for these patients? Portable CT scans may improve feasibility for neuroimaging of patients on ECMO.
- Does ECMO have a direct impact on brain injury and recovery? How might this alter prognostication?

❖ ***Withdrawal of patients from ECMO: Development of ECMO Termination Rules***

Due to a paucity of data and lack of guidelines, clinical practice around the discontinuation of ECMO is heterogeneous. There needs to be a well-defined strategy for terminating ECMO which includes:

- For those patients with optimistic neuroprognosis and recovery of cardiovascular function, what is the best way to wean them off ECMO? Are there indicators such as hemodynamic targets for successful weaning from ECMO with positive outcome?
- What are the criteria for the determination of death by neurological criteria in patients on ECMO? What are the criteria for determination of death by circulatory criteria in patients after discontinuation of ECMO?
- Are there termination rules for stopping ECPR? Should such rules contain both cardiac and neurologic components? Should there be a minimum time interval from the initiation of resuscitation measures to termination of ECPR? How does TTM impact this time interval? Should the cost of ECMO maintenance also be considered in developing termination rules?
- For those patients with confirmed brain death or failure of cardiovascular recovery, what is the best way to manage end-of-life decision-making and withdrawal of ECMO in the palliative setting?
- What are the other elements of an optimal ECPR exit strategy?

There was concern that patients may be kept on ECMO despite concerns about futility. There may be several reasons for this:

- Given the recent Supreme Court ruling in Canada, physicians cannot unilaterally withdraw treatment against the wishes of patient's family or alternative decision-makers.
- Families can be reluctant to accept the death or poor anticipated outcome of a loved one and can refuse withdrawal of life sustaining therapy, including ECMO.
- Prognostication may be complicated and requires a waiting period. Most guidelines for neuroprognostication after cardiac arrest recommend waiting at least 72 hours.
- There are no standardized guidelines or protocols for when and how to stop ECMO treatment, making this process highly variable.

Experiences from ECPR programs in both Vancouver, British Columbia and Melbourne, Australia indicate this may not be a common challenge. According to Dr. Grunau, the longest time on ECMO for a patient with an unfavorable prognosis in Vancouver was one week. He indicated that in Australia criteria for the decision for removal from ECMO has been developed and is being followed, and the average time on ECMO is 1 – 3 days.

- ***Outcomes***
  - What are the most important outcomes for ECPR and at what time points should these outcomes be measured? Should both short and long-term outcomes be reported? What neurologic measure should be used to indicate the level of neurologic recovery? Should quality of life tools also be standardly used? Should outcomes for ECPR include organ donation and transplantation? What outcomes are the most important to patients, their families and society at large?

❖ ***Neurological outcomes of ECPR patients***

The following were identified as the potential outcomes of ECPR patients:

Recovery of system function	Patient outcome
1. Recovery of both heart and brain function	Discharge from hospital (favourable neurological outcome)
2. Recovery of heart function but damaged/diminished neurological function	Discharge from hospital (unfavourable neurological outcome)
3. Recovery of heart function but determination of death by neurological criteria	Death (potential NDD organ donor)
4. Recovery of heart function but proceed to WLST because of irrecoverable anoxic brain damage	Death (potential DCD organ donor)
5. Recovery of brain function but no myocardial recovery	Mechanical bridge to heart recovery, destination therapy (VAD or MCA device) or heart transplant, Or death
6. No recovery of heart function or brain function	Death (potential NDD or DCD donor)
7. Death due to conditions unrelated to cardiac or neurological recovery, including exsanguination, sepsis or multi-organ failure.	Death (unlikely donor)

4. Institutional planning and support

The group identified obtaining support and buy-in from all impacted divisions across the hospital and region including EMS as a potential challenge. Because the clinical process extends from prehospital care by paramedics, through to the ER and ICU and requires interdisciplinary involvement, there is a high degree of coordination, planning and training required from all these groups. More importantly in Canada, health care is publicly funded and allocation of new resources should be evidence-based or tied to planned research of promising and innovative approaches. The evidence in support of ECPR is not substantive enough at present and is unlikely to merit the allocation of new funding to support broad implementation of this intervention.

Like other types of critically ill patients requiring unscheduled intensive care, patients on ECPR could potentially cause disruptions to elective services in the hospital including cardiovascular surgeries (perfusionist availability), coronary angiography, critical care services and the institution's capacity to accept other critically ill patients due to the resource-intense nature of the situation. ECPR preparedness will require equipment and human resources. In addition, because ECMO machines may be a limited resource, placing patients on ECMO will limit an institution's ability to respond to additional cases where ECMO is indicated. Patient selection and the avoidance of ECPR deployment in futile cases will be important because of direct and indirect costs. Meeting participants from centres with existing programs indicated that support and participation in planning from all stakeholders and administrative leaders was critical during implementation.

5. Economic Considerations

The group recognized that establishing the clinical efficacy of ECPR for cardiac arrest is a top research priority, but acknowledged that economic analysis will be essential to make informed decisions about whether or not to pursue broad implementation.

There were many challenges identified with respect to the development of a cost-effectiveness analysis for ECPR. An ECPR program involves a series of interventions, each having different criteria for moving to the next step and each step having different outcomes. There are many uncertainties and any economic model created would require data on each element, however there is a lack of high quality data at present to inform these parameters. A large number of assumptions would be required, pending the availability of high quality data to inform the analyses.

For example, patients treated with ECPR could have a wide range of clinical outcomes with uncertain direct and indirect costs (e.g. family burden, lost wages, etc.). Some patients treated with ECPR could survive with sub-optimal neurological outcomes, including coma, vegetative states or other forms of severe disability requiring long-term care.

Any evaluation of an ECPR program would also need to consider unintended downstream costs and impacts to the health care system. For example, use of beds and perfusionist services in cardiac wards for patients treated with ECPR could potentially increase waiting times for other patients waiting for elective cardiovascular surgery or other hospital-based cardiac services. At a program level, given the financial constraints that health care systems are under, opportunity costs of ECPR implementation would need to be identified, i.e. what other services would need to be stopped in order to implement ECPR if there is no new funding available for the initiative.

While most cost-effectiveness analyses are done from the health care payer perspective, it will be important to consider the societal costs, i.e., workforce and home productivity for both those OHCA patients saved through ECPR and those patients saved as a result of organ donation from ECPR patients who do not survive. For example, the analysis would need to consider the economic impact of organ transplants resulting from ECPR patients who do not survive.

Data required to conduct an economic analysis include: How many additional lives will be saved with ECPR? How many of those saved will have favorable and unfavorable outcomes? What are the cumulative additional health care resources that would be deployed (including prehospital, ED, and in-hospital, as well as post-discharge for survivors)? If an increase in organs available for transplantation is realized, what is the clinical and economic impact of these?

Other estimates required to perform a cost-effectiveness analysis using a model include:

- Incidence of OHCA
- Based on standard criteria, number of potential patients that would be eligible for ECPR
- Potential patient outcomes:
  - Short term survival

- Long term (6 months+) survival
- Proportion of surviving patients with favorable / unfavorable neurological outcomes (including anoxic brain injured survival) as measured by a health utility measurement
- Death without donation
- Anoxic NDD donation
- Anoxic DCD donation
- Transplant organ utilization
- Transplant graft survival
- Transplant recipient survival

- Potential donors and estimated resulting number of organs/transplants
- Cost of ECPR (prehospital, ED, ICU, hospital stay) including program 'readiness', training and maintenance of competency costs
- Cost associated with survival with poor outcomes
- Cost consequences of additional organs available for transplantation

6. Ethics Considerations

Issues and discussion points:

Participants identified several ethical issues that would need further investigation and discussion:

- ***Unfavourable survival outcomes***
  Current evidence suggests that ECPR is associated with increased survival as compared to CPR alone in a subgroup of OHCA patients; however, that increased survival includes patients with poor neurological outcomes, including coma, vegetative states or severe disability. In some cases, patients could be left on ECMO as a "bridge-to-nowhere", where they have some neurologic function, but are not eligible for transplant or left ventricular assist device and not likely to recover.
  - What additional burdens are being placed on patients, families and society at large related to survival with poor neurologic function?

- ***Consent***
  Life-saving treatments delivered to patients in emergency settings have different informed consent/family consent requirements. This is predicated on the presumption that patients would agree to the treatment if they were able to. Given the potential harms and outcomes of ECPR, it is uncertain whether this presumption of consent can extend to ECPR.
  - Do families need to be consulted when initiating ECMO for resuscitative purposes?
  - Is consultation with families or alternative decision-makers feasible given the unexpected and time-sensitive nature of the intervention?
  - If firm exit criteria are established, what are the risks of family disagreement with recommended end-of-life care?

- ***Fair access***
  If decisions on who receives ECPR (both initiation in the field and the hospital) are made on a case-by-case basis, there may be the potential for selection bias and discrimination. To avoid this, clear criteria for inclusion and exclusion need to be developed based on targeting those who will receive benefits.

  Age is becoming increasingly difficult to justify as a cut-off for treatment and is increasingly being challenged on the basis of discrimination. Data will be required from both CPR and ECPR outcomes to inform which patient groups (and age groups) gain additional benefits from ECPR.

- ***Standard of care variation***
  While there is a standard of care for CPR, there is variation in practice. While this data is available in some provinces, it is not available consistently across the country.
  - Is there an ethical issue if ECPR becomes the standard of care in some jurisdictions and not in others?

- Given that in reality there already is a difference in the standard of care between high performing and low performing services, how is this any different?
- Is there a need to optimize existing CPR/ACLS services before considering implementation of an ECPR program?

The issue of criteria for the determination of brain death declaration is coming under some debate in the US. A clear protocol for how a declaration of brain death using the apnea test when a patient is on ECMO should be clearly outlined as a national standard based on expert opinion and/or evidence.

The decision making for initiating or withholding of CPR entails two components: 1) technical and 2) ethical. We currently understand that in many cases decisions related to CPR reflect the values of the treating physicians leading to considerable practice variation. Identified inclusion and exclusion criteria established in protocols for both CPR and ECPR decision-making will help establish a consistent practice standard.

7. Consideration of ECPR implementation in Canada

While hospital-based pilot programs may be in process or under consideration, the general consensus at the meeting was that ECPR is not ready for broad implementation in Canada. The consensus was based on the following observations:

- There is an absence of efficacy data suggesting that ECPR is superior to conventional resuscitation.
- A robust analysis of the cost-effectiveness, risks, and complex ethical considerations are lacking.
- Further work is required to standardize ECPR protocols and to identify and prioritize clinical outcomes of this intervention based on their importance to patients and the general public.
- This lack of data has hindered the development of evidence-based recommendations to inform the creation of ECPR protocols having a high probability of broad implementation and acceptance.

Given the potential high resource utilization with ECPR, higher quality data on effectiveness, harms, and cost-effectiveness is required prior to broad implementation of ECPR outside of a research setting. However, best available evidence from published studies on ECPR suggests benefit in a select patient population that serves as justification for further research. Some institutions across Canada may want to proceed with pilot programs; however this should only be done in the context of a research program. The group was aware of at least one Canadian ECPR pilot program (St. Paul's in Vancouver)(16) and there may be others ready to consider implementation in the context of innovation and carefully designed research.

The group thought that novel ECPR programs are best suited for centres with a well-established ECMO program for inpatients. The centre should receive a sufficient volume of patients to maintain competency, support data collection and program evaluation. Centres and regions considering such a program should undergo a careful and comprehensive examination of impacts prior to implementation.

Challenges to conducting an RCT

In order to obtain high quality evidence related to ECPR treatment, RCTs should be conducted. The group recognized several challenges related to conducting ECPR RCTs in Canada:

- ECPR is logistically complex and the "ECPR-eligible" population is selective with a relatively low incidence. RCTs would likely require multiple centers with ECPR capacity, infrastructure and levels of competence to achieve the necessary sample size.
- Consensus on many critical aspects of the protocol for ECPR, including which population would most benefit from the treatment (i.e. the inclusion and exclusion criteria and time limits at key steps in the process), cannulation and deployment strategies, management strategies, exit criteria and patient outcome measures.
- Ethical issues and cost-effectiveness analyses
- Hospital capacity issues

While the group agreed that an RCT comparing ECPR and conventional resuscitation is indicated, the environment and essential components are not yet available in Canada. However the group agreed that many other more feasible research activities could be undertaken in the present environment to support the development of a randomized controlled trial in the future:

1. **Create a research consortium to plan and monitor research in this area.**
   There was interest in developing an interdisciplinary group to advance research work in this area. In addition to those organizations and programs attending the meeting, other groups that could help with the work were identified.

2. **Submit a planning and dissemination grant to CIHR to consolidate a research agenda/ framework for ECPR.**
   During the working group discussions that took place at the meeting, participants generated a lengthy list of questions that they felt needed to be addressed regarding ECPR in the Canadian context (see Appendix 3). Participants agreed that a logical next step for investigating whether or not ECPR should implemented across Canada would be hold future meetings to consolidate a detailed research agenda to begin to address these questions. Broad areas for this proposed research program would include the subsequent items.

3. **Conduct a systematic review of existing literature.**

4. **Conduct an economic analysis.**

5. **Examine the ethical issues related to ECPR.**
   Normative claims to support the ethical issues related to the practice of ECPR should be developed with consideration of key stakeholders input, available data, and the review of all protocols being considered to support this practice. Inclusive of a trial ECPR program interviews with both survivors and families of deceased patients should be undertaken to understand short and long term implications of this practice.

6. **Develop consensus on inclusion/exclusion criteria for ECPR.**

7. **Develop consensus on a standardized protocol for ECPR**

8. **Develop consensus on outcome measures.**
   Any progression on analysis or evaluation of ECPR programs needs to be based on clear outcome measures that are important to patients and also reflect the efficacy of the process or treatment. Choosing and prioritizing the critical outcomes measures associated with ECPR is difficult given the complex nature of this intervention and the numerous confounding variables inherent to it. Both short-term (e.g. return of spontaneous cardiac activity or wean from ECMO) and long-term measures (e.g. patient survival and neurologic outcome at 1 year) need to be

included. Developments in the field of outcome assessment in the general area of cardiac arrest research will need to be followed closely as this research agenda is developed.

9. **Establish a standardized minimum data set for ECPR studies.**
   Because of the variability of data items collected as part of ECPR studies, a common approach to data definitions and data collection is needed. It was suggested that a standardized data set should be developed for future ECPR work, including the minimum data set that should be collected in any study. Ideally, all ECPR clinical programs in Canada should involve data collection and potentially collaborate with other centres to conduct observational studies. This group could potentially contribute to the effort by setting minimum data sets and providing a forum for a collaborative network and national database to improve the power and generalizability of data generated by individual ECPR programs as they arise.

10. **Consult with patients, families and the public to better inform ECPR clinical practice and research.**
    Public engagement was identified as a critical input to the design of any RCT or program evaluation, and was seen as crucial for the identification of outcomes that are most important to patients and the public. Public engagement was also seen as necessary for any ethics-related discussion around consent, access and acceptable parameters for ECPR RCTs. It was recognized that the ability to provide additional support to families would be an important feature in any ECPR program. This would cover consistency of information provided, family understanding and acceptance of the patient's condition, consent, dealing with family conflict or impasse and end-of-life decision-making. There are several models for providing family care/support and studies related to these models would help to inform ECPR protocols.

11. **Determine ECPR capability and acceptability in Canadian institutions**
    A clearer picture is needed of which programs in Canada are either in the process of planning or of implementing an ECPR program. The development of a national audit will provide valuable information for networking, information sharing, participation in studies, etc. The survey would also include questions for centres that are currently doing ECMO for in-house cardiac arrest. A separate survey could be done to gauge health care professional attitudes towards ECPR, ECMO and organ donation. This would include all specialties and disciplines potentially involved in an ECPR program: e.g. EMS, ED, ICU, neurology, cardiology, etc.

12. **Conduct observational studies.**
    Observational studies could help to determine the feasibility of ECPR in the Canadian setting and provide data to support the design of future clinical trials. Findings from observational studies that have uniform ECPR protocols and minimum data sets that include standardized outcome measures could improve care processes, provide further evidence for the identification of the patient population that would most benefit from this treatment and inform future RCTs. Given the significant ethical considerations inherent with the treatment and the fact that that its benefits have not been proven to outweigh the costs, both financial and societal, many

members of the group felt that a tightly controlled efficacy study is required before a more pragmatic effectiveness study is indicated.

Acronyms

ACLS	Advanced cardiovascular life support
AED	Automated external defibrillator
CPR	Cardiopulmonary resuscitation
CCPR	Conventional cardiopulmonary resuscitation
cDCD	Controlled donation after circulatory determination of death
DCD	Donation after circulatory determination of death
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
ED	Emergency department
EEG	Electroencephalogram
EOL	End-of-life
EMS	Emergency medical services
ER	Emergency room
ILCOR	International Liaison Committee on Resuscitation
MCA Device	Mechanical Circulatory Assist (MCA) device
NDD	Neurologic determination of death
OHCA	Out-of-hospital cardiac arrest
ROSC	Return of spontaneous circulation
RCT	Randomized controlled trial; randomized clinical trial
SSEP	Somatosensory evoked potentials
TTM	Targeted temperature management
VAD	Ventricular assist device
WLST	Withdrawal of life sustaining therapies

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Appendix 1: Meeting Agenda

	Part I: Challenge Address and Context
1.00 – 1.30	***Dr. Steve Brooks,*** *Associate Professor, Queen's University, Department of Emergency Medicine; Meeting Co-Chair* • Participant introductions • Challenge address
1.30 – 2.10	***Dr. Zack Shinar,*** *Emergency Physician, Sharp Memorial Hospital, San Diego, California* • The Sharp Memorial Hospital experience with E-CPR (30 min + 10 min Q&A)
2.10 – 2.40	***Dr. Brian Grunau,*** *Emergency Physician, St. Paul's Hospital, Vancouver* • The Vancouver experience with E-CPR (20 min + 10 min Q&A)
2.40 – 3.10	***Dr. Romer Geocadin,*** *Professor, Departments of Neurology, Anesthesiology/Critical Care Medicine and Neurological Surgery, The John Hopkins University School of Medicine* • Neuroprognostication and end-of-life decision making after cardiac arrest for the ECPR population (20 min + 10 min Q&A)
3:10 – 3:40	***Dr. Sam Shemie****, Critical Care Medicine, Montreal Children's Hospital, McGill University; Medical Advisor, Deceased Donation, Canadian Blood Services; Meeting Co-Chair* • The intersection between E-CPR and Organ Donation- Inherent conflict or natural convergence? (20 min + 10 min Q&A)
3.40 – 4.00	**Break**
	Part II: Clinical Sequence of ECPR
4.00 – 6.00	***Group Work:*** • Reviewing clinical sequences for prehospital care, ED care, ECMO deployment and maintenance, outcomes evaluation: – What are the opportunities, challenges, and barriers? – What are the research questions that need to be answered? – Overarching considerations (ethics, economic analysis, logistics)
6:00	**Working dinner**
6.00 – 7.00	Plenary, summary and next steps/roadmap

Appendix 2: List of Participants

Planning Committee:

Dr. Steve Brooks (Co-Chair)
Associate Professor, Department of Emergency Medicine, Queen's University
Emergency Physician, Kingston General Hospital

Dr. Sam Shemie (Co-Chair)
Division of Critical Care, Montreal Children's Hospital, McGill University Health Centre
Medical Advisor, Deceased Donation, Canadian Blood Services
Professor of Pediatrics, McGill University

Mr. Clay Gillrie
Program Manager, Deceased Donation, Canadian Blood Services
Vancouver, British Columbia

Ms. Laura Hornby
Lead Project Manager, DePPaRT Study, Pediatric Critical Care, CHEO Research Institute
Clinical Research Consultant, Deceased Donation, Canadian Blood Services

Ms. Sylvia Torrance
Associate Director, Centre for Innovation, Canadian Blood Services
Ottawa, Ontario

Group 1: OHCA and prehospital

Mr. Jason Buick
Emergency Medicine, St. Michael's Hospital, Toronto, Ontario

Dr. Jim Christenson
Head, Professor, Department of Emergency Medicine, University of British Columbia
Vancouver, British Columbia

Dr. Frederick D'Aragon
Assistant Professor, Faculty of Medicine, University of Sherbrooke
Clinical Researcher, Centre de Recherche CHUS, Sherbrooke, Quebec

Dr. William Dick
Vice President, Medical Programs, British Columbia Emergency Health Services

Dr. Ian Drennan
Institute of Medical Science, University of Toronto
Rescu, St. Michael's Hospital, Toronto, Ontario

Mr. Clay Gillrie
Program Manager, Deceased Donation, Canadian Blood Services
Vancouver, British Columbia

Dr. Noam Katz
PGY 4 Emergency Medicine, University of Ottawa
Fellow in Resuscitation and Reanimation Medicine, Queen's University

Dr. Laurie J. Morrison
Professor, Clinician Scientist, Division of Emergency Medicine, Department of Medicine, University of Toronto and Li Ka Shing Knowledge Institute, St Michael's Hospital
Director, Rescu, St. Michael's Hospital

Group 2: ED Care & ECMO Deployment

Dr. Steve Brooks
Associate Professor, Department of Emergency Medicine, Queen's University
Emergency Physician, Kingston General Hospital

Dr. Brian Grunau
Emergency Physician, St. Paul's Hospital, Vancouver
Clinical Assistant Professor, Department of Emergency Medicine, Faculty of Medicine, University of British Columbia

Ms. Laura Hornby
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Dr. Steve Lin
Emergency Physician and Trauma Team Leader, St. Michael's Hospital
Scientist, Rescu, Li Ka Shing Knowledge Institute, St. Michael's Hospital
Assistant Professor, Division of Emergency Medicine, Department of Medicine, University of Toronto

Dr. Dave Nagpal
Surgical Director of Heart Transplant and Mechanical Circulatory Support Program, London Health Sciences Centre, Western University, London, Ontario

Dr. Filio Billia
Director of Research, Peter Munk Cardiac Center Medical Director, Mechanical Circulatory Support Program Co-director, PMCC Cardiovascular Biobank Scientist, Toronto General Research Institute Assistant Professor, University of Toronto

Dr. William Stansfield
Assistant Professor, Surgery, University of Toronto
Cardiovascular Surgeon, University Health Network, Peter Munk Cardiac Centre, Toronto General Hospital

Group 3: ECMO Maintenance/Prognosis/Outcomes

Dr. Neill Adhikari
Staff Physician, Department of Critical Care Medicine, Sunnybrook Health Sciences Centre
Medical Co-Director, Cardiovascular ICU, Sunnybrook Health Sciences Centre
Associate Scientist, Sunnybrook Research Institute, Toronto, Ontario

Dr. Andrew Baker
Scientist, Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital
Professor, Departments of Anesthesia and Surgery, University of Toronto
Full Member, Institute of Medical Science, University of Toronto

Dr. J. Gordon Boyd
Assistant Professor, Department of Medicine (Neurology) and Critical Care, Centre for Neuroscience Studies, Queen's University, Kingston, Ontario

Dr. Allan DeCaen
Clinical Associate Professor/Pediatric Intensivist, Department of Pediatrics, Faculty of Medicine, University of Alberta

Dr. Eddy Fan
Assistant Professor of Medicine, Interdepartmental Division of Critical Care Medicine, and Institute of Health Policy, Management and Evaluation, University of Toronto
Medical Director, ECLS Program Director, Critical Care Research University Health Network, Mount Sinai Hospital Toronto, Ontario

Dr. Romergryko Geocadin
Professor, Departments of Neurology, Anesthesiology/Critical Care Medicine, and Neurological Surgery, Division of Neuroscience and Critical Care, Johns Hopkins University of Medicine, Baltimore, Maryland

Dr. John Gill
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Clinical Scientist, Division of Nephrology, St. Paul's Hospital, Vancouver

Dr. Eyal Golan
Critical Care Medicine, University Health Network, Toronto

Dr. Sam Shemie
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Medical Advisor, Deceased Donation, Canadian Blood Services
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Ms. Sylvia Torrance
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Ethics

Mr. Blair Henry
Senior Ethicist, Sunnybrook Health Sciences
Senior Ethicist, North York General Hospital
Assistant Professor, DFCM University of Toronto

Economics

Dr. Scott Klarenbach
Associate Professor, Clinical Scientist,
Nephrology, University of Alberta, Edmonton

Appendix 3: ECPR protocol related questions generated during working group discussions

Prehospital care

1. What are the field screening criteria for paramedics to determine which patients will be rapidly transported to ECPR hospitals?
2. What are the risks to paramedics and public safety with rapid transport?
3. What are the pros and cons of using mechanical compression devices during transport?
4. Are some patients harmed further when put in a rapid transport process?
5. What is risk to the patient in bypassing hospitals that are not set up for ECPR for OHCA patients? What factors would go into this decision (estimated time to hospital? Estimated time to cannulation?)
6. Is it better for patients to be managed for longer times on the scene? What is the optimal time limit for onsite CPR prior to transport to hospital? What are the effects of deployment of a mechanical CPR device early during resuscitation?
7. Should indicators of the quality of CPR delivery be standardly assessed as part of ECPR trials? What measures (compressions of adequate rate and depth and minimizing interruptions between compressions, end-tidal CO2, cerebral oximetry/NIRS) should be used to reflect the quality of CPR delivered?

ED care and ECMO deployment

8. What are the inclusion and exclusion criteria for ECPR patients?
9. What co-morbidities are acceptable? Should patients with co-morbidities that have variable severity, e.g., COPD, diabetes be eligible for ECPR?
10. Are there types of patients in which CPR is less effective that could benefit from a primary strategy of ECPR, e.g. morbidly obese patients?
11. Should ECPR be considered for those who suffer cardiac arrest after admission to the emergency department?
12. Post cardiac arrest shock (ROSC in field) should probably be included but because of worse outcomes in certain shock states, what additional criteria are required?
13. What is the definition of “refractory” cardiac arrest? How long should conventional CPR be continued before considering ECPR?

ECMO maintenance

14. What are the approaches to nutrition, hemodynamic support, and ventilation management, sedation, left ventricle decompression, etc., for the ECMO patient?
15. What are the indications for coronary angiography among patients treated with ECPR?
16. What is the role of TTM in ECPR? What is the optimal target temperature for patients being treated with ECPR? How long should ECPR patients be treated with TTM? Does TTM during

ECPR increase complication rates of ECMO (e.g. severe bleeding) or interfere with neuroprognostication)?

17. What are optimal flow rates for patients treated with ECPR in the emergency department? How should flow rates be titrated?

Prognostication

18. The principle of termination of CPR rules is based on the ability to resuscitate the heart, not to resuscitate the brain. What is the predictive value of absence of return of myocardial function after eCPR?
19. Should the decision making for neuroprognostication be divided into phases: physiologic futility - no recovery of myocardial function versus poor or no recovery of brain function
20. What is the role of clinical evaluations, electrophysiology (EEG, SSEP) measures, neuroimaging, brain blood flow and brain biomarkers with respect to neuroprognostication and how can confounding factors such temperature and drugs be managed?
21. What is the period of observation for neuroprognostication on ECMO and what clinical and imaging criteria must be applied? How does TTM or other therapies affect the length of the period of observation?
22. How feasible is CT neuroimaging for these patients?

Withdrawal of patients from ECMO

23. For those patients with optimistic neuroprognosis and recovery of cardiovascular function, what is the best way to wean them off ECMO? Are there indicators such as hemodynamic targets for successful weaning from ECMO with positive outcome? Is liberation from ECMO trial necessary?
24. What are the criteria for the determination of death by neurological criteria in patients on ECMO? What are the criteria for determination of death by circulatory criteria in patients after discontinuation of ECMO?
25. Are there termination rules for stopping ECPR? Should such rules contain both cardiac and neurologic components? Should there be a minimum time interval from the initiation of resuscitation measures to termination of ECPR? How does TTM impact this time interval? Should the cost of ECMO maintenance also be considered in developing termination rules?
26. For those patients with confirmed brain death or failure of cardiovascular recovery, what is the best way to manage end-of-life decision-making and withdrawal of ECMO in the palliative setting
27. What are the other elements of an optimal ECPR exit strategy?

Outcomes

28. What are the most important outcomes for ECPR and at what time points should these outcomes be measured?
29. Should both short and long-term outcomes be reported?
30. What neurologic measure should be used to indicate the level of neurologic recovery?

31. Should quality of life tools also be standardly used?
32. Should outcomes for ECPR include organ donation and transplantation?
33. What outcomes are the most important to patients, their families and society at large?

Economic analysis

34. How many additional lives would be saved with ECPR?
35. How many of those saved would have unfavorable neurological outcomes?
36. How much would it cost to save one more life?
37. How many additional lives would be saved through organ donation and transplantation?
38. What are the cost implications inclusive of program and outcomes?

Ethics

39. ECPR is associated with increased survival as compared to CPR alone; however, that increased survival includes patients with poor neurological outcomes, including coma, vegetative states or severe disability. What additional burdens are being placed on patients, families and society at large related to survival with poor neurologic function?
40. Do families need to be consulted when initiating ECMO for resuscitative purposes? Would consultation with families or alternative decision-makers be feasible given the unexpected and time-sensitive nature of the intervention?
41. If firm ECMO exit criteria are established, what are the risks of family disagreement with recommended EOL care?
42. Is there an ethical issue if ECPR becomes the standard of care in some jurisdictions and not in others?
43. Given that in reality there already is a difference in the standard of care between high performing and low performing services, how is this any different?
44. Is there a need to optimize existing CPR/ACLS services before considering implementation of an ECPR program?

Appendix 4: Selected bibliography

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