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Commentary and concepts

Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: Ethical considerations

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Abstract

Out-of-hospital cardiac arrest (OHCA) continues to be a leading cause of mortality worldwide. In Canada over 40,000 cardiac arrests that occur each year, a majority occur unexpectedly outside of the hospital setting. However, the reality is that without rapid and appropriate treatment within minutes, most victims will die before reaching the hospital. In the late 1980s case reports identifying favorable outcomes with the use of extracorporeal cardiopulmonary resuscitation (eCPR) in out-of-hospital cardiac arrest (OHCA) began to be reported. Since then case reports, observational studies, propensity analysis, and a systematic review of international practices continues to suggest eCPR as a feasible intervention for refractory ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) in select adult patients. However, in spite of this mounting base of evidence, clinicians continue to report concerns over a paucity of robust data showing definitive eCPR effectiveness compared with conventional resuscitation. This review will explore the ethical issues related to the impact eCPR might have on the orthodoxy pertaining to current resuscitation strategies, the impact of shifting decision-making on families particularly in dealing with a "bridge to nowhere" scenario, a call to accounting for greater data integrity and improved outcome reporting to assess eCPR effectiveness, and addressing the "Should we just do it" question. A recommendation is proposed for the creation of an ethics consultation service to assist families and staff in dealing with the invariable value conflicts and stresses likely to arise.

Keywords: ECMO-CPR, Ethics, Out-of-Hospital Cardiac Arrest

Introduction

Out-of-hospital cardiac arrest (OHCA) continues to be a leading cause of mortality worldwide.[1] Over 400,000 out-of-hospital cardiac arrests (OHCA) occur annually in North America, yet despite attempts to improve the prompt initiation of basic and advanced life supports, on average less than 10% of patients survive to hospital discharge with favorable neurological outcomes.[1,2]

Of the 40,000 cardiac arrests that occur each year in Canada, a majority (85%) of these events strike unexpectedly in places outside of hospital settings.[2] Regrettably, without rapid and appropriate treatment most will die before reaching the hospital. Continued efforts at improving the rate of bystander initiated cardiopulmonary resuscitation (CPR), increasing access to automated external defibrillators, improving the quality of CPR, reducing emergency medical services (EMS) response times, and making enhancements to post-resuscitation care have resulted in the saving of more lives.[3–5] However, it is known that there will continue to be limitations experienced- particularly in cases of sudden cardiac death (SCD) that are refractory to conventional resuscitative measures. [6]

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Traditionally the use of extracorporeal cardiopulmonary resuscitation (eCPR) was largely viewed as a rescue therapy for in-hospital cardiac arrest. [7] In the late 1980's case reports emerged identifying favorable outcomes after eCPR in OHCA.[8] Initially the favorable outcomes were attributed to the differences in demographics between the two groups: out-of-hospital patients experiencing a cardiac arrest tended to be younger, healthier and had less comorbidity than their sicker in-hospital counterparts.

Since then case reports, observational studies, propensity analyses, and a recent systematic review of international practices continues to suggest eCPR as a feasible intervention for refractory OHCA in select adult patients.[9] However, in spite of this mounting base of evidence, clinicians continue to report concerns over a paucity of robust data showing definitive eCPR effectiveness compared with conventional resuscitation. Well-designed randomized studies are required to help clarify key issues such as appropriate patient selection, risk-benefit ratio, and overall cost-effectiveness.[10]

Two laudable benefits to eCPR are cited as important reasons to continue exploring this technology: for appropriately selected patients, eCPR may enable neurologically good survival in those who would have no other alternative; and, to those who could not be saved, eCPR would enhance the donations of solid organs to those in society most at need.[10]

The foundations of all good ethical endeavors begin with good facts.[11] This acknowledges the importance of the scientific rigor brought to this issue and the need for robust evidence to underpin a fulsome consideration of the ethics of eCPR. However, evidence and good science aside, this article will attempt to explore several normative issues related to the development of an ethical eCPR framework. This review will explore the ethical issues related to the impact eCPR might have on the orthodoxy pertaining to the current OHCA resuscitation strategy, the impact of shifting decision-making on families particularly in dealing with a "bridge to nowhere" scenario, a call to accounting for greater data integrity and improved outcome reporting to assess eCPR effectiveness, and addressing the "Should we just do it" question. A recommendation is proposed for the creation of an ethics consultation service to assist families and staff in dealing with the invariable value conflicts and stresses likely to arise.

Ethical issues

Challenging the contemporary orthodoxy pertaining to "stay and play" approaches in refractory VF/VT: harms and benefits reconsidered

The science of resuscitation has evolved with incredible speed over the past two decades. Guidelines emphasizing CPR quality and a focus on post-resuscitation care has seen survival after OHCA improve over time.[4,12,13] Unadjusted survival to discharge increased between 2006 and 2010 for treated OHCA (from 8.2% to 10.4%), as well as for subgroups of VT/VF (21.4% to 29.3%) and bystander witnessed VT/VF (23.5% to 30.3%). [5] Early reports on eCPR have shown some promise, however, it has been suggested that for its successful implementation eCPR programs needs to be considered at a systems level across the continuum of care. Similar to Trauma, STEMI and Stroke care, eCPR cannot be viewed as a set of interdependent and yet distinct pre and in-hospital treatment bundles. It has been demonstrated that an effective eCPR program that relies on well-coordinated out-of-hospital and in-hospital cascading events, referred to as the "chain of survival", needs to be optimized to achieve the best patient outcomes.[14] This "chain of survival" starts with bystander CPR initiation, through to EMS response and start of extracorporeal membrane oxygenation (ECMO) in the Emergency Department, appropriate destination therapy and post arrest care and ends with the patient finally being successfully discharged out-of-hospital. However, recently a new domain of care, focusing on post discharge care has emerged to better appreciate the challenges survivors face after discharge from hospital.[15]

OHCA treatments have been subject to continuous quality improvement and study. As part of this effort, many centers employ EMS paramedics that have been trained to provide ACLS level care such that high-quality CPR, drug administration, and required airway support can all be provided effectively at the scene.[4] As a result of this progress in EMS capability, a realization emerged suggesting that hospitals would unlikely be able to provide any additional resuscitation treatments above what the patient was already receiving in the field. Given the importance of good CPR on return of spontaneous circulation (ROSC), and ultimately patient survival, the risks of negatively impacting CPR quality if a patient were to be bundled and transported, favored the "stay and play" approach to OHCA care.[16] However, this established approach goes against the current thinking for the use of eCPR, in that to be effective, treatable and reversible circulatory downtime needed to be minimized to support survival with good neurological recovery.[17] To support this hypothesis, it has been suggested that EMS would need a modified "load and go" approach to managing OHCA cases. The supportive premise to eCPR's "load and go" claims at effectiveness are based on (a) the ability to diagnose refractory cardiac arrest quickly in the field; and (b) that the dominant underlying cause of these SCA is related to severe coronary artery disease, for which effective treatment could be provided if time allowed. In terms of risk and harms — unnecessarily moving patients who might achieve ROSC if a more prolonged effort of CPR was provided, might involve exposing them to a greater risk if they are transported and subjected to the avoidable risks and harms when placed on ECMO.[18] The counter-argument holds that in cases involving truly refractory VF /VT the "stay and play" approach in these patients will lower odds of survival. It is posited that patients would have a better chance at survival (benefit) if eCPR were made available. A balance of harms and benefits for the "stay and play" versus the "load and go" approaches can only be formally considered with good quality data on survival potential from randomized control trials involving conventional cardiopulmonary resuscitation (CCPR) and eCPR. Data from these trials could be used to inform protocols supporting proper patient selection both in the field and prior to initiation of ECMO in the ED. Though some of the more recent research findings are suggestive that a real potential for a benefit does exist in the judicious use of eCPR — more data is needed to substantiate this claim.[19]

Shifting the decision-making to families and its related tensions

As previously noted, the emergency context of OHCA resuscitation rarely allows for informed first-person or substitute consent to be a consideration when initiating treatment in the field. In the case of OHCA, where the decision is to transfer the patient for eCPR, the decision and consent requirements to continue CPR and transport to hospital for placement on ECMO are unique — in addition to the time-sensitive limitations previously noted, there is virtually no literature to describe how or even whether shared decision-making ought to occur

between EMS and the substitute decision-maker (SDM) regarding transport for eCPR.[20]

In the case of eCPR, as with other in-the-moment lifesaving interventions, the shared decision-making opportunities that could involve a substitute decision-maker are typically shifted to later in the process or in some cases directly to decision involving withdrawal of life supportive interventions. Once on ECMO, additional time to engage family and substitute decision-makers is provided shifting the medical decision making responsibility from the medical practitioner only, to a shared decision-making model that is directed by the family.

The primary aim of placing an OHCA patient on ECMO is to improve their chances for neurologically favorable survival. However, ECMO in and of itself is not a definitive therapy. In eCPR, ECMO is only intended as a bridge to support patients while definitive management of their underlying problems are pursued.[21]

A recent systematic review of the literature identified that most studies reporting on eCPR outcomes were categorized as low to very low in quality.[9] As previously noted robust randomized control trials are needed to properly address efficacy, however, there are predictions that would suggest that even for populations considered ideal for eCPR, survival rates exceeding 30-40 % are unlikely.[10] New data has indicated a 48% functionally intact 3-month survival rate. As impressive as these numbers appear, there does appear to be some element of selection bias as not all patients sustaining refractory VF/VT are taken to the cath lab for ECMO and subsequently PCI.[22] When survival to recovery is no longer attainable, decision-making will need to be directed towards other potential options: death from complications on ECMO with the potential for the patient to become an organ donor, or responding to a condition of stasis or what has become known as the ethically and emotionally troubling "bridge to nowhere" scenario.[21] In this unfortunate situation the patient, while physiologically alive, remains fully dependent on ECMO without any alternative options- creating a distressing and stressful condition for everyone involved.[21]

The standard ethical principle of patient autonomy, combined with the shared decision-making model creates further tensions particularly for the "bridge to nowhere" scenario. The belief continues to exists, on the medical side, that the unique bridge function of ECMO makes it different than other life sustaining therapies in that decisions should be made based on clinical factors alone, and not reliant on the conventional principles of shared decision-making.[23,24] However, further research is needed to determine what benefits or harms might exist by the introduction of the SDM into the emergency department under conditions of both medical uncertainty and complexity.

Programs involved in eCPR need to consider the burdens for both the families and staff relating to the emotionally troubling decision-making points that need to be faced. Time needs to be directed, as early as possible, towards educating and supporting families on the potential risks and benefits of the treatment being provided. Additionally, research is needed to develop clear evidence-based protocols that provide objective guidance on stopping rules and clinical pathways developed to address the complicated psycho-social-spiritual needs of the family.[25] It is known that clinical scenarios involving a low probability of success compounded by high rates of mortality leads to complex caregiver needs and grief, as well as high distress and burnout for staff.[26,27]

eCPR: moving from data to evidence and the ethics of data integrity

Much of the uncertainty surrounding the adoption of eCPR into practice has involved the lack of good, unbiased data to assist in the establishment of its utility and clear benefit. In the evidentiary chain of unfiltered resources, randomized control trials (RCT's) remain the gold standard needed to address the true state of clinical equipoise for this intervention. Though 10 RCT's are currently listed in progress in the RCT registry[28] — much of the support for eCPR continues to rest on data extracted from cohort studies, case-controlled studies, and case series reports.[9]

A major resource in the collection and evaluation of eCPR data is the Extracorporeal Life Support Organization (ELSO). ELSO is a non-profit entity comprised of an international consortium of healthcare institutions. ELSO maintains a registry dedicated to providing data intended to improve quality of care to patients who have been supported on ECMO. Each member institution provides de-identified data on ECMO supported cases using an agreed on limited data set. eCPR cases are also captured in the ELSO registry and have been used for retrospective analysis.[14]

What needs to be considered in the use of either registry data or data directly collected from research studies are the known limitations that can be expected with any data collection activity. In resuscitation science, where the primary task at hand is to save a life, missing data can and should be expected. In many cases, the magnitude of missing data can be significant, or when available, can be subject to observer and recall bias. Imputation methodology is frequently required to address missing data.[29] Similarly, data entry errors are a concern requiring an ongoing process of data validation and verification (particularly when aligning data between prehospital, ED, and ICU capture points).

International cohort studies demonstrate differences in measurements of both the process and outcomes of care after OHCA. In reality, variations currently exist in how the Utstein template is being interpreted, and implemented across settings, and not all registries capture all Utstein core variables as part of their data sets.[30]

In addition to focusing on the existing data collection and reporting processes, the type of data collected should also be reconsidered. Missing in the assessment of current OHCA survival is consistently reported data on the quality of CPR delivered, and documentation of the various tiered EMS response systems that were deployed. Better information may assist in clarifying the actual gain eCPR has over the delivery of good quality CCPR.[31]

Survival is clearly related to time elapse between collapse and definitive care- and all of the processes in between. Ensuring data sets have considered synchronization of times between various service providers (911 call center, EMS arrival on site, arrival to the ED and time on ECMO) is important to consider when minutes count towards overall survival. Similarly registries and research data collection endeavors need to account for and make adjustment on reporting survival for known risk factors that impact outcomes (pre-existing co-morbidities).[32]

From a systems perspective, eCPR data collection needs to recognize the importance of obtaining data related to organ donation, as an important outcome measurement to be include in overall evaluations. [10] Though cerebral performance categories or modified ranking scores are easy to apply when reporting on survival out of hospital, they are not informative of the lived experience of survivors. Patient-reported outcome measures (PROMS) should be established that can reflect the quality of life and its value to the patient and family.[15]

The use of a resource intensive and costly treatment in the face of limited data to establish clear benefit goes to the heart of the primary ethical question — should we do it? However, as outlined in this

section, data collection methodology and research design homogeneity needs to be engineered to ensure good and thorough data is being used in making this important assessment.[30]

eCPR: should we just do it?

There exists an ethical imperative to responsibly pursue science, innovation, and advances in biomedical research and health care directed toward preventing serious harm or providing significant benefits to humankind.[33] However, putting aside any discussion on the value of a life saved — or the lack of high quality evidence suggesting efficacy, an existential question remains: should we just because we can, remains of societal importance.

Deliberations around health care funding decisions rely heavily on the normative ethical theory of consequentialism; wherein, the assessment of the "rightness" of a policy decision is usually based on the anticipated consequences of that act. In times of scarce resources, the ability for any society to fund new or novel health care technologies requires careful assessment of both its economic viability and clinical merit at the macro, meso, and micro levels when developing evidence-based recommendations to support public funding decisions.[34]

New technological assessments must consider data on the incidence and prevalence of the condition being addressed to assess who is most affected by this issue and what percentage of the population would be able to access the new technology.[34] Interestingly, the case of eCPR is unique in that it does not involve the use of a new or novel technology. In this context the technological novelty entails the use of ECMO to replace prolonged CPR in such a way that other interventions can be carried out while the vital organs are being perfused and oxygenated. Economic analysis of eCPR is lacking, however, costs are expected to be substantial, involving the operation of a coordinated eCPR program that includes out-of-hospital EMS services, emergency department or catheterization lab deployment of ECMO, increased demand for access to cardiac interventions, as well as the concomitant cost of the care downstream of eCPR, where additional intensive care unit stays and resources are required.

Practically speaking, eCPR program requirements share many similarities with other specialized emergency-based interventions: ST-Elevation Myocardial Infarction (STEMI) Centers; Stroke Centers; and Trauma Centers. As observed with eCPR, each program requires a set maximum time limit between an event and when treatment is delivered. STEMI requires reperfusion therapy to start within of first medical contact.[35] New guidelines have recommended that stoke centers complete endovascular treatment (EVT) within 6–24 h of stroke onset.[36] and trauma centers speak of the time from event to delivery to a trauma center as the "golden hour" for optimal chances of survival.[37] Data to date on eCPR confirms the critical role "time-to-pump" has on overall survival.[38]

Similarly, any proposed eCPR regional program would be limited to sites that have the requisite expertise to offer the full range of services essential to the program's success. In the case of STEMI, in order to be recognized as qualified center they must be able to provide non-invasive diagnostic testing, cardiac catherization, angioplasty, cardiac surgery and cardiovascular intensive care. Similarly for Stroke and Trauma Centers, highly specialized support services need to be on hand for the center to be successful. These requirements limit accessibility of these programs to established tertiary level care centers with the necessary services and expertise to manage the care that will be required across the continuum.[39]

In most health care allocation decisions, health equity, defined as access to care that is fair and appropriate to one's need regardless of place of residence, socio demographic status, gender, etc. is a prime consideration.[24] However, as noted above, when evidence shows time as a significant factor on mortality — geographical proximity, over equity considerations, becomes a significant factor for the purposes of funding a program.

Given the discussion above, it is reasonable to consider extrapolating the criteria used for assessing funding decisions relating to trauma centers into potential decision-making criteria for eCPR programs. The commitment of resources (human, technology, facilities, and finance) to effectively support an eCPR program would require careful consideration of the following criteria: access, volumes, outcome, population density, rates of OHCA rates refractory to CCPR, work force needs, and availability of healthcare finances.[39]

Ethics consultation services

As previously noted, not all cases involving eCPR will result in a patient's survival to hospital discharge with good neurologic recovery. In some situations decision-making will involves value-laden conflict between families and healthcare teams supporting patients. These cases may involve patients who are in a "bridge to nowhere" scenario and other situations where the team perceives they are providing care that should be considered medically inappropriate or futile.[29] In clinical practice, staff perceptions regarding limitation of futile treatment typically arise from a combination of moral concerns: a duty to preserve dignity, an obligation to minimize suffering, and from a concern over the need to consider the quality rather than quantity of the patient's life.[40]

Ethically based decisions regarding the determination that the care provided is medically inadvisable are dependent on the views of physicians, patient, and/or their family and typically result from a process of conflict negotiation. Historically ethics consultations have been largely adopted as a mechanism for providing patient, family, and staff support in dealing with these types of ethical dilemmas.[41]

In some of these cases, supporting goals of care that aim to maximize benefit and minimize harm for a patient will require reliance on a just and fair decision-making process that can both honor the patients' expressed wishes and hold in tension the individual and cultural value differences among all parties involved.[42] Using clinical ethics consultations in highly stressful end-of-life dilemmas have been observed to improve communication, assist in dispute resolution, and provide support for the moral distress experienced by staff.[43] The main objective of the ethics consultation should be to independently clarify the views of all parties involved in this negotiation, attempt to provide mutual understanding, and propose a path of action acceptable to all.[42]

A recent systematic review and meta-analysis reported on the effectiveness of clinical ethics consultation in ICU's.[44] The study showed that clinical ethics consultations in the ICU were associated with positive user experience, decreased ICU length of stay, and increased family and healthcare provider satisfaction.[44]

Given the medical and ethical complexity of eCPR, consideration might be given to the creation of an automatic trigger for ethics involvement early in the process.[25] Empirical data on the impact of early ethics involvement is lacking, however, Table 1 presents some of the general themes and issues identified from an ethics consultation team involved directly with in-hospital ECMO cases.[23]

Table 1 – Ethics Consultations from an ECMO program.

Themes and issues
Who decides when to stop the circuit?
Under what circumstances would this occur?
Does being on ECMO automatically make a patient a DNR?
Is it justifiable to ask for consent with criteria for how ECMO will be stopped?
Feeling that not enough time has past for a reasonable trial of therapy?
Disagreement related to stopping when patient no longer a candidate for destination.
Limits of prognostication for novel therapies.

Notably the ethical concerns reported in the ECMO cases were similar to those reported when dealing with other end-of-life decisions in a typical ICU setting: the predictable disagreements related to the balance between a therapy being a benefit versus a burden, or deciding when enough time has past to balance uncertainty for both the clinical team and the family. These sources of disagreement create an imperative for proactive and clear communications about key milestones and a need for frequent updates and review — processes that are germane to the work of clinical ethics, and may support the idea of having a triggered or automatic ethics consultation as part of the process.[23]

Conclusions

Understanding the efficacy and the optimal implementation strategy for eCPR is very complex and poorly researched currently. To this end further engagement of not only policy makers and professional groups but of the public as well is needed to ensure this potentially life-saving technology is provided ethically and responsibly during trials and if found to be efficacious, during translation into every day practice.

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REFERENCES

1. Drennan IR, Case E, Verbeek PR, et al. A comparison of the universal TOR Guideline to the absence of prehospital ROSC and duration of resuscitation in predicting futility from out-of-hospital cardiac arrest. Resuscitation 2017;111:96–102.
2. Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. Resuscitation 2017;112:1–10.
3. Ambitious research initiative aims to significantly increase Canadian survival rates from sudden cardiac arrest. http://www.ohri.ca/newsroom/newsstory.asp?ID=716.
4. Buick JE, Drennan IR, Scales DC, et al. Improving temporal trends in survival and neurological outcomes after out-of-hospital cardiac arrest. Circ Cardiovasc Qual Outcomes 2018;11:e003561, doi:http://dx.doi.org/10.1161/CIRCOUTCOMES.117.003561.
5. Daya MR, Schmicker RH, Zive DM, et al. Out-of-hospital cardiac arrest survival improving over time: results from the Resuscitation Outcomes Consortium (ROC). Resuscitation 2015;91:108–15, doi:http://dx.doi.org/10.1016/j.resuscitation.2015.02.003.
6. Katritsis DG, Gersh BJ, Camm AJ. A clinical perspective on sudden cardiac death. Arrhythmia Electrophysiol Rev 2016;5:177–82.
7. Jaski BE, Ortiz B, Alla KR, et al. A 20-year experience with urgent percutaneous cardiopulmonary bypass for salvage of potential survivors of refractory cardiovascular collapse. J Thorac Cardiovasc Surg 2010;139:752–3.
8. Morimura N, Sakamoto T, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a review of the Japanese literature. Resuscitation 2011;82:10–4.
9. Ortega-Deballon I, Hornby L, Shemie SD, Bhanji F, Guadagno E. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes. Resuscitation 2016;101:12–20.
10. Grunau B, Hornby L, Singal RK, et al. Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: the state of the evidence and framework for application. Can J Cardiol 2017.
11. Sujdak Mackiewicz BN. Good ethics begin with good facts. Am J Bioethics 2016;16:66–8.
12. Zive DM, Schmicker R, Daya M, et al. Survival and variability over time from out of hospital cardiac arrest across large geographically diverse communities participating in the Resuscitation Outcomes Consortium. Resuscitation 2018;131:74–82 S0300-9572(18)30366-6 [pii].
13. McNally B, Robb R, Mehta M, et al. Out-of-hospital cardiac arrest surveillance — Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005–December 31, 2010. MMWR Surveill Summ (Washington, DC 2002) 2011;60:1–19 ss6008a1 [pii].
14. Yam N, McMullan DM. Extracorporeal cardiopulmonary resuscitation. Ann Transl Med 2017;5(4):72, doi:http://dx.doi.org/10.21037/atm.2017.01.11.
15. Haywood K, Dainty KN. Life after cardiac arrest: the importance of engaging with the "forgotten patient.". Resuscitation 2018;128:A1–2 S0300-9572(18)30195-3 [pii].
16. Smith RM, Conn AK. Prehospital care — scoop and run or stay and play? Injury 2009;40:S23–6, doi:http://dx.doi.org/10.1016/j.injury.2009.10.033.
17. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). Resuscitation 2015;86:88–94, doi:http://dx.doi.org/10.1016/j.resuscitation.2014.09.010.
18. Holmen J, Hollenberg J, Claesson A, et al. Survival in ventricular fibrillation with emphasis on the number of defibrillations in relation to other factors at resuscitation. Resuscitation 2017;113:33–8 S0300-9572(17)30017-5 [pii].
19. Yannopoulos D, Bartos JA, Martin C, et al. Minnesota resuscitation consortium's advanced perfusion and reperfusion cardiac life support strategy for out-of-hospital refractory ventricular fibrillation. J Am Heart Assoc 20165:, doi:http://dx.doi.org/10.1161/JAHA.116.003732.
20. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal cardiopulmonary resuscitation in adults. Resuscitation 2015;91:73–5.
21. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D. Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. Chest 2014;145:876–82.
22. Bartos JA, Carlson K, Carlson C, et al. Surviving refractory out-of-hospital ventricular fibrillation cardiac arrest: critical care and extracorporeal membrane oxygenation management. Resuscitation 2018;132:47–55 S0300-9572(18)30821-9.
23. Brunner A, Dubois N, Rimensberger PC, Karam O. Identifying prognostic criteria for survival after resuscitation assisted by extracorporeal membrane oxygenation. Crit Care Res Pract 2016;2016:9521091.
24. Meltzer EC, Ivascu NS, Stark M, et al. A survey of physicians' attitudes toward decision-making authority for initiating and withdrawing VA-ECMO: results and ethical implications for shared decision making. J Clin Ethics 2016;27:281–9.

25. Bein T, Brodie D. Understanding ethical decisions for patients on extracorporeal life support. Intensive Care Med 2017;43:1510–1.
26. Barrett T. Understanding how ECMO is changing end of life. Chicago, ILL: MacLean Centre for Bioethics, University of Chicago.
27. Ave AL, Bernat JL. Uncontrolled donation after circulatory determination of death. J Intensive Care Med 2016;885066616682200.
28. ECPR trials globally. Clinical Trials. Gov.; 2018 (Accessed 14 October 2018, at https://clinicaltrials.gov/ct2/results?cond=&term=ECPR&cntry=&state=&city=&dist=).
29. Chen YY, Chu TS, Kao YH, Tsai PR, Huang TS, Ko WJ. To evaluate the effectiveness of health care ethics consultation based on the goals of health care ethics consultation: a prospective cohort study with randomization. BMC Med Ethics 2014;15:1, doi:http://dx.doi.org/10.1186/1472-6939-15-1.
30. Nishiyama C, Brown SP, May S, et al. Apples to apples or apples to oranges? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. Resuscitation 2014;85:1599–609, doi:http://dx.doi.org/10.1016/j.resuscitation.2014.06.031.
31. Brooks SC, Shemie SD, Torrance S, et al. Barriers and opportunities related to extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest in Canada: a report from the first meeting of the Canadian ECPR Research Working Group. CJEM 2018;20:507–17, doi:http://dx.doi.org/10.1017/cem.2017.429.
32. Hirlekar G, Jonsson M, Karlsson T, Hollenberg J, Albertsson P, Herlitz J. Comorbidity and survival in out-of-hospital cardiac arrest. Resuscitation 2018 S0300-9572(18)30988-2 [pii].
33. Brassington I. John Harris' argument for a duty to research. Bioethics 2007;21:160–8 BIOT539 [pii].
34. Health technology assessments: methods and process guide.
35. Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619, doi:http://dx.doi.org/10.1093/eurheartj/ehu278.
36. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46–e110, doi:http://dx.doi.org/10.1161/STR.0000000000000158.
37. Lerner EB, Moscati RM. The golden hour: scientific fact or medical "urban legend"? Acad Emerg Med 2001;8:758–60.
38. Grunau B, Reynolds J, Scheuermeyer F, et al. Relationship between time-to-ROSC and survival in out-of-hospital cardiac arrest ECPR candidates: when is the best time to consider transport to hospital? Prehosp Emerg Care 2016;20:615–22.
39. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. N Engl J Med 2006;354:366–78 354/4/366 [pii].
40. Helft PR, Siegler M, Lantos J. The rise and fall of the futility movement. N Engl J Med 2000;343:293–6, doi:http://dx.doi.org/10.1056/NEJM200007273430411.
41. Tapper EB. Consults for conflict: the history of ethics consultation. Proc (Baylor Univ Center) 2013;26:417–22.
42. Fletcher JC, Siegler M. What are the goals of ethics consultation? A consensus statement. J Clin Ethics 1996;7:122–6.
43. Pronovost P, Angus DC. Economics of end-of-life care in the intensive care unit. Crit Care Med 2001;29:N46–51.
44. Au SS, Couillard P, des Ordons AR, Fiest KM, Lorenzetti DL, Jette N. Outcomes of ethics consultations in adult ICUs: a systematic review and meta-analysis. Crit Care Med 2018;46:799–808, doi:http://dx.doi.org/10.1097/CCM.0000000000002999.