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The Moral Permissiveness of Harms Associated with Extracorporeal Membrane Oxygenation (ECMO): Clinical Reasoning of ECMO Candidacy and the Principle of Double Effect

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Abstract

The Moral Permissiveness of Harms Associated with Extracorporeal Membrane Oxygenation (ECMO): Clinical Reasoning of ECMO Candidacy and the Principle of Double Effect

By Annie Yi-Chun Lai

In the epoch of modern medicine, extracorporeal membrane oxygenation (ECMO), an advanced technology that is evolving in the field of critical care medicine, bears ethical significance as it challenges the moral permissiveness of extraordinary measures to sustain human life. ECMO is part of the extracorporeal life support (ECLS) armamentarium, employed when the heart and/or lungs of the critically ill fail. ECMO is offered to patients of a spectrum of ages, but is clinically indicated only when (1) the underlying medical condition leads to significant organ dysfunction, (2) the medical status is unimproved following the exhaustion of available clinical options, and (3) the pathogenesis of the underlying disease remains reversible. ECMO does not cure but rather 'buys time' against the imminence of death in order to allow organs to recuperate from exogenous or endogenous insults. Problematically, despite being regarded by many as a heroic, life-saving intervention, ECMO poses the potential of considerable patient harms.

ECMO treatment presents a profound fundamental moral dilemma: a tension between strict moral obligations "to save a life" and "to do no harm." This moral paradigm emerges in the practice of extracorporeal cardiopulmonary resuscitation (ECPR) in which patients in active cardiac arrest are emergently transitioned to ECMO support following up to an hour of cardiopulmonary resuscitation (CPR). Since its development, the efficacy of ECMO remains ill-defined due to marked limitations in conducting prospective, randomized clinical trials. Arguably, ECMO has yielded promising outcomes; yet, the means in justifying the ends requires ethical consideration.

This work examines the ethical paradox of choice during clinical reasoning (or double-effect reasoning) in determining ECMO candidacy. The salient factors in determination, particularly the harms-associated with ECMO practice, are described. Central to this examination is determining if the means of performing extraordinary acts that cause harm, in hopes to save a life, are considered morally permissible. Further, the practical translation of the normative theory, Principle of Double Effect (PDE), is assessed in a survey study – a tool commonly used in empirical bioethics. The survey assesses the attitudes of ECMO experts on the four conditions of the PDE. Results are presented and a discussion of the ethical implications on the future practice of ECMO follows.

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Yours,

Annie

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ABBREVIATIONS

AJOB – American Journal Of Bioethics

ARDS – acute respiratory distress syndrome

ARF – acute respiratory failure

ASD – atrial septal defect

CDC - Centers for Disease Control and Prevention

CDH – congenital diaphragmatic hernia

CHF – congestive heart failure

CMV – conventional mechanical ventilation

CPB – cardiopulmonary bypass

CPR – cardiopulmonary resuscitation

CVVH – continuous venovenous hemodialysis

DCD – donation after cardiac death

ECC – extracorporeal circulation

ECLS – extracorporeal life support

ECMO – extracorporeal membrane oxygenation

ECPR – extracorporeal cardiopulmonary resuscitation

ELSO – Extracorporeal Life Support Organization

G1P1 – gravidity one, parity one

H1N1 – hemagglutinin type one, neuraminidase type one

HFOV – high frequency oscillatory ventilation

ICU – intensive care unit

NIH – National Institutes of Health

PDE – Principle of Double Effect

PICU – pediatric intensive care unit

PPHN – persistent pulmonary hypertension of the newborn

PPV – positive pressure ventilation

RCT – randomized clinical trials

RDS - respiratory distress syndrome

TPE – therapeutic plasma exchange

VA – venoarterial

VA ECMO – venoarterial extracorporeal membrane oxygenation

VAP – ventilator-associated pneumonia

VSD – ventricular septal defect

VV – venovenous

VV ECMO – venovenous extracorporeal membrane oxygenation

CHAPTER 1: INTRODUCTION TO ECMO TECHNOLOGY AND THE ETHICS OF ECMO PRACTICE

CASE

A healthy sixteen year-old female with an uncomplicated past medical history developed acute respiratory distress syndrome (ARDS) secondary to influenza A (H1N1) viral infection. The patient was paralyzed, sedated, and intubated to protect her airway prior to an airlift to a higher level-of-care hospital. When the patient arrived to the pediatric intensive care unit (PICU), the patient was tachycardic and had poor heart function (heart rate of 114 beats/min, blood pressure 95/79 (83) mmHg, and pulse pressure of 15 mmHg). The patient only maintained oxygen saturations of 75-80% despite being given the maximum of 100% oxygen support. Physical examination was remarkable for increased work of breathing, high respiratory rate, and diminished breath sounds. Vital signs, physical exam, and laboratory results suggested severe hypoxic respiratory failure and significant acute lung injury.

The patient was unresponsive to all conventional therapies. Mechanical ventilation involving high oxygen concentration and high inflating pressure was required and indicated severe, life-threatening disease; high frequency oscillatory ventilation (HFOV) was initiated. The patient met initial inclusion criteria to reasonably benefit from venovenous (VV) extracorporeal membrane oxygenation (ECMO) support for respiratory failure. However, the transferring hospital informed the ECMO team that the moribund patient had an intrauterine pregnancy at twenty-six weeks gestation (G1P1). The inability to maintain

adequate gas exchange and ventilation resulted in maternal (and fetal) decompensation – heightening the risk of mortality for both lives.

INTRODUCTION

Novel technological advancements in modern medicine have historically shaped clinical practices and continue to present bioethical challenges. This phenomenon is particularly evident in the field of critical care medicine in which machines temporarily support or chronically sustain human life subsequent to heroic life-saving measures. Although artificial mechanisms used as a means to support life yield positive outcomes, the use also involves burdening the critically-ill with a gradient of transient to profound harms. Mechanical interventions are normative clinical tools that characterize modern critical care medicine. However, the proliferative dependence on technology in medicine is coarsely coupled with the intense will to perform extraordinary acts in efforts to preserve life.

To illustrate, mechanical ventilation was once considered an extraordinary medical practice. The Karen Quinlan case (1975), one of the most groundbreaking cases in medical ethics, raised the question about the moral obligation to dying patients (Pence 2011). From the time of Christiaan Barnard's heart-lung bypass machine – regarded as the precursor to the ventilator that kept Quinlan alive (Pence 2011) – and following decades of ongoing modifications in ventilation technology, what was once regarded as an extraordinary practice of

allowing machines to breathe for patients is now considered a “conventional” or ordinary, routine hospital intervention.

In the acute care setting, prolonged conventional mechanical ventilation (CMV) often causes transient ventilator-induced lung injury (Slutsky and Ranieri 2013). Such lung injuries include barotrauma (damage caused by excessive pressure), volutrauma (damage caused by excessive volume), and ventilator-associated pneumonia (VAP). Growing attention to ventilator-induced lung injuries has reshaped practice standards for respiratory failure management (Slutsky and Ranieri 2013). Once considered the standard practice, CMV was operated at settings that mimic the physiological capacity of a non-diseased lung. However, this practice exacerbated rather than alleviated organ stress. More recently, intensivists learned that ventilation settings should correspond to the tolerance of the diseased (rather than non-diseased) lung. Thereafter, ventilator parameters were adjusted as lung function improved (Bohn 2012). This refined approach allows for gradual lung recovery, particularly in trials to wean patients off of CMV.

The technological progression of CMV highlights also the evolutionary phases of other emerging technologies of critical care medicine: first, the technology, itself, is conceptualized and developed; second, the technology is applied to various clinical contexts; and, finally, the specifications of the technology are modified and further refined. CMV has undoubtedly revolutionized medicine and is now ubiquitously found throughout intensive care units (ICUs). However, as more novel technologies permeate the field, the moral salience of the central question posed in the Quinlan case, on what is owed to

dying patients, intensifies. The moral issue concerns balancing the advancement of technology as it moves towards a greater good while examining the justifications of the *means* and to what *end* – the premise for the current discussion. Provided that mechanical interventions can cause transient harms – and, if prolonged, can lead to irreversible harms such as incapacitation and/or patient death – what substantiates the moral permissibility of harmful acts during heroic measures to save the dying provokes ethical inquiry.

A more recent novel technology is extracorporeal life support (ECLS). ECLS is a new breed of technologies that have been evolving in the field of critical care medicine; the practice is of ethical significance because of its extraordinary capacity to sustain human life. The Extracorporeal Life Support Organization (ELSO) defines ECLS as "the use of mechanical devices to temporarily (days to months) support heart or lung function (partial or totally) during cardiopulmonary failure, leading to organ recovery or replacement" (Extracorporeal Life Support Organization 2009). Of note, ECLS and ECMO are often used interchangeably; however, there are other extracorporeal technologies that are employed in the field. Continuous venovenous hemodialysis (CVVH), for instance, is an extracorporeal system used to support kidneys during kidney failure or dysfunction (Hall and Fox 2006). Another example is therapeutic plasma exchange (TPE); it is an extracorporeal apheresis system that selectively filters out undesirable large molecular weight molecules from the plasma (Kaplan 2013). The current discussion focuses on ECMO, an extracorporeal system that supports a failing heart and/or lungs.

ECMO is part of the ECLS armamentarium employed when the native heart and/or lungs of the critically-ill fail despite the body's compensatory mechanisms to physiologically sustain itself. Such organ failure can either be attributed to endogenous and/or exogenous insults. ECMO emulates the primary function of the heart and lungs through extracorporeal circulation (ECC), in which the patient's corpus blood drains from a large vein (by gravity) into a circuitry already primed with heparin and patient-matched blood (ideally).

As the blood mixture flows through the circuit and passes across the gas-exchange interface (the membrane lung), oxygen is added and carbon dioxide is removed – hence, the phrase "membrane oxygenation." Oxygenated blood then returns to the patient to resume the perfusion necessary to support life. If blood returns through an artery, the circuit is termed "venoarterial" mode or VA ECMO; if blood returns through a vein, the circuit is termed "venovenous" mode or VV ECMO. Depending on the mode selected, the circuit selectively bypasses (in part or in whole) the patient's heart and/or lungs to permit organ-specific healing and recovery.

ECMO support can be applied to a spectrum of ages (i.e., neonates, pediatrics, and adults), but it is clinically indicated only when (1) the underlying medical condition leads to significant organ dysfunction, (2) the medical status is unimproved following the exhaustion of all available clinical options, and (3) the pathogenesis of the underlying disease remains reversible (Gaffney, et al. 2010). Of note, the provision of ECMO does not cure but rather 'buys time' to not only allow organs to recuperate but to also, in certain instances, grant the medical team time to identify the causation of injury when it is not immediately apparent.

This holds true during events of cardiopulmonary resuscitation (CPR) when the medical team has not yet determined the underlying cause of biologic dysfunction. Because ECMO is only offered in situations when all other clinical options have been exhausted, the strategic employment of ECMO is key and its use must be initiated prior to the irreversibility of disease pathogenesis – although the state of disease reversibility is not always discernable.

While general practice guidelines outline candidacy for ECMO support, the lack of well-established, specific indications makes difficult choosing candidates who are likely to benefit from it. For example, critical care intensivists have employed ECMO in cases involving substantial barotrauma, when no other alternative therapy to restore lung physiology was available. In more recent years, other nuanced applications of ECMO have been suggested (or even practiced) that further challenge the aim to universally standardize practice guidelines. Such applications include ECMO as a means to bridge patients to organ transplantation (Levi, et al. 2002), as a means of support following primary transplant graft dysfunction (Nguyen, et al. 2000), and as a means of support during toxic cancer therapies (Wolfson, et al. 2005). ECMO has also been suggested for organ procurement in donation after cardiac death (DCD) (Magliocca, et al. 2005). The aspiration to expand the clinical indications of ECMO support for exceedingly medically complex cases, despite reported risks, reinvigorates the normative notion of what is owed to dying patients and the means to the desired end.

Considered a specialized limited resource, ECMO arguably represents an extraordinary practice that has great clinical potential to save lives; yet, ECMO

exposes patients to considerable risks and harms. The notion of harm has a prominent role in both the fields of medicine and in bioethics. In a section devoted to harm in the fourth edition of the encyclopedia *Bioethics*, author Schöne-Seifert highlights the "remarkable tension between harm's undisputed importance in bioethics and the numerous ways in which it comes to be conceptualized and evaluated" (Schöne-Seifert 2014, 1385). This is demonstrated in the moral assessment of harms associated with ECMO practice.

Conceptualizations about what constitutes harm during ECMO intervention vary. For example, renal failure, bleeding, sepsis, and central nervous system complications (Zangrillo, et al. 2013) are physio-physical ascriptions. In contrast, metaphysical ascriptions of harms include moral injury or moral wrongdoing (intentional acts or nonintentional acts). The evaluation of ECMO-associated harms can also differ in degrees of severity and magnitude. Schöne-Seifert describes harm as "context-relative". In other words, "harm is ethically relevant only if it occurs or persists in consequence to human agency, be it by action or omission, from intention or negligence, but not from unavoidable ignorance" (Schöne-Seifert 2014, 1382). While harm may be "contingent on professional knowledge and medico-technical progress" (Schöne-Seifert 2014, 1382), the present work serves to evaluate the constitution of harm, in the context of ECMO being a therapeutic intervention, and general reactions to it.

The adverse complications associated with ECMO therapy have been well documented (Zangrillo, et al. 2013). In general, the incidence of adverse complications for neonatal ECMO support for respiratory failure has improved, largely because ECMO technology emerged and was developed among the

neonatal population (though, initially this was not the case) (Mok, Lee and Cheifetz 2016). Specifically, neonatal ECMO was used for neonates in acute respiratory failure (ARF) secondary to either meconium aspiration, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress syndrome (RDS), or congenital diaphragmatic hernia (CDH) (R. H. Bartlett 2005). Further, Makdisi and Wang state, "children have less complications than adults except for neurologic complications" (Makdisi and Wang 2015, E170); however, more concrete examination is needed. Nevertheless, the number of ECMO cases for cardiorespiratory support in pediatric and adult populations has grown in the last decade (Extracoporeal Life Support Organization 2015). ELSO publishes biannually cumulative international data that reports survival (and mortality) outcomes for each patient population (Extracorporeal Life Support Organization 2016). Details about the kinds of adverse complications of ECMO support and the evaluation of harms-associated with ECMO practice will be discussed further in the chapters following.

ECMO was uniquely featured as a potential rescue therapy during the 2009 H1N1 pandemic (Mitchell, et al. 2010, Gattinoni, Carlesso and Langer 2011). From October 1, 2014 through February 21, 2015, the Centers for Disease Control and Prevention (CDC) reported a total of 14,162 laboratory-confirmed influenza-associated hospitalizations in the United States (Centers for Disease Control and Prevention 2015). Of the 3,118 (22.0%) complete chart reviews, 253 (8.1%) were women of childbearing age (15–44 years); of these, 67 (26.5%) were pregnant (Centers for Disease Control and Prevention 2015). Creanga et al. report that during the 2009 H1N1 pandemic, pregnant women infected with the

virus experienced more severe illness compared to infected non-pregnant women (Creanga, et al. 2010). Of the pregnancies, there were adverse neonatal outcomes that often involved ICU hospitalization and/or sometimes death for both mother and fetus (Creanga, et al. 2010).

During the pandemic (through October 2009), ECMO was shown to improve survival (72%) in patients in ARF if the therapy was employed within six days of initiating mechanical ventilation (Extracorporeal Life Support Organization 2011). Similarly, an observational study conducted by a group from Australia and New Zealand concluded that "ECMO for severe ARDS in pregnant and postpartum women was associated with a 66% survival rate" and "[i]nfants delivered of mothers who had received ECMO had a 71% survival rate" (Nair, et al. 2011, 649). However, the number of patients in this study was relatively small.

Pandemic emergencies are special circumstances where thousands of lives are at risk. The practice of supporting pregnant patients in ARF on ECMO support is an uncommon practice largely because the safety and efficacy are unknown (Cunningham, Devine and Jelic 2006). Instances of having an enlarged, gravid uterus compressing on a major vein, which prevents normal blood flow to the heart and, therefore, encumbering the ECMO circuitry, was a reported complication (Grasselli, et al. 2012). However, this complication can be remedied by better patient positioning. While the risks of obstetric hemorrhaging are presumably likely to occur, Sharma and colleagues state this to be low (Sharma, et al. 2015). While the reports are promising, supporting gravid patients on ECMO is still an unconventional practice.

For the case study, there are three options for consideration: (1) to attempt to rescue both mother and fetus using ECMO support despite the lack of evidence-based knowledge, particularly on the severity of the *in utero* risks (*option a*), (2) to rescue only the mother by employing ECMO support but only following elective cesarean delivery of the fetus (*option b*), or (3) to not offer ECMO given the uncertainty of risks but to continue with exhaustive efforts (like HFOV) yet knowing the probability of foreseeable failure (*option c*).

With *option c*, if exhaustive measures fail, the moribund mother will certainly die, which consequentially results in fetal death. In *option a*, the decision to support both mother and fetus on ECMO would potentially allow for the mother's lungs to recover while perhaps limiting the medical complications that preterm babies unduly suffer due to prematurity. However, this option poses high risk for massive hemorrhaging, strokes, and/or multiple-system organ failure for both mother and, particularly, fetus (Cilley, et al. 1986). Importantly, unknown ECMO-associated risks may imperil fetal survival. With *option b* in which the fetus is surgically delivered and the ECMO-associated complications are evaded, the preterm baby would likely encounter life-long, chronic developmental disabilities as a result of prematurity and underdevelopment (Saigal and Doyle 2008). Medical understanding maintains that ECMO use in gravid patients is an uncommon practice; the difficulty in determining ECMO candidacy was exemplified in this unconventional case. Double-effect reasoning was necessary in assessing the competing interests and risks (both known and unknown) for both mother and fetus.

The ethical questions raised in the case study highlights the juxtaposition of competing moral obligations. The strict moral duty *to save a life* in medicine prescribes the preservation of both lives. Problematically, the competing moral obligation *to do no* harm stipulates that no harm befalls the mother and fetus. Determining ECMO candidacy and the substantive difficulties that arise during clinically aggressive rescue interventions, such as ECMO, require double-effect reasoning; hence, the Principle of Double Effect (PDE) was employed to provide moral guidance.

ECMO practice raises the following broad ethical questions: What burdens ought we impose on the critically ill during and following heroic life-saving measures? Are these burdens or harms morally permissible? Do the potential benefits (such as the patient's functional outcome and quality of life) outweigh the burdens provided the uncertainty of benefits? Does survival, as an endpoint, sufficiently justify the use of the technology?

Since the birth of ECMO in 1953 (Cornish and Arensman 1993), the discussion of the ethics surrounding its use in critical care medicine has been thin. Literature addressing the moral permissiveness of ECMO practice is limited. Problematically, a scarcity of prospective randomized clinical trials (RCTs) regarding ECMO's use and outcomes has hindered the development of a universal standard of practice. Despite previous historical attempts (R. H. Bartlett 2005, O'Rourke, et al. 1989, Bartlett, Roloff, et al. 1985, Peek, et al. 2009), the efficacy of ECMO has yet to be established; though, retrospective research is available from the ELSO whose cumulative database serves to improve ECMO technology and practice (Extracorporeal Life Support

Organization 2010). A primary ECMO resource book titled "ECMO Extracorporeal Cardiopulmonary Support in Critical Care" (also referred to as "The Red Book") provides a collaborative publication about the evolving ECMO experience (Annich, et al. 2012). Notably, only six pages were devoted to the ethics of ECMO practice that included a brief mention of informed consent, best interest standard, and futility (Koogler and Lantos 2012).

The present work seeks to highlight the complexity in clinical reasoning when determining ECMO candidacy, with all things considered, and the provisions under which ECMO is deemed to be a morally acceptable clinical intervention. Chapter two provides a historical overview of the development of extracorporeal technology; the history is divided into three time periods of advancement that lead to modern day ECMO practice. Chapter three outlines the clinical reasoning in determining ECMO candidacy which is intertwined with informing the moral reasoning for evaluating the permissiveness of harms. Part one of chapter three discusses the diseases in which ECMO is applicable, the two disease-dependent modes of the ECMO circuitry (i.e., VV ECMO and VA ECMO), and the three characteristic patient populations (i.e., neonates, pediatrics, and adults) ECMO supports. In part two of the chapter, a substantial amount of the discussion will be devoted to the technical and practical challenges of employing ECMO technology. Here, double-effect, moral reasoning on the permissiveness of ECMO-associated harms is discussed and the PDE is referred to for moral guidance. In chapter four, the evaluative criterion of the PDE is borrowed to appraise the moral propriety of ECMO in a survey study – a tool commonly used in the growing field of empirical bioethics. This chapter sheds light on the

general attitudes of ECMO experts regarding the four conditions of the PDE as it pertains to the permissibility (or impermissibility) of harms associated with ECMO practice. The utility of the proposed moral methodology is discussed. Last, chapter five concludes with the overall ethical implications and future direction of ECMO practice.

CHAPTER 2: HISTORICAL DEVELOPMENTS IN EXTRACORPOREAL TECHNOLOGY AND CURRENT USES

Saving lives using extracorporeal systems was made possible through the ongoing collaborative efforts of multi-interdisciplinary pioneers that have landmarked and continue to make breakthroughs in ECLS technology. The culmination of scientific knowledge, device innovation, pharmacological developments, and practical experience collectively propagated the real potential to employ extracorporeal mechanisms to rescue patients in active cardiac or respiratory failure.

Developments in extracorporealization can be traced back to early 17th century during a time when early thought leaders challenged the then prevailing theories on the structure and function of circulation (Silverman 2007, Souza and Elias n.d.). The pursuit of science and the thirst for knowledge of early scientists uncovered the vital role of the heart and its partial functional independence from the brain (Böckler and Hahn 2011). As deeper understandings grew about the anatomy and physiology of the circulatory system, ensuing theories about the dynamic properties of blood were being tested (Keynes 1967, Roux, Saï and Deschamps 2007, Horsley 1915, Tucker 2011, Cooper 2005, Lim 2006). Soon after, novel apparatuses – like pumps, gas exchange devices, and cannulas – appeared in the operating theater to assist surgeons during complex cardiac repairs (Lim 2006, Hewitt and Creech, Jr. 1966, Stammers 1997). Further, compelling discoveries in pharmaceutics (notably the drug heparin) allowed physicians to chemically tinker and manage, with increasing levels of specificity,

the hemodynamics of a patient's malady (McLean 1959, Barrowcliffe 2012). Such drugs have become quintessential tools for modern medicine.

Together, these developments gave rise to the lifesaving provisions of extracorporeal systems. Although extracorporeal systems have been employed for the last six decades, the practice of extracorporealization has been highly contentious and has even been described as an unethical practice. Before diving into the ethical dimensions that it presents, it is necessary to first explain the technology itself. Thus, this chapter introduces the advent of ECMO and highlights the noteworthy events that have led to current clinical applications of extracorporeal technologies.

ECMO emerged from the birth of open-heart surgery in the early 1950s (Cohn 2003). At the time, surgeons fervently attempted to correct complex congenital defects of the heart but were often paralyzed by the complications that arose (Cornish and Arensman 1993). Complications like massive hemorrhaging decreased the visibility of the sterile field and severely disrupted the interval of time allotted to make repairs, which risked the life of the patient on the operating table. There was a desire for a viable means to provide temporary cardiorespiratory support; a way was needed to temporarily divert blood from the heart while, in the same instance, provide adequate perfusion to the corpus. This need ignited the inception of extracorporeal technologies.

The first successful open-heart surgery was performed on May 6, 1953 by Dr. John H. Gibbon, Jr. using his Gibbon heart-lung bypass machine that allotted total bypass for a then unprecedented time of twenty-six minutes (Cohn 2003). Since then, Gibbon's prototype has evolved and has been the archetype for

generations of extracorporeal devices that impart, not just hours, but weeks of cardiac and/or pulmonary bypass and support. Hence, year 1953 marked the birth of modern day ECMO (Cohn 2003, Cornish and Arensman 1993). This historic achievement in medicine was made possible through a culmination of feats that occurred centuries earlier – hence, a brief review on the evolution of extracorporeal technology is visited.

In a review by Alfred H. Stammers, the author defines three distinct evolutionary periods of cardiopulmonary bypass (CPB) technology – the origins from which ECMO began:

> The developmental sequence of advances in cardiopulmonary bypass has been divided into three nonexclusive periods based on the major changes observed during the time: (1) a conceptual and developmental period, consisting of events that occurred before 1950; (2) an applied technological period, 1950 to 1970; and (3) a refinement period, 1970 to present (Stammers 1997, 266).

Early Conceptual Foundations and Device Innovation (Before 1950)

The discoveries that occurred prior to 1950 focused largely on elementary understandings of human anatomy and physiology – form and function. Basic concepts of CPB and ECMO have roots in these fundamental principles. The extracorporeal investigations performed by the pioneers of this period were crude and involved experimentation using both animals and humans.

The first noteworthy figure of this period is English physician William Harvey (1578 – 1657). In his seminal 1628 publication *Exercitatio anatomica de motu cordis et sanguinis in animalibus* (originally written in Latin and translated as *An anatomical disputation of the movement of the heart and blood in animals)* (Silverman 2007), Harvey proposed a then implausible theory of the circulature. Also known as *De Motu Cordis*, his work described not only the function of the heart but also the existence of an interconnected arterial and venous anatomical highway that the heart supplied (Souza and Elias n.d.) – an interwoven system that carries blood both away and towards the heart.

Harvey's proposal of a complimentary transit system was heavily criticized because it challenged the then dominant teachings of the prominent Greek physician, Galen. As the medical authority of the time, Galen established that the venous circulation was a completely separate system of distribution from the arterial system. It was not until two decades after his death that Harvey's theory was substantiated.

The distinguishing features of the structure and function of both the arterial and venous systems are prerequisite to understanding ECC. Harvey proved, among other things, that the motion of the heart is timed (a normal sinus rhythm), that the heart is the source of propulsive force, and that its valves promote propelling blood forward while preventing reflux (Silverman 2007). Considered to be the "father of Cardiology" (Souza and Elias n.d.), Harvey's work is revered as the "inescapable… starting point" of the field of medicine that also gave rise to specialized fields like critical care medicine (Treacher 2008) – under which ECMO is classified. The book *Classic Papers in Critical Care* provides a

compilation of additional seminal works that shaped modern critical care medicine (Fink, Hayes and Soni 2008).

A second noteworthy figure also from the 17th century is Jean-Baptiste Denis (1635 – 1704), a French physician who made significant contributions as a perfusionist. During his time, contrary to what was deemed controversial, Denis attempted to transfuse blood in humans and did so on several occasions (Roux, Saï and Deschamps 2007). As described in a paper by Roux et al., on July 15, 1667, Denis performed a therapeutic transfusion on a 15 year-old boy. The boy was suffering from intractable fevers. As a remedy, physicians bled the boy deliberately twenty times. Alternatively, Denis believed that the loss in blood volume was causing the patient's condition. Denis infused into the arm of the boy nine ounces of lamb's blood in exchange for three ounces of corpus blood (a volume replacement of three to one). Thereafter, the boy went back to work and ate normally. Other than suffering from a minor nosebleed, the boy's results were encouraging. This case became the first documented cross-species blood transfusion or xenotransfusion involving humans (Roux, Saï and Deschamps 2007).

Denis's second case was an experimental transfusion that involved a healthy 45 year-old butcher. 10 ounces of the butcher's blood was drained and 10 ounces (or 20, depending on the source) of lamb's blood was replaced (Keynes 1967). The butcher survived, but experienced considerable side effects. Denis's third case involved an ill-stricken Swedish nobleman, Baron Bonde (Keynes 1967, Roux, Saï and Deschamps 2007). On June 24, 1667, Denis's transfusion of 6

ounces of calf's blood revived the unconscious Bonde, but the results were short lived and Bonde ultimately succumbed to his illness.

On December 19, 1667, Denis performed his fourth patient transfusion on the mentally-ill patient, Antoine Mauroy, by using the blood from a "peaceful calf" (Keynes 1967, Roux, Saï and Deschamps 2007). Like his previous transfusions, Denis held that "the blood of animals is less full of impurities than that of men" (Roux, Saï and Deschamps 2007, 208). It was also believed that lamb's blood was more efficacious due to the smaller size of the red blood cells compared to those of men (Horsley 1915). Although Mauroy's mental illness faded, his disease reoccurred three months later. Following an unsuccessful attempt to access Mauroy's vein, Denis's patient quickly died and Denis was consequently charged with murder and tried on April 16, 1668. He was later acquitted. Mauroy's death prompted the French parliament to officially ban human blood transfusions in France in December 1669 (Tucker 2011).

However elementary and investigational, Denis's cross-species xenotransfusion experiments served as a benchmark for downstream experimentations that involved human-to-human transfusions. These findings (along with others) led to John Henry Leacock's discovery (1816) of incompatible perfusate properties when mixing blood derived from different organisms or heterologous blood (Roux, Saï and Deschamps 2007). It wasn't until 1818 when Englishman James Blundell successfully performed the first human-to-human blood transfusion (Tucker 2011). In *Blood Work: A Tale of Medicine and Murder in the Scientific Revolution,* author Holly Tucker provides a rich account of the history of blood transfusions (Tucker 2011). Roux and colleagues further

describe the reemergence of xenotransfusion in the 21st century with the discovery of blood groups in 1900 (Roux, Saï and Deschamps 2007). Methods and techniques in both blood transfusion and perfusion technologies have continued to refine how extracorporeal systems are managed to date.

French physiologist Julien Jean César le Gallois (also known as Legallois) (1770 – 1814) was another laudable figure who was also engrossed in perfusion studies (Böckler and Hahn 2011). In his "memoirs" (or experimental journals), Legallois sought to answer "the great question of the exact seat of the principle of life" – on the relationship between the brain, heart, and lungs. Legallois's rabbit decapitation experiments reflected on "[a] situation truly extraordinary, in which both the head and the body possesses life separately" (Le Gallois, et al. 1813, 5).

In 1812, Legallois attempted to resuscitate severed rabbit heads by perfusing oxygen-rich arterial blood into the carotid artery of the heads (Lim 2006), however unsuccessfully. Unexpectedly, he observed intriguing involuntary animations of the trunk post-decapitation. Known to be a pioneer in vivisection, "Legallois developed a primitive isolated heart-lung preparation in rabbits in which he ligated the inferior vena cava, aorta, carotid arteries, and jugular veins and ventilated the lungs through a pewter syringe inserted into the trachea of a decapitated rabbit" (Fye 1995, 599). Although the perfusions failed (due to blood coagulation, a yet to be discovered property at the time), Legallois's early organ perfusion experiments anticipated the invention of the heart-lung machine 150 years later.

First published in 1812 in French under the title *Expériences sur le principe de la vie*, Legallois made an important conclusion about the role of the heart, lungs, and brain in maintaining life:

> What is said of the heart, being applicable to the other organs of the involuntary functions, the question may be more generally considered as the determination of the seat of that principle which presides over this order of function … the brain could no longer be considered as the exclusive seat of this power" (Le Gallois, et al. 1813, 1, 40).

Further, given that the heart plays a central role in life, if supplied by arterial injections of either natural or artificial means, life can extraordinarily be maintained (Fye 1995). Today, surgically connecting the circuit to the patient (ECMO cannulation) similarly involves the methodologies that were published by Legallois. Thus, Legallois's memoirs laid the groundwork for the foundation of extracorporeal principles.

From the mid to the end of the 19th century, investigations about the properties of blood ensued; particular attention focused on the properties that caused hindrances to continuous circulatory flow. A greater understanding of the coagulative properties of blood grew (Lim 2006, Stammers 1997). In 1821, Prevost and Dumas's experiments on blood defibrination led to the development of a method to remove fibrin – the protein that causes blood to clot. This method

allowed others like Lobell to successfully, in 1849, perfuse arterial blood into an isolated kidney (Lim 2006). In 1858, Brown-Sequard arterialized (or added oxygen) to desaturated (or unoxygenated) blood by "whipping" air into it (Stammers 1997). Sir William Osler was the first to recognize the small cell fragments in blood that contributed to clotting (1874); the cell fragments were latter known as platelets (Cooper 2005, Stone 2003).

Developments in artificial devices also occurred late in the 19th century. Devices called oxygenators introduced oxygen into blood; types of oxygenators included bubble and film oxygenators. The "Bubble"-type oxygenators "bubbled" pure oxygen through an extracorporeal reservoir of blood and were reported as early as 1882 by von Schroeder (Lim 2006, Hewitt and Creech, Jr. 1966). Unlike bubble oxygenators, film-type oxygenators create a thin film of blood where gas exchange is facilitated. The year 1884 was the earliest report of its use by von Frey and Gruber whose apparatus is considered the first heart-lung machine prototype (Stammers 1997, Hewitt and Creech, Jr. 1966). Near the end of the 19th century, in 1890, Jacobj introduced a bubble oxygenator that provided pulsatile flow (Lim 2006, Hewitt and Creech, Jr. 1966) – an important feature of perfusion hemodynamics.

The first half of the 20th century was marked by the monumental discovery of heparin in 1916 by then medical student Jay McLean who was working in the lab of physiologist William H. Howell (1860 – 1945) (McLean 1959). In "The Discovery of Heparin", McLean provides a personal account on how he accidentally discovered the natural, but potent, anticoagulant (McLean 1959). Heparin became commercially available in the 1920s and went into clinical trials

in the 1930s (Barrowcliffe 2012). In addition to use in extracorporeal therapies, current therapeutic uses of heparin include acute myocardial infarctions, deep vein thrombosis, peripheral artery diseases, and hemodialysis (Freedman 1992). Now next generation heparins, like low-dose heparin and low-molecular weight heparin, are clinically available to treat a multitude of diseases.

Around the same time that heparin was discovered, the next generation of film oxygenators were being developed: screen oxygenators and disc oxygenators (Hewitt and Creech, Jr. 1966, Stammers 1997). Film oxygenators with the screen feature pass venous (deoxygenated) blood over a series of screens. As described, a thin film of blood is formed on each screen and it's the site where gas exchange occurs. Film oxygenators with the disc feature, in contrast, passes blood over a series of parallel rotating disks. Similarly, a thin film of blood forms on the surface of the disks and it's the interface for gas exchange. Hooker's rubber disk (1915) was the forerunner for the disc oxygenator and was utilized in early human perfusions that occurred in 1950s and 1960s (Hewitt and Creech, Jr. 1966). Other contributors in the development of film oxygenators include Richards and Drinker's perforated silk screen (1915), Dale and Schuster valved pump that delivered pulsatile wave (1928), Cruickshank's spiral wound copper oxygenator (1934), Gibbon's vertical rotating cylinder used in the first successful total CPB in a cat (1937), Bjork's multiple vertical rotating disks (1948), and Jongbloes's multiple rotating spiral coils (1949) (Stammers 1997).

First recognized in 1944 by Kolff and Berk in their experiments using artificial kidney membranes (Short and Pearson 1986), the key to advancing oxygenator technology was the membranous barrier where gas exchange takes

place. Oxygenators are the central component of the extracorporeal circuit, acting like an artificial lung. For a more detailed account, authors Robert L. Hewitt and Oscar Creech, Jr. provide a rich and descriptive history (including original illustrations) on the evolution of pump oxygenators (Hewitt and Creech, Jr. 1966). These events prior to 1950 highlights the early conceptual and innovative foundations of ECMO that promoted the next era in development – clinical applications.

From Testable Experiments to Extracorporeal Practice (1950-1970)

Successes in the extracorporealization of blood from the years prior spring-boarded total corpus perfusion during what Stammers calls the *applied technological period* from 1950 to 1970 (Stammers 1997) – the era of cardiac surgery. Before 1950, surgeries that involved repairing complicated congenital cardiac conditions were stricken with failures (Cornish and Arensman 1993). Such conditions included ostium primum atrial septal defect (ASD) – an abnormality in the valves of the heart, atrioventricularis communis – an abnormal partitioning of the walls of the heart, and ventricular septal defects (VSD) – an abnormal hole between the bottom right and left chambers of the heart (Cornish and Arensman 1993). Corrective surgeries required massive blood replacement and risked both hemorrhaging and embolization. Also, blood pooling often visually impaired the surgical field. Thus, a better method that would grant surgeons direct visual access and, importantly, the opportunity to correct such abnormalities was highly desired by the medical field.

Champions for the challenge were three prominent surgeons whose early achievements catapulted the implementation of extracorporeal systems. These surgeons - Drs. John H. Gibbon, Jr., Clarence Walton Lillehei, and Robert H. Bartlett - are thought of as the "fathers of ECMO" in the industry. The first notable figure, Gibbon, conducted canine experiments with the intent to develop a technique to treat massive pulmonary embolism (R. H. Bartlett 2005). He did so by using the pump oxygenator that he had invented fifteen years prior (1937) and had developed gradually since (R. H. Bartlett 2005). Gibbon's device effectively supported the survival of 60 percent of his canine patients following a surgically created VSD (R. H. Bartlett 2005). With this success Gibbon embarked on testing his pump oxygenator in clinical applications (Lillehei 1993). Many surgical attempts to repair complex cardiac abnormalities in humans, at the time, were largely unsuccessful; Gibbon's enthusiasm of utilizing his apparatus in such cases also failed (Cornish and Arensman 1993). Ongoing failures in the field left Gibbon (and others) with a sense of tremendous pessimism and doubt. Gibbon's device that sought to temporarily function as heart and lung damaged elements of blood as it circulated; it also caused fatal complications if used for longer than two hours (R. H. Bartlett 2005). Unbeknownst to Gibbon at the time, his invention played a crucial role in the success of ECMO on the first human patient two decades later. Gibbon (September 29, 1903 – February 5, 1973) has been credited as the "father of cardiopulmonary bypass" (Golab 2011).

Like Gibbon, Lillehei also utilized canine models for his perfusion experiments. Lillehei discovered that the required blood flow needed to perfuse vital organs (i.e., brain, liver, heart, and kidneys) was remarkably lower than

what was universally accepted at the time (Cornish and Arensman 1993). Lillehei and his research team discovered that perfusion from the azygos vein alone (deemed "physiologic flow") was sufficient enough to sustain crucial organ support for a period of thirty minutes at normal body temperature (or normothermia) (Cornish and Arensman 1993). This phenomenon became known as the "azygos flow concept" and had significant clinical implications in perfusion technology (Cornish and Arensman 1993). Lillehei also proposed a process of cross-circulation where a donor subject would partially provide circulation (and supportive gas exchange) to a patient; he referred to it as "placental" circulation (Cornish and Arensman 1993, Stammers 1997). Lillehei's technique allotted 19 minutes of time to correct a VSD in an 11-year-old by who was being directly supported by the blood of his father, the oxygenator (Cooley 1999). For the first time, in March 1954, the diagnosis of having a cardiac defect no longer meant having a death sentence.

The following year, Lillehei and colleague Richard A. Wall developed an apparatus dubbed the DeWall-Lillehei bubble oxygenator (Cooley 1999). The device became the first clinically accessible bubble oxygenator due to its practical advantages (e.g., economical, easy assemblage, efficient, disposable) and was used as the ECMO device for the field until the late 1970s. The portability of the DeWall-Lillehei oxygenator allowed other institutions to begin developing their own extracorporeal techniques. It was prolific. From a single center in the world performing open-heart surgery using ECC at the University of Minnesota Hospital, the practice of ECMO appeared throughout the US due to the commercialization of the DeWall-Lillehei device. There are now almost two

hundred recognized ECMO centers in the U.S. and hundreds throughout the world (Extracorporeal Life Support Organization n.d.). Lillehei also innovated wearable cardiac pacemakers and developed prosthetic heart valves, among other things (Cooley 1999). Lillehei (October 23, 1918 – July 5, 1999) has been credited as the "father of open-heart surgery" (Cooley 1999).

The last of the fathers of ECMO, Bartlett, painstakingly continued to improve both ECMO technology and application. His early animal model studies, like those of Gibbon and Lillehei, sought to develop membrane oxygenators and to achieve prolonged extracorporeal circulation (R. H. Bartlett 2005). In one of his initial reports, Bartlett described partial bypass on a dog for up to four days of artificial oxygenation (Bartlett, Isherwood, et al. 1969). Seven years later, Bartlett reported the first neonatal ECMO survivor from respiratory failure due to meconium aspiration. The baby, named "Esperanza" (or Spanish for "Hope"), was left orphaned by a mother who illegally crossed the Mexican border (Bartlett, et al. 1976). In March 2011, the University of Michigan Health System reported that the oldest of the so-called "ECMO Babies" is married, has children, and resides in Missouri. Once the only institution to practice ECMO, they also celebrated treating their 2,000th ECMO patient (University of Michican Health System 2011).

Although retired from clinical practice in 2005 (Ann Arbor News 2005), Bartlett still continues to make significant contributions to the clinical application of extracorporeal technology. Since the 1960s, Bartlett has authorship in 563 works that include books, book chapters, scientific publications, and book reviews (University of Michigan n.d.). Together, Drs.

Gibbon, Lillehei, and Bartlett are the revered founders of modern ECMO technology that is being practiced in ECMO centers across the world.

Refining ECMO Practice (1970 – present)

By the 1970s, following years of intense research on materials and techniques, components of extracorporeal systems continued to evolve. For instance, oxygenators transitioned from being biologic oxygenators (canine lungs and monkey lungs) to non-biologic, mechanical oxygenators. Collectively, the advancements noted herein precipitated the era of critical care medicine. In 1971, J. Donald Hill and Maury Bramson reported the first successful use of prolonged life support with a heart-lung machine on a 24-year-old, male trauma patient (Shankar, Kapoor and Goel 2014, R. H. Bartlett 2005). The patient had a ruptured aorta following a motorcycle accident. The following year, Bartlett announced the first successful case of extracorporeal support for postoperative cardiopulmonary failure in children (published in 1974) (Bartlett, et al. 1976).

These reports along with other promising results sparked national interest to conduct studies to evaluate prolonged ECMO. This research-intensive period was marked by three attempts to conduct for the first time prospective RCTs (considered to be the "gold standard" in conducting clinical trials). The National Institutes of Health (NIH) organized a multi-center clinical trial, commissioned in 1975 (R. H. Bartlett 2005, Bartlett, et al. 1976). By this time there were 150 ECMO-supported ARF cases reporting only a 10-20% survival rate (Zapol, et al. 1979).

The first RCT compared adults in ARF supported by VA ECMO (partial bypass) and mechanical ventilation (n = 42) versus conventional therapy alone (n=48) (Zapol, et al. 1979). In the study, the difference in survival between ECMO bypass and conventional therapy (9.5% and 8.3%, respectively) was not found to be statistically significant; thus ECMO for adults in ARF was not considered superior to conventional care (Dalton 2011). Many aspects of the study were criticized (e.g., absence of controlled variables, reversibility versus irreversibility of disease) (Short and Pearson 1986) and the low survival rates precluded adult ECMO for many years (Dalton 2011). The study lasted for four years and ended in 1979.

While adult ECMO was largely abandoned, the survival rates for the non-adult population gradually improved in the 1980s. In 1980, Bartlett and colleagues were attributed to having improved the survival rate of the pediatric population with ARF supported on ECMO from 10% to 25%, when compared to CMV (Short and Pearson 1986). Shortly after, in 1981, Hardesty and colleagues successfully used prolonged ECMO for congenital diaphragmatic hernia repair in neonates (Short and Pearson 1986). Such reports prompted interest to conduct RCTs on the assessment of non-adult ECMO. The second RCT, which involved neonatal ECMO, was conducted by Bartlett et al. (Bartlett, et al. 1976). The third RCT, conducted by O'Rourke et al., also involved ECMO support for neonates (O'Rourke, et al. 1989).

Following the success of the 1975 Baby Esperanza case at the University of California, Irvine, Bartlett's group began conducting a phase I trial that enrolled 55 infants in severe respiratory failure across three centers over a nine year

period (Bartlett, Roloff, et al. 1985). From their reported 56% overall survival, the Michigan group followed with a phase II trial (Bartlett, Roloff, et al. 1985). The phase II "prospective controlled randomized study" utilized a "randomized play-the-winner" statistical method – a method first introduced by M. Zelen in 1969 (Zelen 1969) that assigns moribund infants with alacrity to the better treatment arm.

The Play the Winner Rule (PWR) states: *A success on a particular treatment generates a future trial on the same treatment with a new patient. A failure on a treatment generates a future trial on the alternative treatment* (Zelen 1969, 132, emphasis in original). The premise for the PWR is based on what Zelen calls an ethical principle "of not prolonging a trial longer than necessary, for a trial which is unduly prolonged may result in an excessive number of patients being given the less beneficial treatment" (Zelen 1969, 131). The conclusion of Bartlett's phase II trial was that "ECMO allows lung rest and improves survival compared to conventional ventilator therapy in newborn infants with severe respiratory failure" (Bartlett, Roloff, et al. 1985, 479). However, the conclusion was controversial because only one patient was assigned to the control group under the PWR.

In 1989, O'Rourke et al. at Harvard conducted the second RCT for the assessment of neonatal ECMO. Still, no single standard protocol for supporting patients on ECMO existed (O'Rourke, et al. 1989). In this study, infants with the diagnosis of PPHN were considered. The study involved 39 infants – 19 infants in a "phase I" cohort and 20 infants in a "phase II" cohort. In the phase I cohort, 4 of 10 selected into the CMV group died, whereas none died in the VA ECMO

group (O'Rourke, et al. 1989). Their rule was that if four deaths were to occur in either arm, randomization to the less superior arm was to be halted. Hence, the phase II cohort were all selected to the ECMO arm; 19 of the 20 infants in the ECMO group survived (O'Rourke, et al. 1989). O'Rourke et al. concluded that ECMO was superior treatment of PPHN (97% overall survival) compared to CMV (60% overall survival).

While the Michigan group utilized both VA and VV modes, the Harvard group only employed VA ECMO. Of note, VV ECMO is considered the common mode for respiratory failure albeit it was not well developed at the time. But before the Harvard group published their findings, harsh criticism throughout the nation labeled the study as being unethical because (1) mortally ill newborns were being withheld from this promising new therapy and (2) consenting parents to assign their infants to the CMV group was intentionally avoided by the researchers (Knox 1989). The 1989 Harvard study became a highly cited study as it was situated during a time when the conduct of clinical research was being heavily scrutinized. Further interest to conduct another ECMO RCT in the U.S. was at a halt. It wasn't until almost three decades later, in 1996, that the next neonatal RCT was conducted; it was led by a collaborative group in the United Kingdom (UK Collaborative ECMO Trial Group 1996). This was the only trial undertaken that looked at efficacy and compared mortality and disability following ECMO support (Nichani 2010).

In 1989, the Extracorporeal Life Support Organization (ELSO) was formed. The goal was to maintain a central database of all reported ECMO cases, establish practice guidelines, and facilitate practice standardization (Nichani

2010). Importantly, ELSO publishes an "ECLS Registry Report, International Summary", a report released bi-annually that aggregates cumulative data from ECMO centers across the world (Extracoporeal Life Support Organization 2015). The data also allows researchers to conduct retrospective analysis and is available to all ELSO members.

More recently, ECMO drew public health interest during the 2009 H1N1 epidemic. "Early reports of survival in patients with severe respiratory or multiple organ failure due to H1N1" (Dalton 2011, 1449) generated renewed interest for ECMO use in adults. Another adult ECMO RCT was attempted thirty-five years after the first, by another UK group examining "Conventional ventilation or ECMO for Severe Adult Respiratory Failure" (study known as the CESAR trial) (Dalton 2011, 1448). The study showed that adults with severe but potentially reversible respiratory ECMO are associated with better rates of survival than with conventional ventilation. However, the CESAR trial was equally criticized as much as it was praised (Dalton 2011). ELSO developed an online site to collect this data. In 2011, Dalton reported 263 patients entered into the ELSO H1N1 database with 63% survival (Dalton 2011).

Although the goal to substantiate the efficacy of ECMO in RCTs has been historically largely unsuccessful, ECMO support continues to be practiced throughout ECMO centers across the world. In 1990, there were 1,644 reported cases across 83 centers. The number of cases doubled in 2010. In 2014, the number of cases and centers has tripled (5,037 cases across 251 ECMO centers) (Extracoporeal Life Support Organization 2015).

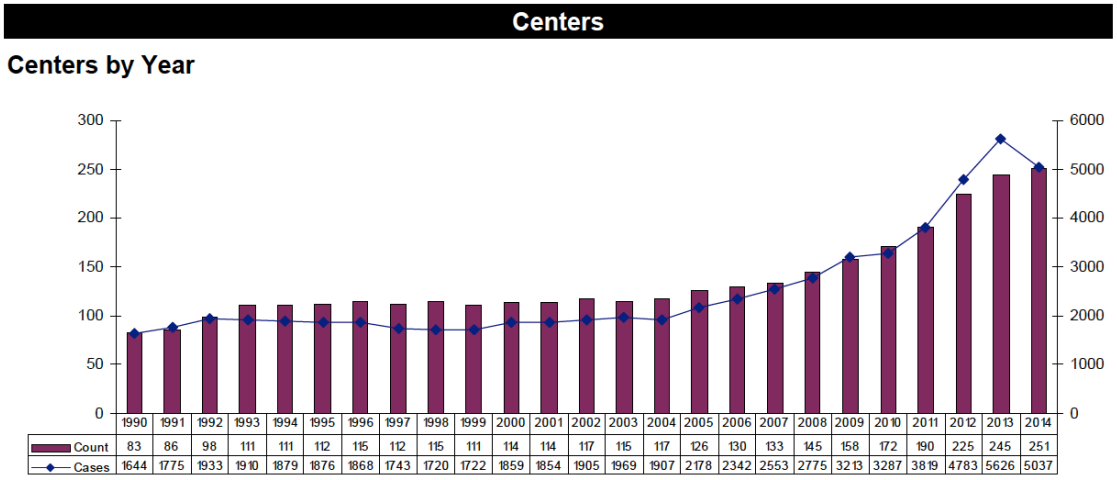

Figure 2.1: ECLS Centers by Year. The left y-axis is the number of ECLS centers; the right y-axis is the number of cases reported. ECMO Registry of the Extracorporeal Life Support Organization (ELSO), Ann Arbor, Michigan, January, 2015.

From the time of Harvey, Denis, and Legallois, the complexity of ECMO technology itself and the complexity of managing the critically ill have certainly grown. Traditionally, ECMO has been indicated for patients with profound cardiac and respiratory failure – at times when the body is no longer able to support cardiopulmonary tissues required for living function. In acute conditions that cause significant heart and/or lung dysfunction, introducing ECMO as a critical clinical intervention has arguably been recognized as a life-saving technology. As new generations of pumps, oxygenators, and cannulas evolve, improvements are made in the safety of the circuitry (e.g., lower priming volumes, reducing bleeding complications). However, the implications of ECMO use in new disease categories have grown to include multiple organ failure, septic shock, burns, trauma, airway abnormalities that require complicated surgical repair, and bridge to organ transplantation (Dalton 2011). Although the efficacy of ECMO support still has yet to be proven, the number of ECMO cases continues

to grow. The January 2015 ECLS Registry Report captured 65,171 total reported cases (34,650 (53.2%) neonatal, 16,253 (24.9%) pediatric, 14,268 (21.9%) adult) (Extracoporeal Life Support Organization 2015). Each patient population is further categorized into cases requiring respiratory support, cardiac support, or emergent ECMO. Chapter three discusses the clinical reasoning in determining ECMO candidacy and the moral reasoning in assessing harms associated with ECMO practice.

CHAPTER 3: CLINICAL REASONING IN ECMO CANDIDACY

Purifying the vital fluid that sustains human life through extracorporealization is an extraordinary feat of modern day medicine; though, the clinical implementation of the practice has major challenges. ECMO, as primarily practiced in highly sophisticated ICUs across the nation, is both clinically complex and requires technical specialization. Factors that contribute to its complexity relate to the rigor in the clinical management of the patient, the scrupulosity of the ICU environment, the intense consumption of resources, and the demanding cognitive and emotional toll on the human psyche.

Concomitantly, technical factors of the circuitry itself propagate the complexities in extracorporealization management. Understanding the mechanical intricacies of the circuitry and its components and, importantly, the ability to troubleshoot the system in the event of system failure, are a requisite for a successful ECMO run. Lequier and colleagues describe these components (i.e., pump, gas exchange device, heat exchanger, blood flow monitor, pressure monitor, circuit access sites, etc.) in greater detail (Lequier, et al. 2013).

Other ancillary factors that contribute to the complexities of extracorporealization include institutional training and experience in the field. To account for such factors that risk potential for complications, practice guidelines have been developed, even though the efficacy of ECMO has yet to be established. ELSO is the primary resource for providing industry guidelines on patient care practices, special topics, and on ECMO center and training (Extracorporeal Life Support Organization n.d.). However, the universality and

consistency of standardizing practice guidelines has yet to be adopted across (or even within) hospital institutions.

While there are many hospitals across the nation (and abroad) that are ELSO registered members, not all hospitals that practice ECMO are members of the Organization. In practice, clinical decisions are based on a combination of retrospective data analysis, evidence-based practice (if available), reliance upon clinical intuitions, and sometimes on heedful experimentation. Not surprising then, clinical reasoning in ECMO practice is often a comparative or case-based process – often referring to historical, clinical paradigm cases. Despite its advancement in the last thirty-years, such factorial inconsistencies during the clinical implementation of ECMO can heighten the risk for complications, which adversely impacts patients as a consequence.

According to ELSO's 2009 guidelines, a patient having a risk of 50% mortality is considered for ECMO support. When patient risk for mortality is at or exceeds 80%, ECMO is clinically indicated (Extracorporeal Life Support Organization 2009). ECMO supports a range of ages but the following inclusion criteria are proportionally considered when determining ECMO candidacy: (1) if the patient's underlying medical condition leads to significant organ dysfunction, (2) if the patient's medical status is unimproved following the exhaustion of available clinical options, and (3) if the pathogenesis of the patient's underlying disease remains reversible (Gaffney, et al. 2010).

In a survey study (discussed in chapter 4), ECMO experts were asked to respond to some descriptive statements that pertained to ethical aspects of ECMO practice, and they were given the option to provide comments at the end

of the survey. ECMO experts are defined as those who initiate, manage, and discontinue the clinical implementation of the technology. These experts were self-identified largely as physicians, nurses, respiratory therapists, primers, and/or ECMO specialists. One expert stated, “ECMO presents high risk for high reward.” Another expert emphasized, “Every patient on ECMO support is different…” because survival outcomes are different for different patient populations and also different based on the mode of the ECMO circuitry; hence, “…That's why ethically it's a challenge to support these patients.” These statements are tacit indicators of the clinical reasoning behind issues surrounding ECMO practice and are, thus, the subject-matter for this chapter. The goal of this chapter is to assess clinical reasoning utilized by ECMO experts when presented with moribund patients for ECMO evaluation. Describing the salient features of determining ECMO candidacy are particularly key given the inconsistencies in practice and lack of predictable outcomes.

This chapter is sectioned into two parts. Part one is offered as necessary background that informs the discussion in part two, on the moral assessment of ECMO-associated harms. Part one introduces the archetypal diseases that cause cardiac and respiratory failure that lead to ECMO consideration, and the respective modes of the ECMO circuitry (i.e., VA ECMO and VV ECMO) required for the type of organ support needed. Also discussed are the age-dependent applications (i.e., neonatal ECMO, pediatric ECMO, and adults ECMO) and the successes and failures among the age cohorts. In this section, the clinical paradigms under which ECMO is classically employed are highlighted.

An ECMO expert that participated in the survey stated, “there are no simple answers in ECMO… ECMO clearly saves lives, ECMO clearly has risks and does not work in all cases. ECMO can be problematic. I do think sometimes ECMO prolongs death, however more times I have seen it save a life.” Because ECMO practice involves significant risks, in part two of the chapter the notion of harm is introduced in relevance to the risks of ECMO practice. These risks include both mechanical and patient-related complications. Together, the risks discussed in part two, in association with the clinical paradigms discussed in part one, construct the dynamic factors of the ‘clinical picture’, all things considered, for which double-effect reasoning assesses. Central to this assessment is determining the moral permissiveness of harms as a means to saving a life.

In sum, ECMO candidacy depends on the disease state, mode of ECMO support required, age group of the patient, and the overall clinical experience (at both the institution and industry levels). Determining candidacy is primarily case-based and evaluated against historical clinical paradigms and exposure to risks (in return for benefit) while being supported on ECMO. However, a number of events of harm occur throughout an ECMO ‘run’ in hopes for some benefit. This chapter draws attention to the multifactorial features required for moral consideration in determining ECMO candidacy.

PART 1

Disease-Dependent Applications and Modes of the ECMO Circuitry

One of the first questions in determining whether ECMO is to be

considered in a case is ‘what is the underlying medical condition?’ and ‘is the severity of disease a significant cause for heart or lung dysfunction?’ Also, ‘is the disease pathogenesis reversible?’ Based on the clinical situation, ELSO provides online resources that describe general inclusion and exclusion criteria in which ECMO is either indicated or contraindicated (Extracorporeal Life Support Organization 2009). For instance, general disease-related contraindications include “conditions incompatible with normal life if the patient recovers” and “preexisting conditions which affect the quality of life” (Extracorporeal Life Support Organization 2013). An ECMO expert stated that “Survival rates vary widely with patient population and diagnosis” and that “the acceptability of risk is dependent on the patient's clinical picture.” One of the aspects in defining the clinical picture are the diseases that cause profound cardiac or respiratory failure which can be either organ-specific or non-organ-specific.

Cardiac Failure and VA ECMO

Cardiac Failure. Diseases that cause cardiac failure are either congenital or acquired. There are a variety of myocardial diseases that can significantly decrease heart function and lead to congestive heart failure (CHF). Myocarditis, ischemic heart disease, and severe aortic stenosis are organ-specific as they directly impact the heart (Magnani and Dec 2006, Thames, Sease and Damian 2004, Sawaya, et al. 2012). Non-organ-specific diseases such as vascular diseases may not directly involve the heart but can indirectly effect the heart by increasing its resistive workload (Gornik and Beckman 2005). The body attempts to

counteract the effects caused by the diseases using its natural compensatory mechanisms to adapt to these stressful conditions. However, when the body's adaptive measures are overwhelmed by the state of disease, the cardiovascular system decompensates or functionally deteriorates. Decompensation results in poor organ perfusion, tissue hypoxia, increased acid production (metabolic acidosis), end-organ dysfunction, and (if left untreated) ultimately death (Joseph, et al. 2009). In turn, the patient quickly deteriorates within hours (or sometimes even within minutes) and death is imminent. In such instances of cardiac failure, ECMO is utilized to support cardiovascular function.

Venoarterial (VA) ECMO. VA ECMO was the original technique that evolved from traditional cardiopulmonary bypass (CPB) performed in the 1950s (Cornish and Arensman 1993). This particular circuitry diverts blood from the systemic venous circulation from entering the right atrium and is accomplished by inserting a water hose-sized cannula into either the right internal jugular vein or femoral vein. The oxygen-depleted, systemic venous blood is circulated through the artificial lung via extracorporeal circulation (ECC) where oxygen is added and carbon dioxide removed. The oxygenated blood is then returned to the body via cannulation of the right common carotid artery or femoral artery in which blood flow to the systemic arterial circulation is resumed. VA ECMO is considered a *partial* bypass because the arterial or return blood mixes in the aorta with left ventricular blood that, in normal conditions, has traversed the lungs (R. H. Bartlett, Physiology of Extracorporeal Life Support 2012). The VA mode of the artificial lung is in parallel with the native lungs as it replaces part or all of both

heart and lung function (R. H. Bartlett, Physiology of Extracorporeal Life Support 2012). This mode allows for the left ventricle to unload, which promotes coronary blood flow and reduces the myocardial stretch; therefore, it allows myocardial rest and recovery. VA ECMO is the technique of choice for patients in severe cardiac failure but can also be employed in instances when VV ECMO (discussed below) cannot be accomplished. Overall, VA ECMO chiefly provides cardiac support but can also provide respiratory support when necessary (Pranikoff and Hines 2012). Cardiac failure (due to one or more of the medical conditions described) and VA ECMO represents a major clinical paradigm for ECMO practice. Makdisi and Wang list more recent clinical indications for VA ECMO, which includes bridge to heart transplantation, primary graft failure post heart transplant, and bridge to decision (Makdisi and Wang 2015).

Emergent ECMO or ECPR. Emergent ECMO or extracorporeal cardiopulmonary resuscitation (ECPR) is defined as "the use of ECLS for patients in cardiac arrest when conventional resuscitative measures have failed" or "when repetitive arrest events occur without return of spontaneous circulation" (Brown and Dalton 2012, 331). Both of the congenital and acquired cardiac conditions described can increase risk for events of cardiac arrest that could require ECPR support. ECPR is typically performed in ICUs, operating rooms, or catheterization laboratories (although attempts in emergency departments have been made). ECPR is another clinical paradigm of ECMO practice where patients in active cardiac arrest are "crashed onto ECMO".

Respiratory Failure and VV ECMO

Respiratory Failure. Diseases that cause respiratory failure (either from an endogenous or exogenous source) induce pathological changes that perturb the normal functioning of the lungs. Acute respiratory failure (ARF) is the most common medical condition for the pediatric and adult populations that require ECMO support (Gattinoni, Carlesso and Langer 2011). ARF is caused by either inhalational injury (i.e., aspiration, smoke inhalation, drowning), systemic disease (i.e., sepsis, trauma, embolism), infectious agents (e.g., bacterial or viral pneumonia), or surfactant deficiency (Wheeler and Bernard 2007). Positive pressure mechanical ventilation (PPV) is another source of causing lung injury (termed barotrauma); severe lung injury from barotrauma can also lead to ECMO intervention (Cordell-Smith, et al. 2006). The pathological changes that result from ARF and barotrauma are characterized as diffuse collapsing of the lungs, fluid build-up in the lungs, and decreased lung elasticity (Bhatia and Moochhala 2004). The pathology greatly inhibits the patient's capacity to breathe. In such instances, ECMO is utilized to support pulmonary function.

Venovenous (VV) ECMO. Whereas the VA mode functions in parallel with the native lungs, VV mode functions "in series with the native lungs and replaces part or all of native lung function" (R. H. Bartlett 2012, 11). This circuit drains and returns blood from the venous circulation by using (1) one double lumen cannula inserted into the jugular vein where one lumen serves to drain blood while the other lumen serves to return blood, or (2) inserting two single lumen cannulas at separate sites – one into the femoral vein where blood is drained, and

the other into the jugular vein where blood is returned. The double lumen cannula method is preferential as it involves only one major insertion site, which reduces the risk of introducing infections. Importantly, in VV mode, the patient must be able to self regulate as this mode does not support the patient hemodynamically. VV ECMO support has fewer complications compared to VA ECMO support (Makdisi and Wang 2015). Respiratory failure (due to one or more of the medical conditions described) and VV ECMO represents another major clinical paradigm for ECMO support. Makdisi and Wang also list the recent clinical indications for ECMO for respiratory support, which includes bridge to lung transplantation, primary graft failure post lung transplant, and status asthmaticus (Makdisi and Wang 2015).

Age-Dependent Applications

Another aspect that further defines the clinical picture is determining the age-dependent applications and the ECMO experience among the age cohorts. According to one ECMO expert, "Patient selection is key to making good clinical and ethical decisions as well determining at any point of time whether the risks outweigh the benefits." ECMO can be applied to a spectrum of ages, however outcomes in survival (or mortality) vary depending on the support-associated requirement (i.e., respiratory-associated support, cardiac-associated support, or emergency-associated support) for each of the patient cohorts.

In the January 2015 International Summary ELSO Registry Report, 65,171 cumulative ECLS cases were reported (Extracoporeal Life Support Organization

2015). Of these cases, overall survivability from ECLS intervention across all three modes of support among all age groups was 71% (46,490 patients) and survival to hospital discharge or transfer out of the unit was 59% (38,636 patients) (Extracoporeal Life Support Organization 2015). Among the three age groups, cumulative number of neonatal cases that employed ECLS for respiratory support was about four times that of the pediatric cases and adult cases requiring the same type of support (Extracoporeal Life Support Organization 2015). This data is not surprising given the early history of the technology being employed in the neonatal cohort. While the cumulative number of total respiratory-associated cases reported by ELSO is higher in neonates, there are comparable numbers of cardiac-associated ECLS cases across age cohorts (Extracoporeal Life Support Organization 2015). Complex cardiac abnormalities were once considered contraindicated for ECMO consideration (Cornish and Arensman 1993); the data reflects this. Of the cumulative number of ECPR cases, the number of total pediatric cases is double compared to neonatal or adult ECPR cases. These age- (and support)-dependent outcomes (shown in Figure 3.1) are relevant factors in clinical reasoning when considering ECMO candidacy.

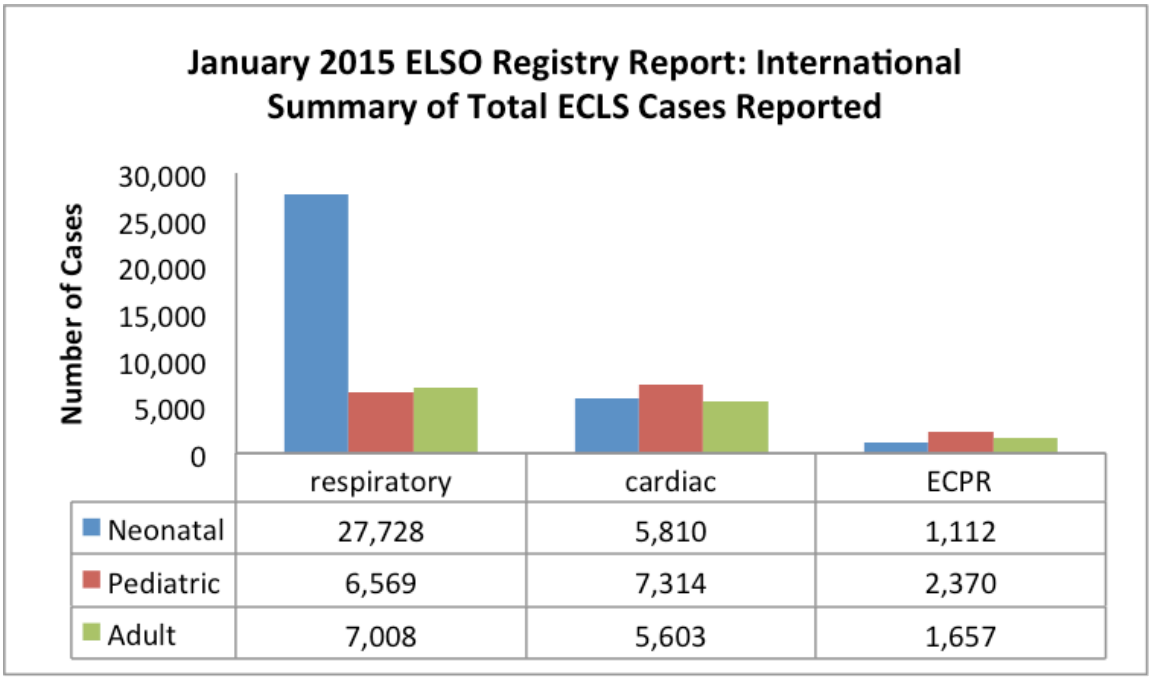

Figure 3.1: Total ECLS Cases Reported by ELSO Registry International Summary, January 2015. This figure was generated using data from the ELSO Registry, January 2015, with permission from the Protocol and Registry Committee (Extracoporeal Life Support Organization 2015). The cumulative number of neonatal ECMO cases for respiratory, cardiac, and ECPR support are represented in blue, pediatric ECMO cases in red, and adult ECMO cases in green.

Neonatal ECMO. It is understood in the field that ECMO intervention on a patient who is at least 34 weeks gestational age and less than thirty days old is considered to be on 'neonatal ECMO' (Hintz, et al. 2000, Chapman, et al. 2009). Age-related contraindications include neonates that are less than 2 kg in weight or less than 34 weeks post-menstrual age due to the elevated risk for intracranial hemorrhaging (Extracorporeal Life Support Organization 2013, Cilley, et al. 1986). The January 2015 International Summary ELSO Registry Report (Extracoporeal Life Support Organization 2015) references 34,650 cumulative neonatal cases, 27,728 that required respiratory support, 5,810 cases requiring cardiac support, and 1,112 cases involving ECPR (see Figure 3.1).

Of the neonatal respiratory group, 16% did not survive while on ECMO and 10% survived but not to hospital discharge or transfer. These are the lowest percentages of mortality, which reflects the overall success in employing respiratory-associated ECMO as compared to the other age groups, regardless of support. This distinction is less apparent in survivability among cardiac- and emergency-associated ECLS cases. In neonatal cases requiring cardiac support, 38% did not survive while on ECMO and 21% survived but not to hospital discharge or transfer. Of the neonatal ECPR group, 36% did not survive while on ECMO and 24% survived but not to hospital discharge or transfer. These results are shown in Figure 3.2 in blue. The level of impairment at the time of hospital discharge is unknown.

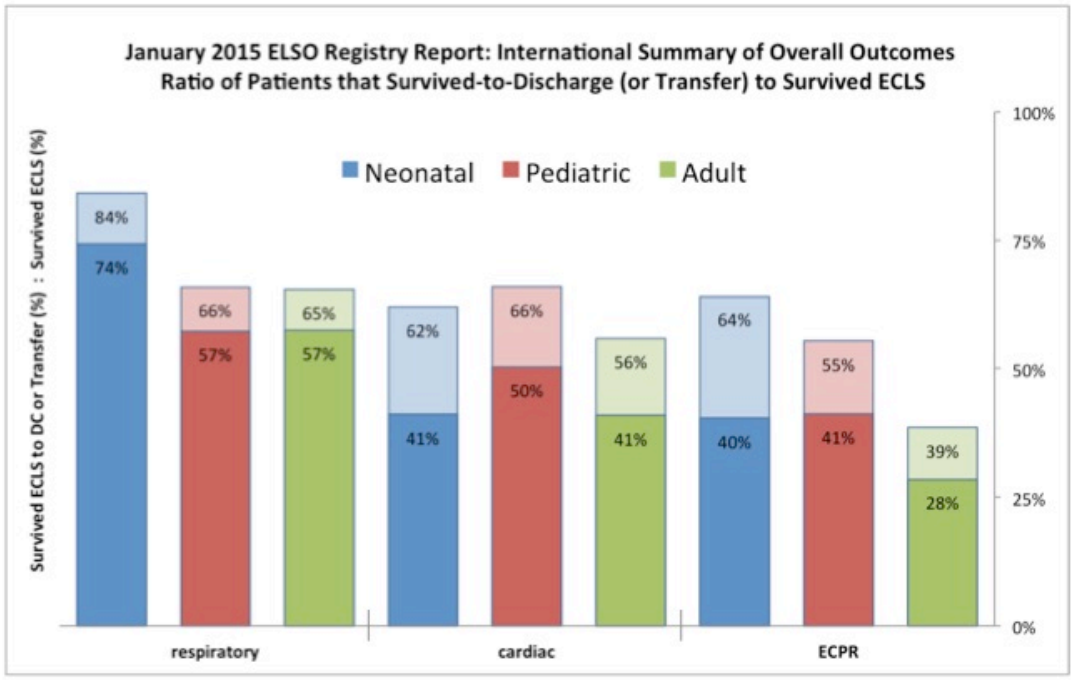

Figure 3.2: January 2015 ELSO Registry Report, International Summary of Overall Outcomes. Ratio of Patients that Survived-to-Discharge (or Transfer) to Survived ELCS. This figure was generated using data from the ELSO Registry, January 2015, with permission from the Protocol and Registry Committee (Extracoporeal Life Support Organization 2015). Of the percentage of patients that survived ECLS, for each age cohort, a percentage fewer survived to hospital discharge (or transfer). The cumulative number of neonatal ECMO cases for respiratory, cardiac, and ECPR support are represented in blue, pediatric ECMO cases in red, and adult ECMO cases in green.

Pediatric ECMO. As understood in the field, ECMO intervention on a patient who is more than thirty days and less than eighteen years of age is considered to be on 'pediatric ECMO' (Extracorporeal Life Support Organization 2013). ELSO provides guidelines for pediatric cardiac (Extracorporeal Life Support Organization 2013) and respiratory (Extracorporeal Life Support Organization 2015) failure. The guidelines state that there are "no absolute indicators" for pediatric patients in respiratory failure but "consideration for ECMO is best within the first 7 days of mechanical ventilation at high levels of support" (Extracorporeal Life Support Organization 2013). In ELSO's January 2015

Registry Report (Extracoporeal Life Support Organization 2015), there were 16,253 cumulative pediatric cases, 6,569 that required respiratory support, 7,314 cases requiring cardiac support, and 2,370 cases involving ECPR (see Figure 3.1).

Of the pediatric respiratory group, 34% did not survive while on ECMO and 9% survived but not to hospital discharge or transfer. In pediatric cases requiring cardiac support, 34% did not survive while on ECMO and 16% survived but not to hospital discharge or transfer. Of the pediatric ECPR group, 45% did not survive while on ECMO and 14% survived but not to hospital discharge or transfer. The results are shown in Figure 3.2, in red. Again, the level of impairment at the time of hospital discharge was unknown.

Adult ECMO. Lastly, ECMO intervention on a patient that is over 18 years of age is considered in the industry to be on 'adult ECMO' (Extracorporeal Life Support Organization 2013, Extracorporeal Life Support Organization 2013). ELSO's guidelines on adults in respiratory failure states "There are no absolute contraindications to ECLS, as each patient is considered individually with respect to risks and benefits" (Extracorporeal Life Support Organization 2013, 3). For adults in cardiac failure, the indication is cardiogenic shock (and sometimes septic shock). An absolute contraindication is "[u]nrecoverable heart and not a candidate for transplant or VAD, Advanced age, Chronic organ dysfunction…, Compliance…, Prolonged CPR without adequate tissue perfusion" (Extracorporeal Life Support Organization 2013, 3). Obesity is considered a relative contraindication in adults whereas this is not the case in pediatrics.

Supporting adults on ECMO is less frequent compared to its younger counterparts. In the January 2015 report (Extracoporeal Life Support Organization 2015), there were only 14,268 cumulative adult cases, 7,008 that required respiratory support, 5,603 cases requiring cardiac support, and 1,657 cases involving ECPR (see Figure 3.1).

In adult cases requiring respiratory support, 35% did not survive while on ECMO and 8% survived but not to hospital discharge or transfer. Of the adult cardiac group, 44% did not survive while on ECMO and 15% survived but not to hospital discharge or transfer. Of the emergent ECMO adult cases, 61% did not survive while on ECMO and 11% survived ECPR but not to hospital discharge or transfer (Extracoporeal Life Support Organization 2015). The results are shown in Figure 3.2, in green. Again, the level of impairment at the time of hospital discharge was unknown.

To summarize, clinical reasoning during consideration for ECMO candidacy is dependent on the entirety of the clinical picture; the clinical picture includes the underlying disease and its severity, the type of ECMO support needed, and the patient age category. Neonatal ECMO for respiratory support represents the primary clinical ECMO paradigm given its success. The eight remaining paradigms gradually undergo further refinement as the number of ECMO cases continues to grow. As discussed, not all patients that survive ECMO continue to hospital discharge or unit transfer. The second part of the chapter focuses on the adverse events that greatly impact patient survivability.

PART 2

"High Risk" ECMO and Harm

"We always seek to do no harm. ECMO is an intervention to save a life", stated an ECMO expert who participated in the current survey. While promising, ECMO intervention does not always save lives, rather "you are typically taking a patient with 80%-100% mortality and giving a patient a chance survival," stated another expert. The process of extracorporealization exposes patients to a unique array of risks and complications (not otherwise encountered without intervention) that exacerbates the criticality of the patient's medical condition. An argument for exposing ECMO candidates to such risks is that "The chance of survival without ECMO is usually 0%" and "Even 'poor stats' like saving 3 in 100 is great compared to 100% mortality!", stated another ECMO expert. The clinical reasoning, here, evokes an ethically profound paradox of choice – to impose harm as a means to the end of potentially saving a life. This section examines the moral paradox found in employing 'high risk ECMO' and patient exposure to harm.

First, what is *harm*? The notion of *harm* has intrigued moralists and scholars for centuries. *Bioethics* (formerly the *Encyclopedia of Bioethics*) adopts the *Oxford English Dictionary*'s definition of *harm* as an "evil (physical or otherwise) as done to or suffered by some person or thing; hurt, injury, damage, mischief" (Schöne-Seifert 2014). Throughout history, the term has appeared in various seminal texts that either construct harm broadly or narrowly. In the *Principles of Biomedical Ethics*, Tom Beauchamp and James Childress notes this

difference (Beauchamp and Childress, Nonmaleficence 2009). When constructed broadly, harm concerns "setbacks to interests in reputation, property, privacy, and liberty" that cause "discomfort, humiliation, offense, and annoyance" (Beauchamp and Childress, Nonmaleficence 2009, 152). When constructed narrowly, as it suggests, harm concerns exclusivity to only the "physical and psychological interests, such as those in health and survival" (Beauchamp and Childress, Nonmaleficence 2009, 152). In *The Metaphysics of Harm*, author Hanser describes competing accounts of harm (Hanser 2008). He presents that the most widely accepted views of harm are state-based – "to be [in or] put into… a certain sort of bad state or condition" (Hanser 2008, 421) – and comparative accounts: (1) counterfactual comparison account and (2) temporal comparison account. Each view also has its corresponding parallel accounts of states of benefit. The non-comparative account is another view on harm. These different conceptualizations of harm will be discussed in more detail.

As referenced in the very first quote, the oldest known, prominent and morally authoritative medical text that mentions *harm* is the Hippocratic Oath. In the Oath, the proclamation "I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice" conveys a high, normative ethical prescription for medical practitioners to 'do no harm' towards those who they provide care (Edelstein 1943, Tyson 2001). Often in association with the Oath is the Latin aphorism *primum non nocere* – translated as "Above all [or first] do no harm" (Beauchamp and Childress, Nonmaleficence 2009). Here, the interpretation of *harm* found in the Oath narrowly concerns the setbacks to health and survival rather than to

reputation, property, privacy, or liberties. To date, the Oath remains to hold ethical prominence within the medical profession and has considerable bearing on the current discussion.

For the following, we bear in mind this normative, narrow notion and the different accounts on harm during clinical reasoning of high risk ECMO practice. In clinical reasoning, with all things considered – the underlying disease and its severity, the type of ECMO support necessary, and the patient age category – further, mechanical- and patient-related complications are, too, equitably considered. The following sections highlight the major mechanical- and patient-related complications that have been reported.

Mechanical Complications. Before and during the process of extracorporealization, having technical expertise in the mechanical intricacies of the ECMO circuitry and its components, and the ability to quickly troubleshoot system failures is key to maintaining a successful ECMO 'run'. Otherwise, system failure (within minutes) can lead to patient death. Mechanical complications that have been reported include oxygenator failure, tubing rupture, pump malfunction, and cannula problems (Conrad, Rycus and Dalton 2005). Conrad and colleagues report that from the 2004 ELSO Registry Report, adult ECMO for respiratory support had the highest incidence of mechanical complications (18.2% oxygenator failure, 4.0% tubing rupture, 4.1% pump malfunction), except for cannula problems (which was highest in the neonatal cohort at 11.1%) (Conrad, Rycus and Dalton 2005). Similarly, 16.4% incidence of oxygenator failure was also reported for patients 16-years or older on ECMO for cardiac

support (Conrad, Rycus and Dalton 2005). Another source of mechanical complications include clots that can appear throughout the circuitry. ELSO continues to serve as the primary resource for tracking the incidence of mechanical complications in reported cases.

Patient-Related Complications. While the body's natural compensatory mechanisms can temporarily sustain itself during technical adjustments made during circuitry malfunctions, the added physiological stress from patient-related complications is more difficult to manage. The ECMO circuitry must be primed with heparin, a potent blood anticoagulant that prevents blood clots from forming throughout the circuitry. Heparinization also prevents blood clots from entering the patient's bloodstream which could lead to heart attacks, strokes, and death (Lequier, Annich and Massicotte 2012). In doing so, heparin is perfused into the patient systematically, thereby offsetting patient hemodynamics – favoring an anitcoagulative state. This particular state increases the hemorrhagic potential and, thus, massive hemorrhaging is a significant risk of ECMO intervention (Zangrillo, et al. 2013). Hemorrhaging (whether it be gastrointestinal, at the cannula site, or at the surgical site) has an incidence of 10-30% (Bartlett and Gattinoni 2010), and is particularly higher in VA ECMO (34%) compared to VV ECMO (Makdisi and Wang 2015). Of note, cannulation-related complications are unique to VA ECMO, and include accidental artery or vein perforations with hemorrhage, and downstream hypoxia of the heart and brain (Makdisi and Wang 2015). Conrad and colleagues report that from the 2004 ELSO Registry, adult ECMO for respiratory support had the highest incidence of

gastrointestinal hemorrhage (4.3%), cannula site bleeding (11.5%), and surgical site bleeding (22.4%). About a third of all ECMO cases for cardiac support, despite age cohort, had reported incidence of surgical site bleeding (Conrad, Rycus and Dalton 2005). During an exsanguinating hemorrhage crisis, the massive transfusion protocol is initiated but it does not necessarily guarantee patient survival (Young, Cotton and Goodnough 2011).

The medical severity for patients on ECMO is also amplified with the heightened risk of neurologic complications that are associated with ECMO intervention (Zangrillo, et al. 2013). Intracranial hemorrhaging and neurological injuries and impairments can result from patient systematic heparinization; these events are major contraindications. Neurologic complications are common in neonatal ECMO, at 10.9% incidence (Conrad, Rycus and Dalton 2005), and are associated with increased mortality (Polito, et al. 2013). In addition, poor perfusion or low oxygen saturations (as a result of mechanical malfunctions, for instance) can cause serious anoxic brain injuries. Both intracranial hemorrhaging and anoxia of the brain are the most undesirable complications of ECMO practice as it can neurologically devastate the patient. In such events, ECMO is deemed futile and must be discontinued.

Further, aggressive drug therapy and chemical intervention that take place prior to and during ECMO support can significantly disrupt the normophysiologic electrolyte balance and can overwhelm the kidneys. Thus, providing renal supportive therapy is often necessary to counteract the detrimental effects of ECMO intervention and the chemical therapies that preceded it (Fleming and Brophy 2012). CVVH technology, part of the ECLS

armamentarium, is a supportive measure when continuous renal dialysis is needed.

Last, implementing ECMO introduces potentially life-threatening infections that can overwhelm the body's already compromised state (Lynch 2012). First, ECMO initiation requires cannulation, a surgical procedure in which one or two hose-sized tubes are inserted into a major artery and/or vein (Pranikoff and Hines 2012). As with any invasive procedure, cannulation risks the direct introduction of microbial infections into the blood stream (or sepsis), which can cause an overwhelming immune response (septic shock) that can lead to multiple organ failure and ultimately death. From 1998 through 2008, it was reported that of the 20,741 ECMO patients in ELSO's registry, there were 2,418 culture-proven infections (Lynch 2012, Bizzarro, et al. 2011). Second, since ECMO support requires massive volumes of blood replacement, blood transfusion-related complications risks introducing the potential of blood-borne infections (such as hepatitis and HIV) and blood product reactions (such as haemolysis and graft versus host disease), albeit, at a low risk (Bjerke, et al. 1992). Collectively, massive hemorrhaging, neurologic devastation, renal failure, and sepsis pose additive risks and further exaggerate the medical criticality of the patient.

DISCUSSION

The overarching ethical question is 'what is morally owed to dying patients (and to what ends)?' and 'are there limits to performing extraordinary acts in

efforts to preserve life?' Determining ECMO candidacy is multifactorial and undoubtedly complex. With all things considered, the path of sound clinical reasoning requires comprehensive evaluation that proportionally addresses the following questions: (1) What is the underlying medical condition? (2) Have all clinical options been exhausted without improvement? (3) Is the pathogenesis of disease reversible? (4) What type of ECMO support is needed (5) What successes and failures are known about the relevant clinical paradigm? (6) What are the indications and contraindications that favor or disfavor ECMO employment? (7) What are the known and unknown risks? and (8) What is the likelihood of functional survival? Given all the salient factors to be considered and the narrowness in normative guidance, determining ECMO candidacy is primarily conducted on a case-by-case basis and often refers to historical, clinical paradigm cases under which ECMO is classically employed. Yet, a profound ethical paradox is central to these deliberations; ECMO practice presents a tension between strict moral obligations 'to save a life' and 'to do no harm'.

ECMO practice risks violating the strict moral obligation 'to do no harm'. As discussed, harm has considerable ethical bearing on employing high risk ECMO. Now that the major ECMO-associated risks have been described, the competing accounts of harm (listed previously) require some further attention. The goal, here, is to not settle on one particular definition or account of harm, but to highlight the various ways in its conceptualization and evaluation, particularly when arriving at collective, sound clinical decisions. The two common state-based, comparative accounts of harm follow.

First, the counterfactual comparison account of harm, as Hanser defines, is the state that is "to come to be worse off than one otherwise would have been" (Hanser 2008, 422). In a more formulaic version, "a person suffers harm if and only there occurs some event *e* such that he would have been better off had *e* not occurred" (Hanser 2008, 422-423). If, for instance, event *e* is VV ECMO intervention on a neonate diagnosed with meconium aspiration, and the occurrence of event *e* results in saving a life, then the patient (according to this account) does not suffer harm. Related, if death results regardless of the occurrence of event *e*, then the patient is no more better off than if event *e* were to not occur; therefore, the patient does not suffer harm. What if, for instance, the occurrence of event *e* causes an intracranial head bleed – a major clinical contraindication – and the neonate is now worse off medically; it follows, then, that the patient is harmed. Similarly, if event *e* causes an exsanguinating hemorrhage crisis that results in the neonate being worse of medically, then, it also follows, that the patient is harmed. But if ultimately the neonate survives the crisis and survives to hospital discharge, then the patient, according to this counterfactual comparison account, does not necessarily suffer harm. Yet, numerous events (both in states of harm and in states of benefit) occur throughout an ECMO run (which can span up to weeks or months). What if, for instance, VA ECMO intervention on a pediatric patient diagnosed with myocarditis, causes hemorrhaging yet cardiac stress is reduced such that the heart is allotted time to heal. In this scenario, whether the patient is better off is more difficult to discern. Moreover, whether ECMO suits the condition as event *e*

is indeterminate. Here, the counterfactual comparison account does not seem to hold.

In such instances, as Hanser describes, there is a parallel account of benefit where "a person can be simultaneously in both a harmed and a benefited state, so long as the harm is relative to the occurrence of one event and the benefit is relative to the occurrence of another" (Hanser 2008, 423). This is called the "extended counterfactual comparison account". In a more formulaic take, "a person receives a benefit if and only if there occurs an event *e* such that he would have been worse off had *e* not occurred" (Hanser 2008, 423). If event *e* is VA ECMO intervention and the occurrence of event *e* resulted in reducing cardiac stress, promoting cardiac healing, then the pediatric patient (as it follows) must benefit from VA ECMO intervention (particularly if the patient survives to hospital discharge). But what if the hemorrhaging caused by the occurrence of event *e*, despite promoting cardiac healing, leads to anoxic brain injury? Is the patient better off or worse off? The patient is both in a simultaneously benefited state (heart is better off with VA ECMO intervention) and harmed state (brain is worse had VA ECMO intervention not occurred). The intuitive appeal of the counterfactual comparison account and its extension diminishes as the substantive difficulties expand.

The other widely accepted comparative view is the temporal comparison account. According to this view, "harm is a matter of becoming less well off than one was before" (Hanser 2008, 425). In the formulaic version, "a person suffers harm if and only if there are a time *t1* and a later time *t2* such that the person is in some respect worse off at *t2* than he was at *t1*" (Hanser 2008, 425). If, for

instance, event *e* is ECPR intervention on an adult patient in active cardiac arrest during time *t1* and the occurrence of event *e* deescalated the cardiac event at time *t2*, then because at time *t2* the patient is better off the patient does not suffer harm. Further, if at time *t2* an ensanguining hemorrhagic crisis occurs and the patient is not only in active cardiac arrest but also bleeding to death, then the patient (being worse off at time *t2*) suffers harm.

In a parallel account of benefit, Hanser summarizes that "a person can be simultaneously in both a harmed and a benefited state with respect to a single aspect of his well-being, so long as the harm and the benefit are relative to different earlier times" (Hanser 2008, 425). If for instance, in the adult ECPR example, the events preceding ECPR caused renal failure (state at time *t1*) requiring CVVH (state at time *t2*) and the occurrence of event *e* (ECPR) deescalates the cardiac event (state at time *t1)*, then the patient is simultaneously in both a harmed state (kidney failure at time *t1* being worse off on CVVH at time *t2*) and a benefited state (deescalated cardiac arrest at time *t2* being better off compared to activated cardiac arrest at time *t1*). Further, Hanser describes:

> He can also be for a time in a harmed state, with respect to a certain aspect of his well-being and relative to a certain earlier time, and then later in a benefited state, with respect to that same aspect of this well-being and relative to that same earlier time (Hanser 2008, 425).

Clearly, reasoning becomes progressively more and more complex as the number of adverse events occurs within a single ECMO case. What, then, if there are multiple states of harm? multiple states of benefit? that occur at multiple points in time (*t1*, *t2*, *t3*, *t4*, …)? Is, then, the moral calculus additive? Does one harm carry more (or less) moral weight compared to another harm? The same is true for benefits. Are states of benefit additive? Does one benefit carry more (or less) moral weight compared to another benefit? This would necessitate constructing axioms of priority.

Whether one's prescription towards a counterfactual comparison account of harm, extended counterfactual comparison account of harm, or temporal comparison account of harm is more or less determinant, the point of doing such an exercise is to not test the plausibility to settle on a single view of harm. The exercise illustrates the multifactorial complexities involved in proportionately assessing and weighing harms (and benefits) and questioning whether such magnitude and/or severity of harms are morally permissible in ECMO practice.

There are other accounts of harm when, regardless of the occurrence of event *e* (ECMO intervention), the patient is in a state of harm simply by being in a non-comparatively bad state. This is called the "non-comparative account of harm" (Hanser 2008), particularly evident in cases where ECMO is contraindicated. For example, having a lethal chromosomal malformation (like trisomy 13 or trisomy 18) in which the median age of death is 10 days (Rasmussen, et al. 2003), is a clinical contraindication because the initial state, itself, is considered a state of harm; that is, a state that is incompatible with life.

Alternatively, another venerable approach to redress this issue of harms (perhaps an approach that holds greater prominence in the clinical context) is the Principle of Double Effect (PDE). Also known as the Rule of Double Effect (RDE), and Doctrine of Double Effect (DDE), or simply referred to as "double effect" (Beauchamp and Childress, Nonmaleficence 2009, McIntyre 2014, Timmons 2002), this formulation inspects harms as either an intended or unintended and foreseen or unforeseen event rather than based on some arbitrary moral calculus of the value of the harm itself. Another important distinction, here, is that the ultimate goal affectedly shapes the choices in which one arrives at achieving the goal (the means-to-an-end).

In ECMO practice, the end goal is to save lives; however, the means and the clinical reasoning in achieving this goal are what are being tested. In the study of bioethics, the PDE is a principle of moral reasoning that contends the conditions under which an otherwise absolute prohibitive act (for example, killing) can be morally permissible; specifically, when an agent performs an act that, although knowingly brings about bad results (also regarded as 'side effects') aims towards ultimately a good end. The most recognizable hypothetical moral dilemma that illustrates the PDE is "the trolley problem" introduced by Foot in 1967 (Foot 2002, Thomson 1985). Foot states:

> The words "double effect" refer to the two effects that an action may produce: the one aimed at, and the one foreseen but in no way desired. By "the doctrine of the double effect" I mean the thesis that it is sometimes permissible to bring about by oblique intention

> what one may not directly intend. Thus the distinction is held to be relevant to moral decision in certain difficult cases (Foot 2002, 1).

In 2007, Hauser and colleagues borrowed Foot's case study of "the trolley problem" and used it to develop further hypothetical moral dilemmas in a study that assessed how voluntary participants responded to conditions under which harm to the innocent is considered morally permissible (Hauser, et al. 2007). The authors concluded with "the principle of the double effect may be operative in our moral judgments but not open to conscious introspection" and "the need to consider the unconscious appraisal system that mentally represents the causal and intentional properties of human action" (Hauser, et al. 2007, 1).

The algorithm in determining the moral permissibility (or impermissibility) of an act in question is understood as when an action produces two foreseen effects – one good effect and one bad effect – then one is permitted to perform the act under the constraints of the bad effect if and only if the list of criteria are all satisfied. Various versions of the criteria generally involve (1) the nature-of-the-act condition, (2) right-intention condition, (3) means-end condition, and (4) proportionality condition. Hereafter, I defer to the classical formulation described by Beauchamp and Childress in *Principles of Biomedical Ethics* (Beauchamp and Childress, Nonmaleficence 2009). The formulation of the PDE is as follows (Beauchamp and Childress, Nonmaleficence 2009, 162-163):

1. *The nature of the act*. The act must be good, or at least morally neutral, independent of its consequences.

2. *The agent's intention*. The agent intends only the good effect, not the bad effect. The bad effect can be foreseen, tolerated, and permitted, but it must not be intended.
3. *The distinction between means and effects*. The bad effect must not be a means to the good effect. If the good effect were the causal result of the bad effect, the agent would intend the bad effect in pursuit of the good effect.
4. *Proportionality between the good effect and the bad effect*. The good effect must outweigh the bad effect. That is, the bad effect is permissible only if a proportionate reason compensates for permitting the foreseen bad effect.

From this, the PDE is applied to determine the moral permissibility of ECMO-associated harms. For the *nature of the act* condition, the act of ECMO intervention itself is for the purpose of saving a life that is at 80% or greater risk for death. Albeit extraordinary, the nature of the act is good aside from its consequences (of which there are many). For the right-intention condition, it is reasonable to assume that ECMO experts anticipate that some good will come about the intervention (e.g., organ rest and healing, sufficient systemic perfusion, allocating time for organ retrieval and transplantation, etc.). Good, here, corresponds to Hanser's state(s) of benefit.

In the same instance, the bad effects have been well documented and reported (Zangrillo, et al. 2013). It is reasonable to assume that the ongoing research and funding towards improving ECLS technology is so that its components can be further refined and risks reduced, with the goal of improving

patient outcomes. Thus, the bad effects are foreseen or predicted based on past experiences, and tolerated or managed when they do occur; but, the bad effects are not intended.

For the third condition on means-and-ends, the relationship of causation is more discreet. As previously discussed about Hanser's temporal comparison account, many states of harm and many states of benefit arise throughout an ECMO 'run'. The good effect(s) or the states of benefit are thought to be causal results of the act itself (ECMO intervention) and not as a consequence of the bad effect(s) or the states of harm. The bad effects that arise, because they are quite bad, lead to the patient being worse off rather than being better off. For example, hemorrhaging and clotting may be a risk of heparinization; perforations and exsanguination may be a risk of cannulation. These bad effects lead to worse off states like strokes and anoxic brain injury, respectively.

Further, the most difficult of the conditions of the PDE is the condition on proportionality. Proportionality raises the issue of constructing axioms of priority. Is it possible to assign moral weight to harms? Similarly, is it possible to assign moral weight to benefits? and are they additive? This level of specification arises in clinical reasoning and it impacts clinical decision-making. The moral methodology in chapter four is attentive to and reflects, in part, these particular challenges.

The notion of *harm* continues to be a pervasive topic in the field of clinical bioethics. In the most recent 2014 version of the encyclopedia *Bioethics*, authors Schöne-Seifert and Bettina state, "harm remains a vague and contested concept that in and of itself does not provide much moral guidance. What counts as harm

varies greatly, as do the scope and relative importance of the prescriptions not to inflict, to prevent, or to remove harm" (Schöne-Seifert 2014, 1381). Hanser argues that "A full account of harm should (a) tell us what it is to suffer harm, (b) explain why it is bad to suffer harm, and (c) give us some idea how to measure the relative seriousness of different harms" (Hanser 2008, 421-422). Discussing normative theories on the prioritization and specification of harms (and benefits) related to ECMO practice is reserved for future study. Whether it is possible to construct a prescriptive theory that better guides the ethics of ECMO practice, is also a topic for further exploration.

CHAPTER 4: THE SURVEY STUDY

AN EMPIRICAL APPROACH TO CLINICAL REASONING

A growing dimension of bioethical research is empirical study. Empirical bioethics is the discipline of examining ethical issues (qualitatively and/or quantitatively) using the methodologies of social science research to focus on 'ethics-in-action' (Have and Lelie 1998). Prior to 1980, traditional normative reflections on ethical reasoning and theoretical analysis have directly appealed to philosophical and theological inquiry (Borry, Schotsmans and Dierickx 2005). While some may argue that the empirical approach is "epiphenomenonal and peripheral to dominant bioethical thought" (Borry, Schotsmans and Dierickx 2005, 60), since the birth of the empirical turn in bioethics in the early 1980s, the incorporation of empirical-ethical research in bioethics has only expanded (Borry, Schotsmans and Dierickx 2005).

Feudtner and colleagues state that the "[e]mpirical studies of bioethics issues are valuable: they can help us to evaluate theory, suggest the need to revise policy, inspire new ideas and hypotheses, and address novel questions that cannot be resolved solely through reflection and analysis" (Feudtner, et al. 2014, 1). The *American Journal Of Bioethics (AJOB) Empirical Bioethics*, formerly *AJOB Primary Research*, serves to promote the aim of empirical bioethics scholarship. An important aspect of the approach, particularly as it relates to medical ethics, is that it enhances practical decision making by "giv[ing] representation to diverse participants and stakeholders and may offer important

perspectives and values" (Feudtner, et al. 2014, 1) which are not otherwise appreciated.

This empirical approach to bioethical analysis, through either a sociological, anthropological, epidemiological, and/or psychological lens, underscores and contextualizes the sociocultural and historical aspects of morality (the dynamic values, preferences, norms, and actions of the moral landscape). This has particular relevance in morally pluralistic societies. Thus, the value of empirical examinations with respect to what it can add to mainstream ethical analysis is worth further exploration.

Although empirical research in bioethics has been growing since the 1980s, Borry and colleagues discussed its emergence during the mainstream normative tradition of ethical analysis (Borry, Schotsmans and Dierickx 2005). The authors offered three reasons for this – first, for pragmatic reasons and second, for historical reasons – but for the current discussion, the third reason (a meta-ethical reason) is the focus. The meta-ethical reason focuses on the 'is-ought' distinction. A normative approach to bioethical issues is prescriptive in that it determines how one ought to act according to a set of *a priori* ethical standards, rules, and principles (Beauchamp and Childress, Moral Norms 2009). It requires logical reasoning, rational justification, coherence, and conceptual clarity.

Normative notions, like that of virtue theory, emphasize upholding high moral character (Beauchamp and Childress, Moral Character 2009). In ECMO practice, for example, the self-cultivation of benevolence in moral character enables disposition of ECMO practitioners to act in ways that benefits the

patient's well-being. Another normative concept in virtue theory includes acting in service of justice (or fairness). For example, just acts involve the ability of ECMO practitioners to discern, particularly during situations where resources are limited, which patients should be offered ECMO therapy while excluding those who (although qualify) would least likely benefit from it. Simply, normative approaches prescribe the ethical action to be performed based on ethical ideals.

At tension with the normative tradition, empirical bioethics is descriptive. It describes what 'is' or what actually happens in reality. This account is not necessarily value-free. In ECMO practice, consistency in reasoning is often at risk; the environment is often highly intense, patient critical, and partakers emotionally charged. As an emerging, modern-day technology, its practice obscures the formulaic reasoning that a normative approach prescribes and, rather, reinvigorates old philosophical questions (such as *what is owed to dying patients?*) in a contextually nuanced way.

For instance, employing ECMO elevates patient risks and harms, and one may not be able to differentiate what choice is most benevolent (given that the predictability of ECMO outcomes are unclear). It has been observed that unlisted patients are placed on ECMO support as a 'bridge to organ transplantation' yet survivability has been observed to be inversely proportional to the duration of the ECMO run (Gupta, et al. 2012). Here, the means does not justify the end. Thus, in ECMO practice, ethical action as determined by moral standards quickly depreciates. So, normative analysis alone, on what ought to occur, is not enough.

An empirical examination of the ethics of ECMO practice is of particular interest. Of note, this discussion does not attempt to rectify the discourse

between the normative tradition versus the descriptive aspect of empirical bioethics; rather it highlights how both approaches could compliment one another. Importantly, introducing an empirical dimension invites greater moral participation of the stakeholders involved, whose diverse perspectives are otherwise overlooked in normative reflection alone. Because the 'stakes are high' in ECMO practice, moral participation is an essential component in fostering ethically-driven clinical practices. Overall, empirical-ethical analysis, here, serves to complement traditional normative reasoning and theoretical analysis in moral decision-making (Strech, Synofzik and Marckmann 2008, Sugarman and Sulmasy 2001, Berry, Schotsmans and Dierickx 2006) and is the impetus for the present survey study.

Moral Methodology

First, some general remarks about moral reasoning are needed. "Moral reasoning is individual or collective practical reasoning about what, morally, one ought to do" (Richardson 2014, 1). From a practical account, reasoning is a formulation of a moral judgment in which one logically reasons from some start point to some end point – resulting in a decision or act. From a theoretical account, hypothetical situations are constructed as thought exercises to examine prospectively what is morally required if the event (or a similar event) is to occur. From a philosophical account, reasoning as norms of thinking are underpinned by metaphysical examinations of morality. But, moral reasoning, itself, is often performed tacitly.

In medicine, for instance, the medical team is often confronted with having to cope with moral conflicts and is morally compelled (and obligated) to think clearly and responsibly in a timely manner. Yet, as Richardson highlights, "moral dumbfounding" – presented as inconsistencies in reasoning – occur as a result of many contiguous external stimuli that greatly influence when and what things are morally considered (Haidt 2001, Schwitzgebel and Cushman 2012, Sneddon 2007, Richardson 2014), a phenomenon not considered in normative theory. Inconsistency in moral reasoning is true with ECMO practice where factors like training, experience, environment, emotions, and availability of resources greatly influences clinical (and perhaps ethical) outcomes. Thus, the overt evaluation of contextual influences that describe what 'is' happening in reality during practical moral reasoning ought to be examined in more detail.

The quintessential methods on how moral justifications are formed are the top-down and bottom-up models. However, each method has been critiqued to have its own major limitations. In *The Principles of Biomedical Ethics*, Beauchamp and Childress highlight these limitations (Beauchamp and Childress 2009). A common critique of the top-down model, in which general norms are deductively applied to real cases, are that sometimes theories, principles, or rules are abstractly indeterminate in offering a conclusive prescription. This is the case with applying ethics to ECMO practice. By the same token, bottom-up models, in which cross-case analogical reasoning is inductively applied to morally relevant norms, pose problems with inconsistencies in case interpretation, which can then lead to conflicting analogical reasoning. For instance, interpreters' biases introduce conflicting analogical reasoning when making case-based judgments

and, problematically, morally relevant features are overlooked (Beauchamp and Childress, Method and Moral Justification 2009).

Alternatively, a new methodology of examining the 'is' juxtaposed with the 'ought' through an empirical lens is proposed here. This nuanced approach collects data from moral agents and how they reflectively reason through difficult clinical situations according to normative standards. Examining bioethical issues through an empirical lens offers a profound facet in bioethics; it can aid in systematically unpacking and assessing complex bioethical issues, which could result in moral prescriptions having, for instance, greater practical coherence. Practical moral reasoning does not happen in a vacuum; empirical-ethical analysis helps to better understand, descriptively, inconsistencies in moral reasoning in ethically complex clinical situations.

To date, a method that examines how moral agents explicitly navigate through complex moral issues (or what Hauser calls "conscious introspection") (Hauser, et al. 2007) during clinical reasoning is limited. The absence of a testable and reliable model in the literature prompted developing and constructing such an approach. The proposed method of collecting empirical data from morally-driven situations borrows from the tools of social science research methods. A common social science research tool, exercised here, is survey research, defined as "a research method involving the use of standardized questionnaires or interviews to collect data about people and their preferences, thoughts, and behaviors in a systematic manner" (Bhattacherjee 2012, 73). Arlene Fink describes the method as "a major means of collecting data to answer

questions about health and social, economic, and political life" (A. Fink 2006, 16).

In the overlay with bioethics, the use of surveys can informatively (in hierarchal order) "1) assess the *Lay of the Land*, 2) determine *Ideal versus Reality*, 3) seek to *Improving Care*, and 4) yields *Changing Ethical Norms*" [emphasis in the original] (Kon 2009). Hence, conducting online survey research presented to be the most reasonable and appealing sensible starting point. Because the practice of ECMO is multifaceted and quite complex (as discussed in chapter three), and because the practice is value-laden with variations in people's moral ascriptions, preferences, and thoughts about ECMO, the current study aims to gauge the "Lay of the Land" in the constitution (rather than quantification) of harm. The study examines the attitudes underlying ECMO practice, particularly the attitudes of those who play a central role in the technology's clinical implementation.

Of note, attitude is defined by "a psychological tendency that is expressed by evaluating a particular entity with some degree of favor or disfavor" (Eagly and Chaiken 2007, 582). According to Eagly and Chaiken's "umbrella" definition, evaluation can be overt or covert, or cognitive (referring to one's beliefs and thoughts), affective (referring to one's feelings and emotions), or behavioral (referring to one's intentions and overt behavior). The current study focuses primarily on the cognitive aspect of attitude assessment, albeit affect is likely to also play a central role.

The purpose of collecting data on the attitudes of ECMO experts is to supplement theoretical analysis in a non-speculative, non-hypothetical manner.

The goal of introducing empirical data into normative analysis is to maximize coherence, minimize biases, and emphasize collective reasoning rather than reliance on some single authoritative, moral (theoretical) prescription. Moreover, both consistencies and inconsistencies in reasoning among individuals and/or between groups can be captured through empirical data. In practice, ECMO has been described as being ethically contentious; thus, examining the issue further, specifically its moral permissiveness, is of practical importance.

STUDY METHODOLOGY

The current study is a cross-sectional, self-administered questionnaire that seeks to examine the moral permissibility (or impermissibility) of ECMO practice according to the Principle of Double Effect (PDE) (introduced in chapter three). The survey was directed towards a national sample of interdisciplinary healthcare teams who participate in the clinical employment of ECMO (i.e., ICU intensivists, cardiothoracic surgeons, ECMO specialists, ECMO nurses, ECMO respiratory therapists, ECMO circuit primers, and perfusionists). The presumption is that the moral attitudes of the healthcare team regarding the practice of ECMO vary across clinical roles (and perhaps even vary within the same role); thus, there exists variations or inconsistencies in the moral deliberations among the healthcare team in cases involving ECMO.

The objectives are (1) to determine if there are differences in professional attitudes towards the practice of ECMO, (2) to delineate if these differences are role-specific (e.g. physicians versus nurses), (3) to find correlations between

professional attitudes, if any, and (4) to elucidate the ethical implications of these attitudes as it pertains to the ethical management of ECMO patients. The results of the survey will be analyzed through an empirical-ethical lens and seeks to contribute to the field of critical care medicine and medical ethics education.

Survey Development

Of the variety of social science research tools, conducting an online survey served to be the most advantageous qualitative research methodology given the scope of the current discussion. The first advantage of online surveys is that they have a large geographical reach. Attentive to bias reducibility, targeting ECMO centers nationwide (rather than a single center) was of great importance (albeit the greatest number of responses were from the author's home institution). The target population was sourced from a publically available list of 157 domestic ECMO centers registered through ELSO (Extracorporeal Life Support Organization 2006); thus, convenience sampling was exploited.

Given the relatively small size of the ECMO community, survey sampling was non-random; each targeted ECMO center included a list of center directors and/or coordinators. However, given that a list of non-ELSO registered domestic centers was unavailable, for the purpose of promoting participation inclusion, ELSO-registered participants who received a survey were encouraged to field others (either internally and/or externally) through the participants' extended ECMO network. Thus, in order to maximize participation of the standard convenience sampling technique while also being sensitive to non-ELSO

registered ECMO centers, snowball sampling (Alexander and Wynia 2008) was tactical.

Although an international reach was considered, developing cross-cultural iterations of the primary survey (having both cultural accuracy and sensitivity) posed a greater resource challenge and was, thus, reserved for future exploration. The survey was distributed electronically in accordance with this model.

The second appeal of online surveys is the ease of technological accessibility. In the era of electronic medical records documentation, the targeted sampling population had both assumed ease of computer access and computer competency. A third appeal to online surveys is that they are relatively inexpensive and less time consuming compared to, for instance, conducting paper surveys or in-person (or phone) interviews. Paper surveys involve mailing costs and accurate address searches while interviewing requires a standard script and potential calling charges. The electronic survey methodology also best favors the scheduling and attention demands of healthcare workers. The last appeal to online surveys is that they are complied in real-time and the data collected is easily stored and accessible.

The survey form was developed using Adobe® FormsCentral, a web-based form-building service. In absence of a testable standard model, 17 descriptive statements were written in expert guidance from a practicing clinical psychologist. The survey statements were also constructed to align with Fink's criteria (e.g. questions being meaningful to the respondents, use of standard language rules, avoid use of biased words and phrases, avoid surveyor bias, etc.) (A. Fink 2006). Statement construction also borrowed terminology found in the

PDE. Table 4.1 lists the descriptive statements that appear in the survey. A point of clarification, here, is that this was a first attempt at conducting a national survey that trials participants to systematically reflect on double-effect reasoning; thus, statement construction was knowingly broad (and conditional). For instance, most people would absolutely agree with the statement "It is important to save a life"; however, conditionally, this may not be the case if say a patient has terminal cancer or a lethal genetic malformation. Future surveys could be refined for further clarity and greater specificity.

Participants were asked to voluntarily respond to the descriptive statements by selecting an answer choice among a five-point graded bidirectional Likert scale. The scale measured ordinal levels of agreeance or disagreeance (i.e., **SD** = strongly disagree, **D** = disagree, **N** = neutral, **A** = agree, **SA** = strongly agree). The overall goal of the survey was to determine, systematically, if each of the four conditions of the PDE were either being satisfied or not satisfied, based on descriptive statement clustering for each condition. In totality, if all of the conditions are satisfied, the harms associated with ECMO practice are deemed morally permissible.

The survey study was approved by Emory University Institutional Review Board under study number IRB00067907; the study met the criteria for exemption of human subjects research under 45 CFR 46.101(b)(2).

Table 4.1: DESCRIPTIVE STATEMENTS
1. Please indicate your professional role:
2. Please indicate your primary clinical environment:
3. Please indicate the primary patient population in which you specialize in or have expert knowledge about:
4. Please indicate the state (if domestic) or country (if international) in which your ECMO center is located.
For questions 5 through 21, please select the response that most closely represents your position:
5. The role of ethics is of primary importance in the practice of ECMO.
6. It is important to save a life.
7. It is important to do no harm.
8. ECMO support has both good and bad effects.
9. ECMO support saves the lives of patients.
10. ECMO support harms patients.
11. The risks of ECMO support are a necessary means to saving a patient's life.
12. ECMO support prolongs death.
13. The burdens of ECMO support are proportional to the benefits.
14. The benefits of ECMO support outweigh the burdens.
15. Survival to hospital discharge following ECMO support is an adequate outcome.
16. The use of ECMO technology is morally problematic.
17. Saving a life, doing harm, not saving a life, and not doing harm are each foreseen when employing ECMO.
18. 61% survival to hospital discharge (39% mortality) is an acceptable outcome of ECMO support.
19. 40% survival to hospital discharge (60% mortality) is an acceptable outcome of ECMO support.
20. 28% survival to hospital discharge (72% mortality) is an acceptable outcome of ECMO support.
21. Any percentage of survival is an acceptable outcome of ECMO support.

Table 4.1: Survey study descriptive statements. Statements 1-4 captures participant demographics. Statements 5-21 attempts to reflect of the four conditions of the Principle of Double Effect (PDE). Statements 6 and 9 reflect the first condition of the PDE on *nature of the act*. Statements 8 and 17 reflect the second condition of the PDE on *agent's intention*. Statements 7, 10, and 11 reflect the third condition of the PDE on *means-end*. Statements 12, 13, and 18-21 reflect the fourth condition of the PDE on *proportionality*.

Piloting

A large ECMO center, comprised of 118 members, was targeted for a pilot survey study. From the 118 members, 20 fellows and 6 midlevel providers were excluded due to limitations in ECMO training, expertise, and membership. From the remaining list of 92 members, 8 were randomly selected to participate voluntarily in the pilot. Of the 92, the majority of the members worked in the ICU setting (25% cardiac, 25% neonatal, and 29% pediatric). The remaining

worked in a surgical (10%) or in an administrative setting (10%). As it relates to technical training and professional rank, 42% of the members were attending physicians, while 16% were cross-trained as nurse-ECMO specialists or 15% respiratory therapists-ECMO specialists. Of the 8 randomly selected for piloting, 25% of each of the technical categories was represented. The pilot survey was distributed electronically via email. 75% participated in the pilot study and were interviewed after survey submission for feedback on survey length, clarity of instructions, general appeal of form, and if any electronic disruptions were experienced. Feedback on piloting was positive and no changes were made.

SURVEY RESULTS

455 surveys were electronically disseminated to a public list of ELSO-registered, domestic ECMO center directors and coordinators and the distribution methodology relied on "snowball sampling" (Alexander and Wynia 2008). 286 (62.9%) completed surveys were returned from 37 states (duplications or incomplete surveys were omitted). Participants self-identified as being either a physician (21%), nurse (44%), respiratory therapist (12%), ECMO specialist (38%), or other (9%) who primarily worked in the ICU setting (90%). Some participants were cross-trained as both nurse-ECMO specialist (17%) or respiratory therapists-ECMO specialists (8%). The survey form was built, distributed, and collected using Adobe® FormsCentral. Survey data was coded and analyzed using the IBM Statistical Package for the Social Sciences (SPSS) (version 23, Release 23.0.0.0) statistics predictive analytics software.

Is ECMO practice morally permissible?

Providing exhaustive medical care to moribund patients in active respiratory or cardiac failure can be a physically, mentally, emotionally, and morally paralyzing situation for the medical team (particularly if the primary source of causation is unknown). If such patient is believed to benefit from membrane oxygenation, factors of risk and harm must be considered in ethically justifying its use. The ethics of ECMO practice involves two primary normative concepts that are prescriptively at odds: *To save a life* and *To do no harm*. Employing ECMO technology (the act), when all clinical options have failed, has both good and bad effects. The good effect is that ECMO support has been shown to saves lives. The bad effect is that, in doing so, imposes heightened risks and burdens on the critically-ill. The most noteworthy bad effect is that ECMO support prolongs dying. The central question, then, is whether ECMO practice is ethically permissible (or impermissible) – a provocative question that can morally paralyzes the medical team during patient management. In order to determine if ECMO practice is morally permissible, the four conditions of the PDE – *the nature of the act, the agent's intention, the distinction between means and effects, and proportionality between the good effect and the bad effect* – as discussed in chapter three, must be all satisfied.

Descriptive statements in Table 4.1 were clustered in an attempt to express each of the four conditions of the PDE. These conditions, then, were used as the evaluative criteria to appraise the moral propriety of ECMO practice by examining attitudes of ECMO experts towards moral prescriptions.

RESULTS

The first condition of the PDE, on the *nature of the act* (see Figure 4.1):

- 94% of the participants agree with the statement "It is important to save a life" (0% SD, 1% D, 5% N, 47% A, 47% SA).
- 92% of the participants agree with the statement "ECMO support saves the lives of patients" (0% SD, 0% D, 8% N, 48% A, 44% SA).

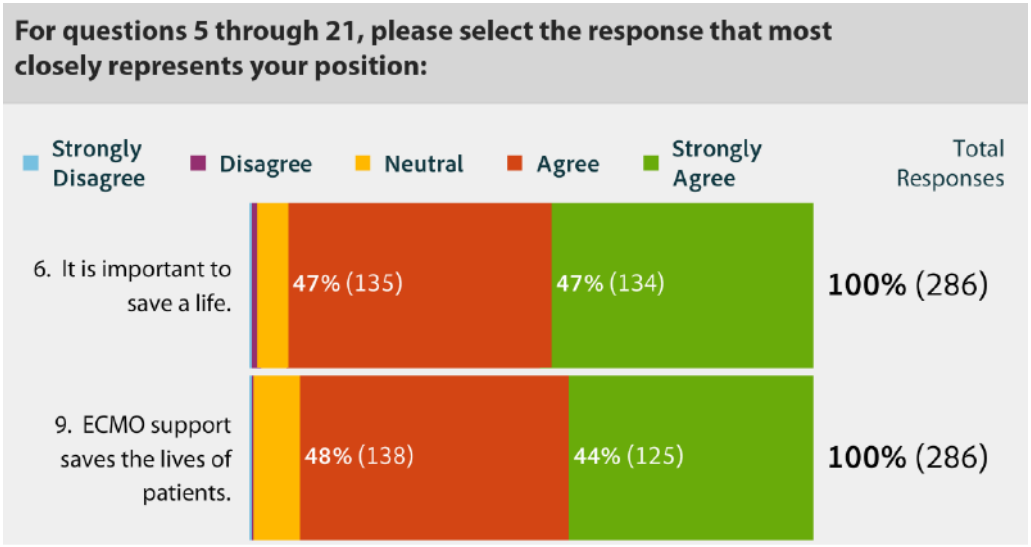

Figure 4.1: Nature of the act. Statements 6 and 9 reflect the first condition of the PDE on the *nature of the act*. Numerical values found within the colored bars (in parenthesis) represent the actual number of respondents who selected either Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree on the 5-point Likert scale. Numerical percentages found within the colored bars represent the proportion per hundred.

The second condition of the PDE, on the *agent's intention* (see Figure 4.2):

- 94% of the participants agree with the statement "ECMO support has both good and bad effects" (0% SD, 1% D, 4% N, 45% A, 49% SA).

- 62% of participants agree with the statement "Saving a life, doing harm, not saving a life, and not doing harm are each foreseen when employing ECMO" (1% SD; 17% D, 19% N, 51% A, 11% SA).
- 18% disagree on what is foreseeable when employing ECMO, while 19% remain neutral.

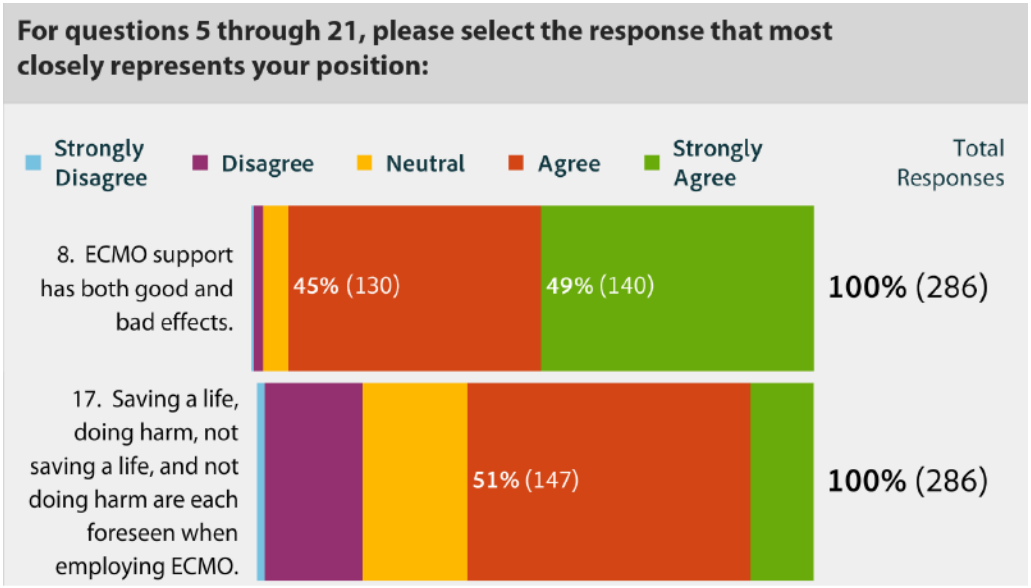

Figure 4.2: Agent's intention. Statements 8 and 17 reflect the second condition of the PDE on the *agent's intention*. Numerical values found within the colored bars (in parenthesis) represent the actual number of respondents who selected either Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree on the 5-point Likert scale. Numerical percentages found within the colored bars represent the proportion per hundred.

The third condition of the PDE, on the *distinction between means and effects* (see Figure 4.3):

- 96% of the participants agree with the statement "It is important to do no harm" (0% SD, 1% D, 2% N, 27% A, 69% SA).

- 47% of the participants disagree with the statement “ECMO support harms patients” (7% SD; 40% D, 32% N, 20% A, 2% SA). In contrast, 22% agree with this statement.
- 87% of the participants agree with the statement “The risks of ECMO support are a necessary means to saving a patient’s life” (0% SD; 1% D, 12% N, 59% A, 28% SA).

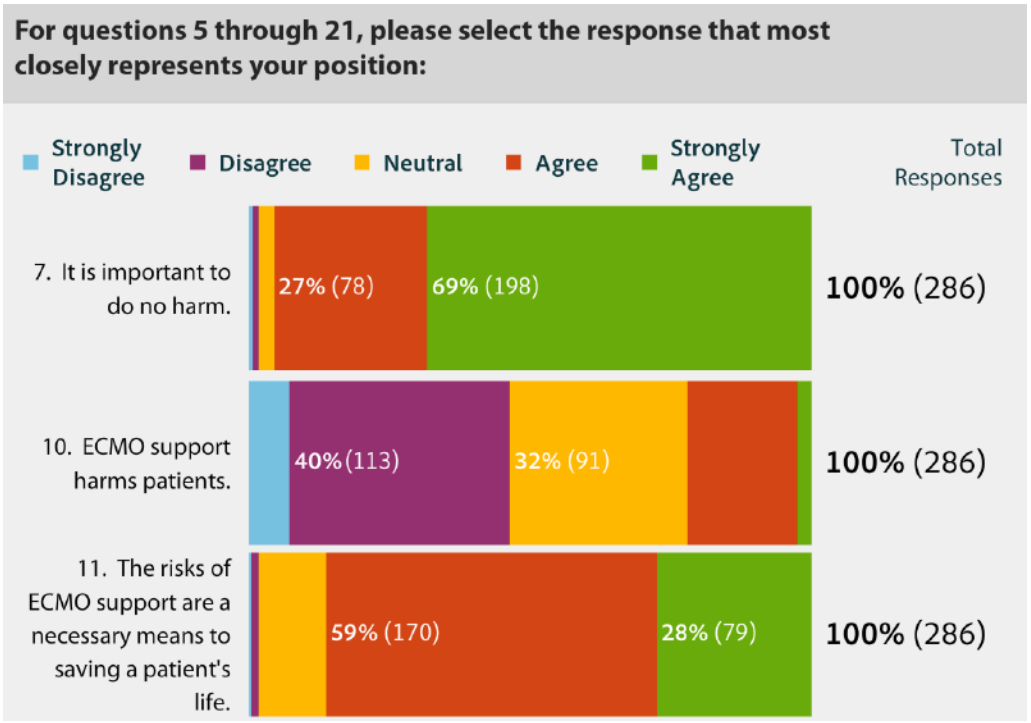

Figure 4.3: Means and effects. Statements 7, 10, and 11 reflect the third condition of the PDE on *means and effects*. Numerical values found within the colored bars (in parenthesis) represent the actual number of respondents who selected either Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree on the 5-point Likert scale. Numerical percentages found within the colored bars represent the proportion per hundred.

The fourth condition of the PDE, on *proportionality between the good effect and the bad effect* (see Figure 4.4):

- 47% of the participants agree with the statement "The burdens of ECMO support are proportional to the benefits" (1% SD, 27% D, 24% N, 37% A, 10% SA). In contrast, 28% disagreed on proportionality.
- 77% of the participants agree with the statement "The benefits of ECMO support outweigh the burdens" (0% SD, 2% D, 20% N, 58% A, 19% SA). However, 20% remained neutral.
- 56% of the participants disagree with the statement "Any percentage of survival is an acceptable outcome of ECMO support" (19% SD; 37% D, 23% N, 16% A, 5% SA). On the other hand, 21% agree on any percentage of survival.
- 50% of the participants disagree with the statement "ECMO support prolongs death" (10% SD; 40% D, 29% N, 19% A, 2% SA). In contrast, 21% agree with the statement.

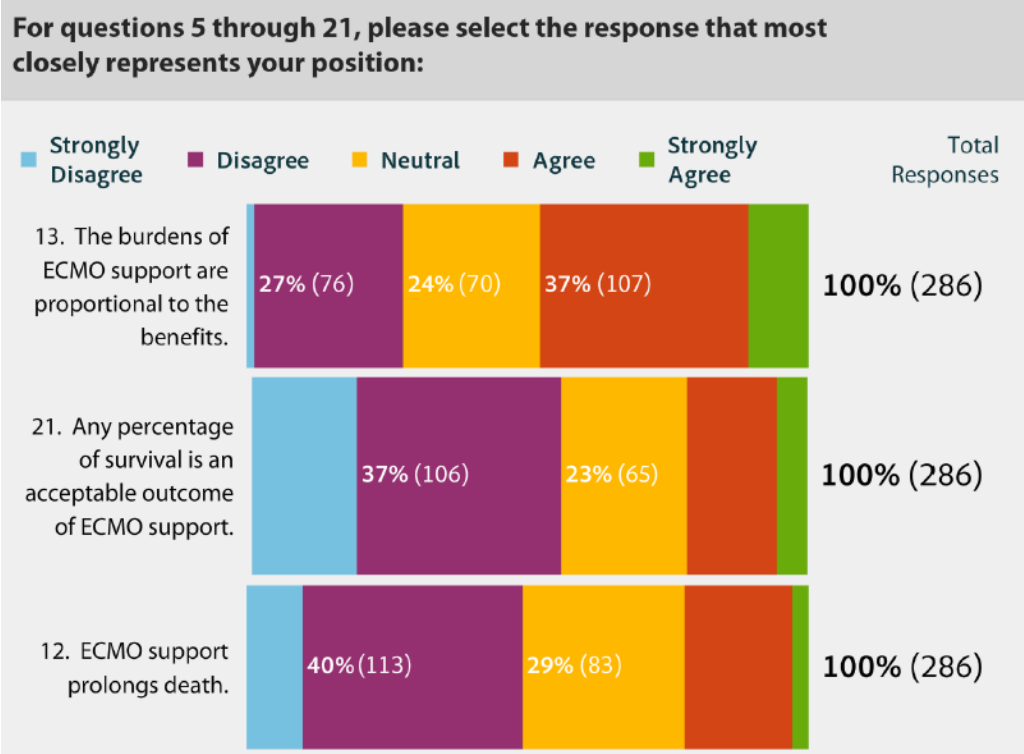

Figure 4.4: Proportionality. Statements 12, 13, and 21 reflect the fourth condition of the PDE on *proportionality between the good effect and the bad effect*. Numerical values found within the colored bars (in parenthesis) represent the actual number of respondents who selected either Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree on the 5-point Likert scale. Numerical percentages found within the colored bars represent the proportion per hundred.

Further on the fourth condition of the PDE, on *proportionality* (see Figure 4.5):

- 72% of the participants agree with the statement "61% survival to hospital discharge (39% mortality) is an acceptable outcome of ECMO support" (0% SD; 6% D, 22% N, 58% A, 14% SA). However, 22% remained neutral.
- 39% of the participants agree with the statement "40% survival to hospital discharge (60% mortality) is an acceptable outcome of ECMO support" (4% SD; 25% D, 33% N, 31% A, 8% SA). In contrast, 29% disagree.

- 49% of the participants disagree with the statement "28% survival to hospital discharge (72% mortality) is an acceptable outcome of ECMO support" (14% SD; 35% D, 26% N, 20% A, 5% SA). In contrast, 25% agree with the statement.

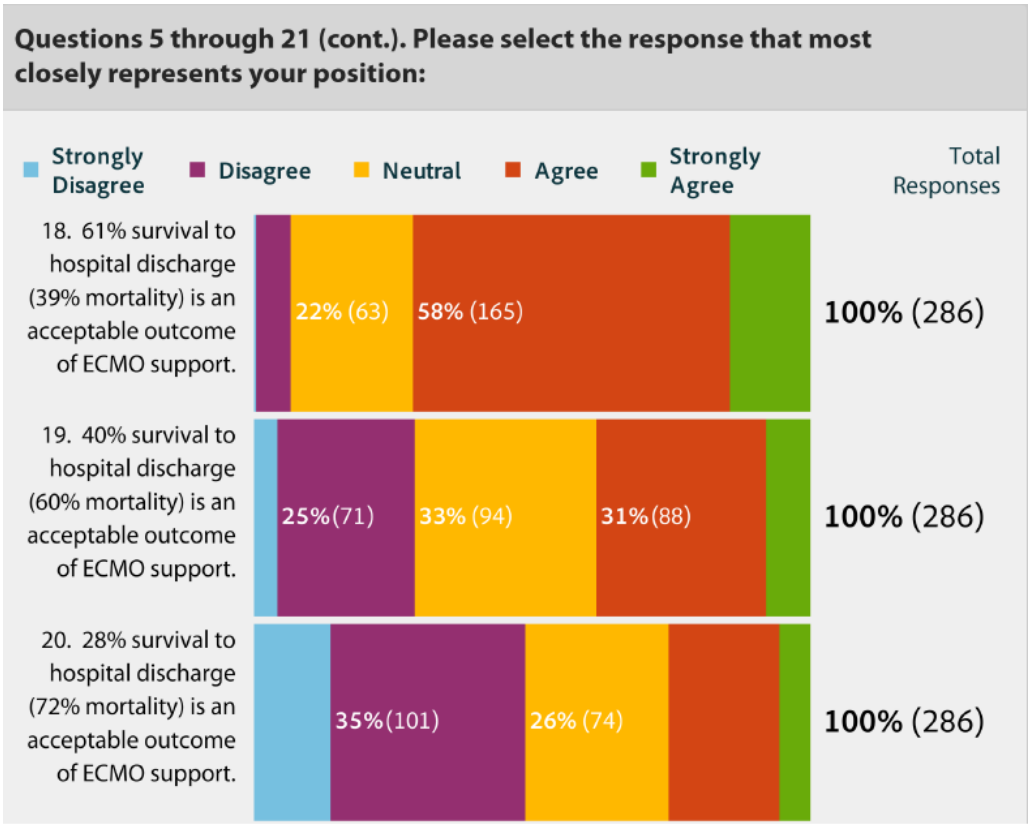

Figure 4.5: Proportionality of overall outcomes. Numerical values found within the colored bars (in parenthesis) represent the actual number of respondents who selected either Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree on the 5-point Likert scale. Numerical percentages found within the colored bars represent the proportion per hundred. Percentage found in descriptive statements represents actual percentages reported in the January 2013 ECLS International Summary Registry Report (Extracorporeal Life Support Organization 2013). 61% survival to hospital discharge is the overall outcome reported across neonatal, pediatric, and adult cohorts for respiratory, cardiac, and ECPR support. 40% survival to hospital discharge is the overall outcome reported for neonatal ECMO for cardiac support. 28% survival to hospital discharge is the overall outcome for adult ECPR reported.

On the overall outcome of ECMO practice:

- 50% of the participants agree with the statement "Survival to hospital discharge following ECMO support is an adequate outcome" (3% SD; 26% D, 21% N, 40% A, 10% SA). In contrast, 29% disagree with the statement.

Last, responses to the descriptive statements 5. through 21. (see Table 4.1) were analyzed according to professional roles (Supplementary Table S.1). The aims were (1) to determine if there are differences in professional attitudes towards the practice of ECMO, (2) to delineate if these differences are role-specific (e.g. physicians versus nurses), (3) to find correlations between professional attitudes, if any, and (4) to elucidate the ethical implications of these attitudes as it pertains to how ECMO patients were being clinically managed. While snowball sampling generated a participation rate of 62.9%, drawing role-specific conclusions was indeterminate due to the small sample size for each role [physician (n = 60), nurse (n = 79), respiratory therapist (n = 12), ECMO specialist (n = 37), cross-trained nurse-ECMO specialist (n = 48), cross-trained respiratory therapists-ECMO specialists (n = 24), or other (n = 26)].

DISCUSSION

The clinical practice of ECMO is multifaceted and quite complex; the practice is value-laden with moral ascriptions, preferences, and thoughts of those who specialize in its clinical implementation. The survey study assessed the "Lay

of the Land" on the moral permissibility (or impermissibility) of ECMO practice according to the PDE. The nationwide scope reduced opportunities for speculation and emphasized collective reasoning rather than reliance on some single authoritative moral (theoretical) prescription. Through general inquiry, survey participants were asked to respond to the statement "The role of ethics is of primary importance in the practice of ECMO." Almost 9 out of 10 ECMO experts agreed that the role of ethics (however it is perceived) is of primary importance (0% SD; 3% D, 9% N, 48% A, 40% SA). Given the heightened risks and harms associated with ECMO practice, this result is reassuring. Interestingly, 3% disagreed while 9% remained neutral; justification for why this is the case is intriguing.

In order to evaluate the moral propriety of ECMO practice, the four conditions of the PDE were borrowed to serve as the normative criteria through which permissiveness of harms could be judged. All conditions must be met in order for harm(s) to be deemed morally permissible. For the first condition of the PDE, on *the nature of the act*, the act (i.e., ECMO intervention) must be good (or considered morally neutral), despite its consequences. Confidently, 9 out of 10 ECMO experts agree that saving a life is important. Similarly, the same ratio agrees that ECMO intervention saves lives. These results served as an evaluative baseline that suggests that the moral maxim *To Save A Life* must be morally obligatory. Here, the nature of the act of providing ECMO support must be good, independent of its consequences.

Under the second condition of the PDE, regarding *the agent's intention*, the agent (i.e., ECMO experts, collectively) intends only the good and not the bad

effects. Importantly, bad effect(s) can be foreseen, tolerated, and permitted, but it cannot be intended. About 9 out of 10 ECMO experts agree that supporting a patient on ECMO has both good and bad effects. This result suggests that ECMO experts recognize implicitly that the moral maxims *To Save A Life* and *To Do No Harm* apply in morally conflicting ways: in satisfying one moral maxim, the competing maxim is inadvertently violated. Further, whether the bad effects are foreseeable is less determinate. 6 out of 10 ECMO experts agree that saving a life, doing harm, not saving a life, and avoiding harm are each foreseeable. Roughly 2 out of 10 ECMO experts disagree with this and another 2 out of 10 remain neutral on the subject. Reasons for this observation are unclear. It is reasonable to assert that perhaps each act, itself, is too conditional hence, the difficulty in selecting a more confident answer choice (note: 19% remained neutral). Future study that examines closer the foreseeable events of ECMO practice would provide greater clarity. Together, it can be inferred that experts generally intend the good effects of ECMO and not the bad effects (yet foresee them). Further study on intention is needed.

For the third condition of the PDE, on *the distinction between means and effects*, the bad effect must not be a means to the good effect. The good effect must not be the causal result of the bad effect; otherwise the bad effect is intended in pursuit of the good effect. Confidently, 9 out of 10 ECMO experts agreed that it is important to do no harm. On the issue of whether "ECMO support harms patients", almost 5 out of 10 ECMO experts believe it does not harm patients. These results serve as another evaluative baseline that suggests

the moral maxim *To Do No Harm* (much like the maxim *To Save A Life)* must be morally obligatory.

However, 2 out of 10 believe that ECMO support can harm patients (note: 1 in 3 remain neutral on the issue). Again, the conditionality of the statement may have been a factor on answer choice selection. Further, almost 9 out of 10 confidently agree that, despite the harms, the risks are a necessary means to saving a patient's life. Together, the data suggests that the constitution of harm has an important role in ECMO practice. The data suggests that the harms of ECMO support are neither a chosen end nor an intended (but necessary) means in achieving the good effects of ECMO support – the primary good effect being saving a life – however, inferred with caution. A quantitative evaluation of harms would answer this more clearly and is reserved for future study.

Concerning the fourth condition of the PDE, on *proportionality between the good effect and the bad effect*, the good effect(s) must outweigh the bad effect(s). Almost 8 out of 10 agree that the benefits of ECMO support outweigh the burdens. Here, the good outweighs the bad, however is the bad proportionate to the good? To test raters' consistency, when asked to respond to the statement "The burdens of ECMO support are proportional to the benefits", only about 5 out of 10 agree that the burdens are proportional to the benefits. Yet, about 1 in 3 ECMO experts disagree on this proportionality (note: about a quarter remain neutral). This suggests an imbalance on how good/benefits and bad/burdens are appraised. So, then, is survival itself a good effect? 2 out of 10 agree that any percentage of survival is an acceptable outcome, whereas 5 of 10 believe survival to hospital discharge is more adequate. Of note, 5 out of 10 believe that ECMO

support does not prolong dying. In contrast, almost 6 out of 10 believe that any percentage of survival is unacceptable; interestingly, only 2 out of 10 believe ECMO support prolongs dying.

Related to outcomes, participants were asked to evaluate the quantification of permissiveness in terms of percentage of acceptable survivability (or mortality) outcomes (see Figure 3.2). Recall, ECMO candidates have an 80% chance or greater for death. First, participants were asked to respond to the statement "61% survival to hospital discharge (39% mortality) is an acceptable outcome of ECMO support". Essentially, if 6 out of 10 patients survive to hospital discharge, 7 out of 10 ECMO experts agree with this outcome. Participants were then asked to respond to whether "40% survival to hospital discharge (60% mortality) is an acceptable outcome of ECMO support". A shift occurred: if only 4 out of 10 patients survive to hospital discharge, about 4 out of 10 ECMO experts agree with this outcome. To further probe, participants were asked to respond to if "28% survival to hospital discharge (72% mortality) is an acceptable outcome of ECMO support". If 3 out of 10 patients survive to hospital discharge, 6 out of 10 ECMO experts disagree with this outcome. This favors that almost 6 out of 10 believing that any percentage of survival is unacceptable.

The present survey study systematically collected data about the cognitive attitudes (and perhaps attitudes influenced by affect) of ECMO experts on the ethical issues that arise in practice. Specifically, the study assessed the moral propriety of the permissiveness of ECMO-associated harms according to the PDE. Although, as Hauser describes, "the principle of the double effect may be operative in our moral judgments", this study was the first attempt at evaluating

ECMO experts' "conscious introspection" (Hauser, et al. 2007, 1). The proposed moral methodology attempted to "consider the unconscious appraisal system that mentally represents the causal and intentional properties of human action" (Hauser, et al. 2007, 1) as it pertained to the ethics of ECMO practice.

It was hypothesized that moral attitudes of the experts on the practice of the technology vary across clinical roles (and even within the same role). However, it is certain that, despite the role, the moral maxim *To Save A Life* and the moral maxim *To Do No Harm* are both morally obligatory and 9 out of 10 believe this to be true. Yet, the stakes are high in ECMO practice. So, to determine the permissiveness of ECMO-associated harms, the four conditions of the normative criteria posed in the PDE must be all satisfied.

It was collectively agreed upon that the nature of the act of providing ECMO support must be good, independent of its consequences. On intentionality, while it is clear that the good effects of ECMO support are intended, the bad effects are unintended yet foreseeable. However, future study on intention is required to gain further clarity. Concerning the means and its effects condition, the data suggests that the harms of ECMO support are neither a chosen end nor an intended (but necessary) means in saving a life. While the results highlight the importance of harm consideration, this conclusion is drawn with caution.

Based on the survey valuation, PDE conditions 1 – 3 were in general satisfied; however, the last condition on proportionality was less apparent. 1 out of 3 ECMO experts believe that the burdens of being on ECMO are disproportionate to the benefits. The moral appraisal on assessing the moral

weight and magnitude of the good/benefits and bad/burdens/harms are reserved for future investigations. Thus, determining the moral permissiveness of ECMO practice requires greater empirical clarity. Importantly, this preliminary study showed the validity of the PDE as a useful, moral analytic tool. Also, the moral methodology employed here judged the moral propriety of ECMO practice using the normative criteria of the PDE from which the permissiveness of harms could be evaluated. Further, the current study is pivotal in that it demonstrated a cross-section of the "Lay of the Land", in a non-speculative manner, of the moral landscape as it pertains to an ethical issue of ECMO practice.

In light of the small sample size, role-specific attitudes could not be statistically correlated to the descriptive statements (particularly statements in which inconsistencies in attitudes was observed). The data is included in the supplemental (Supplementary Table S.1). Limitations in sample sizing was not surprising given the limited number of ELSO-registered ECMO centers across the nation. Georgia had the greatest number of participation (76; 26.6%) followed by Arizona (26; 9.1%) and Minnesota (19; 6.6%). Nonetheless, the methodology discussed is a nuanced way of examining how normative bioethical concepts are translated (and studied empirically) in practice.

Limitations

Although the survey captured the attitudes of ECMO experts, it is worth noting the limitations of the survey study. First, although it was known that 157 ECMO centers exist in the U.S., the number of non-ELSO registered centers – institutions that practice ECMO but do not report their cases – is largely

unknown. Thus, while a known sample size of directors or coordinators was distributed surveys (n = 455) the actual domestic population of ECMO specialists was unknown – an important factor given that the n-value is relatively small. For instance, membership of ECMO specialists varies across ECMO centers. A large ECMO center may have membership of 100 whereas a smaller center has 20 members. Given the exploratory nature of the current study, convenience sampling was used and, although the response rate was 62.9% (albeit from snowball sampling), the sample may not be representative of the whole target population of ECMO experts. Although snowball sampling is typically utilized for socially marginalized or hidden populations, given the experimental nature and ethical sensitivity of ECMO practice, this non-probability sampling technique was used to reach also non-ELSO registered institutions. Drawing statistical inferences on the current sample that is generalizable to the actual population of ECMO experts was, thus, limited. Although over- or underrepresentation of the sample size was difficult to determine, at minimum, the study revealed an interest in the ethics of ECMO practice.

A second limitation of the study concerns intrarater reliability. Participants may answer differently depending on time, clinical experience, training, and role; hence, future results of this cross-sectional study may slightly vary. The third limitation concerns whether the clustering of the descriptive statements had correlative strength to each of the four conditions of the PDE. Although having a greater number of statements would increase correlative strength, the time limitations of participants was the primary consideration that determined the duration of participation in the survey study. Further, the

conditionality of the descriptive statements may have impacted participants' ability to select answer choices that accurately reflects their attitudes. Hence, participants were given the opportunity at the end of the survey to freely provide comments or thoughts that the survey evoked. Future studies would provide greater substantive clarity.

Importantly, introducing an empirical dimension invited greater moral participation rather than reliance on a single moral authority. The participation of doctors, nurses, respiratory therapists, ECMO specialists, etc., whose diverse perspectives are otherwise overlooked in normative reflection alone, was of ethical significance. With the stakes being high in ECMO practice, moral participation was an essential component in determining the ethical implications. In the participant comments section of the survey, of the 286 completed surveys, 50 (17%) provided comments. Comments were clustered based on issue participants thought to address: informed consent, quality of life, proportionality, justice, futility, and prolonging dying (see Supplementary Table S.2).

In summary, the empirical-ethical analysis helped to better understand, descriptively, the problem and highlighted the inconsistencies in reasoning concerning the ethics of ECMO practice. A nuanced methodology was presented. The methodology helped to address and examine the question about the moral permissiveness of ECMO practice – a question that could not have been answered through reflection alone.

CONCLUSION

In the preliminary study, two primary normative concepts were examined: *To save a life* and *To do no harm*. Being that ECMO is an emerging, modern-day technology, consistency in reasoning is often at risk due to the intensity of the environment, critical status of the patient, and raw emotions involved. As demonstrated, double effect reasoning has primary ethical significance in 'high risk ECMO'. In active efforts to save a life by employing ECMO, harm is inadvertently introduced; in omissive efforts to do no harm, a life is inadvertently lost. If the initial premise is that regardless of what normative rule is being followed, a violation is to occur, then inconsistencies in moral reasoning are to be expected. To address this "moral dumbfounding" phenomenon (Sneddon 2007), both the prescriptive and descriptive approaches were explored for the analysis.

To summarize, first, consistency in collective reasoning was observed for the first condition of the PDE suggesting that the nature of the act *to save a life* by means of providing ECMO support, apart from its harms, is not thought to be intrinsically wrong. Second, consistency in collective reasoning was also observed for certain aspects of the second and third condition of the PDE which suggests that the harms associated with ECMO support are morally salient in ECMO practice To further answer completely whether harm is not a chosen end, and are thus not intended but merely foreseen as a side effect in ECMO practice, requires further investigation and clarity. Similarly, on the proportionality (between the good effects and the bad effects) condition of the PDE, participant attitudes were less homogenous. While 5 out of 10 ECMO experts agree that

burdens of ECMO are proportional to the benefits, about 3 out of 10 disagree. While the study unlocks more questions than answers, the study demonstrates the validity of the PDE as a morally analytic tool and the utility of the moral methodology.

To discuss this further, a comprehensive evaluation that addresses the issue of proportionally requires that all salient factors be considered: the underlying medical condition and type of ECMO support needed, the exhaustion of all clinical options yet early employment of ECMO, the comparative consideration of past successes and failures, and the indications and contraindications specific to the age cohort. From the clinical picture in its entirety, the burdens (both known and unknown) are considered. Still, the competing accounts on how harm is characterized and calculated are largely subjective. The counterfactual comparison account affirms harm is a matter of being "worse off than one otherwise would have been" whereas the temporal comparison account affirms harm is a matter of being "less well off than one was before" (Hanser 2008, 422, 425). Yet judging whether an event makes a patient "worse off" or "less well off" requires additional moral specification – performing a moral calculus of some sort.

In addition, clinical reasoning of ECMO practice is largely a bottom-up approach, in which cross-case analogical reasoning is inductively applied to morally relevant norms; it is not surprising, then, to find inconsistencies in interpretations. On proportionality, it is probable that subjectivities in interpretation led to conflicting analogical reasonings, and interpreters' biases (as affected by people's moral ascriptions, preferences, and thoughts about ECMO)

likely also played a role. Since the survey study was a cross-sectional study that captured data reflecting one specific point in time, case interpretation then can vary. For example, a person having a recent bad experience with an ECMO patient (e.g., events of strokes, massive hemorrhaging, traumatic death) is perhaps more likely to agree that the burdens are not proportional to the benefits for more visceral reasons. Conversely, a person having a recent good experience is perhaps more like to agree that burdens are proportional to the benefits.

Further, there was also a lack of consensus on the collective reasoning about survivability outcomes. While 2 out of 10 ECMO experts agree that any percentage of survival is acceptable, at least 5 out of 10 disagree. About 5 out of 10 ECMO experts disagree on an outcome of 7 out of 10 not surviving to hospital discharge, still at least 2 out of 10 ECMO experts agree that this odds of mortality is an acceptable one. Subjectivities in interpretation and interpreters' biases also likely influenced results here. For example, a novice expert (one having 1-2 years of ECMO experience) is perhaps more likely to disagree that any percentage of survival is acceptable simply based on mere statistics (overall, across all age cohorts and type of support, about 6 out of 10 patients survive ECMO to hospital discharge) and statistically would experience more failures than successes early in their career. In contrast, a seasoned expert (one having 7 years or more ECMO experience) is perhaps more likely to accept any percentage of survival, as informed by the number of years of ECMO experience, and the statistical successes he or she experienced across those years.

Lastly, consensus on collective reasoning about whether ECMO prolongs dying was also not evident. 5 out of 10 ECMO experts disagree that ECMO

support prolongs dying, whereas 2 out of 10 agree that dying is prolonged. Again, subjective interpretations and interpreters' biases could have played a role. For example, a participant from a more robust ECMO center (one having numerous cases, well-trained staff, and solid practice manuals) is perhaps less likely to believe that ECMO prolongs death due to high success rates (high percentages of survival). On the other hand, a participant from a lesser established ECMO center (one having few cases, ill-trained staff, and loose practice manuals) is perhaps more likely to believe that ECMO prolongs death due to high failure rates (high percentages of mortality).

However, such inferences about the causation of the inconsistencies found within the fourth condition of the PDE are of course anecdotal and speculative. To ascertain this observation on why there is a lack of consensus on proportionality requires further non-speculative, empirical exploration. Together, the data reflects the competing claims on how the maxims *To Save A Life* and *To Do No Harm* are rationally framed and operationalized in practice. The subsequent examination on further specifying moral justifications and whether a normative theory that guides ECMO practice is feasible to construct, are both of great interest for future study.

The overarching question at hand is whether the use of ECMO technology is morally problematic. Interestingly, 74% of ECMO experts did not believe that ECMO use was morally problematic (26% SD; 48% D, 16% N, 10% A, 1% SA). Inconsistencies in the data on proportionality and percentage survival to hospital discharge suggests otherwise. In order to determine the moral permissiveness of ECMO practice, all conditions of the PDE must be satisfied. Although

consistency was observed in the collective reasoning for condition one, aspects of condition two and three, consistency was not observed for condition four. While the satisfaction of the first three conditions of the PDE, thus far, suggests that the moral permissiveness of ECMO practice is favorable, more detailed examination on the fourth condition of the PDE is required. It would prove fruitful for the field of ECLS and medical ethics to build upon and expand this knowledge.

CHAPTER 5: ETHICS OF ECMO PRACTICE, FUTURE DIRECTIONS

The history of ECMO and extracorporealization technologies has rich and aspirational beginnings and, throughout the last decade, the technology has sustained greater permanency as a life-saving intervention. From the time of its origins in the early 1950s with the birth of open-heart surgery, interdisciplinary collaborations have painstakingly toiled to continue to revolutionize and to improve ECMO technology. As new generations of pumps, oxygenators, and cannulas continue to improve, so does safety in its application. In the same instance, the clinical applications of ECMO are expanding to include new patient categories of diseases such as support for airway abnormalities, trauma, burns, multiple organ failure, septic shock, and bridge to organ transplantation (Dalton 2011, Levi, et al. 2002, Nguyen, et al. 2000). While the efficacy of ECMO still remains ill-defined, the numbers of ECMO cases are on the rise. Since ELSO began collecting both national and international cumulative data on the total number of reported cases in 1990, there has been two decades of steady growth until 2010 – when the number of cases doubled (see Figure 2.3). In a short timespan of just two to three years later, the number of ECMO cases exponentially tripled and, if the trend continues, is projected to quadruple in the year coming. Accordingly, ECMO is here to stay.

Limitations in conducting prospective, randomized clinical trials entail having a heavy reliance on retrospective data analysis, evidence-based practice, and mere clinical intuitions in efforts to make sound clinical decisions. Yet, consistency in reasoning is often at risk due to the intensity of the environment,

criticalness of the patient, and uncensored emotions that lead to "moral dumbfounding". Further, the practice itself raises an ethically provocative tension between strict moral obligations *to save a life* and *to do no harm*. The intense will to rescue and perform extraordinary acts in efforts to save lives and the means in which one (or a team) achieves the goal requires considerable ethical rigor. Conducting such rigor is three-fold as it requires: (1) observational assessment of the practical challenges, (2) normative reflection on moral prescriptions, and (3) descriptive evaluation through empirical design. ECMO has been described as being ethically contentious; this work described why this is so. In ECMO practice, normative reflection could not alone guide clinical reasoning. However, the PDE proved to be a useful analytic tool to measure the collective, double-effect reasoning of experts about the permissiveness of ECMO-associated harms.

ECMO intervention has its challenges; massive hemorrhaging, neurologic devastation, renal failure, and sepsis are some patient risks it introduces (Zangrillo, et al. 2013). ELSO continues to serve as the primary organizational resource that tracks and records adverse events and patient outcomes. As reported in the January 2015 ELSO Registry Report (Extracoporeal Life Support Organization 2015), of the total number of neonatal patients that survive ECMO for respiratory failure (84%), 10% do not survive to transfer or hospital discharge. For pediatric patients that survive ECMO for respiratory failure (66%), 9% do not survive to transfer or hospital discharge. Similarly, 8% of the adult patients that survive ECMO for respiratory failure do not survive to transfer or hospital discharge. Of the 62% neonatal patients that survive ECMO for cardiac failure, a

greater reported percentage (21%) do not survive to transfer or hospital discharge. For pediatric patients that survive ECMO for cardiac failure (66%), 16% do not survive to transfer or hospital discharge. Similarly, 15% of the adult patients that survive ECMO for cardiac failure do not survive to transfer or hospital discharge. Of the total number of neonatal patients that survive ECPR (64%), 24% do not survive to transfer or hospital discharge. For pediatric patients that survive ECPR (55%), 14% do not survive to transfer or hospital discharge. Of the 39% adult patients that survive ECPR, 11% do not survive to transfer or hospital discharge. The data summary is illustrated in Figure 3.2. Knowing the level of impairment following hospital discharge requires longitudinal studies, but these studies take time.

The data suggests that, of those that survive ECMO, about 1 or 2 patients out of 10 do not survive to unit transfer or hospital discharge (Extracoporeal Life Support Organization 2015). Almost 6 out of 10 ECMO experts believe that any percentage of survival is unacceptable outcome. In contrast, proponents (2 out of 10) believe that any percentage of survival is acceptable based on the justification that ECMO patients already have a starting 80% risk of mortality. The issue of quality of life following ECMO survival is an important aspect to evaluate, albeit is difficult to assess without longitudinal studies. For instance, post-survival evaluations on those who survived clinical events of seizures while on ECMO are limited. Further, the quality of life for patients that survived following more than one clinical admission for ECMO support is also unclear. Data is limited.

In Stammers's review article he defines three distinct, nonexclusive evolutionary periods from which ECMO had its roots: (1) a conceptual and

developmental period (before 1950); (2) an applied technological period (1950 – 1970); and (3) a refinement period (1970 to 1990s) (Stammers 1997). What was once conceived as being organ-specific and restricted to only a couple of hours in the operating theatre, extracorporealization has now arguably been declared as "standard care" (since 1990 for newborns and children and 2009 for adults with severe heart and lung failure) (R. H. Bartlett 2016). Industrious efforts to improve the efficiency of extracorporeal technologies have now reshaped the current outlook for the future of ECMO.

In a forthcoming article, Bartlett delineates three new eras of ECMO practice (R. H. Bartlett, ECMO: The next ten years 2016). The first era is "ECMO 1" (1980 – 2008) and is marked by patients being heavily sedated and chemically paralyzed, having irreversible lung damage, having no options for organ transplantation, and having high incidence for barotrauma, pneumothorax, and hemorrhaging. As ECMO devices and systems improved over the last few years, the current era called "ECMO 2" (2009 – 2017) is being marked by minimally sedated, early mobility patients (potentially extubated), having greater opportunities to bridge to organ transplantation. Hemorrhaging is also more manageable and less of a major complication. Extracorporeal support is being applied to other underlying etiologies like status asthmaticus (acute severe asthma), massive pulmonary embolism, and post-Cesarean section amniotic fluid emboli (Agerstrand, Bacchetta and Brodie 2014). As ECMO technology continues to advance, Bartlett predicts patients who can easily ambulate on ECMO or "ambulatory ECMO" that is "automatically controlled with care out of ICU or at home" (R. H. Bartlett, ECMO: The next ten years 2016). Anticoagulating agents

will no longer be necessary due to improvements in the biocompatibility of circuits. "True artificial lungs" or "wearable membrane lungs" are also predicted to be on the horizon (Bartlett 2016, Agerstrand, Bacchetta and Brodie 2014). Bartlett defines this era as "ECMO 3" (2018 – 20??).

Given the current trends in the rising number of cases, developments in devices requiring experimentation, and push towards ambulatory ECMO, it is difficult to reliably evaluate and predict future, unintended risks associated with such practices; thus, the cautionary heed to examine more formally the ethical implications of current (and future) practices. For instance, an Australian and New Zealand group revealed that in their single center study, ECMO patients are at high risk for exposure to previously reported general and ICU-related post-traumatic stress disorder (PTSD) (Tramm, et al. 2015). Examples of risk factors include perceived threat to life, peri-traumatic emotional responses (or dissociation), and distressful ICU experiences like the use of physical restraints. Also, there are logistical issues in maintaining the "awake" state in neonates and pediatric patients compared to adults on ambulatory ECMO. Further, in a letter to the editor, a group from Alabama state "The uncertainty regarding ECMO benefits raises ethical concerns about organ waste and preferential use of marginal allografts or cadaveric lobar transplants" and argue for a national registry for ECMO patients awaiting lung transplantation (Venado, Hoopes and Diaz-Guzman 2014, 184).

ECMO has been described as "one of the most expensive, invasive and potentially life threatening rescue therapies for acute heart and/or lung failure" (Tramm, et al. 2015, 31) and remains still true to this day.

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Supplemental Data

Supplementary Table S.1: Survey responses to descriptive statements according to professional role.

Statement 5. The role of ethics is of primary importance in the practice of ECMO.					
	SD	D	N	A	SA
	0% (1)	3% (9)	9% (25)	48% (136)	40% (115)
MD, MD/PhD		5% (3)	8% (5)	48% (29)	38% (23)
ECMO Specialist (ES)		5% (2)	5% (2)	41% (15)	49% (18)
RN		3% (2)	13% (10)	53% (42)	32% (25)
RT	8% (1)		17% (2)	25% (3)	50% (6)
RN/ES			8% (4)	46% (22)	46% (22)
RT/ES		4% (1)	8% (2)	42% (10)	46% (11)
Other		4% (1)		58% (15)	38% (10)

Statement 6. It is important to save a life.					
	SD	D	N	A	SA
	0% (0)	1% (2)	5% (15)	47% (135)	47% (134)
MD, MD/PhD		2% (1)	3% (2)	52% (31)	43% (26)
ECMO Specialist (ES)			16% (6)	32% (12)	51% (19)
RN		1% (1)	3% (2)	44% (35)	52% (41)
RT			8% (1)	50% (6)	42% (5)
RN/ES			8% (4)	60% (29)	31% (15)
RT/ES				46% (11)	54% (13)
Other				42% (11)	58% (15)

Statement 7. It is important to do no harm.					
	SD	D	N	A	SA
	0% (1)	1% (2)	2% (7)	27% (78)	69% (198)
MD, MD/PhD		2% (1)	3% (2)	28% (17)	67% (40)
ECMO Specialist (ES)				32% (12)	68% (25)
RN	1% (1)	1% (1)	1% (1)	24% (19)	72% (57)
RT			8% (1)	8% (1)	83% (10)
RN/ES			4% (2)	33% (16)	63% (30)
RT/ES			4% (1)	25% (6)	71% (17)
Other				27% (7)	73% (19)

Statement 8. ECMO support has both good and bad effects.					
	SD	D	N	A	SA
	0% (0)	1% (4)	4% (12)	45% (130)	49% (140)
MD, MD/PhD		3% (2)	2% (1)	42% (25)	53% (32)
ECMO Specialist (ES)			5% (2)	62% (23)	32% (12)
RN			6% (5)	38% (30)	56% (44)
RT		8% (1)	8% (1)	8% (1)	75% (9)
RN/ES		2% (1)	2% (1)	56% (27)	40% (19)
RT/ES				54% (13)	46% (11)
Other			8% (2)	42% (11)	50% (13)

Statement 9. ECMO support saves the lives of patients.					
	SD	D	N	A	SA
	0% (0)	0% (0)	8% (23)	48% (138)	44% (125)
MD, MD/PhD			8% (5)	37% (22)	55% (33)
ECMO Specialist (ES)			19% (7)	35% (13)	46% (17)
RN			6% (5)	49% (39)	44% (35)
RT			17% (2)	33% (4)	50% (6)
RN/ES			6% (3)	60% (29)	33% (16)
RT/ES				54% (13)	46% (11)
Other			4% (1)	69%(18)	27% (7)

Statement 10. ECMO support harms patients.					
	SD	D	N	A	SA
	7% (20)	40% (113)	32% (91)	20% (56)	2% (6)
MD, MD/PhD	7% (4)	43% (26)	20% (12)	28% (17)	2% (1)
ECMO Specialist (ES)	5% (2)	43% (16)	43% (16)	8% (3)	
RN	6% (5)	44% (35)	28% (22)	22% (17)	
RT	17% (2)	25% (3)	50% (6)	8% (1)	
RN/ES	8% (4)	33% (16)	33% (16)	21% (10)	4% (2)
RT/ES	4% (1)	33% (8)	38% (9)	17% (4)	8% (2)
Other	8%(2)	35% (9)	38% (10)	15% (4)	4% (1)

Supplementary Table S.1 (continued)

Statement 11. The risks of ECMO support are a necessary means to saving a patient's life.					
	SD	D	N	A	SA
	0% (0)	1% (3)	12% (34)	59% (170)	28% (79)
MD, MD/PhD		2% (1)	12% (7)	58% (35)	28% (17)
ECMO Specialist (ES)			16% (6)	57% (21)	27% (10)
RN			13% (10)	56% (44)	32% (25)
RT		8% (1)	17% (2)	25% (3)	50% (6)
RN/ES			8% (4)	73% (35)	19% (9)
RT/ES				75% (18)	25% (6)
Other		4% (1)	19% (5)	54% (14)	23% (6)

Statement 12. ECMO support prolongs death.					
	SD	D	N	A	SA
	10% (28)	40% (113)	29% (83)	19% (55)	2% (7)
MD, MD/PhD	13% (8)	33% (20)	27% (16)	27% (16)	
ECMO Specialist (ES)	11% (4)	46% (17)	24% (9)	16% (6)	3% (1)
RN	9% (7)	47% (37)	25% (20)	18% (14)	1% (1)
RT		42% (5)	25% (3)	25% (3)	8% (1)
RN/ES		42% (20)	42% (20)	17% (8)	
RT/ES	21% (5)	17% (4)	25% (6)	25% (6)	13% (3)
Other	15% (4)	38% (10)	35% (9)	8% (2)	4% (1)

Statement 13. The burdens of ECMO support are proportional to the benefits.					
	SD	D	N	A	SA
	1% (3)	27% (76)	24% (70)	37% (107)	10% (30)
MD, MD/PhD	2% (1)	27% (16)	27% (16)	32% (19)	13% (8)
ECMO Specialist (ES)		35% (13)	27% (10)	24% (9)	14% (5)
RN		20% (16)	28% (22)	41% (32)	11% (9)
RT	8% (1)	25% (3)	25% (3)	25% (3)	17% (2)
RN/ES		27% (13)	17% (8)	48% (23)	8% (4)
RT/ES		38% (9)	17% (4)	42% (10)	4% (1)
Other	4% (1)	23% (6)	27% (7)	42% (11)	4% (1)

Statement 14. The benefits of ECMO support outweigh the burdens.					
	SD	D	N	A	SA
	0% (0)	2% (7)	20% (58)	58% (167)	19% (54)
MD, MD/PhD		3% (2)	18% (11)	58% (35)	20% (12)
ECMO Specialist (ES)			35% (13)	41% (15)	24% (9)
RN		4% (3)	16% (13)	59% (47)	20% (16)
RT			17% (2)	42% (5)	42% (5)
RN/ES		4% (2)	17% (8)	69% (33)	10% (5)
RT/ES			17% (4)	58% (14)	25% (6)
Other			27% (7)	69% (18)	4% (1)

Statement 15. Survival to hospital discharge following ECMO support is an adequate outcome.					
	SD	D	N	A	SA
	3% (10)	26% (73)	21% (60)	40% (114)	10% (29)
MD, MD/PhD	12% (7)	33% (20)	20% (12)	27% (16)	8% (5)
ECMO Specialist (ES)	5% (2)	19% (7)	19% (7)	49% (18)	8% (3)
RN		23% (18)	29% (23)	39% (31)	9% (7)
RT			25% (3)	50% (6)	25% (3)
RN/ES	2% (1)	29% (14)	19% (9)	42% (20)	8% (4)
RT/ES		29% (7)	8% (2)	42% (10)	21% (5)
Other		27% (7)	15% (4)	50% (13)	8% (2)

Statement 16. The use of ECMO technology is morally problematic.					
	SD	D	N	A	SA
	26% (73)	48% (136)	16% (46)	9% (27)	1% (4)
MD, MD/PhD	35% (21)	40% (24)	15% (9)	10% (6)	
ECMO Specialist (ES)	27% (10)	51% 1(9)	16% (6)	5% (2)	
RN	27% (21)	47% (37)	16% (13)	9% (7)	1% (1)
RT	8% (1)	50% (6)	17% (2)	8% (1)	17% (2)
RN/ES	19% (9)	50% (24)	21% (10)	10% (5)	
RT/ES	21% (5)	50% 1(2)	8% (2)	21% (5)	
Other	23% (6)	54% 1(4)	15% (4)	4% (1)	4% (1)

Supplementary Table S.1 (continued)

Statement 17. Saving a life, doing harm, not saving a life, and not doing harm are each foreseen when employing ECMO.					
	SD	D	N	A	SA
	1% (3)	17% (50)	19% (54)	51% (147)	11% (32)
MD, MD/PhD	3% (2)	13% (8)	18% (11)	48% (29)	17% (10)
ECMO Specialist (ES)		27% (10)	22% (8)	43% (16)	8% (3)
RN		11% (9)	15% (12)	57% (45)	16% (13)
RT		17% (2)	25% (3)	58% (7)	
RN/ES		29% (14)	23% (11)	35% (17)	13% (6)
RT/ES	4% (1)	21% (5)	17% (4)	58% (14)	
Other		8% (2)	19% (5)	73% (19)	

Statement 18. 61% survival to hospital discharge (39% mortality) is an acceptable outcome of ECMO support.					
	SD	D	N	A	SA
	0% (0)	6% (17)	22% (63)	58% (165)	14% (41)
MD, MD/PhD		7% (4)	18% (11)	55% (33)	20% (12)
ECMO Specialist (ES)		11% (4)	14% (5)	62% (23)	14% (5)
RN		5% (4)	20% (16)	61% (48)	14% (11)
RT			42% (5)	42% (5)	17% (2)
RN/ES		2% (1)	35% (17)	50% (24)	13% (6)
RT/ES		8% (2)	17% (4)	58% (14)	17% (4)
Other		8% (2)	19% (5)	69% 1(8)	4% (1)

Statement 19. 40% survival to hospital discharge (60% mortality) is an acceptable outcome of ECMO support.					
	SD	D	N	A	SA
	4% (11)	25% (71)	33% (94)	31% (88)	8% (22)
MD, MD/PhD		22% (13)	32% (19)	37% (22)	10% (6)
ECMO Specialist (ES)	3% (1)	35% (13)	27% (10)	30% (11)	5% (2)
RN	8% (6)	19% (15)	33% (26)	32% (25)	9% (7)
RT	17% (2)	8% (1)	58% (7)	17% (2)	
RN/ES	2% (1)	25% (12)	35% (17)	27% (13)	10% (5)
RT/ES	4% (1)	29% (7)	25% (6)	38% (9)	4% (1)
Other		38% (10)	35% (9)	23% (6)	4% (1)

Statement 20. 28% survival to hospital discharge (72% mortality) is an acceptable outcome of ECMO support.					
	SD	D	N	A	SA
	14% (39)	35% (101)	26% (74)	20% (57)	5% (15)
MD, MD/PhD	10% (6)	33% (20)	23% (14)	28% (17)	5% (3)
ECMO Specialist (ES)	16% (6)	30% (11)	35% (13)	16% (6)	3% (1)
RN	15% (12)	34% (27)	19% (15)	23% (18)	9% (7)
RT	17% (2)	33% (4)	33% (4)	17% (2)	
RN/ES	8% (4)	44% (21)	25% (12)	19% (9)	4% (2)
RT/ES	17% (4)	29% (7)	42% (10)	8% (2)	4% (1)
Other	19% (5)	42% (11)	23% (6)	12% (3)	4% (1)

Statement 21. Any percentage of survival is an acceptable outcome of ECMO support.					
	SD	D	N	A	SA
	19% (54)	37% (106)	23% (65)	16% (46)	5% (15)
MD, MD/PhD	32% (19)	33% (20)	17% (10)	15% (9)	3% (2)
ECMO Specialist (ES)	14% (5)	35% (13)	27% (10)	19% (7)	5% (2)
RN	15% (12)	35% (28)	23% (18)	16% (13)	10% (8)
RT	17% (2)	33% (4)	33% (4)	17% (2)	
RN/ES	10% (5)	46% (22)	21% (10)	19% (9)	4% (2)
RT/ES	17% (4)	29% (7)	38% (9)	13% (3)	4% (1)
Other	27% (7)	46% (12)	15% (4)	12% (3)	

Supplementary Table S.2

1	Patients placed on ECMO need to have reversable condition
2	I think that saving a life is important. I also think Ethics need to play a huge role in ECMO. I sometimes feel that we set criteria for ECMO, but that we dont always follow it. I have worked at 2 institutions, and I feel this was true at both places. I am not sure how I feel about putting a child on ECMO for the 3 or 4th time on the same visit. I guess, ultimately, the decision resides with the guardian-as long as they are WELL INFORMED (notewell, informed) of the risks and the mortality associated with ECMO.
3	Difficult to quantify questions 18-21: Depending on circumstances, saving at least one life is beneficial, but clearly the more quality of life patients that survive to discharge is the best option.
4	We have 80+% survival, so darn well worth it!
5	A more interesting discussion would be about the circumstances for not initiating support and when support should be discontinued, even if the family objects
6	When the level of harm outweighs the benefits, the ethical conundrums begin
7	ECMO is a chance. It represents hope. We do our best to give ECMO support only to patients who can recover, but we cannot predict the future. I am glad we use ECMO here and know of many kids who would not be here if we did not take that chance for them.
8	Patients who need ecmo support are already so sick that they will not survive without it, so I feel that however poor the statistics are for surviving it are worthwhile, since without ecmo the patients is guaranteed to die.
9	#16 I would say that it is ethically problematic
10	Relating to questions 18-20 the outcomes must be looked at in relation to the patient population so it is hard to state one way or the other on what is an acceptable mortality rate. I think the primary reason for reduced ECMO outcomes is not placing patients on ECMO earlier in their course of care. Too often ECMO is looked at as a "last ditch effort" instead of a therapeutic tool.
11	12/16 Sometimes ECMO is used in a way that prolongs death and in such cases is morally problematic 18-21 Even "poor stats" like saving 3 in 100 is great compared to 100% mortality! and in my opinion worth the try if the resources are available and the family is desiring to try.
12	ECMO selection Criteria play a big role, and help facilitate decision making. Remember you are typically taking a patient with 80%-100% mortality and giving a patient a chance survival only if the underlying cause of illness is potentially reversible.
13	Patient selection is very important.
14	Questions 18,19,20- I feel that every perecentage is good, obviously the better the outcome the better I feel about it, but really if the patient is sick enough to be on ECMO they probably wouldn't have survived without it, so any percentage survived is a good outcome.

15	So first: there are no simple answers in ECMO, therefore answering the survey is a challenge for me with the options offered. ECMO is commonly done in an emergecny when delay may result in patient death. Therefore there is not time for the discussions that would perhaps be ideal. The other challenge for me is that any parent, or in fact physician faced with death or ECMO would likely choose ECMO in the moment. I'm not sure how one addresses the challenges and the urgency adequately. One bent I thinmk you may get is that all who answr your survey are in afct supportive of ECMO as htey are all involved somehow in programs with it. Might be intereseting to ask non- ECMO people their thoughts. ECMO clearly saves lives, ECMO clearly has risks and does not work in all cases. ECMO can be problematic. I do think sometimes ECMO prolongs death, however more times I have seen it save a life. I cant answer the % question without thinking in my head....is 100% death when ECMO could have been tried na acceptable utcome?? I feel that this answer is no! Also it is my opinion that in not "ECMO", that causes issues but the egos/ beliefs/ hopes and desires of the MD's /team caring for the patient.
16	For questions 18-21, what should be considered acceptable for a specific percentage of ECMO patients who survive to hospital discharge depends on the indications for being placed on ECMO. If your center focuses on neonatal/infant congential cardiac surgery, and you are putting mostly patients on ECMO with single ventricle physiology, then a survival of 30% would be expected. However, if your patient population is mostly neonatal respiratory failure then your surival should be much higher.
17	Complex ethical questions; numbers, percentages are, of course not enough information to make decisions to start, stop ECMO. Important to keep asking these ethical questions of ourselves and each other but also trainees, nursing staff, and anyone involved with these patients. Thanks.
18	Survival rates vary widely with patient population and diagnosis. A single figure does not tell the whole story. Venovenous ECMO in the face of respiratory failure is dramatically more sucessful than Venoarterial ECMO in the post operative patient with complex cardiac anomalies. An acceptable survival rate must be compared to the survival rate of those patients who need ECMO but do not get it. In some cases ECMO does prolong death but this is a small percentage of the total. do not fully understand what you are seeking in question 17. To many factors put into one question will not give you a clear picture of what is valued. Your questions are opposites of one another. What is the information that you are seeking? We always seek to do no harm. ECMO is an intervention to save a life.
19	The chance of survival without ECMO is usually 0%. Patient selection is key to making good clinical and ethical decisions as well determining at any point of time whether the risks outweigh the benefits. Begining ecmo the benefits should outweigh the risks with reasonable chance of a successful outcome. However this can change though during an run when nfo becomes available and the patients clinical status and response change.
20	ECMO presents high risk for high reward. It is difficult to remain neutral when sitting at the bedside of an ECMO patient for 8-16 hours. The number of patients who have survived and gone on to rejoin their lives, at the same level they had been, has encouraged me to continue to support this high risk/high cost method of Life Support. The gift of returning a newborn safely to his parents after a severe meconium aspiration recently has encouraged me even more.

21	From a parent standpoint, any percentage of survival is an acceptable outcome of ECMO if you child is in the surviving group. I believe there is a drop off between 0.1% and 33% in terms of what is acceptable primarily in terms of resources - cost benefit, stress on staff, turnover etc. Taking the emotion out of it, unfortunately like anything in healthcare, there is a financial/resources aspect to consider. A good question to the organization and not just to care provider would be, "At what percentage of survival does the cost no longer justify providing ECMO therapy; if actions cannot be applied to improve survival percentages." I think that the responses of a survey like this change dramatically from a staff point-of-view between an ECMO center that has high survival rates vs. a center with consistently poor survival rates. Being involved with ECMO is a very sought after and prestigious mark for staff at CHOA, I would suspect that the staff attitude at a poor survival rate center is much different. Great study Annie, good luck.
22	The risk of mortality must be considered in the disease process prior to initiation of ECMO to validate whether a low percentage of survival is acceptable. If the patients were predicted to have an 85% chance of mortality and with ECMO that is decreased to 75% then you have added benefit to 10 out of 100 patients. For those 10 it is most certainly acceptable.
23	Application of this type of support is ALWAYS contextual. No single statement about acceptable levels of survival or death can be answered in a vacuum. I feel strongly that functional survival should be our primary goal, rather than just survival to hospital discharge.
24	Risks outweigh the benefits if careful screening is done. The only time that ECMO should not be considered is if patient's outcome will not be what is desired by patient and their families. i.e. Patient will end up being in a long term care facility for the rest of their life even though they have stated that they would never want to "live this way".
25	Survival to discharge is inadequate, but our only current option. Long term studies are needed.
26	There is much more that goes into the decision of offering ECMO support than mortality risk and an acceptable outcome.
27	The survival is in our experience largely based on good selection criteria and a team that is willing to use them. We have a mandatory ethics consult on every ecmo patient.
28	Outcomes for ECMO supported patients are related to the primary cause and not always related to the fact the patient was on ECMO. ECMO provides time for the patient to heal from the primary cause of illness.
29	When the option of NOT doing ECMO equates to or approaches 100% fatality then any survival rate is better than not doing ecmo.
30	I really think the acceptability of risk is dependent on the patient's clinical picture. Do we think the patient can survive if ECMO support is used? What do we think the neurological outcome is going to be?
31	any opportunity to save a life, when there will still be a quality of life to live is an acceptable outcome. Putting a pt on ECMO that will not survive or that will have a poor quality of life, just because we can, is unacceptable.

32	That is a tough question. ECMO patients have a high risk of mortality which is often reflected in the survival rate. The point that should be looked at is not their outcome but were they a good candidate. If they are not a good candidate and their chance of survival is not good, should they have been put on ecmo? If these type patients are put on ecmo then it would have a huge impact on survival rates. If the patients are good candidates, any outcome percentage is acceptable. Because ECMO is heroic effort that the patient would otherwise die with out.
33	Question 3, I would like to put all patient populations. Some Centers work with neonates, pediatrics, and adults. For question 12 you could also say intubating a patient prolongs death. The problem is not the use of these interventions but having the conversation with family members and health personnel on when it is futile to continue.
34	I think your survey neglects to look at the age of a patient. If the patient population is over the age of 70 maybe the efforts are not worth the benefit - however we are not God and can't make that call. We have very good results in this patient population. In young people and children I believe we try every avenue available in our bag of tricks to help them.
35	thank you
36	Not enough info to answer 18-21 hypothetically
37	it is not about ecmo the questions in my mind are wrong. it is about the provider and family and how ecmo is presented and knowing when to stop
38	Most families feel if ecmo may save their child it is worth a try.
39	The survey is simplistic. The outcome in the last few questions depends on what the outcome of alternative questions are. Perhaps you could have rather presented clinical cases
40	Surgery can be associated with harm; Chemotherapy can be associated with harm; TPA for stroke therapy was at one point assoc with sig risk of stroke; in Europe >50% of babies with certain anomalies are aborted; and many folks would consider lung Tx futile care and perhaps unethical given the consequences of therapy and quality of life following Rx
41	All of this depends on where you work and what the physicians want. Ethics/morality be damned if you have a physician who keeps a pt. on ECMO for 20,30,40 days until they rot or finally code. We who are under the physicians orders have no say in the pt. we take care of. Doesn't matter if it's ethically or morally wrong. We have to follow orders or lose our jobs. This is an obtuse survey.
42	ECMO is generally a last stitch effort. These patients will most likely die without the support of ECMO. Mortality rates are misleading. If they died from lack of care than it's not acceptable. If they died because ECMO just didn't work on their disease, that's different. Patient selection is also a major factor is successful vs unsuccessful ECMO cases. I'm sure everyone knows this, but it's not included in the descriptions of these questions and therefore, somewhat hard to answer.
43	Too Vague with the questions. All forms of ECMO support, the risks and benefits are weighed to decide if ECMO is worth the risk in our institution. The survival stats need to be diagnostic specific to determine if those are acceptable outcomes or not.

44	It is impossible to answer 18-21 without knowing the population and underlying rate of mortality with ECMO support
45	these questions are too gray and I entered neutral because most have qualifiers. If you were talking MAS then none of these survival #s are acceptable. If you are talking cardiac ecmo or ECPR then it might be. What is of vital importance and morally right is to include the family in the discussion of pros and cons and probable outcomes and let them help in the decision making.
46	Each potential ECMO candidate's circumstances, if the patient is indeed a candidate, must be taken in to consideration. I'm not sure that a survival to discharge percentage can really capture the need for ECMO in any one circumstance....necessarily. A multidisciplinary approach is essential in determining each individual candidate's appropriateness for ECMO support.
47	It's difficult to generalize ECMO patiens to these answers. Every patient on ECMO support is different. That's why ethically it's a challenge to support these patients.
48	In some (but not all) instances, ECMO does prolong death. If a patient's risk of mortality was 100% without ECMO, then ANY percentage of survival would be acceptable. Most patients, however, have a lower mortality risk, therefore a higher survival to hospital discharge should be expected. The mortality rate of ECMO will ALWAYS be higher than more common treatments of disease, as the patients requiring ECMO have an extremely high mortality rate. In my opinon, it's more important to compare a patient's mortality rate without ECMO to the mortality rate of ECMO.
49	Each case is different and there are times when I feel it is prolonging death in specific cases (especially in CICU)
50	I think it would be important to clarify what "type" of ECMO...i.e. neo resp, ped resp, adult resp vs neo card, ped card or adult card. A survival of 40% in neo resp is unacceptable to me, but that is totally acceptable (and the norm) for neo card ECMO