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Technology Assessment Unit of the McGill University Health Centre (MUHC)

Use of Extracorporeal Membrane Oxygenation for Cardiac Life Support in adult subjects

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Report prepared for the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC)

by

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Approved by the Committee of the TAU on Tuesday, June 6, 2017

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REPORT REQUESTOR

This report was requested by the chief of the Intensive Care Unit, Dr. Peter Goldberg, and the Director of Quality and Risk Management, Ms. Patricia Lefebvre, on May 11, 2016.

The date of the first review was at the TAU Policy Committee meeting held on Monday, March 13, 2017.

The date of the final review was at the TAU Policy Committee meeting held on Wednesday, May 10, 2017.

TYPES OF RECOMMENDATIONS ISSUED BY TAU

Type of recommendation	Explanation
Approval	• Evidence of efficacy, safety, and cost is sufficiently strong to justify a recommendation that the technology be accepted, used and funded through the institutional operating budget
Approved for evaluation	• There is a *high probability* that the technology is effective but the evidence is not yet sufficiently strong to support a recommendation for permanent approval; • The evidence is sufficiently strong to recommend a *temporary* approval for the purposes of evaluation, funded through the institutional operating budget; • Other context-specific factors are favorable such as MUHC experience, feasibility, improved efficiency, and availability of alternatives.
Not approved	• There is lack of evidence or conflicting evidence, and real uncertainty (equipoise) of efficacy and/or safety; • The costs of any use of the technology (e.g. for research purposes) should not normally be covered by the institutional budget.

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ABSTRACT

- Extracorporeal membrane oxygenation (ECMO) uses a modified cardiopulmonary bypass system to create an external circuit for the exchange of blood gases, thus helping to prolong the life of patients in acute respiratory or cardiac failure. ECMO configurations include veno-venous (VV) ECMO and veno-arterial (VA) ECMO. When VA-ECMO is used in conjunction with cardiopulmonary resuscitation (CPR), it is known as ECPR.

- Since 2010, ECMO use in adults has greatly increased, but it remains unclear whether ECMO prolongs survival and results in better neurological outcomes relative to alternative treatments, particularly for cardiac arrest patients.

- The objective of this report is to review the evidence on outcomes, efficacy, and safety of VA-ECMO. A further objective is to review the literature to identify optimal patient selection variables, and to identify programmatic factors that promote optimal ECMO utilization. Finally, we estimate the total costs and projected budget impact of using VA-ECMO at the MUHC.

- No randomized controlled trials of VA-ECMO in adults have been published so far. Data on survival rates for VA-ECMO relative to alternative options are inconclusive, given the limited evidence base, heterogeneous study populations and inconsistent results. There is a suggestion of improved survival with ECPR compared with conventional CPR for in-hospital and out-of-hospital cardiac arrest.

- We identified two documents offering guidelines for the optimal use of ECMO, but the current literature has not yet established clear normative guidelines due to the heterogeneous study population and limited body of evidence on clear indicators for survival.

- We also identified three models that predict survival after ECMO, but their utility to help patient selection remains unclear.

- Given the possible, but inconclusive, evidence for greater neurologically-intact survival with VA-ECMO relative to alternative options, there is a clear need for the MUHC to systematically document baseline characteristics and outcomes for each ECMO case.

- Spending on the 41 adults supported with ECMO at the MUHC since 2013 was $765,149. The estimated total cost of treating the next 20 patients with VA-ECMO is $361,211, assuming each patient spends 3 days on ECMO.

- At the MUHC, the decision to insert ECMO is made by cardiac surgeons or intensivists. However, a designated ECMO team comprising personnel from these specialities has not yet been created. Such an ECMO team would lead to faster deployment of ECMO, greater efficiency, and possibly improved clinical outcomes.
- ECMO is a resource-intensive technology, and the recent rise in ECMO cases at the MUHC has placed an increased burden on limited resources, including perfusionists. Perfusionist time allocated to ECMO has increased from 7% to 29% since 2014, although the number of perfusionists has not increased.
- The integration of this resource-intensive technology can only be sustained with a dedicated budget. Given that the MUHC also receives referrals from other hospitals, a dedicated budget is necessary to meet its role as a quaternary centre.

RÉSUMÉ

- L'oxygénation par membrane extracorporelle (OMEC) utilise un système de "bypass" cardiopulmonaire modifié de façon à créer un circuit externe pour l'échange des gaz sanguins, aidant ainsi à prolonger la vie des patients en insuffisance respiratoire aiguë ou en insuffisance cardiaque. Les différentes configurations OMEC incluent l'OMEC véno-veineuse (VV) et l'OMEC véno-artérielle (VA). Lorsque l'OMEC-VA est utilisée conjointement avec la ressuscitation cardiopulmonaire (RCP), l'appellation RCPE est utilisée.

- Depuis 2010, l'utilisation de l'OMEC chez l'adulte a beaucoup augmentée mais il demeure incertain que l'OMEC prolonge la survie et se traduit par de meilleurs résultats neurologiques relativement à des traitements alternatifs, particulièrement chez les patients en arrêt cardiaque.

- L'objectif de ce rapport est de revoir les preuves des résultats, de l'efficacité et de l'innocuité de l'OMEC-VA. Un autre objectif est de revoir la littérature pour identifier les variables correspondant à une sélection optimale des patients et pour identifier les facteurs programmatiques favorisant l'utilisation optimale de l'OMEC. Enfin, nous évaluons les coûts totaux ainsi que l'impact budgétaire projeté correspondant à l'utilisation de l'OMEC-VA au CUSM.

- Aucune étude randomisée de l'OMEC-VA chez l'adulte n'a été publiée à ce jour. Les données sur les taux de survie suite à l'OMEC-VA, comparativement aux options alternatives, ne sont pas concluantes étant donné le peu de données probantes, les populations hétérogènes étudiées ainsi que les résultats incohérents. Par contre, il y a indication d'une survie améliorée avec la RCPE comparativement à la RCP conventionnelle lors d'arrêts cardiaques intra-hospitaliers et extra-hospitaliers.

- Nous avons identifié deux documents proposant des lignes directrices pour l'utilisation optimale de l'OMEC mais la littérature actuelle n'a toujours pas établi des lignes directrices normatives dues aux populations hétérogènes étudiées ainsi qu'à un nombre limité de preuves sur des indicateurs précis de survie.

- Nous avons aussi identifié trois modèles prédisant la survie après l'OMEC mais leur utilité pour aider à la sélection des patients demeure incertaine.

- Étant donné les preuves possibles mais non concluantes pour une plus grande survie sans dommage neurologique avec l'OMEC-VA relativement à des options

alternatives, il existe un besoin évident pour que le CUSM documente systématiquement les caractéristiques de base et les résultats de chaque cas impliquant l'OMEC.

- Au CUSM, les dépenses pour les 41 adultes supportés avec l'OMEC depuis 2013 se chiffrent à 765 149 $. Le coût total estimé pour traiter les 20 prochains patients avec l'OMEC-VA est de 361 211 $ en supposant que chaque patient soit supporté 3 jours par l'OMEC.

- Au CUSM, la décision d'utiliser l'OMEC est prise par les chirurgiens cardiaques ou par les intensivistes. Cependant, une équipe OMEC dédiée comprenant du personnel de ces spécialités n'a pas encore été créée. Une telle équipe OMEC permettrait un déploiement plus rapide de l'OMEC, une plus grande efficience et possiblement, une amélioration des résultats cliniques.

- L'OMEC est une technologie qui nécessite un personnel important et l'augmentation récente des cas OMEC au CUSM a créé un fardeau accru sur les ressources limitées, incluant les perfusionnistes. Le temps perfusionniste alloué à l'OMEC a augmenté de 7% à 29% depuis 2014, bien que le nombre de perfusionnistes n'ait pas augmenté.

- L'intégration de cette technologie nécessitant un personnel important ne peut être soutenue qu'à l'aide d'un budget dédié. Étant donné que le CUSM reçoit des patients référés d'autres hospitaux, un budget dédié s'impose pour que celui-ci joue son rôle de centre quaternaire.

LIST OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
CI	Confidence interval
CPB	Cardio pulmonary bypass
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal membrane oxygenation during cardiopulmonary resuscitation
ELSO	Extracorporeal Life Support Organization
HTA	Health technology assessment
ICU	Intensive care unit
MUHC	McGill University Health Centre
MV	Mechanical ventilation
NICE	National Institutes for Health and Clinical Excellence
QoL	Quality of life
RCT	Randomized controlled trial
TAU	MUHC Technology Assessment Unit
VAD	Ventricular assist device
VA-ECMO	Veno-venous extracorporeal membrane oxygenation
VV-ECMO	Veno-arterial extracorporeal membrane oxygenation

EXECUTIVE SUMMARY

Background

Extracorporeal membrane oxygenation (ECMO) uses the creation of an external blood gas exchange circuit to provide temporary life support to patients in acute respiratory or cardiac failure, and includes veno-venous (VV) ECMO and veno-arterial (VA) ECMO. When VA-ECMO is used during cardiopulmonary resuscitation, it is known as ECPR. ECMO has a long history of use to support neonates in respiratory failure. ECMO use in adults has greatly increased since 2010, with expanding cardiac failure indications.

Objectives

This report will focus primarily on use of VA-ECMO in adults, because that is the modality used by the majority of McGill University Health Centre (MUHC) cases, i.e. those with acute heart failure requiring cardiac support. The objectives of this report are to:

1. review the evidence on the outcomes, efficacy and safety of VA-ECMO
2. review the literature to identify optimal patient selection variables for VA-ECMO
3. review the literature to identify programmatic factors that promote optimal ECMO utilization,
4. summarize the MUHC experience with ECMO, focusing primarily on outcomes and cost

Methods

We performed a literature search to identify recent HTAs, systematic reviews and meta-analyses that have reviewed the efficacy and safety of VA-ECMO. Results were extracted separately for VA-ECMO for cardiogenic shock and ECPR for cardiac arrest. We also carried out a search for any HTAs, protocols or guidelines describing criteria for patient selection for VA-ECMO in adults and for observational studies that have identified predictors of survival following VA-ECMO. We searched for protocols or guidelines describing organizational characteristics necessary for achieving optimal outcomes following ECMO. We reviewed the outcomes in patients who have received ECMO (either VA or VV) at the MUHC. Finally, we evaluated the cost and budget impact of ECMO support in adults at the MUHC.

Results: Literature review

Outcomes, efficacy and safety following VA-ECMO:

Survival following use of the VA-ECMO is determined largely by the nature and severity of the pathology being treated. Overall, evidence from case series indicate that VA-ECMO is associated with 40% survival to discharge in adults.

There has been a particular surge in ECPR use, according to an analysis of data from the Extracorporeal Life Support Organization (ELSO) database that indicates a 10-fold increase from 2003 to 2014, from 35 annual cases to 400. This same study reported survival rates at discharge for ECPR to be 29%, which has not changed over time.

No randomized controlled trials of VA-ECMO in adults have been published so far. We identified 5 observational studies of VA-ECMO in cardiogenic shock patients, and 8 studies of ECPR in in-hospital and out-of-hospital cardiac arrest patients that reported neurologically-intact survival:

- VA-ECMO for cardiogenic shock: 5 studies compared VA-ECMO to various alternatives, including ventricular assist devices (VAD), cardiopulmonary bypass (CPB), or mechanical ventilation. The ECMO groups had small number of patients, ranging from 15 to 61. Only the study comparing VA-ECMO to CPB in lung transplant found a higher survival rate in the ECMO group [87% vs 61%].
- ECPR for in-hospital cardiac arrest: Of 4 studies, all reported improved neurologically-intact survival in the ECPR group vs. the CPR group (improvement in survival ranging from 7% to 18%), but only 1 (n=120) showed statistically significant improvements at discharge, and at 2 years.
- ECPR for out-of-hospital cardiac arrest: 3 of 4 studies reported statistically significant benefit in the ECPR group for neurologically-intact survival (improvement ranged from 11% to 33%). The largest of these (n=454, prospective, not propensity-matched) reported an improvement in survival of 11% that persisted at 6 months.

In summary, data on survival rates for VA-ECMO relative to alternative options (such as ventricular assist devices or cardiopulmonary bypass) are inconclusive, given the limited evidence base, heterogeneous study populations and inconsistent results. Limited evidence from observational studies suggest that there may be improved neurologically-

intact survival with ECPR compared with conventional CPR for both in-hospital and out-of-hospital cardiac arrest.

In terms of safety, a meta-analysis of case series found a high rate of complications with VA-ECMO including major bleeding (41%), infection (30%) and neurological complications (13%).

A few small studies evaluated health-related quality of life (QoL) after VA-ECMO, and in general concluded that cardiac patients who survive ECMO have similar QoL scores to those patients who did not receive ECMO, suggesting that ECMO does not greatly diminish quality of life in patients with pre-existing chronic illness.

Patient selection for VA-ECMO:

Proper patient selection can influence clinical outcomes; however, evidence-based guidelines do not currently exist. The Extracorporeal Life Support Organization (ELSO), an international body that maintains a registry of ECMO cases, and The Alfred Hospital in Melbourne, Australia, which has a well-established ECMO program, have published indications and contra-indications for ECMO. According to these guidelines, VA-ECMO is indicated for refractory life-threatening forms of reversible respiratory and/or cardiac failure where the benefit to risk ratio of VA-ECMO is greater than that of other less invasive life-support techniques.

We also identified three statistical models that can be used to estimate a patient's probability of survival following VA-ECMO based on characteristics such as patient's age and comorbidities. But more validation studies are needed before we can comment on the utility of such models in practice.

Programmatic considerations for ECMO:

A position paper by international ECMO experts as well as guidelines from ELSO have put forward various considerations for establishing an ECMO program. Though not evidence based, these guidelines make several recommendations including the acquisition of appropriate infrastructure and the establishment of a specialized ECMO team comprising highly experienced personnel from cardiovascular surgery, perfusion and intensive care. Recent evidence suggests that patients receiving ECMO at centres treating more than 30 adult ECMO cases per year have lower mortality rates than those treated at centres with fewer than six adult cases annually, making the case for concentrating ECMO treatment in a few high-volume centres.

Experience with ECMO at the MUHC

From March 2013 to September 2016, 41 adults have been supported with ECMO at the MUHC: 35 (85%) received VA-ECMO, including 14 (34%) who received ECPR; 6 (15%) received VV-ECMO. There has been a particular increase in ECPR use, from 2 cases in the 2013-14 fiscal year (constituting 17% of all ECMO cases that year), to 6 cases in the first half of the 2016-17 fiscal year (60% of all ECMO cases). ECMO cases originated from various units, including the operating room, the ICU, the catheterization laboratory, and the cardiac care unit. The decision to insert ECMO is made by intensivists in the ICU, or by cardiac surgeons; a designated ECMO team comprising personnel from these units does not currently exist. The increase in ECMO cases has resulted in an increase in perfusionist time allocated to ECMO from 7% to 29% since 2014, and a parallel decrease in time allocated to other services. This increase is independent of the number of perfusionists at the MUHC (10 perfusionists), which has not increased in this time period. Patients were mainly male (68%), with an average age of 55 years (range: 21 to 89 years), and spent a median of 3 days on ECMO (range: 0 to 13 days). Overall survival at weaning was 49% (vs 56% reported by the ELSO registry), and 30-day survival was 38% (compared to 41% at discharge reported by ELSO).

Costs

To determine the cost of ECMO we considered nursing and ICU costs, device and disposable costs, and perfusionist costs. The estimated cost of treating a patient with VA-ECMO for 3 days is $18,060.55. Thus, the total cost of treating 20 such patients is $361,211. The estimated budget impact (additional costs incurred by the use of ECMO) of treating a patient with VA-ECMO for 3 days is $13,289.35.

CONCLUSIONS

- ECMO is a temporary life support technique to support patients with acute heart or respiratory failure and high risk of mortality. Since 2010, ECMO use in adults has increased, and indications have expanded to adults in cardiac failure.
- Given the limited evidence base, it remains unclear whether VA-ECMO prolongs survival and results in better neurological outcomes relative to alternative treatments such as ventricular assist devices, cardiopulmonary bypass and mechanical ventilation. Data from comparative studies suggest some evidence of improved survival with ECPR relative to conventional CPR. However, ongoing RCTs of ECPR vs conventional CPR in cardiac arrest patients indicate continued equipoise

for trials of ECMO in this population. Data from case series indicate that survival to discharge after VA-ECMO for cardiogenic shock is approximately 40%.

- Although some organizations have attempted to develop guidelines for indications of ECMO use, the current literature has not established clear normative guidelines due to the heterogeneous study population and limited body of evidence on clear indicators for survival.

- Recent evidence suggests that patients receiving ECMO at high-volume centres (>30 adult ECMO cases per year) have lower mortality rates than those treated at centres with fewer than six adult cases annually, making the case for concentrating ECMO treatment in a few high-volume centres.

- At the MUHC, 41 adults have been supported with ECMO since 2013. Survival was comparable to data reported in large case series (49% at weaning and 38% at 30 days). The estimated total cost of treating 20 patients with VA-ECMO is $361,211 assuming each patient spends 3 days on ECMO. The estimated budget impact (additional costs incurred by the use of ECMO) of treating a patient with VA-ECMO for 3 days is $13,289.35.

- ECMO is a resource-intensive technology, and the recent rise in ECMO cases at the MUHC has placed an increased burden on limited resources, including perfusionist time. There is a need for dedicated funding to ease this burden and avoid unwanted delays in access to care.

RECOMMENDATIONS

- VA-ECMO for cardiogenic shock: Despite the absence of convincing evidence of superiority of VA-ECMO over alternative treatments for patients in cardiogenic shock, this technology has become widely accepted. We thus recommend an approval for evaluation of VA-ECMO in selected cardiogenic shock patients. [Please see Page ii for an overview of recommendation types issued by the TAU.]

- ECPR for in-hospital cardiac arrest: In view of the limited evidence that ECPR may improve survival rates compared to CPR alone, as well as the wide acceptance of this technology, it is recommended that this intervention continue to be made available within the MUHC. We thus recommend an approval for evaluation of ECPR for in-hospital cardiac arrest patients.

- ECPR for out-of-hospital cardiac arrest: Currently, these cases are not treated with ECMO at the MUHC. Given the limited evidence that ECPR may improve

neurologically-intact survival in out-of-hospital cardiac arrest patients, and the availability of ECMO at the MUHC, we recommend an approval for evaluation of ECPR for out-of-hospital cardiac arrest patients, which is conditional on:

  - procurement of dedicated funding to ease the burden on resources associated with an increase in ECMO use;
  - establishment of an ECMO team.

- All of the above recommendations are conditional on:
  - systematic documentation of each case;
  - re-evaluation of the evidence as new data, or new technology, become available.
- The following recommendations apply to VA-ECMO (including ECPR) and VV-ECMO:
  - Any further increase in ECMO cases performed at the MUHC must be preceded by dedicated funding to sustain the increased use, including funding for outside referrals, and for perfusionists or nurses trained to replace perfusionists at the bedside. Such a dedicated budget is necessary to avoid unwanted delays in access to care due to a diversion of perfusionist services, and to reduce the burden on perfusionists.
  - Given that the decision to insert ECMO is made by cardiac surgeons and intensivists, the creation of a designated multi-disciplinary ECMO team comprising personnel from these specialties is necessary to foster efficient decision-making and faster deployment of ECMO, which may improve clinical outcomes.
  - We strongly recommend that the following variables be systematically documented for each case of ECMO: indications for use, reasons for choosing ECMO over alternative treatments, patient characteristics identified as relevant in the literature, time to deployment, complications, survival, and neurological outcomes.
  - A protocol should be developed outlining potential indications and contraindications, weaning criteria, and ethical considerations, to establish clear guidelines for the use of ECMO at the MUHC,
  - In order to promote optimal resource utilization, a quality review process for ECMO should be established.

    - The MUHC should register its adult ECMO site with ELSO, thus contributing valuable data to this vast, international registry.

- Given the limited evidence base and that ECMO is a rapidly evolving technology, this report should be updated as new information becomes available.

SOMMAIRE

Contexte

L'oxygénation par membrane extracorporelle (OMEC) utilise un circuit sanguin extérieur pour les échanges gazeux, permettant un support vital temporaire aux patients en insuffisance respiratoire aiguë ou en insuffisance cardiaque, et comprend l'OMEC véno-veineuse (OMEC-VV) et l'OMEC véno-artérielle (OMEC-VA). Lorsque l'OMEC-VA est utilisée conjointement avec la ressuscitation cardiopulmonaire, l'appellation RCPE est utilisée. L'OMEC est utilisée depuis longtemps pour supporter les nouveaux-nés en insuffisance respiratoire. L'utilisation de l'OMEC chez l'adulte a beaucoup augmenté depuis 2010, liée à l'augmentation des indications d'insuffisance cardiaque.

Objectifs

Ce rapport se concentrera principalement sur l'utilisation de l'OMEC-VA chez l'adulte car c'est la modalité que l'on retrouve chez la majorité des cas traités au Centre universitaire de santé McGill (CUSM), soit ceux montrant une défaillance cardiaque aiguë nécessitant un support cardiaque. Les objectifs de ce rapport sont:

1. Revoir les preuves des résultats, de l'efficacité et de l'innocuité de l'OMEC-VA.
2. Revoir la littérature pour identifier les variables correspondant à une sélection optimale des patients pour l'ECMO-VA.
3. Revoir la littérature pour identifier les facteurs programmatiques favorisant l'utilisation optimale de l'OMEC.
4. Résumer l'expérience du CUSM en regard de l'OMEC en se concentrant principalement sur les résultats et les coûts.

Méthodologie

Nous avons effectué une revue de la littérature pour identifier les récents rapports d'évaluation des technologies (HTA), les revues systématiques et les méta-analyses ayant revu l'efficacité et l'innocuité de l'OMEC-VA. Les résultats furent compilés séparément pour l'OMEC-VA lors de chocs cardiogéniques et pour la RCPE lors d'arrêts cardiaques. De même, nous avons aussi recherché des rapports d'évaluation des technologies (HTA), des protocoles ou des lignes directrices décrivant des critères pour la sélection de patients adultes pouvant être supportés par l'OMEC-VA, et des études d'observation ayant identifié des prédicteurs de survie après traitement avec l'OMEC-VA. Nous avons

recherché des protocoles ou des lignes directrices décrivant les caractéristiques organisationnelles requises pour atteindre des résultats optimaux suivant un support par OMEC. Nous avons revu les résultats des patients ayant été traités par OMEC-VA ou OMEC-VV au CUSM. Enfin, nous avons évalué les coûts et l'impact budgétaire du support OMEC chez l'adulte au CUSM.

Résultats

Résultats, efficacité et innocuité de l'OMEC-VA:

La survie suite à l'utilisation de l'OMEC-VA est largement déterminée par la nature et la sévérité de la pathologie traitée. De façon globale, les preuves des différentes séries de cas nous indiquent que l'OMEC-VA est associée à une survie de 40% chez l'adulte, au moment du congé de l'hôpital.

L'organisme "Extracorporeal Life Support Organization" (ELSO) a noté une augmentation singulière de l'utilisation de la RCPE, suite à l'analyse des chiffres de leur base de données qui indique qu'il y a eu 10 fois plus de cas traités entre 2003 et 2014, soit une augmentation de 35 à 400 cas par année. La même étude rapporte que le taux de survie au moment du congé hospitalier suivant la RCPE est de 29%, taux qui n'a pas changé avec le temps.

Aucune étude randomisée de l'OMEC-VA chez l'adulte n'a encore été publiée à ce jour. Nous avons identifié 5 études d'observation de l'utilisation de l'OMEC-VA chez les patients en choc cardiogénique ainsi que 8 études de la RCPE intra-hospitalière et extra-hospitalière chez les patients en arrêt cardiaque, qui rapportaient une survie sans dommage neurologique:

- L'ECMO-VA lors de chocs cardiogéniques: 5 études ont comparé l'OMEC-VA à diverses alternatives incluant les dispositifs d'assistance ventriculaire (DAV), le pontage cardiopulmonaire (PCP) ou la ventilation mécanique. Les groupes OMEC-VA avaient moins de patients, variant de 15 à 61. Seule l'étude comparant l'OMEC-VA au PCP lors de la transplantation pulmonaire identifia un plus haut taux de survie chez les groupes OMEC (87% vs 61%).
- La RCPE lors d'arrêts cardiaques intra-hospitaliers: 4 études ont unanimement mentionné une amélioration de la survie sans dommage neurologique chez le groupe RCPE vs le groupe RCP (amélioration de la survie variant de 7% à 18%), mais

une seule étude (n=120) montra des améliorations statistiquement significatives après congé et après 2 ans.

- La RCPE lors d'arrêts cardiaques extra-hospitaliers: 3 études sur 4 ont rapporté un bénéfice statistiquement significatif chez le groupe RCPE pour une survie sans dommage neurologique (amélioration variant de 11% à 33%). Le groupe le plus important (n=454, prospectif, sans l'appariement des coefficients de propension) rapporta une amélioration de la survie de 11% qui demeura après 6 mois.

En résumé, les données des taux de survie pour l'OMEC-VA, comparativement aux options alternatives (tel que les dispositifs d'assistance ventriculaire ou le pontage cardiopulmonaire), ne sont pas concluantes étant donné le peu de données probantes, les populations hétérogènes étudiées ainsi que les résultats incohérents. Le peu de preuves des études d'observation suggère qu'il peut y avoir une amélioration de la survie sans dommage neurologique avec la RCPE, comparativement à la RCP conventionnelle lors d'arrêts cardiaques intra-hospitaliers et extra-hospitaliers.

Concernant l'innocuité, une méta-analyse des séries de cas identifia un haut taux de complications liées à l'OMEC-VA incluant des saignements majeurs (41%), des infections (30%) et des complications neurologiques (13%).

Quelques petites études évaluèrent la qualité de vie (QoL) après l'OMEC-VA et de façon générale, ont conclu que les patients ayant survécu après support OMEC-VA avaient des scores QoL similaires à ceux des patients n'ayant pas été traités par l'OMEC-VA, suggérant que l'OMEC ne diminue pas considérablement la qualité de vie des patients ayant des maladies chroniques préexistantes.

Sélection des patients pour l'OMEC-VA:

Une sélection judicieuse des patients peut influencer les résultats cliniques; cependant, des lignes directrices fondées sur des données probantes n'existent pas actuellement. L'organisme international ELSO (Extracorporeal Life Support Organisation) qui tient un registre des cas OMEC et "The Alfred Hospital" de Melbourne (Australie) qui possède un programme OMEC bien établi, ont publié des indications et des contre-indications pour l'utilisation de l'OMEC. Selon ces lignes directrices, l'OMEC-VA est indiquée pour les formes mortelles et réfractaires d'insuffisance respiratoire et/ou cardiaque réversibles lorsque le rapport "bénéfices vs risques" de l'OMEC-VA est plus grand que celui des autres techniques de support non-invasives.

Nous avons aussi identifié trois modèles statisques pouvant être utilisés pour estimer la probabilité de survie d'un patient suite à l'OMEC-VA, fondée sur ses caractéristiques telles que son âge et ses comorbidités. Mais plus d'études sont requises pour valider ces modèles avant que nous puissions commenter leur utilité en pratique.

Considérations programmatiques pour l'OMEC:

Un exposé de principes par des experts internationaux en OMEC ainsi que des lignes directrices de l'organisme ELSO ont mis de l'avant diverses considérations pour la mise en place d'un programme OMEC. Même si elles ne sont pas fondées sur des données probantes, ces lignes directrices font plusieurs recommandations incluant la mise en place d'une infracstructure appropriée et d'une équipe OMEC spécialisée comprenant un personnel hautement qualifié issu de la chirurgie cardiovasculaire, de la perfusion et des soins intensifs. Des preuves récentes suggèrent que les patients supportés par l'OMEC dans des centres traitant plus de 30 cas OMEC par année chez l'adulte ont des taux de mortalité plus bas que ceux des patients traités dans des centres recevant moins de six cas adultes par année, ce qui suggère fortement de concentrer les traitements OMEC dans quelques centres hospitaliers à fort débit.

L'Expérience du CUSM avec l'OMEC

De mars 2013 à septembre 2016, 41 adultes ont été supportés par l'OMEC au CUSM: 35 patients (85%) ont été traités par l'OMEC-VA, incluant 14 patients (34%) qui ont été traités par RCPE; 6 patients (15%) ont été traités par l'OMEC-VV. Il y a eu une augmentation singulière de l'utilisation de la RCPE, de 2 cas pour l'année fiscale 2013-2014 (soit 17% de tous les cas OMEC de l'année) à 6 cas durant la première demie de l'année fiscale 2016-2017 (60% de tous les cas OMEC). Les cas OMEC provenaient de différentes unités incluant le bloc opératoire, l'unité des soins intensifs, le laboratoire de cathétérisme et l'unité cardiaque. La décision de traiter avec l'OMEC est prise par les intensivistes à l'unité des soins intensifs ou par les chirurgiens cardiaques; une équipe OMEC dédiée comprenant du personnel de ces unités n'existe pas actuellement. L'augmentation des cas OMEC s'est traduite par une augmentation du temps perfusionniste alloué à l'OMEC, de 7% à 29% depuis 2014, ainsi qu'une diminution correspondante du temps consacré aux autres services. Cette augmentation est indépendante du nombre de perfusionnistes au CUSM (10 perfusionnistes), qui n'a pas augmenté durant cette période. Les patients étaient surtout des hommes (68%), d'un âge moyen de 55 ans (étendue: 21 à 89 ans) et qui ont été traités 3 jours en moyenne par l'OMEC (étendue: 0 à 13 jours). La survie

globale après sevrage était de 49% (vs 56% rapportée par le registre ELSO) et la survie à 30 jours était de 38% (comparée à 41% après congé, rapportée par l'organisme ELSO).

Coûts

Pour évaluer le coût de l'OMEC, nous avons considéré les coûts des soins infirmiers et de l'unité des soins intensifs, de l'appareillage et des disposables ainsi que les coûts des perfusionnistes. Le coût estimé pour traiter un patient par l'OMEC-VA pour 3 jours est de 18 060,55 $. Ainsi, le coût total pour traiter 20 patients est de 361 211 $. L'impact budgétaire estimé (soit les coûts supplémentaires encourus par l'utilisation de l'OMEC) pour traiter un patient par l'OMEC-VA pendant 3 jours est de 13 289,35 $.

CONCLUSIONS

- L'OMEC est une technique temporaire de soutien à la vie pour supporter les patients en insuffisance cardiaque ou respiratoire aiguë, et présentant un haut risque de mortalité. Depuis 2010, l'utilisation de l'OMEC chez les patients adultes a augmenté de même que les indications chez les patients adultes en insuffisance cardiaque.

- Étant donné le peu de données probantes, il demeure incertain que l'OMEC-VA prolonge la survie et entraîne de meilleurs résultats neurologiques, comparativement à des traitements alternatifs tels les dispositifs d'assistance ventriculaire, le pontage cardiopulmonaire et la ventilation mécanique. Les données d'études comparatives nous suggèrent quelques preuves d'une amélioration de la survie avec la CPRE par rapport à la CPR conventionnelle. Cependant, des études randomisées en cours portant sur la CPRE vs la CPR conventionnelle chez les patients en arrêt cardiaque indique un équilibre clinique, incitant à d'autres études sur l'OMEC chez cette population. Les données des séries de cas indiquent que la survie au moment du congé de l'OMEC-VA pour choc cardiogénique, est d'environ 40%.

- Malgré le fait que quelques organismes ont essayé de développer des lignes directrices concernant l'utilisation de l'OMEC, la littérature actuelle n'a pas établi de directives normatives claires dues à la population hétérogène étudiée et le peu de preuves concernant des indicateurs précis de survie.

- Des preuves récentes suggèrent que les patients traités par l'OMEC dans les centres traitant un nombre important de patients (> 30 cas OMEC chez l'adulte par année) ont des taux de mortalité inférieurs à ceux des patients traités dans des

centres acceptant moins de six patients par année, ce qui suggère fortement de concentrer les traitements OMEC dans quelques centres hospitaliers à fort débit.

- Au CUSM, 41 patients adultes ont été supportés avec l'OMEC depuis 2013. Le taux de survie était comparable aux données des séries de cas importantes (49% après sevrage et 38% après 30 jours). Le coût total estimé pour traiter 20 patients avec l'OMEC-VA est de 361 211 $ en supposant que chaque patient est supporté 3 jours avec l'OMEC. L'impact budgétaire estimé (soit les coûts supplémentaires encourus par l'utilisation de l'OMEC) pour traiter un patient par l'OMEC-VA pendant 3 jours est de 13 289,35 $.

- L'OMEC est une technologie qui nécessite un personnel important et l'augmentation récente des cas OMEC au CUSM a créé un fardeau accru sur les ressources limitées, incluant le temps des perfusionnistes. Un besoin s'impose pour des fonds dédiés de façon à alléger ce fardeau et éviter ainsi des délais indésirables pour accéder aux soins.

RECOMMANDATIONS

- L'OMEC-VA lors de chocs cardiogéniques: Malgré l'absence de preuves concluantes de la supériorité de l'OMEC-VA par rapport aux traitements alternatifs chez les patients en choc cardiogénique, cette technologie est maintenant largement acceptée. Nous recommandons ainsi une approbation pour l'évaluation de l'OMEC-VA chez les patients en choc cardiogénique préalablement choisis. (S'il vous plaît, veuillez-vous référer à la Page ii pour un aperçu des types de recommandations émises par le TAU).

- La RCPE lors d'arrêts cardiaques intra-hospitaliers: En tenant compte des preuves insuffisantes selon lesquelles la RCPE peut améliorer les taux de survie comparativement à la RCP seule, de même que l'acceptation répandue de cette technologie, il est recommandé que cette intervention soit maintenue au CUSM. Nous recommandons ainsi une approbation pour l'évaluation de la RCPE pour les patients intra-hospitaliers en arrêt cardiaque.

- La RCPE lors d'arrêts cardiaques extra-hospitaliers: Actuellement, ces cas ne sont pas traités avec l'OMEC au CUSM. Étant donné les preuves insuffisantes selon lesquelles la RCPE peut améliorer la survie sans dommage neurologique des patients extra-hospitaliers en arrêt cardiaque ainsi que la disponibilité de l'OMEC au CUSM, nous recommandons une approbation pour l'évaluation de la RCPE pour les patients extra-hospitaliers en arrêt cardiaque, conditionnellement à:

  - l'obtention d'un fond dédié pour alléger le fardeau sur les ressources découlant de l'augmentation de l'utilisation de l'OMEC;
  - la mise en place d'une équipe OMEC

- Toutes les recommandations précédentes sont conditionnelles à:
  - une documentation systématique de chaque cas;
  - une réévaluation des preuves à mesure que de nouvelles données ou de nouvelles technologies deviennent disponibles.

- Les recommandations suivantes s'appliquent à l'OMEC-VA (incluant la RCPE) et l'OMEC-VV:
  - Toute augmentation supplémentaire des cas OMEC réalisés au CUSM doit être précédée par un fond dédié pour supporter cette utilisation accrue, incluant les perfusionnistes ou les infirmières formées pour remplacer les perfusionnistes au chevet des patients; ceci comprend aussi les fonds pour les références externes.
  - Étant donné que la décision de traiter un patient avec l'OMEC est prise par les chirurgiens cardiaques et les intensivistes, la création d'une équipe OMEC multi-disciplinaire comprenant du personnel de ces disciplines s'impose pour favoriser une prise de décision efficiente ainsi que le déploiement plus rapide de l'OMEC, ce qui peut améliorer les résultats cliniques.
  - Nous recommandons fortement que les variables suivantes soient systématiquement documentées pour chaque cas OMEC: les indications pour l'utilisation, les raisons supportant le choix de l'OMEC par rapport à des traitements alternatifs, les caractéristiques des patients identifiées comme pertinentes dans la littérature, le temps du déploiement, les complications, la survie et les résultats neurologiques.
  - Un protocole devrait être développé, soulignant les indications potentielles et les contre-indications, les critères de sevrage et les considérations éthiques, pour clairement établir des lignes directrices quant à l'utilisation de l'OMEC au CUSM.

  - De façon à promouvoir l'utilisation optimale des ressources, un processus d'évaluation de la qualité pour l'OMEC devrait être mis en place.
  - Le CUSM devrait s'enregistrer auprès de l'ELSO comme site OMEC pour les patients adultes et fournir ainsi des données précieuses à ce vaste registre international.

- Étant donné le peu de données probantes et le fait que l'OMEC est une technologie évoluant rapidement, ce rapport devrait être mis à jour aussitôt que de nouvelles informations deviennent disponibles.

USE OF EXTRACORPOREAL MEMBRANE OXYGENATION FOR CARDIAC LIFE SUPPORT IN ADULTS

1. BACKGROUND

1.1 What is ECMO?

Extracorporeal life support, also known as extracorporeal membrane oxygenation (ECMO), is a temporary life support technique to provide cardiac and/or respiratory support in patients with acute heart or respiratory failure. There are two main configurations of ECMO: venoarterial ECMO (VA-ECMO) (for cardiac and mixed cardiac and respiratory support) and venovenous ECMO (VV-ECMO) (for respiratory support). In both systems, desaturated blood is withdrawn from the venous system and pumped through an oxygenator, where gas exchange of oxygen and carbon dioxide takes place. In VV-ECMO, the oxygenated blood is then returned to the venous system; while in VA-ECMO, blood is returned to the arterial system.[1]

1.2 Indications for VA-ECMO and survival

There are a number of indications for which VA-ECMO is used, the classic indication being cardiogenic shock. VA-ECMO can be used either as a bridge to recovery (allowing the patient adequate time for restoration of their heart or lung function) or while waiting for heart/lung transplantation (bridge to transplant).[1] When VA-ECMO is used during cardiac arrest as an adjunct to cardiopulmonary resuscitation, it is known as ECPR. According to the Heart and Stroke Foundation of Canada, approximately 40,000 cardiac arrests occur annually in Canada, with 85% of these occurring out-of-hospital. Survival in out-of-hospital cardiac arrest patients is estimated at 10%, and ECPR is a potential option to improve survival in this population.

Data from the international ELSO Registry suggest that survival following VA-ECMO in a population of 9,025 patients was 56% to weaning and 41% to discharge or transfer. Survival following ECPR in 2,885 patients was 39% to weaning and 29% to discharge or transfer.[2]

1.3 Alternatives to ECMO and challenges in estimating efficacy

Conventional treatment options for patients in cardiac failure include ventricular assist devices (VAD), intra-aortic balloon pump or inotropic support with mechanical ventilation. ECMO offers different advantages over each of these alternatives. It is easier to implant compared with VADs. The considerably longer time that patients can be supported with ECMO than with conventional CPR, allows time for intrinsic return of heart or lung function, and potentially better neurological outcomes. For cardiac surgery patients, ECMO may be used instead of cardiopulmonary bypass (CPB), which also circulates and oxygenates the patient's blood outside the body. However, CPB requires storage of blood in a reservoir that can generate an intense inflammatory response, which is associated with complications and poor outcomes.[3]

Given the considerable variability in etiology of patients treated with the different life support options and the emergent nature of the patients' condition it is particularly challenging to estimate the efficacy or effectiveness of ECMO relative to alternative treatments. The underlying patient severity and propensity to receive a particular treatment are major confounding variables in non-randomized controlled studies. Such confounding by indication, wherein patients selected for ECMO may have different disease severity compared with patients receiving conventional treatment, can bias relative survival rates in observational studies. Although this bias may be eliminated in randomized controlled trials, there are considerable logistical and ethical hurdles in designing such studies.

1.4 Context of the current report

ECMO has long been used in pediatric care to support neonates with acute respiratory failure. The use of ECMO in adults was rare due to inconsistent results from early randomized controlled trials,[4] until two concurrent events reignited interest in the use of ECMO for this population. First, survival rates as high as 79% after ECMO (VV-ECMO in more than 90% of patients) were reported among patients who developed acute respiratory distress syndrome (ARDS) during the 2009 H1N1 pandemic.[5-7] At the same time, results from the CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) randomized controlled trial comparing VV-ECMO with conventional ventilation support in adults were published, which showed that VV-ECMO resulted in a lower rate of mortality or disability at 6-months post-intervention compared to the control group (RR 0.69; 95% CI 0.05-0.97).[8] However, there was no difference in death before discharge or 6 months between the two groups.

Since the publication of these results and with further advances in technology, ECMO use in adults has greatly increased, and indications have expanded to include adults in acute cardiac failure. However, it remains unclear whether ECMO prolongs survival and results in better neurological outcomes relative to alternative treatments, particularly for cardiac patients. ECMO is a resource intensive intervention. While on ECMO, a patient is continually monitored by a specially trained, inter-disciplinary team of healthcare professionals. Therefore, there is an interest in estimating the average cost of ECMO. Given the uncertain benefit and high cost of using ECMO, there is also an interest in identifying factors that may aid in optimal patient selection.

This report was requested by the chief of the Intensive Care Unit, Dr. Peter Goldberg, and the Director of Quality and Risk Management, Ms. Patricia Lefebvre. This report will focus primarily on use of VA-ECMO in adults, because the majority of cases treated at the McGill University Health Centre (MUHC) are cases of acute heart failure requiring cardiac support.

2. OBJECTIVES

The objectives of this report are to:

1. review the literature for evidence on outcomes including survival rates, neurologically-intact survival, and complications, and on the efficacy and safety of VA-ECMO relative to alternative options;
2. review the literature to identify variables that can be used to define a protocol for patient selection for VA-ECMO;
3. review the literature to identify programmatic factors that promote optimal ECMO utilization;
4. summarize the MUHC experience with ECMO, focus primarily on the outcomes and cost of ECMO in adult patients treated at the MUHC.

3. METHODS

3.1 Literature search

There are no published randomized controlled trials of VA-ECMO in adults. However, there have been several recent health technology assessment (HTA) reports, systematic reviews and meta-analyses summarizing the results of case series and non-randomized controlled studies. Accordingly, our literature search for evidence on the outcomes, efficacy and safety of VA-ECMO included recent HTA reports published by recognized organizations, systematic reviews, meta-analyses and the references therein. We retained studies that were published in 2008 and onwards due to an increase in ECMO use after the H1N1 pandemic. In the case of comparative studies, we excluded studies evaluating a combination of ECMO and another modality, studies using historical controls or studies that reported results based on a mix of patients receiving VA-ECMO for cardiogenic shock or ECPR. We chose not to carry out a meta-analysis due to the small number of studies and heterogeneity between study populations.

We also searched PubMed using the following search strategy: *'((extracorporeal[Title/Abstract] OR VA-ECMO[Title/Abstract] OR ECMO[Title/Abstract] OR OR ECLS[Title/Abstract])) AND (cardiogenic shock[Text Word] OR heart failure[Text Word] OR cardiac failure[Text Word] OR acute cardiac failure[Text Word] OR cardiac life support[Text Word] OR cardiac arrest[Text Word])'* together with terms specifying the type of study, namely *(systematic review[Title/Abstract] OR meta-analysis[Title/Abstract]), 'propensity[Text Word] or propensity-score[Text Word]' and 'prediction model[Text Word]'.* The last search was conducted on December 26, 2016. The literature search was carried out by two authors (LS and ND). The search was limited to English records.

In order to identify criteria for patient selection, we searched for published protocols/guidelines addressing indications/contraindications as well as programmatic considerations for VA-ECMO in cardiogenic shock/cardiac arrest patients. We also searched PubMed for validated prediction models of survival post-ECMO.

3.2 MUHC experience

We consulted experts from the MUHC and the MCH (listed in the Acknowledgements) about the current practice of ECMO at their institutions. We briefly describe the ECMO pediatric programme and summarize the survival rate and costs in the adult programme. When estimating the cost of ECMO we considered only the cost of the intervention and

not downstream costs related to any complications. To estimate the average cost of ECMO we considered device and disposable costs, nursing and ICU costs, and perfusionist costs. To estimate attributable cost of the Maquet console per patient we assumed that 20 patients would be treated annually at the MUHC and that each patient would spend 3 days on ECMO.

4. RESULTS

4.1 Outcomes, efficacy and safety of VA-ECMO

4.1.1 Results of literature search

We included 16 non-randomized studies comparing the efficacy of VA-ECMO or ECPR in prolonging survival relative to alternative options,[9-24] identified through our PubMed search or from references in recently published meta-analyses and HTAs.[25-27] We also identified one meta-analysis summarizing survival rates from case series of VA-ECMO or ECPR,[28] and one meta-analysis of complications following VA-ECMO.[29]

We additionally reviewed HTA reports from four organizations - the National Institute for Care and Excellence (NICE, UK),[1] the Canadian Agency for Drugs and Technologies in Health (CADTH),[30] the Washington Health Authority,[27] and the Centre hospitalier de l'Université de Montréal.

4.1.2 Survival

Survival rates from case series:

A recent descriptive analysis of registry data collected by ELSO of 1796 patients aged >16 years who received ECPR found a 10-fold increase in use from 2003 to 2014, from 35 cases reported annually to 400 per year.[31] The authors reported an overall survival to discharge rate of 29% [95% confidence interval (CI) 27%-31%] , which remained unchanged over time, even after adjusting for changes in ECMO practice over time (such as time to ECMO initiation) and baseline characteristics including age, race, and components of the SAVE score (**Table 7**).

A recent meta-analysis[28] attempted to gather information on survival at discharge as well as survival over a longer period following either VA-ECMO or ECPR. The pooled survival rate to discharge following VA-ECMO across 12 non-comparative studies of 659 patients with refractory cardiogenic shock was 41.2% (95% confidence interval (CI) 32.2-52.4%),

ranging from 14.8% to 65.4% across individual studies, indicating a high degree of heterogeneity. In patients who received ECPR following cardiac arrest, the pooled survival rate at discharge across 5 studies of 277 patients was 35.9% (95% CI 28.1%-44.0%) ranging from 29.1% to 53.3%.[28] Though this study also reports results over a longer period of follow-up, these figures are uninterpretable as they are based on a smaller number of studies and the percentage of loss-to-follow up is neither corrected for nor reported.

Comparative studies of VA-ECMO vs alternative treatments:

A summary of the evidence from five non-randomized studies of the effectiveness of VA-ECMO in prolonging survival in adult cardiac patients relative to alternative treatments appears in **Table 1**. One study each compared VA-ECMO to a ventricular assist device (VAD),[12] to cardiopulmonary bypass (CPB),[16] and to mechanical ventilation (MV).[17] Two studies compared patients who received VA-ECMO to those who did not receive VA-ECMO.[9] Most studies had a small number of patients in the ECMO arm ranging from 15 to 61.

The study by Bougouin et al. was the only one that used a propensity score analysis to adjust for bias due to confounding variables.[11] After the adjustment, there still remained a statistically significant difference in LVEF in the two groups (18% in ECMO group vs. 35% in the control group, $p<0.0001$). The authors reported no difference in the survival at discharge in the two groups.

Only the study comparing VA-ECMO to cardiopulmonary bypass (CPB) in lung transplant found a higher survival rate in the ECMO group; survival rates at discharge of 87% vs 61% ($p=0.04$).[16] This advantage was reported to be maintained at 1 year. Patients in the VA-ECMO group were more likely to have had pulmonary hypertension as the indication for the transplant and were more likely to be admitted to the ICU prior to the transplant. The patients in the CPB group had a lower forces expiratory volume in 1 second, possibly related to a greater prevalence of chronic obstructive pulmonary disease (COPD).

Comparative studies of ECPR

Table 2 summarizes the results of 11 studies comparing ECPR with conventional CPR: five studies each of in-hospital[10,13,15,19,23] and out-of-hospital cardiac arrest,[21,22,24,32,33] and one study including a mix of both in- and out-of-hospital patients, though the majority (74%) were out-of-hospital cardiac arrest patients.[20]

Of the five studies of **in-hospital cardiac arrest** patients (four of which used propensity score matching), [10,13,15,23,33] all reported improved survival in the ECPR group compared to the CPR group (improvement in survival ranging from 9.6% to 36.2%), but only three showed statistically significant improvements.[13,15,23] Two of these articles, which used propensity score matching and survival analysis, found that the survival advantage was maintained at one and two years post-ECMO.[13,23] The study by Chen et al., published in the Lancet in 2008, was among the first to demonstrate a short-term and long-term survival benefit of ECPR over CPR.[13] Although this study used propensity scores to balance covariates between treatment groups, differences remained for cause of cardiac arrest, with more patients with congestive heart failure or acute coronary syndrome receiving CPR, and more patients post-cardiotomy receiving ECPR. The authors reported a hazard ratio of 0.51 (0.35, 0.74; p<0.0001) at discharge, indicating better survival for ECPR vs CPR. Similarly, Shin et al. also used propensity matching (achieving good balance between included covariates) and found a prolonged survival benefit of ECPR, even after 2 years (HR: 0.56 (0.37,0.84; p=0.005).[23] However even for high quality propensity score studies, the possibility of confounding of unmeasured confounders limits the strength of any conclusions.

Results from the six studies of **out-of-hospital cardiac arrest** patients (three of which used propensity score matching) were more equivocal.[20-22,24,32,33] Four reported better survival in ECPR groups compared with the CPR group (improvement in survival ranging from 8.5% to 25%),[20-22,32] but only three studies found statistically significant results.[20-22] Three studies also reported better long-term survival following ECPR.[21,22,24] The largest of these was a prospective, multi-centre (n=26 centres) study by Sakamoto et al. that included 260 ECPR patients and 194 CPR patients. Although this study did not use propensity score matching, they report no differences in baseline characteristics such as age, sex, time to receiving treatment, and cause of arrest. Variables such as duration of CPR, initial rhythm, and comorbidities were not reported. Intention-to-treat (n=454) and per-protocol (n=393) analyses showed similar results favouring ECPR vs CPR, i.e. better neurologically-intact survival in the ECPR group at 1 and 6 months (12.3% vs 1.5% at 1 month, and 11.2% vs 2.6% at 6 months).[22]

Appropriateness of propensity score analyses

Propensity score analysis is a design to render observational groups as similar as possible by attempting to balance treatment groups on all potential confounding factors known to be associated with receiving the treatment.[34] However, while randomization in RCTs ensures that treatment groups are similar on measured *and* unmeasured confounders, propensity score designs can only create balanced treatment groups on measured

confounders, leaving the possibility of confounding by any excluded, unmeasured or poorly measured variables. Thus, although propensity score matching eliminated differences in age and gender, patients in the ECPR group were much more likely to undergo primary revascularization in many of the studies.[25] In the study by Choi the ECPR group was more likely to receive reperfusion therapy and therapeutic hypothermia.[14], while in the study by Chen et al., differences in the cause of cardiac arrest remained between treatment groups after matching.[13]

4.1.3 Morbidity and complications

Complications arising from VA-ECMO are common and may be a result of the procedure itself or may be related to the underlying etiology and pre-existing co-morbidities. Principal complications during ECMO include cannulation site bleeding and limb complications.

Evidence from case series:

A recent meta-analysis[29] of 1866 patients from 20 studies of ECMO for cardiac arrest or cardiogenic shock (studies included populations of post-cardiotomy cardiogenic shock, acute myocardial infarction, or mixed populations) between 2000 and 2012 reported the following associated complications: need for rethoracotomy for postcardiotomy bleeding or tamponade (41.9%; 95% CI: 24.3, 61.8); major or significant bleeding (40.8%; 95% CI: 26.8, 56.6); significant infection (30.4%; 95% CI: 19.5, 44.0); lower extremity ischemia (16.9%; 95% CI: 12.5, 22.6); neurological complications (13.3%; 95% CI: 9.9, 17.7); compartment syndrome or fasciotomy (10.3%); stroke, (5.9%; 95% CI: 4.2, 8.3); and lower extremity amputation (4.7%; 95% CI: 2.3, 9.3).[29]

Evidence from comparative studies:

A study that compared ECMO with miniaturized percutaneous ventricular assist device (mp-VAD) found no difference in limb complications between the two groups.[12] When comparing lung transplant patients who received ECMO vs CPB, another study reported that more CPB patients required dialysis ($p<0.01$) and secondary ECMO ($p<0.01$). There was no difference in vascular complications, stroke, or rethoracotomy for bleeding between the two groups.[16]

4.1.5 Neurologic outcomes post-ECMO

Evidence from case series:

In a recent analysis[35] of 4,522 adults in the ELSO registry who received VA-ECMO, 15% of patients had in-hospital neurological impairments. Brain death (7.9%) was the most frequent neurological impairment, occurring most commonly in ECPR patients, followed by cerebral infarction (3.6%), seizures (1.8%), and cerebral hemorrhage (1.8%).[35] The underlying etiologies were variable including cardiac dysfunction (66.5%), cardiopulmonary resuscitation (19.4%) and respiratory failure (14.1%).

In patients supported with VA-ECMO, the central nervous system (CNS) complication rate peaked in 1999-2001 at 15.6% and then stabilized over the subsequent years to reach 10.6% in 2011-2013. Patients supported with ECPR had a higher rate of CNS impairments at 36.6% in 2002-2004, which declined to 23.9% in 2011-2013. However, the poor outcomes with ECPR should be interpreted carefully due to the high heterogeneity in patient's profiles and the quality of pre-ECMO CPR provided.[36] It is possible that in many patients supported with ECPR, CNS impairment resulted from cardiac arrest prior to VA-ECMO deployment[35].

Evidence from comparative studies:

Eight studies comparing ECPR with CPR reported survival with good neurological outcomes, four each in in-hospital and out-of-hospital cardiac arrest patients (**Table 3**).[10,13,19,22-24,32,33] While all four studies of in-hospital cardiac patients showed better neurologically intact survival in the short and long term,[10,13,19,23] only one study demonstrated statistically significant results. This study by Shin et al. that used propensity score matching, reported consistently better survival with minimal neurological impairment for ECPR patients at 6-months (HR: 0.51; 0.34, 0.77), 1 year (HR: 0.52; 0.35, 0.78), and 2 years (HR: 0.53; 0.36, 0.80) post-ECMO.[23]

In contrast, three of the four studies in out-of-hospital patients reported statistically significant benefit in the ECPR group for neurologically-intact survival.[22,24,33] The largest of these, a prospective, multi-centre analysis by Sakamoto et al. showed persistent benefit for the ECPR group at 6 months (11.2% with good neurological functioning for ECPR vs 2.6% for CPR; p=0.001).[22]

4.1.6 Quality of Life outcomes

There have been a few studies with small sample sizes that assessed health-related quality of life (QoL) in ECMO survivors (**Table 4**). All studies found that QoL scores were consistently lower than population-based controls. However, when compared with patients with other chronic illnesses such as those on hemodialysis, cardiac surgery patients, or survivors of Acute Respiratory Distress Syndrome, ECMO survivors had similar QoL scores.[37-40] Some studies also reported than QoL scores improved with longer follow-up.[40,41]

In conclusion, cardiac patients who survive ECMO appear to have similar QoL scores to those patients with chronic illnesses who did not receive ECMO, with QoL score improving over time, suggesting that ECMO does not greatly diminish quality of life in patients with pre-existing chronic illness.

4.1.7 Recommendations from HTAs

Several recently published HTAs including from NICE,[1] CADTH,[30] the Washington State Health Care Authority,[27] and the HTA of the Centre hospitalier de l'Université de Montréal (CHUM)[42] have summarized the evidence on the efficacy of VA-ECMO in prolonging survival in adult cardiac patients relative to alternative treatments. All organizations concluded that, given the heterogeneous populations, inconsistent results, and limited evidence, the ability to draw definitive recommendations for the use of VA-ECMO in adult cardiac patients was limited.

CADTH and the Washington Health Authority concluded that there was a suggestion of improved survival with ECPR compared with conventional CPR, but the evidence comparing ECMO with VAD or with CPB as a bridge to transplant was extremely limited.[27,30] NICE recommended that ECMO in cardiac patients only be carried out in conjunction with special arrangements for clinical governance, ethics and research.[1] They further recommend that ECMO only be used by specialized teams, and that patient characteristics, indications, survival, quality of life and neurological status following ECMO be systematically documented.

4.1.8 Ongoing randomized controlled trials (RCTs)

We identified one ongoing RCT of VA-ECMO in adult patients with cardiogenic shock in the Czech Republic[43]. Results are expected in September 2019. We also identified two ongoing RCTs, comparing ECPR with conventional CPR in patients with out-of-hospital

cardiac arrest[44,45], assessing survival to discharge, and survival with good neurological outcome up to 6 months. Study sites are in the Czech Republic and Austria. Results of both studies are expected in May 2018.

4.1.9 Summary of the evidence

The available evidence on effectiveness of ECMO is drawn from relatively small, non-randomized studies. Results on long term outcomes are particularly sparse. Only studies comparing ECPR to CPR for in-hospital cardiac arrest have consistently reported a benefit in favour of ECPR. For out-of-hospital cardiac arrest patients, one large prospective study, and a smaller, propensity matched study found evidence of better short and long-term neurologically-intact survival with the use of ECPR. Forthcoming results from ongoing RCTs of ECPR in out-of-hospital cardiac arrest patients may shed further light on the efficacy of this technology in this population. Evidence based on large case series suggest there is a high risk of complications among patients VA-ECMO, though these may be owing to the patient's underlying condition rather than VA-ECMO or ECPR per se.

4.2 Patient selection criteria for VA-ECMO

Below we summarize our review of the indications and contraindications for VA-ECMO use, criteria for using ECMO as an adjunct to cardiopulmonary resuscitation (ECPR), and prediction models of survival after VA-ECMO and ECPRs. It should be noted that these criteria are not evidence-based. The variables identified here may serve to develop a protocol for the MUHC. Systematic recording of these variables may be useful for retrospective evaluation of the MUHC's ECMO program in adults.

4.2.1 Results of literature search

In consultation with experts at the MUHC we identified guidelines published by the Extracorporeal Life Support Organization (ELSO),[46] an international body that maintains a database of ECMO cases, as well as a guideline published by The Alfred Hospital in Melbourne, Australia, where they have a well-established ECMO program[47] (offering both VV and VA-ECMO). Below we briefly summarize the indications/contraindications as well as the programmatic considerations for VA-ECMO provided by these guidelines.

4.2.2 VA-ECMO indications in adults

Table 5 summarizes the criteria for indications for VA-ECMO proposed by the Alfred Hospital[47] and ELSO.[46] According to these guidelines, VA-ECMO is indicated for refractory

life-threatening forms of reversible respiratory and/or cardiac failure where the benefit to risk ratio of VA-ECMO is greater than that of other less invasive life-support techniques. Moreover, the expectation of post-ECMO survival without severe disability should be reasonable.[47],[46] The guidelines from the Alfred Hospital further state that in younger patients (<50 years), VA-ECMO may also be indicated for irreversible forms of cardiac or respiratory failure with the option of a ventricular-assistance device (VAD) or heart transplantation.[47]

ECPR is used to resuscitate patients with cardiac arrest refractory to conventional CPR, and for whom there is a high likelihood of reversing the cause of cardiac arrest by providing artificial circulation. The Alfred Hospital has developed guidelines for the use of ECPR for patients with out-of-hospital or in-hospital cardiac arrest (**Table 5**).

4.2.3 Contraindications for ECMO

ELSO and The Alfred Hospital guidelines also list contraindications for VA-ECMO (**Table 6**).[46,47] These include patients with irreversible conditions and other severe co-morbidities. They recommend that VA-ECMO should not be applied in some conditions in the presence of multiple acute organ failure prior to the initiation of VA-ECMO, as the expected survival is very low. [46,47]

4.2.4 Predictors of survival

A validated prediction of survival following VA-ECMO in cardiogenic shock patients:

We identified one validated survival prediction model that estimates the predicted probability of survival following VA-ECMO given a particular patient profile. The SAVE (Survival After Veno-arterial-ECMO) score was developed by Schmidt *et al*.[48] to help predict survival in patients with cardiogenic shock refractory to conventional medical therapy (available online at http://www.save-score.com/). The authors used a retrospective cohort of 3846 patients documented in the ELSO registry who underwent VA-ECMO for refractory cardiogenic shock between January 2003 and December 2013. The main outcome was survival to discharge from hospital. The predictors included in the model are listed in **Table 7** along with the probability of survival in various scoring categories. By providing an individual patient's values on these variables, it is possible to calculate a predictive score ranging from -35 (lowest probability of survival) to +17 (highest probability of survival), with a score of 0 indicating a 50% probability of survival.

The value of the area under the receiver operating characteristics curve (AUROC) was 0.68 (95%CI 0.64-0.71) indicating a low to moderate predictive performance. The SAVE score has been validated in an external cohort of 161 VA-ECMO patients where an even higher AUROC value was reported [0.9 (95%CI 0.85-0.95)].[48] The predictor variables used in the SAVE score were limited to those recorded in the ELSO database. Consideration of other predictors identified in the literature may further improve its predictive value.

Other prediction models for VA-ECMO and ECPR:

The PubMed search identified two other prediction models that are yet to be validated in an external cohort. The variables identified by these models are also listed in **Table 7**. The ENCOURAGE (prEdictioN of Cardiogenic shock OUtcome foR AMI patients salvaGed by VA-ECMO) risk score was developed by Muller *et al.*[49] to predict mortality in the intensive care unit (ICU)[49]. A model for predicting survival following ECPR in in-hospital cardiac arrest patients has also been published but has yet to be validated[50].

4.3 Organizational considerations

We identified two publications that have made recommendations regarding organizational and staffing considerations necessary for a successful ECMO program in adults. It should be noted that most of these recommendations (besides the one on volume of patients) are not evidence-based.

A position paper prepared by a group of international ECMO experts (physicians, health-care professionals)[51] tried to provide an optimal approach for organizing ECMO programs. The recommendations of the paper can be summarized as follows:

- An ECMO referral centre should have the appropriate infrastructure such as equipment, facilities, and trained and competent personnel.
- The ECMO program should be a component within the organization of the tertiary care unit. The ICU should conform to the relevant national guidelines and be able to offer supportive therapy for multi-organ failure.
- The ECMO centre also should expect to have a relatively high volume of patients (>30 cases/year) to ensure a better quality of care because data from large ECMO centres have shown an association between better survival outcomes and high volume of ECMO patients compared to hospitals with few cases per year (<6).[52]

- ECMO centres should develop specific guidelines and train staff to provide 24-hour-a-day intra-hospital transport of the patient receiving ECMO.

- Formal Policy and Procedures outlining the indications and contraindications for ECMO, clinical management of the ECMO patient, maintenance of equipment, termination of ECMO therapy, and follow-up of the ECMO patient should be available for review.[53]

4.3.1 Staffing

The ELSO has developed a guideline describing the ideal institutional requirements needed for effective use of ECMO in general.[53] The recommendations concerning the staff can be summarized as follows:

- Staff involved in ECMO should have subspecialty training as described by their specific governing medical board.

- A single physician should be the ECMO program director with responsibility for the overall operation of the centre. The medical responsible should be a board-certified critical care specialist; cardiovascular specialist; thoracic, vascular, or trauma surgeon; or other board-certified specialist with specific training and experience in ECMO support.

- An ECMO coordinator with responsibility for the supervision and training of the technical staff, maintenance of equipment, and collection of patient data should be appointed. The ECMO coordinator may be an experienced adult intensive care registered nurse or registered respiratory therapist with a strong ICU background (minimum of 1 year of ICU experience), or a certified clinical perfusionist with ECMO experience.

- An ECMO-trained physician will provide 24-hour on-call coverage for the ECMO patient. The physician may be an adult critical-care specialist, a critical care subspecialty fellow, or other physician who has completed at least three years of post-graduate surgical, or adult medical training and has specific ECMO training.

- There shall be an ECMO clinical specialist in addition to the ICU nurse or an ECMO trained nurse to provide care throughout the course of ECMO. The ECMO specialist should have a strong intensive care background (at least 1 year of NICU, PICU, MICU, CCU or other critical care experience preferred). The ECMO specialist can be a physician, nurse, respiratory therapist, technician who had completed the

requirements by their corresponding boards and have received specific ECMO training.

- Additional support personnel from the permanent hospital staff should be available including: cardiology, cardiology perfusion, biomedical engineer, neurology, nephrology, pulmonology, infectious diseases, occupational therapy, speech/feeding therapy, rehabilitation, palliative care.[53]

5. ECMO AT THE MUHC

5.1 Current treatment policy

While the Montreal's Children Hospital (MCH) has an established ECMO program, introduced in 1991, to support children with heart/lung failure refractory to conventional therapies, the use of ECMO in adults is relatively recent at MUHC, and is anticipated to increase.

5.1.1 In children

The pediatric ECMO program has a 24-hour on-call team consisting of: an ECMO physician, a PICU physician, a cannulating surgeon, and consultants (including cardiology, cardiac surgery, nephrology, surgery, medical imaging). In addition, the ECMO team includes an in-house coverage team consisting of: a perfusionist or ECMO specialist, a PICU fellow and a PICU nurse.

The staff responsible for ECMO have developed their own protocol with inclusion/exclusion criteria, parental consent, checklists, and daily assessment of appropriateness as well as quality improvement questionnaires to check the evolution of candidacy. The ECMO program at the MCH ensures continuing training and education for its members (training sessions every 2 months).

An average of six pediatric cases per year require ECMO support, with a survival rate to discharge of 54% at the MCH compared with 58% reported by the ELSO registry. The majority of cases (65%) are neonates with respiratory failure.

5.1.2 In adults

The adult site of the MUHC has 5 ECMO devices. From May 2013 to September 2016, 41 adult patients have been supported with ECMO at the MUHC. Of these, 35 (85%) received VA-ECMO, including 14 (34%) who received ECPR (**Table 8**). 6 (15%) patients were supported with VV-ECMO. **Figure 1** illustrates the number of procedures done in each year. ECMO cases originated from various units including the main operating room (29%), the ICU (29%), the catheterization laboratory (27%), and the cardiac care unit (12%). 5 of the 41 (12%) ECMO cases were supported at the Montreal General Hospital site. Patients were mainly male (68%), with an average age of 55 years (range: 21 to 89 years), and spent a median of 2.58 and a mean of 3 days on ECMO (range: 0 to 13 days). The average number of days was 2.3 for patients who received VA-ECMO, 6.4 for patients who received VV-ECMO. Overall survival at weaning was 49% (vs 56% reported by the ELSO registry), and 30-day survival was 38% (compared to 41% at discharge reported by ELSO). Survival rates with good neurological outcomes were not available. Currently the MUHC adult site is not registered with ELSO.

5.2 Perfusionist workload

ECMO is a time-intensive procedure, requiring constant bedside surveillance of the patient by a perfusionist. The rise in ECMO cases at the MUHC has placed an increased burden on perfusionists, who also provide services in the operating room (OR) and catheterization laboratory for cardiac surgery and trauma cases. The MUHC currently employs 10 perfusionists. The percentage of perfusionist hours spent on ECMO has increased 300% (7% to 29%) from 2014 to 2016 (Antoinette Di Re, personal communication), which has resulted in a parallel decrease in time spent on other procedures, such as OR cases (**Figure 2**). This increase is independent of the number of perfusionists, which has not increased in this time period. This diversion of perfusionist services can result in unwanted delays of access to care. Furthermore, the increased burden on perfusionists may also result in a high burnout rate.

5.3 Cost of ECMO at MUHC

Table 9 summarizes the cost of keeping a patient on ECMO for one day or for three days. The base cost of ECMO, which is applied to all patients receiving the procedure, is $9,332.05 for VA-ECMO and $10,082.05 for VV-ECMO. Additional costs are proportional to patient-days on ECMO. The estimated cost for a patient who spends 1 week day on VA-ECMO is $12,241.55 while the estimated cost for a patient who spends 3 week days on VA-ECMO is $18,060.55. If 2 of the days fall during the weekend, the cost would increase

to $18,588. The total cost of performing VA-ECMO on 20 patients annually, each of whom spend 3 week days on ECMO, will be approximately $361,211.

It should be noted that the nursing cost in the ICU of $1,590.40 per day will remain the same even if a patient were placed on an alternative treatment, provided the patient survived for the same duration of time as when they were on ECMO (**Table 9**). Therefore, the estimated budget impact of performing VA-ECMO on a patient who spends 3 week days on ECMO will be approximately $13,289.

6. DISCUSSION

The use of ECMO to support adults in acute respiratory or cardiac failure is rapidly increasing. However, evidence for the efficacy of VA-ECMO relative to conventional options is limited with no randomized trials having been published so far. The evidence for VA-ECMO vs alternative therapies for cardiogenic shock is inconsistent given the heterogeneous patient population. Studies of ECPR vs conventional CPR are more consistent, suggesting a beneficial effect for ECPR for patients who suffer an in-hospital cardiac arrest. However, this observation is tempered by the fact that that the reported percentage of patients with a good neurological outcome following ECPR is around 20% to 30% even for in-hospital cardiac arrest.

The evidence for out-of-hospital cardiac arrest is also inconsistent. Neurologically-intact survival rates are generally low for this population, though there is some evidence from two moderate-quality studies that patients receiving ECPR do better than those receiving CPR. However, in the absence of randomization, indication bias as an explanation of the results cannot be excluded. RCT evidence may not be forthcoming before 2017 for ECPR and before 2019 for VA-ECMO for cardiogenic shock. These ongoing studies point to the fact that equipoise remains between ECMO and alternative treatments, at least for cardiac failure in adults.

Given the lack of evidence, high cost and the continued growth in the use of this emerging technology there has been a lot of interest in developing protocols that will aid in patient selection. Our review identified some of the protocols and predictor variables that have been described in the literature. However, once again, the evidence to support their use is limited and it is unlikely these measures can be used to make decisions for individual patients. Nonetheless, systematic documentation of all important variables, including baseline characteristics and outcomes (e.g. survival,

neurological outcomes) may help to retrospectively identify patient characteristics or predictors of survival specific to the MUHC. Furthermore, the collection of such data will enable regular quality reviews of each case that may identify areas for improvement.

Recent evidence suggests that patients receiving ECMO at centres treating more than 30 adult ECMO cases per year have lower mortality rates than those treated at centres with fewer than six adult cases annually.[52] It would thus be beneficial to concentrate ECMO cases within a few high-volume centres in Montreal.

Though not evidence-based, some publications on the development of ECMO centres have strongly recommended the establishment of an ECMO team to enable rapid decision-making and ensure more efficient deployment of ECMO, which can impact survival outcomes. Given that ECMO cases at the MUHC arise from different hospital units, including the ICU, the operating room, and the catheterization laboratory, drawing on the personnel and resources from each of these departments, the creation of a multi-disciplinary ECMO team would increase efficiency and allow for standardization of the deployment protocol. Such a team is particularly necessary if the MUHC wishes to treat out-of-hospital cardiac arrest cases with ECPR. A pre-established ECMO team also encourages timely review of each case.

The rise in ECMO cases at the MUHC has placed an increased burden on perfusionists, whose services are also required during other elective and emergent procedures in the operating room and catheterization laboratory. To ease the burden on perfusionists, and to avoid unwanted delays in access to care due to a diversion of perfusionist services to ECMO, a parallel infusion of funds to accompany the increase in ECMO cases is warranted.

With respect to the societal benefit of ECMO, there is the possibility that the use of ECMO may expand the organ donor pool, because of ECMO's ability to prolong oxygen perfusion of organs in cardiac arrest patients. Research is ongoing to evaluate outcomes following organ procurement from ECMO donors.[54]

7. CONCLUSIONS

- ECMO is a temporary life support technique to support patients with acute heart or respiratory failure and high risk of mortality. Since 2010, ECMO use in adults has increased, and indications have expanded to adults in cardiac failure.

- Given the limited evidence base, it remains unclear whether VA-ECMO prolongs survival and results in better neurological outcomes relative to alternative treatments such as ventricular assist devices, cardiopulmonary bypass and mechanical ventilation. Data from comparative studies suggest some evidence of improved survival with ECPR relative to conventional CPR. However, ongoing RCTs of ECPR vs conventional CPR in cardiac arrest patients indicate continued equipoise for trials of ECMO in this population. Data from case series indicate that survival to discharge after VA-ECMO for cardiogenic shock is approximately 40%.

- Although some organizations have attempted to develop guidelines for indications of ECMO use, the current literature has not established clear normative guidelines due to the heterogeneous study population and limited body of evidence on clear indicators for survival.

- Recent evidence suggests that patients receiving ECMO at high-volume centres (>30 adult ECMO cases per year) have lower mortality rates than those treated at centres with fewer than six adult cases annually, making the case for concentrating ECMO treatment in a few high-volume centres.

- At the MUHC, 41 adults have been supported with ECMO since 2013. Survival was comparable to data reported in large case series (49% at weaning and 38% at 30 days). The estimated total cost of treating 20 patients with VA-ECMO is $361,211 assuming each patient spends 3 days on ECMO.

- ECMO is a resource-intensive technology, and the recent rise in ECMO cases at the MUHC has placed an increased burden on limited resources, including perfusionist time. There is a need for dedicated funding to ease this burden and avoid unwanted delays in access to care.

8. RECOMMENDATIONS

- VA-ECMO for cardiogenic shock: Despite the absence of convincing evidence of superiority of VA-ECMO over alternative treatments for patients in cardiogenic shock, this technology has become widely accepted. We thus recommend an approval for evaluation of VA-ECMO in selected cardiogenic shock patients. [Please see Page ii for an overview of recommendation types issued by the TAU.]

- ECPR for in-hospital cardiac arrest: In view of the limited evidence that ECPR may improve survival rates compared to CPR alone, as well as the wide acceptance of

this technology, it is recommended that this intervention continue to be made available within the MUHC. We thus recommend an approval for evaluation of ECPR for in-hospital cardiac arrest patients.

- ECPR for out-of-hospital cardiac arrest: Currently, these cases are not treated with ECMO at the MUHC. Given the limited evidence that ECPR may improve neurologically-intact survival in out-of-hospital cardiac arrest patients, and the availability of ECMO at the MUHC, we recommend an approval for evaluation of ECPR for out-of-hospital cardiac arrest patients, which is conditional on:
    - procurement of dedicated funding to ease the burden on resources associated with an increase in ECMO use;
    - establishment of an ECMO team.
- All of the above recommendations are conditional on:
    - systematic documentation of each case;
    - re-evaluation of the evidence as new data, or new technology, become available.
- The following recommendations apply to VA-ECMO (including ECPR) and VV-ECMO:
    - Any further increase in ECMO cases performed at the MUHC must be preceded by dedicated funding to sustain the increased use, including funding for outside referrals, and for perfusionists or nurses trained to replace perfusionists at the bedside. Such a dedicated budget is particularly necessary to avoid unwanted delays in access to care due to a diversion of perfusionist services, and to reduce the burden on perfusionists.
    - Given that the decision to insert ECMO is made by cardiac surgeons and intensivists, the creation of a designated multi-disciplinary ECMO team comprising personnel from these specialties is necessary to foster efficient decision-making and faster deployment of ECMO, which may improve clinical outcomes.
    - We strongly recommend that the following variables be systematically documented for each case of ECMO: indications for use, reasons for choosing ECMO over alternative treatments, patient characteristics identified as relevant in the literature, time to deployment, complications, survival, and neurological outcomes.

  - A protocol should be developed outlining potential indications and contraindications, weaning criteria, and ethical considerations, to establish clear guidelines for the use of ECMO at the MUHC,
  - In order to promote optimal resource utilization, a quality review process for ECMO should be established.
  - The MUHC should register its adult ECMO site with ELSO, thus contributing valuable data to this vast, international registry.

- Given the limited evidence base and that ECMO is a rapidly evolving technology, this report should be updated as new information becomes available.

FIGURES

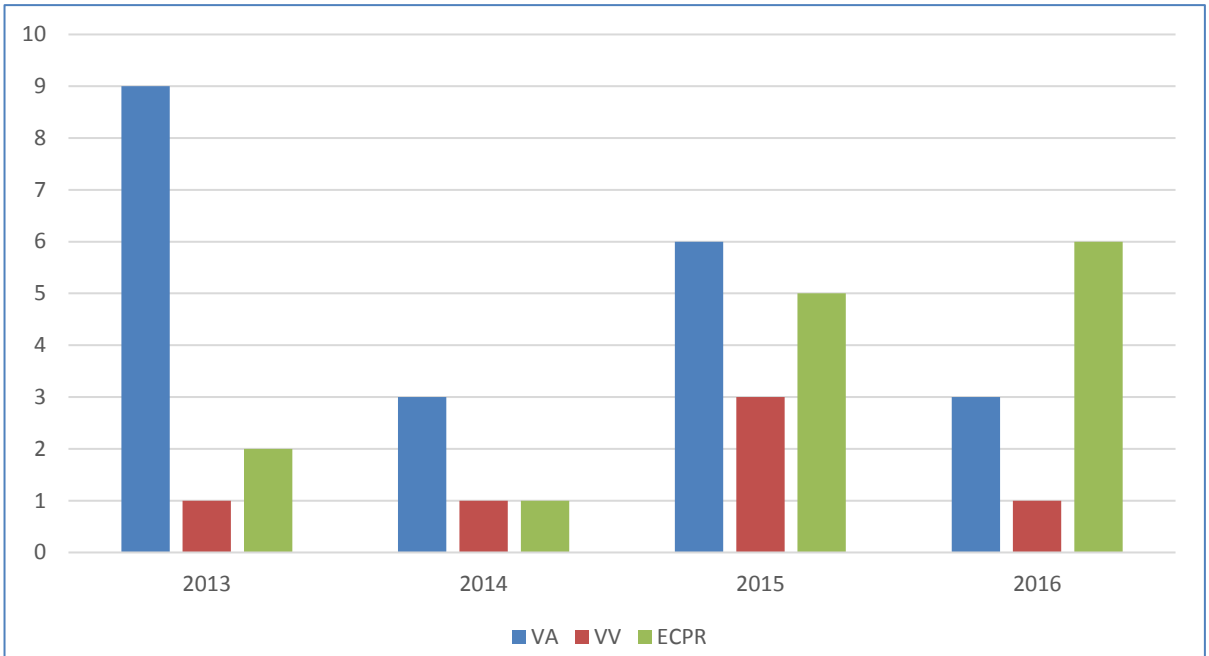
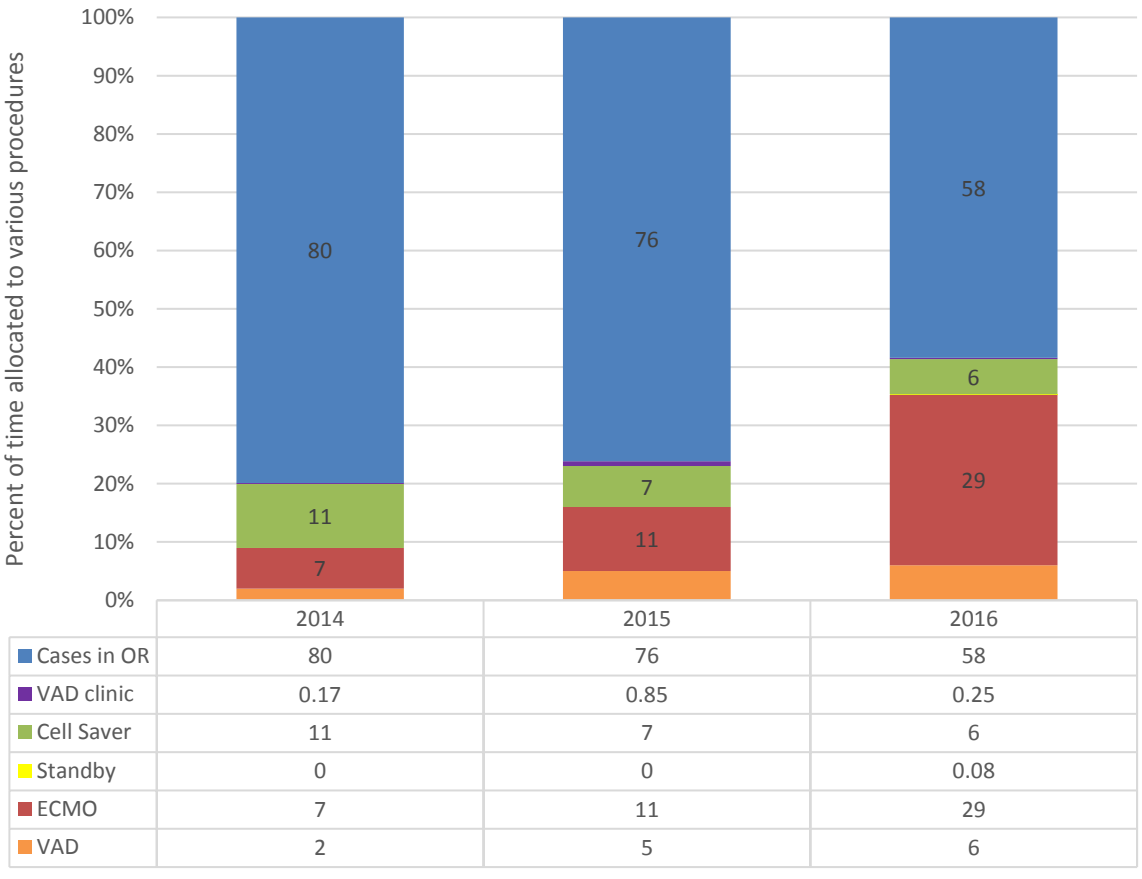


Figure 1. Number of cases of VA-ECMO, VV-ECMO and ECPR at the MUHC over time.



	2014	2015	2016
Cases in OR	80	76	58
VAD clinic	0.17	0.85	0.25
Cell Saver	11	7	6
Standby	0	0	0.08
ECMO	7	11	29
VAD	2	5	6

Figure 2. Perfusionist workload at the MUHC as a percentage of total hours worked per calendar year, 2014 to 2016

TABLES

Table 1. Summary of evidence for survival rates associated with VA-ECMO relative to alternative treatments in cardiac failure patients

Study, Year, Country, Study Design	Population	Treatment groups	N	Outcome			
				Survival to discharge		Long term survival	
				Estimate	Risk difference of ratio (95% CI)	Estimate	Risk difference of ratio (95% CI)
Chamogeorgakis, 2013, US Retrospective chart review	Cardiogenic shock	VA-ECMO	61	14.8%	RD: -7.5% (-31.4, 9.7)		
		mp-VAD	18	22.2%			
Bittner, 2012, Germany Retrospective chart review	Bridge to lung transplant	VA-ECMO	27	30 day: 63%	RD: -35.6% (-53.4, -17.9)	1 year: 33%	RD: -49.4% (-65.5, -28.2)
		Not requiring ECMO	81	30 day: 97%		1 year: 83%	
Bougouin, 2017, France Prospective cohort study, Propensity score matched	Cardiogenic shock	VA-ECMO	37	24%	RD: 0.0% (-19.2, 19.2)		
		Not requiring ECMO	37	24%			
Ius, 2012, Germany Retrospective chart review	Lung transplant recipients	VA-ECMO	46	87%	RD: 26.1% (8.2, 42.1)	1 year: 81%	RD: 23.9% (4.9, 40.7)
		CPB	46	61%		1 year: 56%	
Jayarajan, 2014, US Retrospective chart review	Combined Heart-lung transplant recipients	VA-ECMO	15	30 day: 20%	RD: -64.0% (-77.2, -38.5)	5-year: 20%	RD: -26.9% (-40.6, -1.4)
		MV	22	30 day: 77%	RD: -6.7% (-27.6, 6.4)	5-year: 27%	RD: -19.7% (-34.4, 1.7)
		Neither	505	30 day: 84%	reference	5-year: 47%	reference

RD: Risk difference; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; mp-VAD: miniaturized percutaneous ventricular assist device; MV: mechanical ventilation; VA-ECMO: venoarterial extracorporeal membrane oxygenation

Table 2. Summary of evidence for survival rates associated with ECPR relative to CPR

Author, Year, Country, Study design	Treatment groups	N	Outcome			
			Survival to discharge		Long term survival	
			Estimate	Risk difference or ratio (95% CI)	Estimate	Risk difference or ratio (95% CI)
In-hospital cardiac arrest						
Blumenstein, 2016, Germany retrospective, propensity matched	ECPR	52	26.9%	RD: 9.6% (-6.4, 25.1)	1 year: 23.1%	RD: 9.6% (-5.5, 24.3)
	CPR	52	17.3%		1 year: 13.5%	
Chen, 2008, Taiwan, prospective, propensity matched	ECPR	46	32.6%	HR: 0.51 (0.35, 0.74)	1 year: 19.6%	HR: 0.53 (0.33, 0.83)
	CPR	46	17.4%		1 year: 13.0%	
Chou, 2014, Taiwan retrospective	ECPR	43	63%	RD: 36.7% (11.4, 55.4)	1 year: 35%	RD: 13.1% (-10.6, 32.4)
	CPR	23	26%		1 year: 22%	
Lin, 2010, Taiwan, retrospective, propensity matched	ECPR	27	30 day: 33.3%	RD: 7.4% (-16.4, 30.2)	1 year: 22.2%	RD: 11.1% (-9.4, 31.0)
	CPR	27	30 day: 25.9%		1 year: 11.1%	
Shin, 2011, 2013, Korea, retrospective, propensity matched	ECPR	60	28 day: 31.7%	HR: 0.51 (0.33, 0.78)	2 year: 20.0%	HR: 0.56 (0.37, 0.84)
	CPR	60	28 day: 10.0%		2 year: 8.3%	
Out-of-hospital cardiac arrest						
Choi, 2016, Korea Retrospective, propensity matched	ECPR	320	18%	OR: 0.63 (0.39, 1.02)		
	CPR	320	16%			
Kim, 2014, Korea, retrospective, propensity matched	ECPR	52	17%	RD: -3.9% (-19.0, 11.4)	3-month: 15.4%	RD: 9.6% (-2.7, 22.3)
	CPR	52	21%		3-month: 5.8%	
Lee, 2015, Korea, retrospective [mix of in-hospital and out-of-hospital (74%) patients]	ECPR	81	22.2%	RD: 8.5% (0.4, 18.9)		
	CPR	874	13.7%			
Maekawa, 2013, Japan retrospective, propensity matched	ECPR	24	37.5%	RD: 25.0% (0.3, 46.4)	3-month: 37.5	RD: 29.2% (5.2, 50.0)
	CPR	24	12.5%		3-month: 8.3	
Sakamoto, 2014, Japan, prospective	ECPR	260	30 day: 26.5%	RD: 20.4% (13.8, 26.6)	6-month: 21.5%	RD: 17.4% (11.5, 23.2)
	CPR	194	30 day: 6.2%		6-month: 4.1%	

Author, Year, Country, Study design	Treatment groups	N	Outcome			
			Survival to discharge		Long term survival	
			Estimate	Risk difference or ratio (95% CI)	Estimate	Risk difference or ratio (95% CI)
Siao, 2015, Taiwan, retrospective	ECPR	20	50%	RD: 22.5% (-2.8, 45.6)	1 year: 50%	RD: 30% (5.1, 52.2)
	CPR	40	27.5%		1 year: 20%	

HR: Hazard ratio; OR: odds ratio; RD: Risk difference; CPR: cardiopulmonary resuscitation; ECPR: Extra corporeal cardiopulmonary resuscitation

Table 3. Summary of evidence for survival rates with good neurological function associated with ECPR relative to CPR

Author, Year, Country, Study design	Treatment groups	N	Outcome			
			At discharge		Long term outcome	
			Estimate	Risk difference or ratio (confidence interval)	Estimate	Risk difference or ratio (confidence interval)
In-hospital cardiac arrest						
Blumenstein, 2016, Germany retrospective, propensity matched	ECPR	52	21.2%	RD: 7.7% (-7.1, 22.3)	19.2%	RD: 7.7% (-6.5, 21.8)
	CPR	52	13.5%		11.5%	
Chen, 2008, Taiwan, prospective, propensity matched	ECPR	46	30.4%	RD: 15.2% (-2.0, 31.5)	19.5%	RD: 8.7% (-6.4, 23.6)
	CPR	46	15.2%		10.8%	
Lin, 2010, Taiwan, retrospective, propensity matched	ECPR	27	25.9%	RD: 7.4 (-14.8, 28.8)	1 year: 18.5%	RD: 7.4% (-12.4, 27.0)
	CPR	27	18.5%		1 year: 11.1%	
Shin, 2011, 2013, Korea, retrospective, propensity matched	ECPR	60	6-month: 23.3%	HR: 0.51 (0.34, 0.77)	2 year: 20.0%	HR: 0.53 (0.36, 0.80)
	CPR	60	6 month: 5.0%		2 year: 5.0%	
Out-of-hospital cardiac arrest						
Choi, 2016, Korea Retrospective, propensity matched	ECPR	320	9%	OR: 0.94 (0.14, 2.14)		
	CPR	320	6%			
Kim, 2014, Korea, retrospective, propensity matched	ECPR	52	15.4%	RD: 13.5% (2.4, 25.7)	3-month: 15.4%	RD: 13.5% (2.4, 25.7)
	CPR	52	1.9%		3-month: 1.9%	
Sakamoto, 2014, Japan, prospective	ECPR	260	30 day: 12.3%	RD: 10.8% (6.3, 15.4) ;<0.0001	6-month: 11.2%	RD: 8.6% (3.9, 13.2); 0.001
	CPR	194	30 day: 1.6%		6-month: 2.6%	
Siao, 2015, Taiwan, retrospective	ECPR	20	40%	RD: 32.5% (10.6, 54.4)		
	CPR	40	7.5%			

HR: Hazard ratio; OR: odds ratio; RD: Risk difference; CPR: cardiopulmonary resuscitation; ECPR: Extra corporeal cardiopulmonary resuscitation

Table 4. Results of studies assessing quality of life (QoL) in VA-ECMO survivors

Author (year)	N (Included/ Alive at follow-up)	Indication for ECMO	Tool	Follow-up	Comparator	QoL
Hayes (2016)[37]	25/20	Pre- or post-heart transplant pts	6MWD, leg complications, mobility, QOL	At hospital discharge & 3 mos	1. General Australian population 2. ARDS patients with ECMO	1. Lower for all domains 2. Similar for role emotion, mental health, vitality; Lower for physical health
Hsieh (2016)[41]	363/100	CS, severe heart failure, respiratory distress	SF-36*	9-51 mos post discharge	1. Healthy controls	1. Lower
Schoenrath (2016)[55]	57/16	Pts with acute cardiogenic shock	SF-36	34 mos	1. Age-matched healthy controls	1. Lower for the combined physical score but not combined mental score
Mirabel (2011)[38]	41/26	Fulminant myocarditis	SF-36	1.4 years (median)	1. Age- and sex-matched controls 2. VAD pts bridged to transplant or 1-year ARDS survivors	1. Lower 2. Similar
Wang (2009)[39]	62/32	Pts undergoing cardiac surgery	SF-36	2.3 years (mean)	1. General Chinese population 2. Cardiac surgery pts without ECMO	1. Lower 2. Similar (lower for mental health and vitality)
Combes (2008)[40]	34/28	Refractory CS	SF-36	11 mos (median)	1. Matched healthy controls 2. Patients on hemodialysis, with NYHA III HF, or 1-yr survivors of ARDS	1. Lower 2. Higher

*****The Short Form 26 (SF-36) is a widely used and validated questionnaire to assess self-report quality of life. It consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Scores for these eight domains are combined into a physical health component score and mental health component score. Domain scores range from 0 (worst) to 100 (best), and are standardized for population data.

Table 5. Indications/considerations for VA-ECMO listed by Alfred Health[47] and ELSO[46]

Alfred Health	ELSO
VA-ECMO is indicated for the following conditions	
• Cardiogenic shock • Acute Myocardial infarction- without multiple organ failure • Acute fulminant myocarditis • Cardiomyopathy first presentation • Post-cardiac surgery • Primary graft failure: post heart/lung-heart transplantation • Drug-overdose with profound cardiac depression or arrhythmia • Pulmonary embolism with cardiogenic shock • In-hospital cardiac arrest (with a fast ECMO entry, < 60 min)	• Cardiogenic shock • Mortality risk > 80% • Acute Myocardial infarction • Myocarditis • Peripartum Cardiomyopathy • Post cardiotomy shock • Heart failure with severe pulmonary failure • Decompensated *chronic* (?)heart failure • Septic shock
VA-ECMO may be considered for the following conditions	
• Chronic cardiomyopathy with severe heart failure • Ischemic cardiogenic shock with multiple organ failure • Heart transplant recipient with chronic rejection and suitable for VAD and re-transplantation	
ECPR is indicated for the following conditions	

1. Patients with out-of-hospital cardiac arrest refractory to standard CPR with:
• ALL the following:
  • Primary cause is respiratory or cardiac
  • Cardiac arrest was witnessed
  • Chest compressions started within 10 mins
  • Cardiac arrest duration<60 mins
  • Patient 12-70 years
  • No major co-morbidities
• Profound hypothermia (<32C)
• Overdose of vaso-active drugs
• Other reversible cause of cardiac arrest	

Alfred Health	ELSO
2. Patients with in-hospital cardiac arrest refractory to standard CPR such as patients: • With suspected acute coronary syndrome AND the cause is likely to be reversible • Undergoing coronary angiography in cardiac catheterization lab • With suspected massive pulmonary embolism • With other reversible cause of cardiac arrest	

Table 6. Contraindications for ECMO listed by Alfred Health[47] and ELSO[46]

Alfred Health	ELSO
• Advanced age • Irreversible conditions • Central nervous system injuries • Chronic respiratory diseases • Multiple organ failure • Malignancy • Immunosuppression • Intracranial hemorrhage • Aortic dissections or severe aortic regurgitation • Unrecoverable heart disease • Prolonged cardiac arrest • Non-transplant or ventricular assist device candidates	• Advanced age • Chronic organ dysfunction (emphysema, cirrhosis, renal failure) • Unrecoverable cardiac function • No transplantation or durable mechanical support candidates • Prolonged cardiopulmonary resuscitation (CPR) without adequate tissue perfusion • Compliance limitations (financial, cognitive, psychiatric, and social limitations)

Table 7. Variables included in prediction models for predicting survival after VA-ECMO or ECPR

SAVE Score for VA-ECMO	ENCOURAGE score for VA-ECMO	ECPR score for in-hospital cardiac arrest
• Myocarditis, • Post heart or Lung transplants • Refractory VT/VF • Congenital heart disease • Other diagnoses • Age • Weight • Pulse pressure pre ECMO ≤20 mmHg • Diastolic BP pre ECMO ≥40 mmHg • Pre-ECMO cardiac arrest • Peak inspiratory pressure ≤20 cmH_2O • Intubation duration pre- ECMO (hrs) • Acute renal failure • Chronic renal failure • HCO_3 pre ECMO ≤15 mmol/L • Central nervous system dysfunction • Liver failure	• Age >60, • Female sex • Body mass index >25 kg/m^2 • Glasgow coma score <6 • Creatinine >150 µmol/L • Lactate (<2, 2-8, or >8 mmol/L) • Prothrombin activity <50%	Pre-ECPR factors: • Age ≤ 66 years • Diabetes • First monitored arrest rhythm • Asystole • Pulseless electrical activity • VF/pulseless VT • Ischemic cardiomyopathy Intra-ECR factors: • CPR to ECMO time ≤ 38 min • Initial pulse pressure ≥ 24 mm Hg Post-ECPR factors: • Initial MAP ≥ 57 mm Hg • Initial SOFA score ≤ 14

Table 8. Descriptive summary of patients who received ECMO between 2013-2016 at the MUHC

	VA-ECMO	ECPR	VV-ECMO
Number of patients	20	14	6
Length of stay (days)			
Mean	2.28	2.92	6.41
Median	2.17	1.30	6.02
Number survived (n, (%))			
At weaning	9 (45%)	7 (50%)	3 (50%)
At 30 days	8 (40%)	4 (32.5%)	3 (50%)

Table 9. Average cost per patient who receives ECMO for 1 day or 3 days during the work week

Item	Unit cost	1 day of use		3 day of use		Budget impact per patient for 3 days*
		Resource use	Average cost	Resource use	Average cost	
	a	b	a x b	b	a x b	
Per procedure costs						
1. Maquet console†	$432.05/console‡	1 console	$ 432.05	1 console	$ 432.05	$ 432.05
2. Maquet circuit	$7300/circuit	1 circuit	$ 7,300.00	1 circuit	$ 7,300.00	$ 7,300.00
3. VA-ECMO cannula	$800/cannula	2 cannulae	$ 1,600.00	2 cannulae	$ 1,600.00	$ 1,600.00
4. VV-ECMO cannula	$2,350/cannula	1 cannula	$ 2,350.00	1 cannula	$ 2,350.00	$ 2,350.00
Hourly costs						
5. Nursing and ICU costs	$1,590.40/day	1 days	$ 1,590.40	3 days	4,771.20	
6. Perfusionist costs						
a. Regular hours	$43.97/hr	12 hours	$ 527.64	36 hours	1,582.92	1,582.92
b. Overtime	$43.97*1.5/hr	12 hours	$ 791.46	36 hours	2,374.38	2,374.38
Cost of VA-ECMO (1+2+3+5+6a+6b)			$ 12,241.55		$18,060.55	$13,289.35
Cost of VV-ECMO (1+2+4+5+6a+6b)			$12,991.55		$18,810.55	$14,039.35

† Equivalent Annual Cost (EAC) of Maquet console = $\frac{Capital\ cost}{\frac{1-(\frac{1}{1+r})^t}{r}}$, where t is the service life = 7 years, and r is the annual discount rate=5%, and capital cost of the console=CAD 30,000. EAC = $5185.

‡ The MUHC owns 5 Maquet consoles, and each machine is used for an average of 3 days. Thus, for 20 cases per year (60 patient days), the EAC per machine = 5185/ (60/5) =432.05

* Additional cost of ECMO versus alternative treatment

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APPENDICES

APPENDIX A: DEFINITIONS

Cardiogenic shock

Cardiogenic shock is the inability of the heart to pump an adequate amount of blood to the tissues and is defined by both hemodynamic and clinical criteria. Hemodynamic criteria include persistent hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure 30 mmHg lower than baseline) with severe reduction in cardiac index (<1.8 l/min/m² without support or <2.0 to 2.2 l/min/m² with inotropic support) and adequate or elevated filling pressures (left ventricular end-diastolic pressure >18 mmHg or right ventricular end-diastolic pressure >10 to 15 mmHg). It may result of an acute ischemic event or a non-ischemic process, with or without underlying chronic heart failure[56].

Current management techniques of cardiogenic shock

Cardiogenic shock is managed primarily by administrating inotropic agents and vasopressors. This treatment may improve cardiac output but at the expense of increased myocardial oxygen demand, myocardial ischemia, arrhythmogenicity, and compromise of tissue microcirculation and may be associated with increased risk for mortality[57].

The second line of treatment is the mechanical circulatory support systems, which include several percutaneous procedures. These systems have the potential to attenuate the inflammatory response by improving tissue perfusion without the adverse effects of medical therapies. These procedures include: intra-aortic balloon pump (IABP), left ventricular assist device (LVAD), Impella devices and the extracorporeal membrane oxygenation system (ECMO). ECMO has the advantages over the other support systems by the rapidity of insertion, the ability to support right ventricular, left ventricular or biventricular failure and the possibility to support patients with concomitant lung injury when applicable[58].

Ventricular assist device (VAD)

VADs are mechanical pumps used to support cardiac function in patients with acute cardiac failure. VADs help to circulate blood, but do not oxygenate it, unlike ECMO devices. They can be either left (LVAD), right (RVAD) or bi- ventricular assist devices (BIVAD), depending on the type of cardiac support required. These devices come in two configurations: transcutaneous VADs where the pump is located outside the body, and which are used for short term support, such as after cardiac surgery; and implantable VADs, where the pump is located inside the body and are used as a longer-

term solution. Impella devices are miniaturized percutaneous LVADs, which require minimally invasive techniques to implant compared with conventional VADs.