WITHDRAWAL OF LIFE SUPPORT THERAPY: PROCESSES AND PATTERNS OF DEATH IN THE INTENSIVE CARE UNIT

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ABSTRACT

Withdrawal of life support therapy involves controlled removal of life support modalities including artificial respiration and circulation with intent to provide a comfortable death. Withdrawal of life support therapy is necessary prior to procedures such as organ donation after cardio-circulatory death, but remains poorly explored in current literature. To enhance the current evidence, we conducted a thorough structured review, an observational study, and a qualitative comparison of components comprising withdrawal of life support therapy in both donor and non-donor patient groups. At all stages, we considered how results impacted donation after cardio-circulatory death. Withdrawal of life support therapy processes vary between countries, hospitals, practitioners, and patients. Variability in practice impacts care and outcomes for both donor and non-donor patients. Improved definitions and consensus about the process of withdrawal of life support therapy may improve patient care, success of organ donation after cardio-circulatory death, and uptake of donation protocols.

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SUMMARY OF CONTRIBUTIONS

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Amanda has completed the required one year of course credits for her MSc and written the entirety of this thesis project as primary author. With guidance and input from the thesis committee, Amanda created and designed all three components of this project. She is the primary author on all three manuscripts and is taking responsibility as submitting and corresponding author on all submitted papers. Submission of the manuscripts presented here are currently pending acceptance of the original Determination of Death Practices in Intensive Care Units pilot study manuscript, with anticipated submission in January 2014. Amanda has also presented this thesis work in the form of a scientific poster at both the Canadian Society for Epidemiology and Biostatistics Biennial Conference and Student Conference in St. John's Newfoundland in June of 2013.

1.0 INTRODUCTION

Organ transplantation offers one of the only cures for end stage organ failure to millions of patients worldwide. Transplantation procedures provide chronically ill patients a chance to return to their prior quality of life and significantly reduce morbidity and mortality. Unfortunately, wait lists for solid organ transplants continue to prevent a large number of those in need from accessing this lifesaving treatment. The number of people requiring organs continues to surpass the available organ supply in almost all countries and healthcare systems. Unequal supply of organs for transplantation results in poorer health outcomes for disadvantaged and increasingly chronically ill populations, and can also encourage unethical practices such as organ trafficking (1). Deficiencies in the supply of organs from deceased donors causes an increased reliance on donations from living relatives, posing unnecessary health risks to healthy persons and further heightening the potential for exploitation (2). Improving the supply of organs from deceased donors, and decreasing the overall demand for transplants have thus been identified as important health research objectives worldwide (1). Processes surrounding deceased organ donation present multiple potential target areas in which improvements in efficiency, effectiveness, and social acceptability could help to increase the organ supply. The withdrawal of life sustaining therapies is one such area of clinical practice with potential impacts on organ donation and the broader scope of end of life care.

1.1 DONATION AFTER CARDIO-CIRCULATORY DEATH (DCD)

When deceased organ donation began with the transplantation of kidneys in the 1960s, all organs procured from deceased donors were obtained after donors were

declared dead using cardiovascular criteria, i.e. the cessation of circulation (3). During the 1970s, an increasing number of organs were procured from patients declared dead using newly developed neurological death criteria (3). Donors declared using neurological criteria remained connected to breathing machines and other systemic support systems even after a declaration of death, and organs procured from such patients were of superior quality compared to those declared using traditional cardiovascular criteria. With widespread acceptance of these new neurological death criteria and expansion of donation after neurological death programs, donation after cardio-circulatory death (DCD) largely fell out of fashion with transplant programs across the western world (3). Up until the early 1990s, organ donation from patients declared using neurological criteria was the only deceased donation practiced in many western countries.

Recently, growing numbers of patients on transplant waiting lists and improvements in transplant procurement procedures for DCD organs have led to the reappearance of this once overlooked method of deceased donation. DCD, also sometimes referred to as "expanded category" or "non-heart beating" donation, offers patients who do not meet criteria for neurological definitions of death the option to donate. While only about 2% of all hospital deaths are confirmed neurologically dead (4), up to 90% of deaths in the intensive care unit (15% of all deaths annually) occur after controlled withdrawal of life support therapy leading to cardio-circulatory death (5-7). With substantially increased numbers of patients potentially eligible for this method of organ donation, donation after cardio-circulatory determination of death has the potential to significantly increase the number of potential donors, some estimate by up to 30% (8-11).

Potentially eligible DCD patients are most commonly first identified in the intensive care unit where they are comatose and maintained on life support therapy. The patients are critically ill, but have not been identified as meeting criteria for neurologic determination of death. Families are approached for consent for DCD organ donation only after a decision has already been made by the family and treating physician to change the goals of patient care from curative to maintenance of patient comfort only. In these patients, the care team and family have agreed that further life sustaining therapy is unlikely to change patient outcomes, and the best option for the patient is to withdraw any invasive medical interventions. Once families have consented to organ donation, withdrawal of life support therapies begins. Life support therapy, also referred to as "life support treatment", "life-sustaining therapy," and "life-sustaining treatment," consists of a combination of medical interventions including both drugs and therapeutic technologies. Life support therapy is used to artificially maintain circulation and respiration in critically ill patients unable to sustain these vital functions on their own. During the withdrawal of life support therapies, breathing tubes, oxygen support, and other life support therapy modalities such as hemodialysis are removed in an order and manner decided upon by the treating care team (Figure 1).

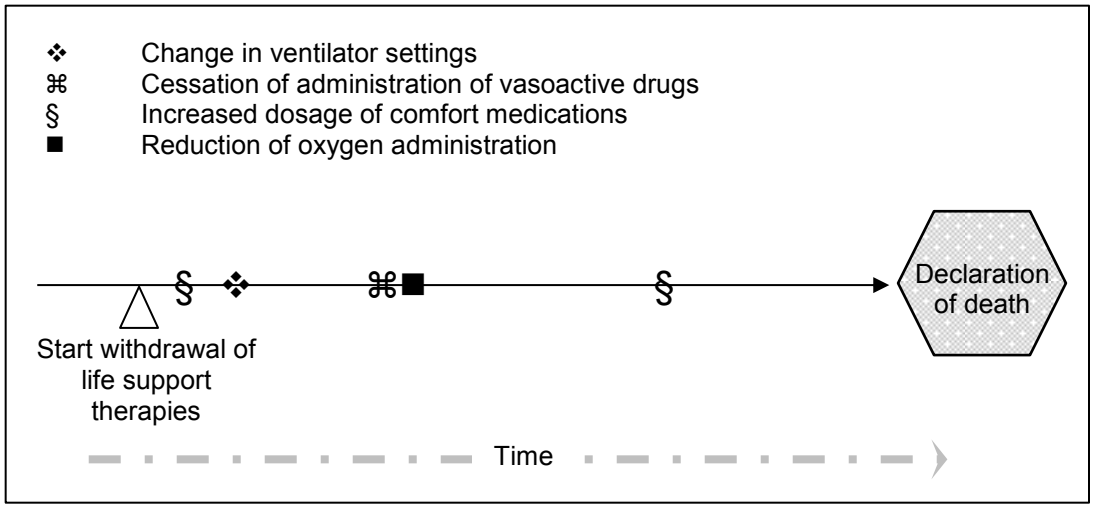

Figure 1 – Schematic diagram of example life support therapy withdrawal process

Mechanical ventilation, a combination of machines, tubes, and oxygen support used to provide artificial respiration for critically ill patients, may be stopped completely if patients are extubated (i.e. have breathing tube removed). For some patients, mechanical ventilation may be weaned gradually, or continued, depending on the severity of illness or requests from family. Therapeutic medications such as vasoactive drugs (used to maintain blood pressure), anti-arrhythmic drugs (used to maintain a normal heart rhythm), and diuretics (used to maintain fluid balance) are stopped during the withdrawal of life support therapy. Analgesics and sedatives (also referred to collectively as "comfort medications") are maintained and may be increased during the withdrawal of life support therapy to minimize pain and discomfort.

The general process of withdrawal of life support therapy is common for both non-donor and donor patients in the intensive care unit in cases where a decision to change the goals of care from curative to "comfort only" has been made. The exact process, including if, how, and when certain interventions are withdrawn is decided by the treating care team, sometimes with input from the patient's family. For patients who

wish to donate organs through DCD, it is imperative that death is declared no more than 1-2 hours after the start of life support therapy withdrawal in order to ensure sufficient organ quality (12). A surgical team is assembled and waits in the operating room for a declaration of death to be made so organ procurement can proceed in a timely manner. So far, DCD processes have been utilized to procure kidneys, livers, lungs, and hearts in eligible and consenting patients (13, 14).

1.2 Controversy and Concerns with DCD Process

Although DCD programs offer a greater number of potential donors the option to donate and could substantially increase the number of available organs, their acceptance and implementation has not been universal (15). DCD continues to be hindered by a number of concerns regarding the ethical and practical components of the process. Patients, healthcare workers, and the public have raised concerns regarding the quality of organs procured via DCD (16), the uncertainty in predicting which patients will proceed to successful donation (17), the quality of end of life care for DCD donors (18), and the role of healthcare professionals in the DCD process (19). In particular, questions abound regarding whether DCD satisfies moral principles of organ donation, and whether organs procured are safe and usable for transplantation. These concerns are situated in the larger ethical-legal context of organ donation practices, economic pressures to reduce the burden of disease and limit black market profits, as well as the philanthropic goal of improving the lives of persons with end stage organ disease. Addressing these concerns is a major focus of research in the field of DCD.

1.2.1 DCD and the "Dead Donor Rule"

A major underlying principle of all deceased organ donation is the "dead donor rule", an ethical and moral understanding that donation processes should not be the cause of death for organ donors (20). To ensure adherence to this rule, clear and consistent criteria used for the declaration of death are necessary. For organ donors, criteria for either cardiovascular or neurological death are used. Criteria for the neurological definition of death have been outlined and accepted, but agreement on a clear definition of the criteria for cardiovascular death is still forthcoming in the medico-legal community (21). While debate over the correct definition of cardiovascular death ensues, DCD programs across the world have adopted slightly different definitions of when death is determined to occur and thus the timing of when organ procurement can proceed (22). Acceptance of DCD programs has been considerably affected by the ongoing uncertainty surrounding definitions of cardio-circulatory death and whether the DCD process acceptably satisfies the dead donor rule.

As an extension of the dead donor rule, consensus for organ donation practice is that processes of organ procurement should be kept separate from patient care (20). DCD protocols recommend the responsibility of patient and donor care are delegated to separate care teams, and that withdrawal of life support therapy be carried out with the best interests of the patient, rather than with organ donation goals in mind (12). Concerns over whether this separation actually occurs in practice have become a barrier to acceptance of DCD protocols in some cases (19, 23).

1.2.2 The DCD process and organ quality

Originally, DCD practice was replaced due to the suboptimal quality of organs procured compared to those obtained through donation after neurological declaration of death. Not surprisingly, organ quality remains a central concern for those critical of DCD. While technological and pharmacological medical advances have made the process of organ procurement more advanced and precise than ever before, fundamental differences exist between DCD and the better-known, procurement after neurological declaration of death. Donors can be declared dead using neurological criteria for death while they remain connected to life support modalities that maintain circulation and oxygenation to organs. Once death has been declared in these donors, organs can be procured with almost no interruption in organ perfusion, resulting in high quality organs comparable to those obtained through living kidney, liver, and lung donations (3).

DCD donors are not declared using neurological criteria, but instead are determined to be dead using clinical cardiovascular criteria such as the absence of a pulse and the inability to detect an arterial wave form using invasive arterial monitors (12). In most DCD donors, this death occurs as a result of a controlled withdrawal of life support therapy; the removal of breathing machines and drugs that maintain blood pressure. As part of the withdrawal process, breathing slows and blood pressure gradually drops until it ceases to sustain life. A natural side effect of the dying process is a decline in adequate organ perfusion. The process of withdrawal of life support therapy gradually deprives organs of oxygen. The longer the dying process, the more oxygen deprived organs become, and the larger the amount of potential ischemic damage they suffer as a result. Ischemic organ damage is difficult to measure directly, so the length of time from

beginning of life-support therapy withdrawal to death is used as a proxy estimation of oxygen deprivation. Most DCD protocols stipulate a maximum time limit from the start of life support therapy withdrawal to the declaration of death, beyond which organs are deemed unusable for transplantation (12, 24, 25). Time limits vary between centers and between countries, and are different depending on the organs to be procured (12). A significant challenge with DCD is predicting which patients will meet the time limit cut off for organ donation eligibility and which will be "donation failures". Current prediction algorithms focus on baseline assessments of patients and often fail to include the withdrawal of life support process as an important variable (26). Though some have shown promise, few have been validated, and many lack the sensitivity and/or specificity to accurately identify successful donors (27-30). Additionally, concern remains regarding whether organs procured from patients with a longer time from initiation of life support therapy withdrawal to death retain enough function to be used for transplantation.

1.3 CENTRAL ROLE OF WITHDRAWAL OF LIFE SUPPORT THERAPY

A common theme for many of the concerns with DCD is the process of withdrawal of life support therapy itself, a process which occurs for all donors and potential donors identified in the intensive care unit (Figure 2).

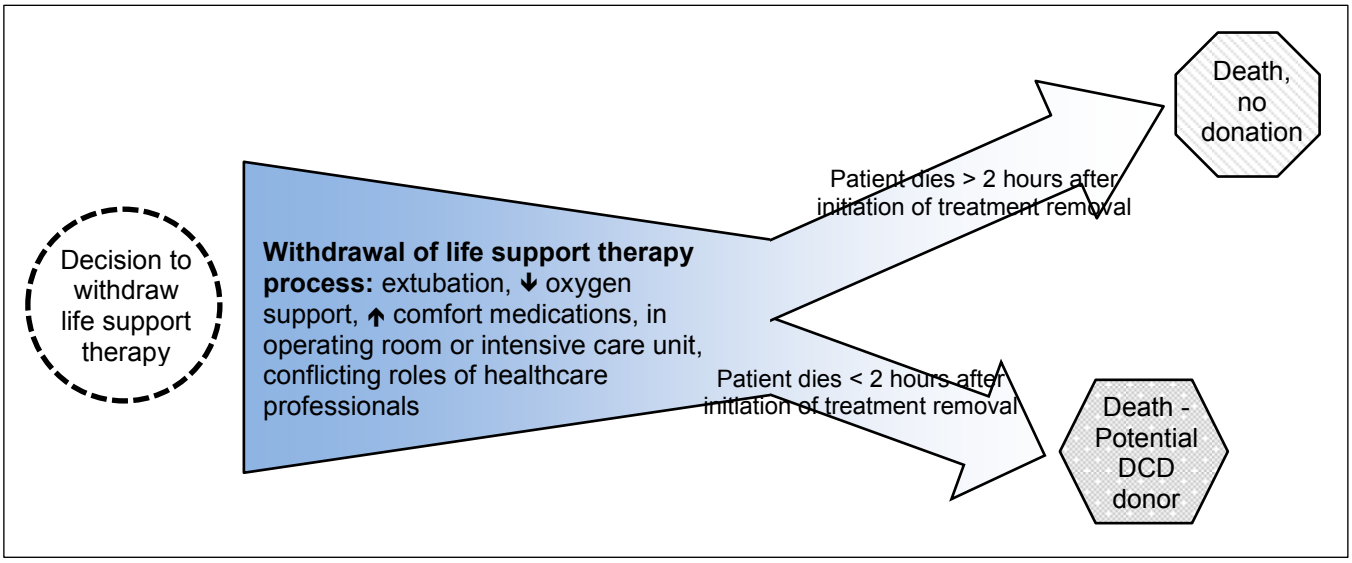

Figure 2 – Conceptual diagram of role of withdrawal of life support therapy processes in DCD

Withdrawal of life support therapy encompasses a large number of decisions made in the last hours of a patient's life. The process has the potential to impact both time to death and physiologic stability of the donor during the dying period, both of which can influence donation success (12, 25, 31). Through their impact on length of ischemia, the trajectory and location of dying may also impact organ functionality after procurement, another important outcome in organ donation (25, 32-34). In addition to playing a major role in DCD, the process of withdrawal of life support therapy is a significant contributing factor of end of life care quality outcomes such as patient comfort and family satisfaction with care (18, 35). Withdrawal of life support therapy constitutes the final clinical treatment pathway where healthcare professionals who have been caring for patients prior to a decision to change the goals of care may transition into an alternative or additional position of caring for a potential organ donor and assisting with transplantation protocols. For cardio-circulatory deceased donation, the process of life support therapy withdrawal plays a central role and is inextricably tied to ongoing concerns about the DCD practice.

1.4 Knowledge Gap in Process of Withdrawal of Life Support Therapy

Despite having both a central role in DCD and comprising a key component of quality critical care, limited research has been completed on the process of life support therapy withdrawal. The Society of Critical Care Medicine describes withdrawal of life support therapy as comprised of two processes: the decision to withdrawal medical interventions and switch to comfort care, and the "actions that are taken once this shift in goals has been made" (36). Over the past decade, the medico-legal community has focused intensely on the ethical and clinical discussions necessary for making the decision to withdraw medical interventions (36-38). General consensus exists about the need for clear communication, documentation, and ethical considerations in the decision to withdraw life support therapy, especially for patients whose families additionally consent for them to become organ donors. The second, "action" part of the process of withdrawal of life support therapy has been considered in less detail, and a number of questions pertaining to what should occur during the removal of specific life support modalities remain unanswered.

Once a decision to withdraw life support therapy is made, the process of withdrawal of life support therapy can be further divided into ethical considerations, and actual physical actions or inactions of removing medical interventions and titrating drugs. The ethical considerations of adequate pain relief during the dying process have been widely discussed in the literature, resulting in the accepted concept of "double effect" (12). Most practitioners have agreed that administration of pain medications as required is warranted during the dying process, even if the same doses of drugs could lead to respiratory depression and death (35). Questions regarding which drugs should be used,

in what amounts, and when, have yet to be answered. Whether this concept remains well accepted in cases of DCD donation is also a key consideration.

A number of empirical studies exist describing practices of withdrawal of life support therapy in intensive care units worldwide (39-42), but consensus on exactly how to withdraw life-sustaining therapies in usual practice has been comprised mainly of vague recommendations based on expert opinion (35). Recommendations for processes of withdrawal of life support therapy in potential organ donors are even scarcer, and usually refer practitioners to the use of "standard care practices" (12, 26). A lack of consensus about optimal practices for processes of life support therapy withdrawal may lead to increased stress in healthcare workers and patient families at the bedside (15, 19). Since the order of life support therapy withdrawal is at least conceptually associated with time to death, bedside staff may feel apprehensive about removing certain life support modalities for fear of the perception that they are hastening death and potentially violating the 'dead donor rule'. Anxiety over the perception of hastening death may be even more pronounced in healthcare workers caring for organ donors, and has the potential to impact the quality of end of life care (43, 44). Current studies provide a cursory description of key interventions removed, but few link processes of life support therapy withdrawal with important outcomes in addition to patient death. A significant amount of detail and guidance is missing from this central component of end of life care processes for both donors and non-donors in the intensive care unit. Further information about the process of withdrawal of life support therapy has the potential to impact end of life care for all patients in the intensive care unit, both donors and non-donors, as well as

to improve comfort levels with and perhaps uptake of DCD protocols by helping to assuage concerns about the donation process.

No current formal consensus exists about the best way to withdraw life-sustaining therapy, in what order, or with what complement of drug dosing, and considerable variability exists in clinical practice. Knowledge of present variability and scope of practice will help to inform future policy and help to guide discussion about what processes are acceptable when DCD donation is a goal after life support therapy withdrawal.

2.0 GOALS AND OBJECTIVES OF THE STUDY

Withdrawal of life support therapy plays a central role in the process of DCD but remains vaguely described in the literature. The overarching goal of this project was to contribute to a clearer definition and understanding of the process of withdrawal of life support therapy as it relates to both standard practices in the intensive care unit and organ donation after cardio-circulatory declaration of death. The first objective of the project was to describe the most common process of life support therapy withdrawal in adult intensive care units according to currently published literature, including an exploration of the most common time sequences, medications, and modes of life-support therapies withdrawn. Our second objective was to analyze observations of actions taken during withdrawal of life support therapy as it occurs in selected Canadian intensive care units, creating a detailed description of time sequences and resulting in a conclusion about common patterns of life support therapy withdrawal on a regional and national level. Our final project objective was to identify and examine the goals of life support therapy

withdrawal for non-donor patients, compared to the goals of life support therapy withdrawal for DCD donors, and consider qualitatively how aligning these goals may benefit all participants in end of life care.

3.0 METHODOLOGY

To meet the goals and objectives of this exploration of withdrawal of life support therapy we undertook a three-part thesis project in manuscript form. Three separate but interlinked projects were designed and completed with each part informing the design of the next. At each stage of the project, we considered our results and re-assessed the most effective manner to proceed with future work. Each subsequent project was created out of the knowledge gap highlighted by our prior research.

The manuscript model was utilized due to the relatively new nature of the DCD topic and the interest of the global medical and ethical community in further information and discussion about the DCD process. Publications on the role of processes of life support therapy withdrawal in DCD are timely given recent incentives and encouragement by North American governments to include DCD protocols within the healthcare system (11), and improve organ transplantation programs (45). The completion of a manuscript-based thesis ensures that findings about the role of processes of life support therapy withdrawal in DCD will be disseminated in a timely manner to the broader community.

3.1 PROJECT LAYOUT

The thesis is comprised of three stand-alone manuscript papers that also complement one another. Each paper completes one objective of the thesis through the exploration of several sub-objectives. The manuscripts are presented with complete individual abstracts, introductions, methodologies, and discussions. The manuscripts presented as part of this thesis have had additional detail added to methods and results sections for clarity and comprehensiveness. Between manuscripts follows a reflection of findings and a discussion of how new information gained through each body of research was used to shape subsequent projects. Following all three papers is a final reflection of the findings and a discussion of how results from this project will be used going forward in organ donation research in Canada.

4.0 PART I – PATTERNS AND VARIABILITY IN THE OPERATIONAL PROCESS OF WITHDRAWAL OF LIFE SUPPORT THERAPY: WHY IT MATTERS FOR DONATION AFTER CARDIO-CIRCULATORY DEATH

4.1 ABSTRACT

Objective: DCD has the potential to increase the availability of organs for transplantation. Concerns surrounding violation of the "dead donor rule" and the potential for overlap between end of life care and actions to facilitate organ donation eligibility hinder uptake of this practice. We conducted a structured review to examine the physical process of withdrawal of life support therapy in standard intensive care unit practice. The purpose was to describe a common practice of withdrawal of life support therapy in non-DCD patients and consider its relationship to DCD in terms of modifying time to death and preserving the moral principle of the dead donor rule. **Data Sources:** Electronic

journal databases were searched from date of first issue of each journal until October 2012. **Study Selection:** Original research articles describing the physical process of life support therapy withdrawal in North American, European, and Australian intensive care units were included. **Data Extraction:** For included papers, we extracted operational definitions of life support therapy withdrawal, descriptions of life support modalities withdrawn, order of life support therapies withdrawn, drugs administered, and timing from life support withdrawal until death. **Data Synthesis:** 14 papers met inclusion criteria. Definitions of life support therapy withdrawal varied between studies and focused on withdrawal of mechanical ventilation. Two studies did not present an operational definition of withdrawal of life support therapy processes. All 14 studies described different aspects of the process of life support therapy withdrawal and measured different time periods leading up to death. Staggered patterns of life support therapy withdrawal were reported in all studies describing order of withdrawal of life support modalities, with vasoactive drugs withdrawn first followed by gradual withdrawal of mechanical ventilation. Processes of life support therapy withdrawal did not seem to influence time to death. **Conclusions:** Defined time periods and interventions removed as part of life support therapy withdrawal are not consistent between reports; a description of the average life support therapy withdrawal process was not possible. A clearer definition of the practical process of life support therapy withdrawal and when it begins is necessary before robust comparisons between withdrawal of life support therapy and DCD protocols can be made.

4.2 INTRODUCTION

The severe shortage of organs urgently needed for transplantation remains an international problem. People across the globe must wait months or years before getting transplant therapy they need (46). The shortage persists due to both a lack of eligible donors and inefficiencies of the organ procurement system. Traditional organ donation from deceased donors has focused on patients who have been declared "brain dead" according to specific neurological criteria, but brain death is rare, comprising only 2% of hospital deaths (3, 4). In contrast, patients who are comatose on a ventilator but do not meet specific brain death criteria represent a large pool of potential organ donors. These patients are declared dead according to cardio-circulatory criteria that confirm the irreversible cessation of respiration and pulse after controlled withdrawal of life sustaining medical therapy. According to some estimates, these patients comprise up to 20% of all hospital deaths and could increase the number of available organs by 10-30% (5, 11).

Despite its potential to improve the shortage of organs, widespread acceptance of DCD has been slow. Concerns have focused on whether the "dead donor rule", a central principle in organ donation requiring deceased donors to be declared dead before any organ procurement process begins (3), is upheld during DCD. As part of the "dead donor rule", organ procurement actions are to be kept separate from the withdrawal of life support therapy; patients should not have interventions given or withheld solely for the purposes of organ donation (13). Withdrawal of life support therapy must therefore be completed according to "standard practice", and the patient declared dead before organ procurement can proceed. Though the process of life support therapy withdrawal is to be

kept separate from DCD, it has an impact on whether patients will be eligible to donate by influencing how and when they die (47). In some cases the time between initiation of withdrawal of life support therapy and death is too long, causing organs to sustain ischemic damage and patients to be excluded from donating (12). "Donation failure" may occur in up to 40% of all potential DCD donors (25), resulting in lost resources and disappointment for families (13).

The standard practice of life support therapy withdrawal is important for both the moral integrity of the dead donor rule and for determining eligibility of patients for DCD. Guidelines for the process of withdrawal of life support therapy during DCD could help provide clearer standards and encourage uptake of DCD protocols in addition to decreasing donation failure. The process of life support withdrawal has a key role in DCD but has not been well described in the literature.

The objective of this review is to describe the most common process of life support therapy withdrawal in adult intensive care units according to currently published literature. The questions of interest include 1) What life support modalities are most commonly withdrawn in the intensive care unit, 2) What is the most common sequence of life support therapy withdrawal, 3) What drugs are given in the last few hours of life, and in what doses, and 4) What is the average time to death after the withdrawal of life support therapy?

4.3 METHODS

4.3.1 Search strategy and selection of studies

Three electronic databases, MEDLINE® (1946 to October 2012), EMBASE® (1947 to October 2012), and EBM Reviews (1991 to October 2012), were searched for articles using MESH and non-indexed keywords related to four main concepts: intensive care units, healthcare practice patterns, life support care, and the withholding and withdrawal of life sustaining technologies (a complete list of search terms used is presented in Appendix A). Results were restricted to English language papers only. No publication date limit was set. Grey literature was searched through a targeted strategy by examining publications from the following national organizations involved in DCD and end of life care: Canadian Medical Association, Canadian Critical Care Society, American Medical Association, Society of Critical Care Medicine, Institute of Medicine, Trillium Gift of Life Network, World Health Organization, World Medical Association, European Society for Organ Transplantation, European Society of Intensive Care Medicine, and the National Institutes of Health. A hand search of reference lists was also done.

4.3.2 Data extraction

Papers were included if they focused on adult patients in an intensive care unit, described any physical processes of life support therapy withdrawal, and took place in North America or in countries with comparable medical practice and socio-demographic patterns (i.e. Western Europe, Australia). We included all publication types. Articles were excluded during a detailed title and abstract review if they did not include direct

quantitative observations of the physical processes of life support therapy withdrawal. A screen of full articles was completed for articles that could not be excluded based on titles or abstracts. One reviewer (AvB) was responsible for determining inclusion eligibility at all stages using a consistent checklist. We wanted our description of current life support therapy withdrawal practices to be broad and inclusive, and did not look for effect size or make practice recommendations as part of this review. Further, the nature of this topic requires the use of observational studies, which are less likely to be considered methodologically robust using conventional rating methods. As no previous review has been completed on the topic, we considered that more benefit would be gained by including all relevant and comparable publications regardless of study quality. Methodological strength of articles was therefore not assessed as part of the eligibility determination for articles. Data was extracted to summary tables using a consistent data collection tool (A sample data extraction table can be found in Appendix B). The articles were grouped according to reported measures of withdrawal of life support therapies. Category-specific data abstraction tools were created and used to collect data for these subgroups.

4.4 RESULTS

The search strategy retrieved 2446 citations after deletion of duplicates (Figure 3). 59 articles met inclusion criteria based on abstracts and were selected for full review. Further appraisal of full texts removed 46 not relevant to the research question. The most common reasons for non-relevance in papers were: related to pediatric or neonatal intensive care units, focus on decision making process of life support withdrawal, no

direct quantitative observations of the physical process of life support withdrawal. Of papers that met inclusion criteria, one review article and two papers based on similar study populations were excluded (7, 48, 49). Four articles were identified through a reference scan. A final 14 original papers were included (Table 1).

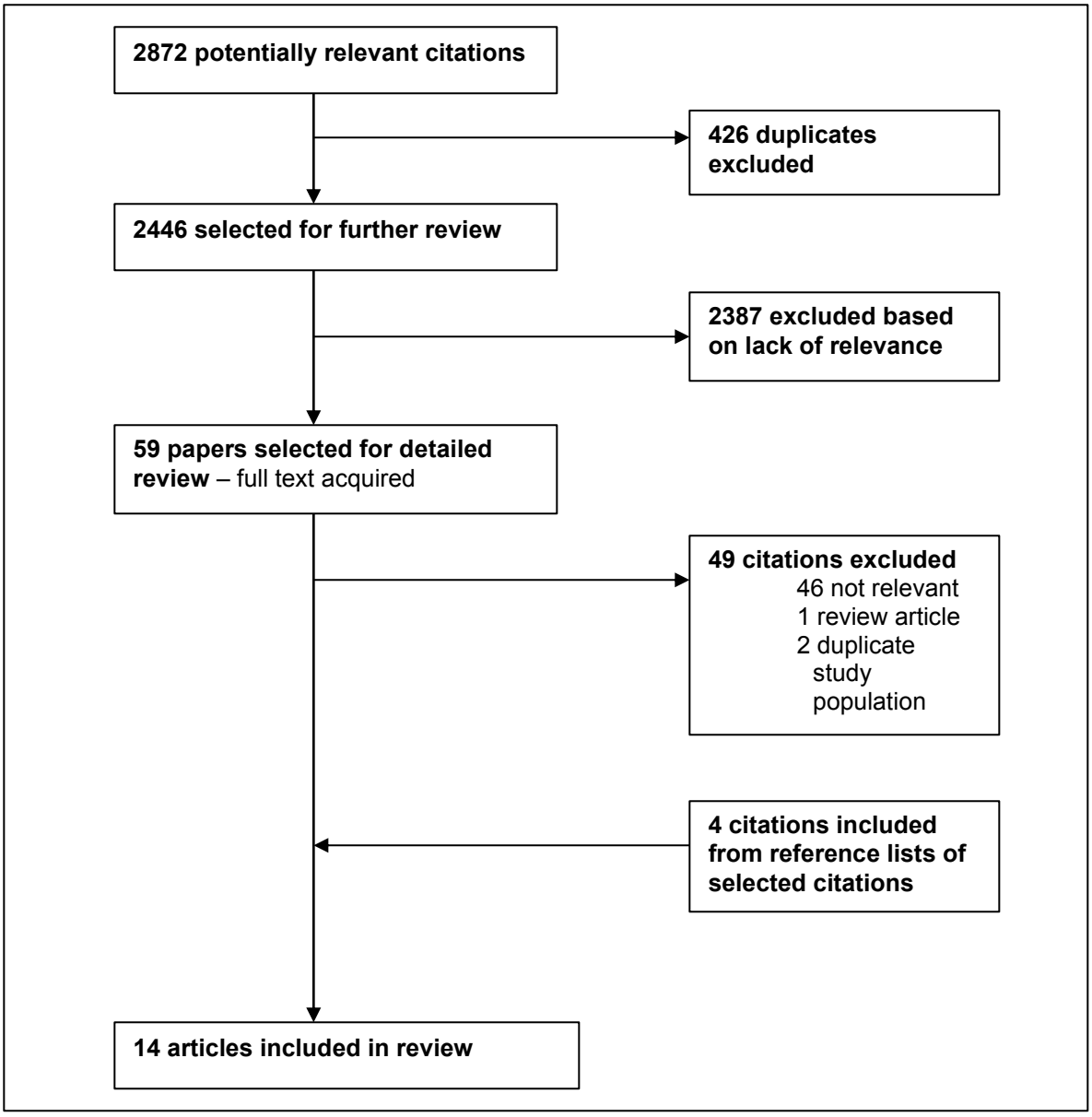

Figure 3 – Flow diagram of review search strategy

Nineteen publications were identified through the targeted Grey Literature search. Most were ethical/legal statements regarding the moral principles of life support therapy withdrawal; others were consensus documents for decision making in life support therapy withdrawal processes based on expert opinion. None of the publications made available by recognized institutions presented quantitative evidence of the *process* of life support therapy withdrawal and therefore none were selected to include for this review.

Table 1: Studies included in review of withdrawal of life support therapy processes

Author, Reference	Year	Country	Study setting (Number of hospitals, type)	Design	N[a]
Smedira et al (50)	1990	United States	2 M/S, U	PC	115
Wilson et al (51)	1992	United States	2 M/S, U	PC	44
Wood and Martin (52)	1995	Canada	1 M/S, U	RCR	71
Keenan et al (53)	1997	Canada	2 M/S, 1 trauma center, U	RCR	293
Keenan et al (41)	1998	Canada	3 M/S, U 6 M/S, C	PC with ~30% data retrospective	292
Hall and Rocker (54)	2000	Canada	2 M/S, U	RCR	174
Esteban et al. (55)	2001	Spain	6 M/S, U	PC	221
Ferrand et al. (40)	2001	France	148 M/S, U	PC	807
Rocker et al (56)	2004	Canada	6 M/S, U	PC	206
Chan et al (39)	2004	United States	1 trauma center, U	RCR	75
Gerstel et al (57)	2008	United States	2 M/S, U 12 M/S, C	RCR	584
White et al (42)	2009	United States	1 medical, U	RCR	78
Bloomer et al. (58)	2010	Australia	1 M/S, U	RCR	70
Wind et al. (29)	2012	Netherlands	Country-wide, any with potential DCD patients	PC	211

PC, prospective cohort; RCR, retrospective chart review; M/S, medical/surgical; U, university hospital; C, community hospital

[a] Number of intensive care unit patients in study who had life support therapy withdrawn

4.4.1 Study characteristics

Within the 14 papers included for review we focused on four main observations relating to the process of life support therapy withdrawal: life support treatment modalities withdrawn, order of life support treatment modalities withdrawal, drugs administered, and timing from life support therapy withdrawal until death. Three of the 14 papers (21%) included all 4 categories (52, 53, 56). Most articles (12 of 14 – 86%) described processes of life support therapy withdrawal in non-DCD patients.

All studies included at least one university-affiliated hospital; three studies (21%) included community hospital intensive care units (50, 52, 53). Mean patient age and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were similar for articles that reported them (Table 2). Primary reasons for admission were medical/surgical diagnoses. Chan et al. (39) and Wind et al. (29) reported more neurologically injured and/or surgical patients. Smedira et al. (50) included brain-dead donors and Wind et al. (29) included cardio-circulatory death donors in their population.

Table 2: Patient characteristics of articles included in review

Study	Age, years	APACHE II score	ICU length of stay, days (range)
Smedira et al (50)	51 ± 23	--	11 ± 13, (<1 – 93)
Wilson et al (51)	--	--	8.9, (1-67)[a]
Wood and Martin (52)	66.5 ± 12.2	26.0 ± 8.4	7.6 ± 6.9
Keenan et al (53)	62.7 ± 16	25.4 ± 7.8	9.8 ± 22.2 (<1 – 247)
Keenan et al (41)	Community ICU: 64.0 ± 10.1 University ICU: 67.4 ± 16.6	--	Community ICU: 4.86 ± 8.37, (1-63) University ICU: 7.39 ± 16.08, (1-177)
Hall and Rocker (54)	65 ± 16	25 ± 9	7.0, (5.5 – 8.5)
Esteban et al. (55)	70 (59-76)*	--	8 (2-6) [a]
Ferrand et al. (40)	72 (62-78)*	--	8 (3-19) [a]
Rocker et al (56)	67.8 ± 14.6	25.8 ± 7.4	7.8 days (4.2-13.4) [a]
Chan et al (39)	59 ± 19	--	4, (1-82)
Gerstel et al (57)	72.4 ± 14.0	--	4, (1-75)
White et al (42)	64 ± 16	--	14 ± 43
Bloomer et al. (58)	69.3	27.3	3.67
Wind et al. (29)	52 ± 13	--	(1-30)

All data presented as mean ±SD except * presented as ranges.
APACHE II, Acute Physiology and Chronic Health Evaluation II score; ICU, intensive care unit.
[a] Length of stay prior to initiation of withdrawal of life support therapy

4.4.2 Definitions of processes of withdrawal of life support therapy

The included studies presented a range of operational definitions of the process of withdrawal of life support therapy (presented in Appendix C – Definitions of process of withdrawal of life support therapy used in included studies). Five articles (36%) separated observations of withholding versus withdrawal of life support therapy (40, 50, 52, 53, 58). We combined values reported in these articles to represent "withheld" and "withdrawn" interventions as a single process, withdrawal of life support therapy.

Three studies (21%) used withdrawal of mechanical ventilation as the start of life support therapy withdrawal (39, 42, 51). Just under half (43%) incorporated additional "life sustaining" technologies such as dialysis and vasoactive drug support in their definitions (40, 41, 53, 54, 57, 58). Two studies (14%) did not outwardly define "withholding or withdrawal" of life support therapy (29, 50), and three studies (21%) included an expectation of patient death as part of their definition (52, 54, 55). A "do-not-resuscitate" order was included as part of the definition of life support therapy withdrawal processes in two studies (41, 53).

4.4.3 Description of life support treatment modalities withdrawn

Twelve of the included articles (86%) reported the numbers and type of life support treatment modalities withdrawn (41, 42, 50, 52-54, 56, 57). Four articles (33%) reported baseline life-sustaining therapies given before or at the time of life support therapy withdrawal. Patients were on an average of 3 (range 1-6) life-sustaining therapies at the time life support therapy withdrawal was initiated (56, 57). Mechanical ventilation was the intervention most commonly withdrawn, with 68 – 85% of patients undergoing some form of reduction of artificial respiration. Rates of withdrawal of mechanical ventilation were lower (20 – 42%) in one Australian and two European studies (40, 55, 58). In Ferrand et al.'s descriptions withdrawal of life support therapy in France, 6% of the 534 intubated and mechanically ventilated patients were extubated (40).

The proportion of patients undergoing withdrawal of drugs used to maintain blood pressure (vasoactive drugs) varied among 9 studies that recorded this variable. Withdrawal of vasoactive drugs was reported for 26 - 100% of the sampled populations.

Hall & Rocker (54) reported 15% of patients in their study remained on blood pressure support with vasoactive drugs at the time of death. Five studies reported the percentage of nutritional support therapies withdrawn, which ranged from 10 – 31% of patients undergoing life support therapy withdrawal (40, 52, 53, 55, 58). Withdrawal of renal replacement therapy occurred for 1 – 38% of patients in 6 studies recording this variable (40, 50, 52, 53, 55, 58).

4.4.4 Order of life support treatment modalities withdrawn

Four of fourteen articles (29%) measured the order of life support treatment modalities withdrawal, shown in Table 3 (52, 53, 56, 57). All 4 noted a staggered pattern of life support therapy withdrawal; Rocker et al (56) reported more staggered life support therapy removal patterns while Gerstel et al (57) observed more patients to undergo a simultaneous withdrawal of life support therapies. All four articles noted vasoactive drugs to be withdrawn prior to mechanical ventilation. Gerstel et al. (57) reported dialysis, hydration, and nutritional interventions were withdrawn prior to vasoactive drugs.

Table 3: Order of interventions withdrawn

Authors, Reference	Staggered withdrawal pattern evident?	Order of interventions withdrawn [a]
Wood and Martin (52)	Yes	VP, O_2 support, MV
Keenan et al (53)	Yes	VP, O_2 support, MV
Rocker et al (56)	Yes	--
Gerstel et al (57)	Yes	RRT, hydration, nutrition, VP, laboratory tests, MV

VP, vasoactive drugs; MV, mechanical ventilation; RRT, renal replacement therapy

[a] order from first to last intervention withdrawn preceding death

4.4.5 Drug administration during withdrawal of life support therapy

Eleven of 14 (79%) articles included observations of drugs administered during life support therapy withdrawal (29, 39, 40, 42, 50-54, 56, 58). Between 40 to 80% of patients received sedative and/or analgesic medication during the process of life support therapy withdrawal (Table 4). The most commonly given medication was Morphine (a type of analgesic), administered to over 50% of patients in 7 of 11 studies capturing data on drug administration.

Table 4: Drugs administered during the process of withdrawal of life support therapy

Authors, Reference	N	Number (%) of patients on analgesics and/or sedatives	Number (%) of patients given morphine
Smedira et al (50)	115	68 (70%)	NR
Wilson et al (51)	44	33 (75%)	31 (70%)
Wood and Martin (52)	71	NR	52 (73.2%)
Keenan et al (53)	293	NR (86%)	NR (86%)
Hall and Rocker (54)	174	NR	125 (71.8%)
Ferrand et al. (40)	807	344 (43%)	NR
Chan et al (39)	75	63 (84%)	NR (90%)
Bloomer et al. (58)	70	46 (66%)	41 (59%)
Wind et al. (29)	211	43% on sedatives 51% analgesics	NR (45%)
Rocker et al (56)	206	NR	NR (57.8%)

NR, not reported

Three (27%) studies noted increased doses of sedatives/analgesics during life support therapy withdrawal (39, 51, 54), while 2 (18%) studies reported no significant changes in drug dosing at the end of life (42, 56).

Chan et al. (39) observed mean Morphine doses given by physicians ranged from 1.4 ± 4.7 mg/h to 12.4 ± 30.2 mg/h. No other studies measured individual physician

dosing. Two articles reported use of muscle relaxants during the process of life support therapy withdrawal (51, 54). Wilson et al. (51) observed 9% of their patients given pancuronium or vecuronium at the time of life support therapy withdrawal for maintenance of adequate ventilation. Hall & Rocker (54) reported 14% of patients in their study received muscle relaxants during life support therapy withdrawal.

4.4.6 Time to death after withdrawal of life support therapies

Times to death after withdrawal of life support therapies ranged from under 1 hour to over 2 days as presented in 12 of the 14 (86%) papers (29, 39, 41, 42, 51-53, 55-58). Five of twelve studies (42%) reported no significant differences in time from life support therapy withdrawal to death between patients having different doses of sedatives (29, 51), simultaneous versus staggered patterns of life support therapy withdrawal (56), extubated versus non extubated patients (29), and whether life support therapy withdrawal took place in an intensive care unit or a long term care home (42). Three of twelve (25%) articles reported life support therapy withdrawal process characteristics including location of hospital (community vs. teaching), doses of benzodiazepines, and family size increased time from life support therapy withdrawal to death (39, 41, 57). Four of twelve articles (33%) did not compare time to death by any characteristics (52, 53, 55, 58).

4.5 DISCUSSION

This review identified 14 papers describing the process of life support therapy withdrawal for non-DCD and potential DCD patients in adult intensive care units in

North America, Europe, and Australia. To our knowledge, it is the first review of standard processes of withdrawal of life support therapies. Most articles described a stepwise process of life support therapy withdrawal involving titration of vasoactive drugs followed by ventilator weaning. Rates of extubation were variable between studies, with lower rates of ventilation withdrawal and extubation reported by studies in Australia and Europe. Sedatives and analgesics were maintained during life support therapy withdrawal in most cases, with some articles reporting an increase in dosing towards the time of death. Time from life support therapy withdrawal to death varied and was not obviously related to any life support therapy removal patterns. However, inconsistencies in measurements between studies made it difficult to come to any meaningful conclusions regarding possible relationships between patterns of life support therapy withdrawal and time to death.

Observed patterns of processes of withdrawal of life support therapies in the included articles are consistent with patterns described in physician practice surveys (59, 60). Of note, the pattern observed by Ferrand et al. (40) differed in that only 6% of patients in their study were extubated.

The greatest variance between studies was between operational definitions of withdrawal of life support therapy. Articles ranged in their definitions of which interventions were included as part of the life sustaining therapies being withdrawn. Less than half of the included studies considered life support modalities in addition to mechanical ventilation as warranting observation in the withdrawal of life support therapy process. Studies also differed in their interpretations of when processes of withdrawal of life support therapy began, with most definitions vaguely outlined and two

studies not defining any clear starting point. Variation in how life support therapy withdrawal was operationally defined resulted in each study measuring different aspects of the process and reporting different outcomes. For studies with broad definitions, withdrawal of life support therapy processes appeared more variable and resulted in longer times from the start of life support therapy withdrawal to death. For studies with narrow definitions of withdrawal of life support therapy processes, patterns seemed more consistent between patients. How life support therapy withdrawal was defined in each study influenced, in turn, how this action was carried out.

Observed variability could have been due to factors not intrinsic to the process of life support therapy withdrawal. Included articles were published between 1990 and 2012, a period in which clinical practice in the intensive care unit has changed along with what is considered medically, legally, and ethically acceptable practice. While all included articles had at least one study center at a university-affiliated hospital, case mixes differed between sites. One study specifically reported more neurologically injured patients, which may have influenced how life support therapy was withdrawn since neurological injuries require different approaches to life support treatments (39, 61). Not all studies reported baseline proportions of patients requiring each life support treatment modality. In addition, this review included articles from countries with different health care funding structures and legislation surrounding life support therapy withdrawal, which may have resulted in differences in practice. Indeed, lower rates of extubation were observed in Ferrand et al.'s (40) observation of life support therapy withdrawal processes in France compared to rates of extubation in North American intensive care units. Rates of extubation in Bloomer et al.'s (58) Australian study were also lower than North

America. This may be due to differences in decision-making surrounding life support therapy withdrawal, influences of legislation and practice guidelines, or economic/institutional differences between healthcare systems and personnel training (62). Life support therapy is expensive, which could influence both timing of a decision for life support therapy withdrawal and the processes that follow. It is unclear whether differences between processes of life support therapy withdrawal are attributable to underlying economic and social factors.

Variation in the definitions of processes of withdrawal of life support therapy is also present in DCD prediction tools. DeVita et al. and Kaufman et al. both reported associations between aspects of life support therapy withdrawal (withdrawal pattern and drug dosing, respectively) and time to death in their populations, and yet neither article describes an operational definition of the life support therapy withdrawal process (63, 64). Because the process of withdrawal of life support therapy remains undefined both in descriptions of standard clinical practice and in DCD protocols, the line between life support therapy withdrawal and the process of organ procurement will continue to be blurred.

While differences in how withdrawal of life support therapy was completed did not appear to influence the time to death (and therefore potential DCD eligibility) in these studies, a firm conclusion cannot be made. Processes of withdrawal of life support therapy were defined, observed, and measured dissimilarly amongst articles, making meaningful comparisons using review data impossible. Keenan et al. (41) and Gerstel et al. (57) reported longer times to death in community hospitals and for larger family sizes, respectively, which could reflect a social element of the withdrawal of life support

therapy process that impacts time to death. Chan et al. (39) observed higher benzodiazepine doses increased time to death, a finding that has been repeated (63). Consistent definitions and measurements of the process of withdrawal of life support therapy are necessary before the impact of patterns of withdrawal of life support therapy on time to death and DCD eligibility can be fully determined.

4.6 CONCLUSIONS

In summary, we identified 14 articles that described the physical process of withdrawal of life support therapy, an aspect of intensive care that has been neglected in published literature. Defining time periods and interventions that the life support therapy withdrawal process encompasses are not consistent between reports, making an accurate description of the average process difficult to produce. However, a broader range of what is acceptable during withdrawal of life support therapy also results in the potential for overlapping with DCD processes. At the least, a clearer, more universal agreement on what constitutes the operational definition of life support therapy withdrawal and when this physical process begins would allow for more robust comparisons between palliative care and DCD literature. Further investigation into the physical processes of life support therapy withdrawal in a more structured manner is needed in order to identify whether true trends and patterns exist, and whether patient-centered patterns of life support therapy withdrawal are compatible with DCD protocols aiming to optimize organ viability.

5.0 REFLECTION ON A REVIEW OF LIFE SUPPORT THERAPY WITHDRAWAL AND FUTURE RESEARCH DIRECTIONS

The review of life support therapy withdrawal patterns in non-organ donors provided useful background information for the remainder of the thesis project. To our knowledge, it is the first review article summarizing the process of life support therapy withdrawal in non organ donor patients. The paper highlights the lack of comprehensive knowledge or direction regarding best practices of life support therapy withdrawal in critical care, as well as the variation across hospital centers and countries. Over the twenty-year period covered by included articles, the practice of withdrawal of life support therapy remained highly variable and poorly defined for non-organ donors. While some degree of commonality initially appeared consistent between observed processes (vasoactive drugs withdrawn first followed by a reduction in mechanical ventilation), a closer look revealed differences in definitions and time periods which meant compilation of observations into an aggregated average was not possible. We hypothesized that an exploration of observations of life support therapy withdrawal using a different study design may be able to determine a clearer common pattern of life support therapy withdrawal.

In the structured review, included papers presented only aggregate estimates of what occurred during withdrawal of life support therapy, rather than the complexities of individual data. Furthermore, descriptions of actions occurring during life support therapy withdrawal, such as how mechanical ventilation was titrated and dosing of drugs administered, were inconsistent and not well presented in the majority of articles. Taking into account the conclusions from the review, we hypothesized that a common picture of withdrawal of life support therapy patterns may become more apparent with additional

information at the patient level. We further hypothesized that certain processes of life support therapy withdrawal may be carried out due to individual patient characteristics not identified at the aggregate, publication level. To explore these questions, an additional examination of life support therapy withdrawal using individual patient data was undertaken with the next part of the thesis project.

6.0 PART II - EXPLORATION OF WITHDRAWAL OF LIFE SUPPORT THERAPY PROCESSES IN PARTICIPATING CANADIAN INTENSIVE CARE UNITS USING DATA FROM A SMALL PILOT STUDY

6.1 ABSTRACT

Objective: Donation after cardio-circulatory death (DCD) has re-emerged as an option for improving the organ supply. The process of DCD is strongly connected with the process of withdrawal of life support therapy, a procedure in standard intensive care unit practice care that remains vaguely explored in the literature. In addition to impacting DCD success, the actions taken as part of life support therapy withdrawal have implications for the quality of palliative care. We examined data from Canadian intensive care units to explore current practices of life support therapy withdrawal in non-organ donor patients and describe the variability in standard practice. **Design:** Secondary analysis of observational data collected for the Determination of Death Practices in Intensive Care pilot study. **Setting:** Four Canadian adult intensive care units. **Patients:** Patients ≥ 18 years in whom a decision to withdraw life support therapy was made and for whom substitute decision makers consented to study participation. Organ donors were not eligible for participation. **Interventions:** None. **Measurements and Main Results:** Complete data on the life support modalities withdrawn, drugs administered, and timing

of life support therapy withdrawal was available for 36 adult patients who had participated in the pilot study. Patients' age, illness severity, and level of consciousness were comparable between sites. Withdrawal of life support therapy processes appeared to follow a general pattern of vasoactive drug withdrawal followed by removal of mechanical ventilation and extubation in most sites, but specific actions taken as part of withdrawal of life support therapy varied. Approaches to extubation and weaning of vasoactive drugs were not consistent. Protocols detailing the process of life support therapy withdrawal were available for 3 of 4 sites and also exhibited differences across sites. 42% of patients died in ≤ 1 hour; median length of time to death varied between sites. **Conclusions:** Standard practice of life support therapy withdrawal appears to differ between the included Canadian sites. Variability in withdrawal of life support therapy may have a potential impact both on rates of DCD success and quality of palliative care.

6.2 INTRODUCTION

The number of patients requiring organ transplantation as a treatment for end stage organ failure is rising in Canada and across much of the globe (3, 46). In contrast, supply of organs remains chronically inadequate (46). Donation after cardio-circulatory death has re-emerged as an opportunity to improve organ availability. Controlled DCD can occur in critically ill patients after a decision to withdraw life-sustaining therapies.

The process of life support therapy withdrawal plays an underlying role in the success of DCD donations. In the period between the start of life support therapy withdrawal and the declaration of death, organs are deprived of adequate oxygenation due to gradual cessation of circulation. Oxygen deprivation of organs during the dying

process can be detrimental to their functionality after procurement, and most DCD protocols call for a focus on minimization of this time period (12, 24). The maximum time acceptable between initiation of life support therapy withdrawal and death is debated, with most protocols setting a cut off of 1 – 2 hours (12, 24, 25). Up to 40% of potential DCD donors fail to successfully donate organs because they die outside this window, a loss both for grieving families and waiting recipients (25). Recent research suggests physiologic characteristics during the dying process may also have direct impact on the functionality of recovered organs (33). The process of life support therapy withdrawal can impact the timing of death as well as the physiologic profile of the donor during the dying period, and has an underlying role in determining DCD success.

Withdrawal of life support therapy is also an important component of quality patient care in the intensive care unit for donors and non-donors. The goal of palliation at the end of life is a "good death" – one without undue suffering and in accord with patient and family values (65). Actions completed during the process of life support therapy withdrawal (removal of life support modalities, increased sedation/analgesia) are done primarily to provide comfort to patients during the dying process. For organ donors, the actions taken during withdrawal of life support therapy have the dual role of providing comfort and influencing DCD eligibility. While administering sedation for pain relief has been deemed ethically acceptable during withdrawal of life support therapy, administering sedatives to achieve successful organ donation has not. Efforts to avoid the perception of hastening death for the purposes of organ donation can lead to changes in how life support therapies are withdrawn in organ donors (20, 47), contributing to prolongation of the dying process and its associated suffering. An exploration of how

quality end of life care can be integrated with optimal DCD eligibility has not yet been undertaken.

Despite its seemingly critical role in DCD donation and for adequate palliation in organ donors, the practical elements of the life support therapy withdrawal procedure remain vaguely explored in the literature. Results of the few observational studies of life support therapy withdrawal practices in non-DCD patients differ substantially in operational definitions used, and the time periods and interventions measured (40-42). Studies of DCD donation processes and DCD protocols focus on measuring, predicting, and reducing oxygen deprivation of organs, but leave applied details of the withdrawal of life support therapy process up to individual practitioners and often do not collect detailed data on the process of withdrawal of life support therapy (63, 64).

The objective of this study was to describe and analyze the actions taken during the process of withdrawal of life support therapy as it occurred in Canadian intensive care units. Specifically, this study 1) described in detail the process of withdrawal of life support therapy as it occurred in participating Canadian adult intensive care unit sites, and 2) explored whether any common pattern of life support therapy withdrawal existed between or within participating sites.

6.3 MATERIALS AND METHODS

6.3.1 The Determination of Death Practices in Intensive Care Units Pilot Study (DDePICt)

The pilot study involved the prospective, continued monitoring of patients undergoing withdrawal of life support therapies in the intensive care unit. Patients' whose families or substitute decision makers consented to their participation had cardiovascular

and respiratory monitoring continued for 30 minutes prior to and 30 minutes following the declaration of death. One site also had neurological monitoring continued during this period. During the process of withdrawal of life support therapy, detailed information was recorded on number, type, dosing, and route of all drugs administered and withdrawn; and timing and method of ventilation withdrawal. A highlighted list of variables collected as part of the pilot study and used for this analysis is presented in Appendix D. Processes of withdrawal of life support therapy were not altered in any way for the study protocol. Only patients who already had the required monitoring devices in place were eligible. Patients who were to become organ donors were not eligible to participate. A total of 5 centers (1 pediatric and 4 adult intensive care units) participated in the pilot study.

6.3.2 Data analysis

Permission was granted from the local research ethics board to use the data collected for the pilot study in a secondary analysis (see Appendix E for copy of ethics board approval letter). Data was available from all 4 participating adult intensive care unit sites. De-identified patient data was obtained in an SPSS dataset, which was modified to exclude all patients < 18 years. Pediatric patients were excluded due to differences in life support therapy withdrawal processes in pediatric intensive care units.

A descriptive analysis was performed using relevant variables; means, medians, and standard deviations were calculated. Univariate comparisons of means were not completed due to small sample size. Data was analyzed along 6 main categories: patient characteristics, artificial airway management, weaning of ventilation, vasoactive drug

weaning, sedation/analgesia, and timing of events. Data was analyzed and compared by site. Timing data was analyzed using Microsoft Excel. All other calculations were done using IBM SPSS© version 20.

Copies of withdrawal of life support therapy protocols were obtained to further explore practice variations between hospitals. Protocols detailing the process of withdrawal of life support therapy were compared along 13 characteristics covering their content, order of steps of withdrawal of life support therapy process, and physical characteristics including document length and use of checklists. A list of characteristics abstracted from each protocol is available in Appendix F.

Statistical significance was not calculated for any comparisons made in this analysis due to the sample size limitations and the descriptive goals of the study.

6.4 RESULTS

A total of 37 patients at 4 adult intensive care unit sites were identified in the dataset as ≥ 18 years. One additional patient was excluded due to missing data (patient died before withdrawal of life support therapy procedures began). A total of 36 adult patients were included in the final analysis (Figure 4).

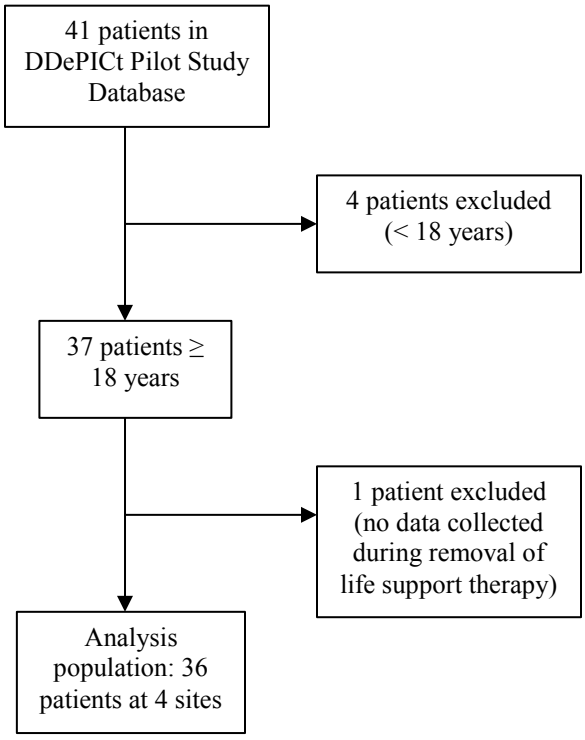

Figure 4 – Flow diagram of patients included for analysis

6.4.1 Patient demographics and characteristics prior to withdrawal of life support therapy

Patients included in the DDePICt pilot study are described in Table 5. Patient age, sex, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores did not seem to differ substantially between sites. Patients' median level of consciousness, measured using the Glasgow Coma Scale, did seem dissimilar between sites. All participating intensive care units were located at university teaching hospitals. Two sites were specialized centers for patients with neurological trauma; the others treat mostly medical and surgical patients.

Table 5: Patient demographics of included patients from DDePICt pilot study

Center #	N	Median age (range), years	Number (%) Male	Median APACHE II score	Median Glasgow Coma Score (range)	Number (%) patients with comorbidity [a]	Median ICU length of stay (days)
1	7	59 (49-64)	4 (57)	27	3 (-)	6 (86)	1.8
2	10	62 (30-85)	6 (60)	28	7 (3-12)	10 (100)	2.0
3	9	69 (36-85)	7 (78)	23	3 (3-10)	8 (89)	7.2
4	10	70 (58-90)	5 (50)	29	4 (3-9)	9 (90)	3.2
ALL	36	64 (30-90)	22 (61)	27	4 (3-12)	33 (92)	2.3

APACHE II, Acute Physiology and Chronic Health Evaluation II score; ICU, intensive care unit.
[a] any chronic pre-existing medical condition as identified by research coordinator

Prior to life support therapy withdrawal, all patients (36, 100%) were endotracheally intubated and mechanically ventilated. No patients had tracheotomies or were supported with non-invasive mechanical ventilation. All patients were administered inspired oxygen (mean FiO_2 range 32-55%). Prior to withdrawal of life support therapy, 12 patients (33%) were administered vasoactive drugs to maintain blood pressure; this ranged from 0% of patients at two sites to 70% of patients at one site (Table 6). Those receiving vasoactive medications had a median of 1 drug infusion. Thirty patients (83%) were administered sedation and/or analgesia just before life support therapy withdrawal. The percentage of patients on any sedation/analgesia just prior to withdrawal of life support therapy varied between sites from 29-100%.

Table 6: Patient management prior to withdrawal of life support therapy

Center #	N	Number (%) on vasoactive drugs	Number (%) on analgesia/sedation	Mean % FiO_2
1	7	0 (0)	2 (29)	35
2	10	7 (70)	10 (100)	40
3	9	5 (56)	8 (89)	55
4	10	0 (0)	10 (100)	32
ALL	36	12 (33)	30 (83)	40

6.4.2 Airway management

Of 36 intubated and mechanically ventilated patients, 27 (75%) were extubated during the withdrawal of life support therapies (Table 7). Fifteen of 27 patients (56%) were extubated immediately at the start of life support therapy withdrawal. Nineteen of 27 extubated patients (70%) had mechanical ventilation and endotracheal tubes withdrawn without any weaning process. Median time to extubation was 0 minutes in 2 of the sites, and ranged from 46 – 60 minutes in the other two study centers.

Table 7: Airway management during withdrawal of life support therapy

Center #	N	Number (%) extubated during life support therapy withdrawal process	Number (%) extubated immediately at start of life support therapy withdrawal process	Median time to extubation (min)
1	7	7 (100)	7 (100)	0
2	10	3 (30)	0 (0)	60
3	9	9 (100)	6 (67)	0
4	10	8 (80)	2 (25)	46
ALL	36	27 (75)	15 (56)	0

6.4.3 Mechanical ventilation and oxygen weaning

Of 36 intubated and mechanically ventilated patients, 15 (42%) had inspired oxygen percentage reduced during life support therapy withdrawal as part of a ventilation weaning process. Patterns of ventilation weaning and extubation (e.g. how inspired oxygen percentage was reduced; whether protected airway was maintained) appeared to vary between sites. Table 8 presents strategies of mechanical ventilation weaning observed during the study.

Table 8: Ventilation weaning during withdrawal of life support therapy

Center #	N	Number (%) had O_2 reduced	Number (%) switched to T-piece	Number (%) extubated without any weaning [a]
1	7	0 (0)	0 (0)	7 (100)
2	10	8 (80)	4 (40)	1 (33)
3	9	1 (11)	0 (0)	8 (89)
4	10	6 (60)	3 (30)	3 (38)
ALL	36	15 (42)	7 (19)	19 (70)

[a] as % of extubated patients

6.4.4 Withdrawal of vasoactive drugs

Twelve patients (33%) had vasoactive drug infusions just prior to the initiation of life support therapy withdrawal. Three of these patients (25%) had the drugs withdrawn immediately at initiation of life support therapy withdrawal. Two study sites weaned vasoactive drugs from the remaining 9 patients, with an average of 2 dose reductions before drugs were completely stopped. Median length of time for weaning vasoactive drugs was 30 minutes at both sites. While one site always weaned vasoactive drugs using at least one step down before cessation, the other site seemed to fluctuate between an abrupt stop and a gradual decrease.

6.4.5 Order of withdrawal of life support modalities

All 12 patients who were receiving vasoactive drugs just prior to the initiation of withdrawal of life support therapy had these drugs withdrawn before or at the same time that mechanical ventilation was removed. One site appeared to withdraw all interventions, including vasoactive drugs and all ventilation/oxygen support, at the start of life support therapy withdrawal. In contrast, another site employed a gradual, staggered withdrawal process (weaning of vasoactive drugs followed by weaning of oxygen and ventilation mode, and finally extubation) for all patients. The remaining two sites utilized

a combination of staggered and simultaneous processes of withdrawal of life support therapy processes.

6.4.6 Administration of analgesia and sedation

Thirty patients (83%) in the pilot study received some form of analgesia/sedation during the process of withdrawal of life support therapy, a number that varied by site (Table 9).

Table 9: Administration of analgesia/sedation during withdrawal of life support therapy

Center #	N	Number (%) given analgesia/sedation	Number (%) had analgesia/sedation increased	Median number of drug increases	Most common drug type administered (% of patients given)
1	7	2 (29)	2 (29)	2	Morphine (100%)
2	10	10 (100)	10 (100)	10	hydromorphone (100%), midazolam (90%)
3	9	8 (89)	5 (56)	4	Morphine (63%), midazolam (63%)
4	10	10 (100)	8 (80)	8	midazolam (80%), fentanyl (70%)
ALL	36	30 (83)	25 (69)	6	midazolam (73%), fentanyl (40%)

Twenty-five patients (69%) who received analgesia/sedation during withdrawal of life support therapy were given increased doses or boluses compared to amounts received prior to life support therapy withdrawal. Median time to first drug increase ranged from 5 to 94 minutes from commencement of life support therapy withdrawal. Drugs most commonly administered were midazolam, given to 22 patients (73%), and fentanyl, given to 12 patients (40%). Morphine was administered to 11 patients (37%) during life support therapy withdrawal. Other drugs administered during life support therapy withdrawal included propofol, given to 2 patients (7%), and lorazepam, given to 1 patient (3%). One

patient (3%) was given a glycopyrrolate injection to reduce secretions. No other drugs were reported as administered during withdrawal of life support therapy. Six patients (17%) did not have analgesia/sedation administered during the process. Five out of these six patients (83%) had severe neurological injuries, all had a GCS score of 3, and 4 (67%) died less than 1 hour after the start of withdrawal of life support therapy. All 6 patients (100%) who did not receive any analgesia/sedation either just prior to or during the process of life support therapy withdrawal died within 2 hours of initiation of this process.

6.4.7 Time to death after initiation of withdrawal of life support therapy

Median time to death for all sites was 1 hour and 51 minutes. Longest time to death was 2 days, 1 hour and 20 minutes, and the shortest was 13 minutes (Table 10). Median times from initiation of life support therapy withdrawal to death varied between sites. Less than half (42%) of all patients died in ≤ 1 hour after the initiation of withdrawal of life support therapy. At 2 hours after commencement of withdrawal of life support therapy, 53% of all patients had died.

Table 10: Time from initiation of life support therapy withdrawal to death

Center #	N	Median time to death, min (h)	Range of times to death, min (h)	Number (%) died in ≤ 1 hour	Number (%) died in ≤ 2 hours	Number (%) died in ≤ 4 hours
1	7	39 (0.5)	13 – 1105 (0.2 – 18.4)	4 (57)	5 (71)	6 (86)
2	10	127 (2.1)	14 – 2960 (0.2 – 49.3)	3 (30)	5 (50)	6 (60)
3	9	67 (1.1)	19 – 825 (0.3 – 13.8)	4 (44)	5 (56)	6 (67)
4	10	390 (6.5)	15 – 1964 (0.3 – 32.7)	4 (40)	4 (40)	4 (40)
ALL	36	111 (1.9)	13 – 2960 (0.2 – 49.3)	15 (42)	19 (53)	22 (61)

6.4.8 Withdrawal of life support therapy protocols

Three of four study centers (75%) used a protocol detailing the process of life support therapy withdrawal for non-donor patients (Table 11).

Table 11: Description of withdrawal of life support therapy protocols

Center #	Has Protocol?	First "Step" in Life Support Therapy Withdrawal Process	"No Drug Limit" Stated	Suggested Drugs	Extubation as Step	Wean of vasoactive drugs outlined	Protocol Length
1	No	--	--	--	--	--	--
2	Yes	Wean vasoactive drugs	Yes	Morphine, midazolam	Yes	Yes	1 page
3	Yes	Discontinue all drugs except sedation	No	Morphine/ fentanyl, midazolam/ lorazepam	Yes	No	2 pages
4	Yes	Increase analgesia/sedation	Yes	Morphine, midazolam/ lorazepam	No	No	1 page checklist + 4 page protocol

One site had a protocol for DCD patients only. This protocol was excluded, as none of the patients enrolled in this pilot study were organ donors. Included protocols varied in their descriptions of what the first action of the life support therapy withdrawal process should be, though all three began withdrawal of life support therapy with a change to patients' drug infusions/doses. Two of three protocols included statements explaining the ethical reasoning for an absence of a dose limit for analgesia/sedation during life support therapy withdrawal. Two of three protocols described specific physical symptoms bedside staff might look for to determine if increases in analgesia/sedation are warranted. While two protocols outlined steps for ventilation withdrawal leading to extubation, one center's protocol left ventilation weaning strategies entirely up to the treating physician.

All three protocols considered the cessation of enteral feeding, laboratory testing, and medical monitoring devices part of the life support therapy withdrawal process. One protocol included an explanation of decision-making and family discussions surrounding withdrawal of life support therapy. Protocols ranged from 1 – 5 pages in total length and featured a combination of checklists and blocks of text.

6.5 DISCUSSION

This analysis of 36 adult intensive care patients enrolled in the DDePICt pilot study provides a unique exploration of withdrawal of life support therapy practices in Canadian intensive care units as they occur in patients who are not organ donors. While previous studies have described general processes of life support therapy withdrawal in adult patients, our analysis included detailed observations relating to the steps of extubation, withdrawal of mechanical ventilation, and administration and weaning of vasoactive drugs and analgesia/sedation.

Observed processes of life support therapy withdrawal involved the cessation of vasoactive drugs, a withdrawal of mechanical ventilation, and increases in analgesia/sedation. The order and degree to which each life support therapy was withdrawn over time differed between sites. In general, vasoactive drugs and mechanical ventilation were withdrawn at a similar time; a pattern identified in surveys of physicians' withdrawal of life support therapy practices (59, 60). The majority (83%) of enrolled patients received some form of analgesia and/or sedation during life support therapy withdrawal, similar to observational studies of comparable populations (39, 50, 51, 53). Types of drug, amounts, and timing of titrations seemed to vary between sites. Just over

half of all patients (53%) died within 2 hours of initiation of withdrawal of life support therapy, consistent with other studies in non-organ donor patients where 28-55% die within 1-2 hours of initiation of life support therapy withdrawal (53, 58). Although there seemed to be a trend between administration of analgesia/sedation and increased time to death, we hesitate to present this data with such a small sample size. Median times from life support therapy withdrawal to death seemed to remain comparable between sites regardless of the pattern of therapy withdrawal. Three out of four sites had protocols outlining the procedures of life support therapy withdrawal for non-donor patients.

While sites appeared comparable in terms of patients' illness severity, sex, and length of stay in the intensive care unit, intensity of patient management prior to life support therapy withdrawal was dissimilar between sites. This may reflect inclusion of neuro-trauma centers in the participating sites. Neurologically injured patients require different approaches to life support therapy due to their hemodynamic stability and need for airway protection (61).

We identified a potential association between administration of analgesia/sedation during life support therapy withdrawal and increased time to death, likely due to confounding by indication. Patients who are more severely ill are less likely to require increased administration of sedation during life support therapy withdrawal due to reduced levels of consciousness. These sicker patients are also more likely to die within a shorter period of time. This finding has been previously identified in several studies observing withdrawal of life support therapy processes (39, 51).

Specific actions of withdrawal of life support therapy appeared to vary between sites. We found contrasting patterns in the degree of staggered versus simultaneous

withdrawal of life support modalities, number and types of drugs used, and methods of ventilation withdrawal. Cook et al. (66) found similar levels of variability between sites in a survey of intensive care unit staff preferences regarding escalation, withholding, and withdrawing of life support therapies for 12 patient scenarios. Keenan et al. (41) also observed variability in length of time from withdrawal of life support therapy to death, and in vasoactive drug weaning strategies between community and teaching hospital intensive care unit sites. Other prospective, multi-center observations of the withdrawal of life support therapy in intensive care units have found variation in the degree to which withdrawal of life support therapy is practiced, but have not examined differences in specific steps of extubation, withdrawal of mechanical ventilation, weaning of vasoactive drugs, and administration of analgesia/sedation (40, 55, 56).

A lack of consistency was also observed between protocols detailing the withdrawal of life support therapy. In this study, 3 of 4 sites used a protocol for life support therapy withdrawal in patients who were not organ donors. Specific steps for airway management, ventilation and vasoactive drug weaning, and administration of analgesia/sedation were different between site protocols. Similarly, Dunne et al. (67) found conflicting practices between guidelines collected at 27 intensive care units in Scotland, of which only 40% had life support therapy withdrawal protocols available.

For a process that is part of standard clinical practice and with implications for the quality of patient care, withdrawal of life support therapy does not appear to be well defined or standardized in terms of intensive care practice guidelines. Variability in the practice of life support therapy withdrawal has a number of potential consequences. Patterns of life support therapy withdrawal likely impact physiologic and hemodynamic

stability of patients during the dying process. According to recent research by Reid et al. (33), physiologic characteristics of patients during life support therapy withdrawal may be a more accurate indication of DCD eligibility than the length of time to death. Variability in withdrawal of life support therapy patterns between sites could therefore differentially impact DCD success and quality of procured organs.

Lack of consistency about what constitutes the process of withdrawal of life support therapy in non-organ donor patients may also leave physicians open to allegations of hastening death in patients who do proceed to DCD. It is difficult to proceed with "standard care" life support therapy withdrawal orders during organ donation when such orders are variable and in some intensive care units may not be clearly stated. From a patient perspective, it is also imperative to provide all patients, including those who go on to donate organs, with the highest quality end of life care. Further research is needed to determine the relationship of certain life support therapy withdrawal patterns to physiologic results in the patient (e.g. hypotension, hypoxia) in order to determine the potential impact of life support therapy withdrawal patterns on DCD eligibility and also on patient experiences at the end of life.

There were limitations to this study including missing information on drug dosing during withdrawal of life support therapies, missing data on whether IV fluids, enteral feeding, dialysis, or laboratory tests were administered, stopped, or withheld, and the small sample size which limited our ability to draw firm conclusions. The small number of patients included per site prevented us from exploring possible variation within sites or determine whether observed differences were statistically significant. In addition, the pilot study did not collect observations of patient comfort and/or suffering during the

dying process, limiting our ability to comment on the social acceptability and quality of deaths resulting from certain patterns of life support therapy withdrawal. Many of these limitations are due to the retrospective nature of this analysis; initial data collection tools and pilot study design did not take into consideration an exploration of questions surrounding the withdrawal of life support therapy process. Future studies should ensure they are adequately powered, and should incorporate objective measures of patient comfort into data collection of life support therapy withdrawal actions to determine whether certain treatment removal patterns are more or less acceptable for patients and families.

6.6 CONCLUSIONS

Variation in life support therapy withdrawal practice appears to exist between 4 Canadian adult intensive care units. Sites approached and completed life support therapy withdrawal processes differently. Median times to death were comparable, but just under half (47%) of all patients died outside the 2 hour maximum window recommended for DCD organ donors. With current variability in airway management, ventilation weaning, and administration of drugs during withdrawal of life support therapies, the practical actions executed during this process are not consistent between sites, leaving room for improvement both for organ donation and end of life care purposes. The impact of life support therapy withdrawal processes on physiologic stability and patient comfort during the dying period requires further exploration if goals of palliation and organ donation are to be optimally aligned for DCD donors.

7.0 COMPARING PATTERNS OF VARIABILITY IN WITHDRAWAL OF LIFE SUPPORT THERAPY PROCESSES BETWEEN REVIEW AND PILOT STUDY DATA

Part I of this thesis project systematically identified published articles describing observational accounts of withdrawal of life support therapy among adult populations of non-organ donors in intensive care units across North America, Europe, and Australia. In the second project, we explored observational data collected during a small pilot study of adult, non-organ donor patients in Canadian intensive care units. Both projects identified variance within the practice of life support therapy withdrawal, with the review in part I highlighting larger country and regional trends while the analysis of pilot study data emphasized variance existing between more closely related locations of practice and between individual patients.

Both explorations of observational data on withdrawal of life support therapy found the time from life support therapy withdrawal to death - a measure critical for DCD donation - to vary and to appear unrelated to patterns of life support therapy withdrawal. While this may seem to point to the irrelevance of withdrawal of life support therapy patterns for DCD donation, a closer consideration of the results show inconsistencies in measurement which may bias conclusions. Definitions of life support therapy withdrawal, including an objective definition of when the process is considered to have begun, are not outlined clearly in almost all observational studies examining this process. In the structured review, definitions of life support therapy withdrawal differed between published studies. In the pilot study, site life support therapy withdrawal protocols revealed inconsistencies in which actions were considered the first steps of withdrawal of life support therapy. The pilot study itself did not outwardly define a process of life

support therapy withdrawal. With withdrawal of life support therapy starting at different times and with different actions measured in almost all observational studies of this process, it is not surprising that time from start of life support therapy withdrawal to death has a large degree of variance and seems to be unrelated to life support withdrawal patterns. Larger studies with clearer operational definitions of life support therapy withdrawal, including the time life support therapy withdrawal is considered to begin, are necessary before firm conclusions about the relationship of withdrawal pattern with time to death can be made.

Results of both the structured review and the analysis of observational pilot study data point to a seemingly wide degree of variance in practice, but neither project considered the potential impacts of this variance. Taking into consideration the degree and type of variance in life support therapy withdrawal process described in parts I and II, we hypothesized that this variance would have considerable potential impact on patients, donors, their families, and healthcare staff. Because variance exists in standard practice for non-donors, and DCD processes of life support therapy withdrawal are recommended to be based on these standard processes, we further hypothesized that any variance in practice for non-donors could also impact processes utilized during DCD donation.

Findings from the review in part I and the analysis of pilot study data in part II were imperative in describing the current variability in life support therapy withdrawal practice and providing detailed examples of actual cases of withdrawal of life support therapy. With the third part of this thesis project we aimed to identify and explore how variance in the process of withdrawal of life support therapy may impact different

participants in end of life care for both donors and non-donors, and to explore how consistency in practice may improve outcomes for all stakeholders.

8.0 PART III - OPTIMIZATION OF ORGAN DONATION OR PATIENT CARE? AN EXPLORATION OF OUTCOME GOALS DURING THE WITHDRAWAL OF LIFE SUPPORT THERAPY IN DCD PATIENTS

8.1 ABSTRACT

Background: Donation after cardio-circulatory death has recently been considered more regularly as a method of organ procurement. The process can take place after a controlled withdrawal of life support therapy in the intensive care unit, a process already commonly undertaken in cases where the family and care team have made a decision of medical futility. Withdrawal of life support therapy has been mostly well accepted by society, though the physical process of life support therapy withdrawal remains highly variable. Inconsistencies in how this process is carried out may raise ethical and practical concerns in situations where organ donation is an additional desired outcome. Variability in the practice of life support therapy withdrawal has been described, but an exploration of whether variability in standard practice is amenable to the goals of organ donation has not been completed. This analysis paper explores whether goals of life support therapy withdrawal in standard care and in cases of organ donation can be aligned, and also considers whether consistency in all cases of life support therapy withdrawal should be attempted in critical care. **Results:** Three components of withdrawal of life support therapy were identified: the physical life support therapy withdrawal process, the role of healthcare professionals, and the expectations of patients and families. While withdrawal of life support therapy in standard care had outcome goals of achieving a good "pain

free" death, a switch from curative to comfort care, and acceptable, quality end-of-life care consistent with patient/family values, situations of DCD organ donation had additional goals of optimal organ functionality and a switch from patient to donor care. **Discussion/Conclusions:** Variability in standard care practice influenced all outcome goals of life support therapy withdrawal for both standard care and donors. Based on identified goals, consistency in how the process of life support therapy withdrawal is defined and carried out has the potential to improve both standard care and DCD donation outcomes. Alignment of goals between DCD and standard care withdrawal of life support therapy is possible if currently variability in practice is addressed.

8.2 INTRODUCTION

In the past decade organ donation programs have renewed their interest in donation after cardio-circulatory death as a possible means of improving the insufficient organ supply. Controlled DCD can occur when a decision is made to withdraw life support therapies from patients with severe neurological injuries. DCD extends the opportunity for organ donation to critically ill patients previously excluded based on stringent criteria for donation after brain death. DCD programs have expanded across much of the western world and have helped increase numbers of available organs (9, 68).

Patients are potentially eligible for DCD if they are critically ill and their treating physician and family members have decided to withdraw further medical treatments. Patients are only fully eligible for donation after a controlled withdrawal of life support therapy has been completed and death is pronounced within a required time limit (usually 1-2 hours). Withdrawal of life support therapy is a common medical practice in the

intensive care unit. The process involves removal of medications, oxygen support, airway protection, and other interventions considered unnecessary given a decision to change goals of patient care to comfort rather than cure. Withdrawal of life support therapy is part of palliative care and also involves the administration of analgesic and sedative medications for patient comfort during the dying process.

Although removal of life support therapies may appear simple, the order and rate at which interventions are withdrawn contributes to different, and possibly more or less painful patterns of death. Mechanical ventilation, for example, can either be withdrawn all at once (called "terminal extubation"), or it can be gradually removed in a series of reductions known as "terminal weaning" (69). The past ten years have seen arguments from both sides as to which method is best for reducing discomfort and which is most relevant for achieving patient and family goals of life support therapy withdrawal. While extubation has been described as more "aesthetically pleasing" and comforting for families, it is also associated with more signs of respiratory distress (69, 70). Arguments for terminal weaning focus on the extra time provided during the process, allowing physicians to observe patients and appropriately increase analgesics and sedatives as respiratory distress gradually increases (71). Some see terminal weans as an unnecessary prolongation of the patient's life and as giving false hope of success to distressed families (36). In practice, physicians continue to vary in their preference for either method (67).

Another highly varied practice in the process of life support therapy removal is the order in which interventions are withdrawn. Whether to remove mechanical ventilation before the titration of vaso-active drugs or vice versa could influence the patient's final life experiences. The dosing and timing of drugs as medical interventions

are withdrawn will contribute to both patients' and families' comfort. All of these details have the added potential of contributing to the timing (either hastening or prolonging) of the patient's death (53).

Timing and methods for removing or weaning medical interventions continue to differ widely (72). Specific actions taken during the withdrawal of life support therapy as part of standard care have not been well explored in the literature, and though recommendations have been made for best practices (35), the process of withdrawal of life support therapy has not been standardized. Published accounts of observed withdrawal of life support therapy processes reveal a wide degree of variation within usual care practice in terms of the order and timing of therapy withdrawal. Processes of life support therapy withdrawal vary between countries, hospitals, and treating care teams (39-41).

The absence of a clear "standard of care" withdrawal of life support therapy process is of particular concern for cases of DCD organ donation. Variability in life support therapy withdrawal affects the time and place of patients' deaths, the quality of deaths, and whether or not patients are able to become organ donors (7). Additionally, national guidelines for DCD highlight the ethical and moral importance of maintaining a boundary between palliative care of the dying patient and optimization of the organ donor (12). DCD protocols request treating physicians follow existing "standard practice" for the withdrawal of life support therapies prior to organ procurement, and underline that withdrawal of life support processes should not be influenced by donation status (12). But without a clear understanding of what constitutes "standard practice" of life support therapy withdrawal in non organ-donor patients, how can we ensure that practices remain

the same for DCD patients? Additionally one may question whether standard practice life support therapy withdrawal should be followed during DCD, since changes in how life support therapy is withdrawn may improve numbers of successful donations. The overlap in goals between palliative care patient management and donor management has not been explored extensively in the current literature.

The following analysis paper will identify and examine goals of withdrawal of life support therapy for non-donor patients versus DCD donors. We will attempt to answer two questions: 1) Given the current variability in standard care practice of withdrawal of life support therapy, can goals of life support therapy withdrawal in standard care and for DCD patients be aligned, and 2) How will aligning these goals improve outcomes for participants in patients' and donors' end of life care?

8.3 METHODOLOGY

We conducted a scoping literature review to identify key concepts and goals of life support therapy withdrawal in both non-donor and DCD patients. Input was also solicited from physicians and experts in the field of DCD and organ donation. We grouped resulting outcome goals of life support therapy withdrawal under three components of the process of life support therapy withdrawal that they related to. Analysis of the outcome goals was based on the literature and on a consideration of DCD and withdrawal of life support therapy within the larger context of critical care medicine.

8.4 RESULTS

From the literature review, we created three key "components" of life support therapy withdrawal: the physical process of life support therapy withdrawal, the role of healthcare professionals, and the goals and expectations of patients and families. Each of these components was related to an outcome goal of the life support therapy withdrawal process (presented in Figure 5). The outcome goals of life support therapy withdrawal seemed similar between non-donor and DCD patients, except that in cases of DCD additional outcome goals were present. The central outcome goal for both donors and non-donors during life support therapy withdrawal was to meet expectations and goals of patients and families.

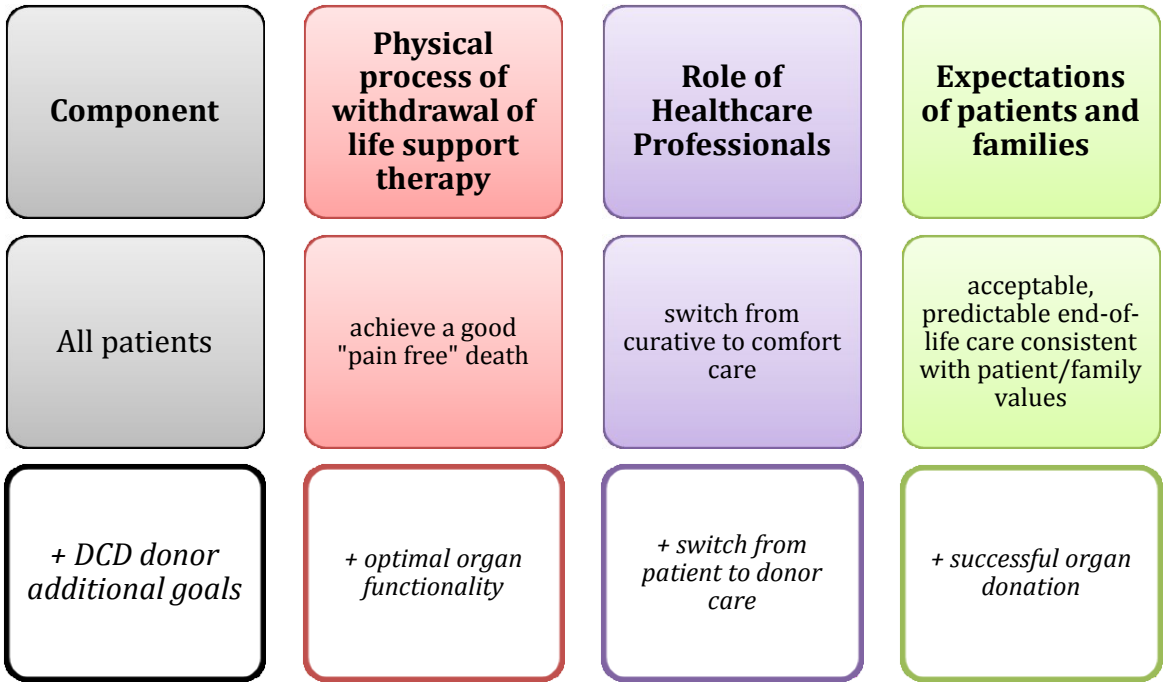

Figure 5 – Framework of components of withdrawal of life support therapy

We found that variability and uncertainty in the process of withdrawal of life support therapy impacted standard care for non-donors. Because the outcome goals of life

support therapy withdrawal for non-donor patients are included within the outcome goals of life support therapy withdrawal components for DCD patients, variability in practice for non-donors has the potential to directly impact outcome goals for donors. This continued impact of variability was identified for all three components of life support therapy withdrawal.

8.4.1 Physical process of withdrawal of life support therapy

The physical process of withdrawal of life support therapy was identified as an important component for both non-donor patients and DCD patients. For non-donors, the goal of the process of life support therapy withdrawal is to ensure a pain-free death (35, 36, 72). This is done by careful titration of analgesic and sedative medications ("comfort medications") as life support modalities are withdrawn. General consensus on the importance of pain relief for critically ill patients at the time of death allows physicians to prescribe increased doses of comfort medications as necessary, even if these doses could hasten death (35, 73). Removing potential sources of pain and discomfort, such as feeding tubes and monitoring lines, is another important step for providing a comfortable death (35). The best order and method for removing medical interventions to relieve pain has not been determined. Debate continues as to whether a short or long ventilator weaning process or immediate extubation is best for patient comfort (73, 74). A wide degree of variability in life support therapy withdrawal processes continues to exist in practice for patients who are not organ donors (40-42, 72). Observational studies of life support therapy withdrawal have shown that despite physicians' and families' best intentions, "non-clinical and potentially irrelevant factors" may play more of a role in

determining how to physically withdraw life support therapy than has been previously considered (75). A lack of consistent method for meeting goals of a pain-free death may leave the life support therapy withdrawal process open to increased influence from non-clinical biases and could lessen the quality of death for these patients.

An additional goal for the process of withdrawal of life support therapy for DCD patients is to ensure death with the highest quality of procurable organs. During the dying process, organs are slowly deprived of oxygen while blood pressure decreases; length of the dying process is inversely related to organ quality. If substantial, ischemic damage suffered during withdrawal of life support therapies can render organs unusable for transplantation. The goals for the physical process of life support therapy withdrawal for DCD patients, then, are centered on minimizing this damage and ensuring optimal organ functionality. Since ischemic organ damage cannot be measured directly, proxy measures of potential damage are used. One such measure is the time from start of life support therapy withdrawal to death. Most DCD protocols recommend that declaration of death occur within 1-2 hours of the initiation of life support therapy withdrawal for organs to be used (12, 76). Patients who die outside of this window are no longer eligible for organ donation. Newer research suggests that hemodynamic stability during life support therapy withdrawal may also be a marker of procured organ functionality (25, 77). The best order and timing of life support therapy withdrawal to ensure death within 1-2 hours and optimal hemodynamic stability has not been determined. Some research points to the importance of method of life support therapy withdrawal for time to death (63) while other researchers have found life support therapy withdrawal patterns make no difference (47). Publications in this field are limited and heterogeneity in definitions of withdrawal

of life support therapy prevents meta-analytic review. To meet goals of ideal organ functionality, many DCD protocols recommend the administration of anti-coagulants during withdrawal of life support therapy (24, 68, 76). Additional pre-mortem interventions may also be performed prior to or during the withdrawal of life support therapies, including administration of additional drugs to improve organ perfusion and insertion of catheters used after death for infusion of preservation fluids (24, 76, 78). Variability also exists in DCD protocols; sites differ in methods of ventilation withdrawal and number of pre-mortem interventions administered (68).

8.4.2 Role of healthcare professionals

Healthcare professionals working in the intensive care unit play a significant role in the withdrawal of life support therapies; they participate and guide decision-making, complete the process of life support therapy withdrawal and are also responsible for ensuring that goals of life support therapy withdrawal are met. For non-donor patients, the process of life support therapy withdrawal requires healthcare professionals to switch from a role of curing disease to one of providing a "good death" (36). The change in focus from cure to comfort may prove difficult for some healthcare workers in an environment where lifesaving measures, not palliative care, is usually the primary aim at patients' admission. Without a consistent recommendation for best practices in life support therapy withdrawal, healthcare workers may become unsure about which processes to perform as part of the highest standard of care. As an example, a tendency to under treat pain in dying patients may be present due to the fear of hastening death, despite principles of double effect that remove this responsibility (79). Physicians'

challenges with the move from curative to palliative care have been evidenced by a tendency for some to prolong the dying process during life support therapy withdrawal and to remove interventions based on personal bias (59, 70, 80). Self-reported satisfaction with the life support therapy withdrawal process varies between nurses, physicians, and other allied health professionals (43, 81). In one study, undefined care roles and other challenges with the shift in goals of care resulted in conflict in 78% of decisions made regarding end of life care in critically ill patients (82). Pressures from patient's family members and fear of being perceived as hastening death may influence nursing practice during this change from cure to comfort (43, 44).

For DCD organ donors, healthcare workers additionally shift their role from patient care to donor care during the withdrawal of life support therapies. This shift may require administration of pre-mortem interventions and additional preparations during the process of life support therapy withdrawal. Surveys of staff in the intensive care unit suggest healthcare workers may be uncomfortable with this shift in care roles (11, 19, 83). Part of this shift may also require healthcare workers to modify their usual bedside setting of care to the operating room, which can lead to conflict between care teams (84, 85). Some institutions have attempted to alleviate this conflict by having anesthesiologists and surgical nurses perform the withdrawal of life support therapy for DCD patients (85), introducing stress both for the original care team who can no longer follow up with their patient, and additional stress on operating room teams not experienced with withdrawal of life support therapy (84). Additionally, asking the operating room staff that will procure the organs to withdraw life support therapy for DCD patients introduces significant conflict of interest into the donation process. Though

many healthcare professionals appear to support DCD protocols (83), some continue to express concern over the uncertainty involved in the switch from patient to donor care (15, 19, 85).

8.4.3 Expectations of patients and families

Perceptions and expectations of patients and families play a significant role in life support therapy withdrawal processes for both donor and non-donor patients. Since the determination of whether a patient has achieved a good death is entirely subjective, outcome data on quality of end of life care often comes from patient's families (65, 72). Families appear to have similar goals for the process of life support therapy withdrawal in both non-donor and DCD patients: they wish to have end of life care completed in a manner consistent with patient and family values, and in a way that meets patient goals (86-88). For non-donor patients, these goals of a good, pain free death can be met when the process of life support therapy withdrawal is clearly explained (89), and the order and location of life support therapy withdrawal is in agreement with patient and family wishes (73).

Expectations of families for a good, pain free death may not be met as often in DCD patients if the process is not clearly explained and family members cannot predict what will happen to their loved one during the process of life support therapy withdrawal (17). Requiring consent for pre-mortem interventions of no benefit to the patient can be concerning for family members who understand withdrawal of life support therapy to be a process of removing unnecessary interventions (87). For DCD patients, an additional patient/family goal is the successful donation of organs after the process of life support

therapy withdrawal. Families' perceptions of whether the patient had a good death may be impacted if the patient fails to die within the required time limit. In one study, families expressed concern that their loved ones would go through pre-mortem interventions and a different life support therapy withdrawal process "for no reason" if organs were found to be unusable (17). Ensuring adequate information is provided to families of organ donors remains an unmet challenge for DCD protocols (90, 91).

8.4.4 Potential benefits of aligning donor and non-donor outcome goals in withdrawal of life support therapy

Current variability in the practice of withdrawal of life support therapy has potential detrimental effects on patient-important outcomes for both DCD donors and non-donor patients. Alignment of goals between these two patient groups and subsequent adoption of a consistent operational process of withdrawal of life support therapy could therefore result in a number of improvements for donation and standard intensive care practice.

The physical process of withdrawal of life support therapies is crucial for maintaining patient comfort and achieving a good, pain free death. Current variability in practice of life support therapy withdrawal for both usual care and organ donor patients raises concerns about whether this goal is consistently being met for all patients. A consistent and common understanding of what should constitute life support therapy withdrawal would help to ensure that goals of pain free death are being met for all patients.

For healthcare workers, a common life support therapy withdrawal pathway may help to alleviate the moral distress that can be experienced at the interface between

patient and donor care. Healthcare workers may find caring for DCD donors morally and ethically challenging when they perceive that end of life care and patient wishes are compromised by the donation process (19, 83, 92). Outlining a consistent process of what is to occur during the process of withdrawal of life support therapy for all patients, as well as outlining the roles of healthcare professionals for meeting patient goals (whether of a pain-free death, organ donation, or both) may help to lessen moral distress and improve uptake of DCD protocols (85).

Finally, and perhaps most importantly, setting a consistent definition of the life support therapy withdrawal process for all patients provides a statement to patients and families that end of life care will not be compromised during organ donation. A clear outline of what is to take place during the withdrawal of life support therapy process for both organ donors and usual care patients will help to gain public trust in DCD protocols (83), and help to ensure patient/family goals of life support therapy withdrawal are met. Up to 40% of all potentially eligible donors fail to die within the required time window for organ donation eligibility (25). For these patients, additional goals of organ donation will be removed part way through the process of withdrawal of life support therapies. If we ensure that the process of life support therapy withdrawal is consistent for both donors and non-donors, a change in goals part way through the dying process will be less likely to impact the perceived quality of end-of-life care (18). Improving perceptions and acceptance of DCD by families also has an impact on other components of life support therapy withdrawal. Healthcare professionals may be more comfortable with their role change from patient to donor care if this shift has been clearly explained, understood, and accepted by patient's families (83). In addition, consent for pre-mortem interventions to

improve organ functionality may be easier for families if they are assured that aside from additional infusions, quality and practices of life support therapy withdrawal will remain consistent with those of usual care provided for non-donor patients.

8.5 DISCUSSION

This review has highlighted three major components of the withdrawal of life support therapy process that appear to differ between DCD donor and non-donor patients. While the goals of life support therapy withdrawal for non-donors are a component of care for organ donor patients, DCD protocols may impose additional goals during end of life care. At times, these additional goals may contradict goals for non-donors. For the physical process of life support therapy withdrawal, care goals for non-donors are to achieve a good, pain-free death. In DCD patients, there is an additional goal of preserving optimal organ function. In this case, administration of pre-mortem interventions for the achievement of optimal organ function may contradict the goal of a pain-free death. Healthcare professionals must make a shift during life support therapy withdrawal from curative to comfort care. For DCD patients, an additional shift from patient to donor care must also be made during this time. Finally, expectations of patients and families play a considerable role in determining whether goals of life support therapy withdrawal have been met. Patient and family expectations appear to be similar for both donors and non-donors, though for DCD donors families also wish to see their loved ones successfully donate organs. Alignment of the process of life support therapy withdrawal to ensure its consistent application for both donors and non-donors appears possible given the

observation that all goals of withdrawal of life support therapy for usual care are contained within the goals of withdrawal of life support therapy for DCD patients.

The question remains, should we attempt to align these goals and ensure a consistent process of life support therapy withdrawal for both non-donor patients and DCD organ donors? Some have argued that withdrawal of life support therapy should be an individualized process and should depend on the patient and family's wishes (93). Resistance to standardization of the life support therapy withdrawal process also centers around the idea that differences in patient characteristics and severity of illness at the end of life make formulation of a common process impossible (73, 93). The standardization of many medical procedures has been met with resistance and the fear of loss of the essential intuitive skill of medicine (94). Despite this, standardized protocols for ventilation weaning and patient sedation, areas closely related to processes commonly done as part of life support therapy withdrawal and also highly correlated to severity and complexity of patient illness, have been well accepted in adult intensive care units (95-97). Implementation of protocols and care pathways for these areas of clinical care has helped healthcare professionals, especially nurses, to feel confident they are carrying out processes safely and in adherence with best practices (95). While past experience with standardized order forms for life support therapy withdrawal did not seem to change perceived quality of death for non-donor populations (98), our findings suggest several ways in which consistency in the process of withdrawal of life support therapy may improve outcomes for each component. Our findings further suggest that these improvements may be beneficial to both non-donors and patients who are DCD donors.

Alignment of life support therapy withdrawal processes between donors and non-donors will require clearer definitions of life support therapy withdrawal processes and a reduction in the current degree of variability in practice for usual care in non-donor patients. Evidence-based recommendations for optimal processes of life support therapy withdrawal are necessary to ensure that goals are met in all three components of life support therapy withdrawal and that all participants: patients, families, donors, and healthcare professionals, are satisfied. Without a move towards a more comprehensive definition and common picture of what withdrawal of life support therapy encompasses, current levels of variability will continue to negatively influence outcomes of withdrawal of life support therapy processes for both non-donors and DCD patients.

8.6 CONCLUSIONS

Goals for withdrawal of life support therapy for DCD patients incorporate the goals of life support therapy withdrawal for usual care, the role of the health care staff, and expectations of the family along with additional goals for optimal organ functionality and successful donation. An alignment of life support therapy withdrawal processes for donors and processes for non-donors is therefore possible and may be additionally beneficial for a number of reasons. Most importantly, a commitment to consistency of processes between donors and non-donors may help to increase public and healthcare worker trust in DCD protocols and set a moral precedent that donors and non-donors will receive the same quality of end of life care. Clearer empirical definitions and outlines of what should occur during standard withdrawal of life support therapy practice is necessary before a practical alignment of goals and processes can occur.

9.0 FINAL THESIS CONCLUSIONS

Our a priori goals with this thesis project were to identify a common pattern of withdrawal of life support therapy and then consider whether this conventional process satisfied the "dead donor rule", was useful for predicting DCD eligibility, and ensured adequate organ functionality for procured organs. While we were unable to distinguish any one common pattern of life support therapy withdrawal within our results, we did highlight a vast degree of variability in a process that has not previously been extensively considered in the current literature. As we explored this resulting variability further, we discovered that inconsistencies in the process of withdrawal of life support therapy had a large potential impact on patient care and outcomes for both DCD donors and non-donors in the intensive care unit. Our exploration of outcome goals in withdrawal of life support therapy described how variability in life support therapy withdrawal practice affects quality of death and quality of organs procured, perceptions and practice of healthcare professionals, and expectations and satisfaction of families. We also presented how a reduction in variation might positively improve outcomes for both DCD donors and non-donors and could lead to improved uptake of DCD donation protocols.

The current variability in practice we identified prevented us from concretely answering the concerns we initially established regarding the withdrawal of life support therapy process for DCD donors. We were unable to show a clear common pattern of life support therapy withdrawal and thus unable to comment on whether current intensive care unit practice can satisfy a clear separation of patient and donor care as recommended through the "dead donor rule". As DCD becomes a cornerstone of deceased organ donation, the possibility for withdrawal of life support therapy processes to be

increasingly influenced by goals of organ donation may become more likely. While future research could eventually deem the standardization of withdrawal of life support therapy impossible, it is nonetheless important for the medical community to be open with patients, families, and those in the medico-legal field about the current variability in end of life care practices, and the resulting potential for overlap in withdrawal of life support therapy goals between donors and non-donors.

Though our limited data seemed to show no association between withdrawal of life support therapy pattern and time to death, again, lack of consistency between definitions and measurements in all studies made this a weak conclusion worthy of further investigation. It also highlighted the need for consistent definitions of withdrawal of life support therapy processes in order for future research studies to be comparable.

Despite the remaining knowledge gap with regard to withdrawal of life support therapy in the intensive care unit, we conclude from our results that optimization and potential standardization of this process could have widespread benefits in the intensive care unit. We found that patients' families and healthcare staff expressed uncertainty and concern regarding end of life care processes, including the process of withdrawal of life support therapy, for both potential DCD donors and non-donor patients. Concerns for families were primarily regarding a fear that life support withdrawal processes would be inadequate, or somehow modified for donors versus non-donor patients. For health care staff, concerns centered around a fear of being perceived as hastening death, especially during the withdrawal of life support therapy process in potential donors. Given the current variability identified in standard withdrawal of life support processes in the intensive care unit, these concerns may be well founded since many different withdrawal

of life support therapy patterns seem accepted as part of usual care. We hypothesize that a clear statement of a common definition of withdrawal of life support therapy and empirically based guidelines to be used for both donors and non-donors in the intensive care unit will assuage these concerns and could help to improve the uptake of DCD protocols at additional sites. Through this thesis project we conclude that further research on optimal withdrawal of life support therapy processes is necessary if these potential gains are to be realized.

10.0 SIGNIFICANCE AND FUTURE DIRECTIONS

Results from this project help to provide a background estimation of the variation in withdrawal of life support therapy practice for non-organ donors in the western world. This information provides a useful baseline for future research examining the process of withdrawal of life support therapy in non-donor patients in the intensive care unit. Baseline information on this subject may be useful for future research aiming to improve end-of-life care or identify areas of practice in the withdrawal of life support therapy process that can be improved.

This project has been the first to highlight the process of withdrawal of life support therapies in adult, non-donor intensive care unit patients. While individual studies have described the process, the review completed as part of this project was the first to collect and summarize similar articles. When presented together, the variability in practice and potential for overlap with DCD processes becomes more evident.

As part of this project, data collected during the Determination of Death Practices in Intensive Care Units Pilot study was analyzed. The pilot study was the first to collect

detailed physiologic data on withdrawal of life support therapy in Canada, and the secondary analysis completed in this thesis presents the first detailed description of life support therapy withdrawal processes in Canadian adult intensive care units. While this study had limited power to detect significant differences between sites, the secondary analysis of descriptive data on withdrawal of life support therapy highlighted trends of variability across centers and identified questions of interest for further research in Canadian intensive care unit practice.

The exploration of goals of life support therapy withdrawal and comparison between usual care and DCD donation will be useful to the transplant community as well as the ethics community for continuing the discussion about the current potential for overlap between the goals of life support therapy withdrawal and the goals of DCD practices. Further research and input from intensive care unit and transplant communities are necessary before a decision can be made as to whether the process of life support therapy withdrawal should be consistent for all patients. This discussion is especially pertinent at this time where increasing recommendations are made for the initiation of DCD in greater numbers of intensive care unit patients due to our inability to accurately predict time to death.

Findings from this project are being integrated into the design of the larger Death Prediction and Physiology after Removal of Therapy (DePPaRT) Study, which has recently received funding as part of the Canadian Institute for Health Research funded Canadian National Transplant Research Program (CNTRP). Part of the objective for the larger, multicenter, observational trial will be to examine patterns of life support therapy withdrawal and determine how they relate to time to death. As part of this study,

outcomes of life support therapy withdrawal will be measured in a more systematic manner, and findings from the final analysis paper of this thesis project will be taken into account when considering which variables will be collected.

12.0 REFERENCES

1. Delmonico FL, Dominguez-Gil B, Matesanz R, Noel L. A call for government accountability to achieve national self-sufficiency in organ donation and transplantation. Lancet. 2011;378: 1414-1418.
2. Riemer V. Organ donors still scarce. [podcast on the Internet]. World Health Organization; 2010 [cited 2013 Feb 10]. Available from: http://www.who.int/mediacentre/multimedia/podcasts/2010/organ_transplants_20100806/en/
3. DeVita MA, Snyder JV, Grenvik A. History of organ donation by patients with cardiac death. Kennedy Inst Ethics J. 1993;3(2): 113-129.
4. Organ Donation [Internet]. Toronto: Trillium Gift of Life Network; [cited 2012 Mar 12]. Available from http://www.giftoflife.on.ca/en/transplant.htm
5. Heyland DK, Lavery JV, Tranmer JE, Shortt SE, Taylor SJ. Dying in Canada: is it an institutionalized, technologically supported experience? J Palliat Care. 2000;16 Suppl: S10-6.
6. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. Am J Respir Crit Care Med. 1997;155(1): 15-20.
7. Rocker GM, Cook DJ, Shemie SD. Brief review: Practice variation in end of life care in the ICU: Implications for patients with severe brain injury. Can J Anesth. 2006;53(8): 814-819.
8. Halpern SD, Barnes B, Hasz RD, Abt PL. Estimated supply of organ donors after circulatory determination of death: A population-based Cohort study. JAMA. 2010;304(23): 2592-2594.
9. Hernadez-Alejandro R, Wall W, Jevnikar A, Luke P, Sharpe M, Russell D et al. Organ donation after cardiac death: Donor and recipient outcomes after the first three years of the Ontario experience. Can J Anaesth. 2011;58(7): 599-605.
10. Moser M, Sharpe M, Weernink C, Brown H, McGregor T, House AA et al. Five-year experience with donation after cardiac death kidney transplantation in a Canadian transplant program: Factors affecting outcomes. Can Urol Assoc J. 2012;6(6): 448-452.
11. D'Alessandro AM. The process of donation after cardiac death: a US perspective. Transplant Rev. 2007;21(4): 230-236.
12. Shemie SD, Baker AJ, Knoll G, Wall W, Rocker G, Howes D et al. National recommendations for donation after cardio-circulatory death in Canada: Donation after cardiocirculatory death in Canada. CMAJ. 2006;175(8 Suppl): S1-S24.
13. Steinbrook R. Organ Donation after Cardiac Death. NEJM. 2007;357 (3): 209-213.
14. Howard RJ, Schold JD, Cornell DL. A 10-year analysis of organ donation after cardiac death in the United States. Transplantation. 2005;80(5): 564-568.
15. Csete M. Editorial: Donation after cardiac death and the anesthesiologist. Anesth Analg. 2010;110(5): 1253-1254.
16. Doshi MD, Hunsicker LG. Short- and Long-Term Outcomes with the Use of Kidneys and Livers Donated after Cardiac Death. Am J Transplant. 2007;7: 122-129.
17. Sque M, Long T, Payne S, Allardyce D. Why relatives do not donate organs for transplants: 'Sacrifice' or 'gift of life'? J Adv Nurs. 2008;61(2): 134-144.

18. Rady MY, Verheijde JL, McGregor J. Organ donation after circulatory death: The forgotten donor? Crit Care. 2006;10(5):166.
19. Mandell MS, Zamudio S, Seem D, McGaw LJ, Wood G, Liehr P et al. National evaluation of healthcare provider attitudes toward organ donation after cardiac death. Crit Care Med. 2006;34(12): 2952-2958.
20. Youngner SJ, Arnold RM. Ethical, psychosocial, and public policy implications of procuring organs from non-heart-beating cadaver donors. JAMA. 1993;269(21): 2769-2774.
21. Evans DW. Seeking an ethical and legal way of procuring transplantable organs from the dying without further attempts to redefine human death. Philos Ethics Humanit Med. 2007;2(1):11.
22. Joffe AR. The ethics of donation and transplantation: Are definitions of death being distorted for organ transplantation? Philos Ethics Humanit Med. 2007;2(1).
23. Rady MY, Verheijde JL, McGregor J. Organ procurement after cardio-circulatory death: A critical analysis. J Intensive Care Med. 2008;23(5): 303-312.
24. Bernat JL, D'Alessandro AM, Port FK et al. Report of a national conference on donation after cardiac death. Am J Transplant. 2006;6(2): 281-291.
25. Bradley JA, Pettigrew GJ, Watson CJ. Time to death after withdrawal of treatment in donation after circulatory death (DCD) donors. Curr Opin Organ Transplant. 2013;18(2): 133-139.
26. Neyrinck A, Van R, D., Monbaliu D. Donation after circulatory death: Current status. Curr Opin Anaesthesio. 2013;26(3): 382-390.
27. Davila D, Ciria R, Jassem W, Briceño J, Littlejohn W, Vilca-Meléndez H et al. Prediction models of donor arrest and graft utilization in liver transplantation from maastricht-3 donors after circulatory death. AmJ Transplant. 2012;12(12): 3414-3424.
28. Rabinstein AA, Yee AH, Mandrekar J, Fugate JE, de G, Y.J., Kompanje EJO et al. Prediction of potential for organ donation after cardiac death in patients in neurocritical state: A prospective observational study. Lancet Neurol. 2012;11(5): 414-419.
29. Wind J, Snoeijs MGJ, Brugman CA, Vervelde J, Zwaveling J, Van M, W.N. et al. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. Crit Care Med. 2012;40(3): 766-769.
30. Lewis J, Peltier J, Nelson H, Snyder W, Schneider K, Steinberger D et al. Development of the University of Wisconsin Donation after Cardiac Death Evaluation Tool. Prog Transplant. 2003;13(4): 265-273.
31. Rady MY, Verheijde JL. Prediction of time to death after terminal withdrawal of life-support in non-heartbeating organ donation: Unaccounted variables and window of opportunity. Crit Care Med. 2012;40(3): 986-988.
32. Levvey BJ, Westall GP, Kotsimbos T, Williams TJ, Snell GI. Definitions of warm ischemic time when using controlled donation after cardiac death lung donors. Transplantation. 2008;86(12): 1702-1706.
33. Reid AWN, Harper S, Jackson CH, Wells AC, Summers DM, Gjorgjimajkoska O et al. Expansion of the kidney donor pool by using cardiac death donors with prolonged time to cardiorespiratory arrest. Am J Transplant. 2011;11(5): 995-1005.

34. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Willingham DL, Kramer DJ et al. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl Int. 2012;25(8): 838-846.
35. Truog RD, Campbell ML, Curtis R, Haas CE, Luce JM, Rubenfeld GD et al. Recommendations for end-of-life care in the intensive care unit: A consensus statement by the American College of Critical Care Medicine. Crit Care Med. 2008;36 (3): 953-963.
36. Truog RD, Cist AFM, Brackett SE, Burns JP, Curley MAQ, Danis M et al. Recommendations for end-of-life care in the intensive care unit: The ethics committee of the society of critical care medicine. Crit Care Med. 2001;29(12): 2332-2348.
37. Luce JM, White DB. A History of Ethics and Law in the Intensive Care Unit. Crit Care Clin. 2009;25(1): 221-237.
38. Schuklenk U, van D, Johannes J M, Downie J, McLean SAM, Upshur R, Weinstock D. End-of-life decision-making in Canada: the report by the Royal Society of Canada expert panel on end-of-life decision-making. Bioethics. 2011;25 Suppl 1: 1-73.
39. Chan JD, Treece PD, Engelberg RA, Crowley L, Rubenfeld GD, Steinberg KP et al. Narcotic and benzodiazepine use after withdrawal of life support: Association with time to death? Chest. 2004;126(1): 286-293.
40. Ferrand E, Robert R, Ingrand P, Lemaire F. Withholding and withdrawal of life support in intensive-care units in France: A prospective survey. Lancet. 2001;357(9249): 9-14.
41. Keenan SP, Busche KD, Chen LM, Esmail R, Inman KJ, Sibbald WJ. Withdrawal and withholding of life support in the intensive care unit: A comparison of teaching and community hospitals. Crit Care Med. 1998;26(2): 245-251.
42. White AC, Joseph B, Gireesh A, Shantilal P, Garpestad E, Hill NS et al. Terminal withdrawal of mechanical ventilation at a long-term acute care hospital: Comparison with a medical ICU. Chest. 2009;136(2): 465-470.
43. Puntillo KA, Benner P, Drought T, Drew B, Stotts N, Stannard D et al. End-of-life issues in intensive care units: A national random survey of nurses' knowledge and beliefs. Am J Crit Care. 2001;10(4): 216-229.
44. Sjokvist P, Berggren L, Cook DJ. Attitudes of Swedish physicians and nurses towards the use of life- sustaining treatment. Acta Anaesthesiol Scand. 1999;43(2): 167-172.
45. Canadian Institutes of Health Research. Harper Government supports Canadian National Transplant Research Program [news release on the Internet]. 2013 Apr 22 [cited 2013 Jul 08]. Available from: http://www.cihr-irsc.gc.ca/e/46632.html.
46. Rudge C, Matesanz R, Delmonico FL, Chapman J. International practices of organ donation. Br J Anaesth. 2012;108(SUPPL. 1): i48-i55.
47. Revelly J-P, Imperatori L, Maravic P, Schaller M-D, Chiolero R. Are terminally ill patients dying in the ICU suitable for non-heart beating organ donation? Intensive Care Med. 2006;32(5): 708-712.

48. Glavan BJ, Engelberg RA, Downey L, Curtis JR. Using the medical record to evaluate the quality of end-of-life care in the intensive care unit. Crit Care Med. 2008;36(4): 1138.
49. Hall RI, Rocker GM, Murray D. Simple changes can improve conduct of end-of-life care in the intensive care unit. Can J Anaesth. 2004;51(6): 631-636.
50. Smedira NG, Evans BH, Grais LS, Cohen NH, Lo B, Cooke M et al. Withholding and withdrawal of life support from the critically ill. N Engl J Med. 1990;322(5): 309-315.
51. Wilson WC, Smedira NG, Fink C, McDowell JA, Luce JM. Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. JAMA. 1992;267(7): 949-953.
52. Wood GG, Martin E. Withholding and withdrawing life-sustaining therapy in a Canadian intensive care unit. Can J Anaesth. 1995;42(3): 186-191.
53. Keenan SP, Busche KD, Chen LM, McCarthy L, Inman KJ, Sibbald WJ. A retrospective review of a large cohort of patients undergoing the process of withholding or withdrawal of life support. Crit Care Med. 1997;25(8): 1324-1331.
54. Hall RI, Rocker GM. End-of-life care in the ICU: treatments provided when life support was or was not withdrawn. Chest. 2000;118(5): 1424-1430.
55. Esteban A, Gordo F, Solsona L, Alia I, Caballero J, Bouza C et al. Withdrawing and withholding life support in the intensive care unit: A Spanish prospective multi-centre observational study. Intensive Care Med. 2001;27(11): 1744-1749.
56. Rocker GM, Heyland DK, Cook DJ, Dodek PM, Kutsogiannis DJ, O'Callaghan CJ. Most critically ill patients are perceived to die in comfort during withdrawal of life support: A Canadian multi-centre study. Can J Anesth. 2004;51(6): 623-630.
57. Gerstel E, Engelberg RA, Koepsell T, Curtis JR. Duration of withdrawal of life support in the intensive care unit and association with family satisfaction. Am J Respir Crit Care Med. 2008;178(8): 798-804.
58. Bloomer MJ, Tiruvoipati R, Tsiripillis M, Botha JA. End of life management of adult patients in an Australian metropolitan intensive care unit: A retrospective observational study. Aust Crit Care. 2010;23(1): 13-19.
59. Asch DA, Christakis NA. Why Do Physicians Prefer to Withdraw Some Forms of Life Support over Others? Intrinsic Attributes of Life-Sustaining Treatments Are Associated with Physicians' Preferences. Med Care. 1996;34(2): 103-111.
60. Christakis NA, Asch DA. Biases in how physicians choose to withdraw life support. Lancet. 1993;342(8872): 642-646.
61. Mayer SA, Kossoff SB. Withdrawal of life support in the neurological intensive care unit. Neurology. 1999;52(8): 1602-1909.
62. Baumann A, Audibert G, Claudot F, Puybasset L. Ethics review: End of life legislation - the French model. Crit Care. 2009;13(1): 204.
63. DeVita MA, Brooks MM, Zawistowski C, Rudich S, Daly B, Chaitin E. Donors after cardiac death: Validation of identification criteria (DVIC) study for predictors of rapid death. Am J Transplant. 2008;8(2): 432-441.
64. Kaufman DA. Factors Predictive of Time to Death After Withdrawal of Life Support. Crit Care Med. 2002;30(12):
65. Field MJ, Cassel CK. Approaching Death: Improving Care at the End of Life. Washington, DC: The National Academies Press; 1997.

66. Cook DJ, Guyatt GH, Jaeschke R, Reeve J, Spanier A, King D et al. Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. JAMA. 1995;273(9): 703-708.
67. Dunne KA, Crutchley N, Puxty AS. National survey on the use of guidelines in the withdrawal of treatment in Intensive Care Units. In: Abstracts of ESICM LIVES 2011, the 24th Annual Congress of the European Society of Intensive Care Medicine: ESICM LIVES 2011; 2011 Oct 1-5; Berlin Germany. Intensive Care Med. 2011;37: S72.
68. Rhee JY, Ruthazer R, O'Connor K, Delmonico FL, Luskin RS, Freeman RB. The impact of variation in donation after cardiac death policies among donor hospitals: A regional analysis. Am J Transplant. 2011;11(8): 1719-1726.
69. Campbell ML. How to withdraw mechanical ventilation: A systematic review of the literature. AACN Adv Crit Care. 2007;18(4): 397-403.
70. Siegel MD, Ryder A, Salon JE, Carlson RW, Campbell ML, Frank RR et al. Life support: The debate continues [1]. Chest. 1996;109(3): 852-853.
71. Grenvik A. 'Terminal weaning'; discontinuance of life-support therapy in the terminally ill patient. Crit Care Med. 1983;11(5): 394-395.
72. Thompson BT, Cox PN, Antonelli M, Carlet JM, Cassell J, Hill NS et al. Challenges in End-of-Life Care in the ICU: Statement of the 5th international consensus conference in critical care: Brussels, Belgium, April 2003: Executive summary. Crit Care Med. 2004;32(8): 1781-1784.
73. Cist AFM, Truog RD, Brackett SE, Hurford WE. Practical guidelines on the withdrawal of life-sustaining therapies. Int Anesthesiol Clin. 2001;39(3): 87-102.
74. Faber-Langendoen K, Lanken PN, Snyder L. Dying patients in the intensive care unit: Forgoing treatment, maintaining care. Ann Intern Med. 2000;133(11): 886-893.
75. Asch DA, Faber-Langendoen K, Shea JA, Christakis NA. The sequence of withdrawing life-sustaining treatment from patients. Am J Med. 1999;107(2): 153-156.
76. Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MMI, D'Alessandro A et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. Am J Transpl. 2009;9(9): 2004-2011.
77. Ho KJ, Owens CD, Johnson SR, Khwaja K, Curry MP, Pavlakis M et al. Donor post-extubation hypotension and age correlate with outcome after donation after cardiac death transplantation. Transplantation. 2008;85(11): 1588-1594.
78. Joffe AR, Carcillo J, Anton N, deCaen A, Han YY, Bell MJ et al. Donation after cardio-circulatory death: A call for a moratorium pending full public disclosure and fully informed consent. Philos Ethics Humanit Med. 2011;6(1):17.
79. Solomon MZ, O'Donnell L, Jennings B, Guilfoy V, Wolf SM, Nolan K et al. Decisions near the end of life: Professional views on life-sustaining treatments. Am J Public Health. 1993;83(1): 14-23.
80. Brody H, Campbell ML, Faber-Langendoen K, Ogle KS. Withdrawing intensive life-sustaining treatment - Recommendations for compassionate clinical management. N Engl J Med. 1997;336(9): 652-657.

81. Keenan SP, Mawdsley C, Plotkin D, Sibbald WJ. Inter-hospital variability in satisfaction with withdrawal of life support: Room for improvement? Crit Care Med. 2003;31(2): 626-631.
82. Breen CM, Abernethy AP, Abbott KH, Tulsky JA. Conflict associated with decisions to limit life-sustaining treatment in intensive care units. J Gen Inter Med. 2001;16(5): 283-289.
83. Bastami S, Matthes O, Krones T, Biller-Andorno N. Systematic review of attitudes toward donation after cardiac death among healthcare providers and the general public. Crit Care Med. 2013;41(3): 897-905.
84. Reed CC, Gerhardt SD, Shaver K, Koebcke M, Mullins D. Case Study: Family Presence in the OR for Donation After Cardiac Death. AORN Journal. 2012;96(1): 34-44.
85. Joris J, Kaba A, Lauwick S, Lamy M, Brichant J-F, Damas P et al. End of life care in the operating room for nonheart-beating donors: Organization at the university hospital of lige. Transplant Proc. 2011;43(9): 3441-3444.
86. Mularski RA, Heine CE, Osborne ML, Ganzini L, Curtis JR. Quality of dying in the ICU: Ratings by family members. Chest. 2005;128(1): 280-287.
87. Rady MY, Verheijde JL, Ali MS. Islam and end-of-life practices in organ donation for transplantation: New questions and serious sociocultural consequences. HEC Forum. 2009;21(2): 175-205.
88. Steinhauser KE, Clipp EC, McNeilly M, Christakis NA, McIntyre LM, Tulsky JA. In search of a good death: Observations of patients, families, and providers. Ann Intern Med. 2000;132(10): 825-832.
89. Keenan SP, Mawdsley C, Plotkin D, Webster GK, Priestap F. Withdrawal of life support: How the family feels, and why. J Palliat Care. 2000;16(SUPPL.): S40-S44.
90. Long T, Sque M, Addington-Hall J. What does a diagnosis of brain death mean to family members approached about organ donation? A review of the literature. Prog Transplant. 2008;18(2): 118-126.
91. Woien S, Rady MY, Verheijde JL, McGregor J. Organ procurement organizations Internet enrollment for organ donation: Abandoning informed consent. BMC Med Ethics. 2006;7:
92. Everidge CS. Donation after cardiac death: Ethical dilemmas and implications for advanced practice nurses. Dimens Crit Care Nurs. 2012;31(4): 228-234.
93. Hawryluck LA, Harvey WRC, Lemieux-Charles L, Singer PA. Consensus guidelines on analgesia and sedation in dying intensive care unit patients. BMC Med Ethics. 2002;3: 1-9.
94. Lehmann CU, Miller MR. Standardization and the Practice of Medicine [editorial]. Journal of Perinatology 2004;24: 135-136.
95. Hansen BS, Severinsson E. Intensive care nurses' perceptions of protocol-directed weaning--a qualitative study. Intensive Crit Care Nurs. 2007;23(4): 196-205.
96. Hansen BS, Severinsson E. Physicians' perceptions of protocol-directed weaning in an intensive care unit in Norway. Nurs Health Sci. 2009;11(1): 71-76.
97. Rose RL, Bucknall T. Staff perceptions on the use of a sedation protocol in the intensive care setting. Aust Crit Care. 2004;17(4): 151-159.

98. Treece PD, Engelberg RA, Crowley L, Chan JD, Rubenfeld GD, Steinberg KP et al. Evaluation of a standardized order form for the withdrawal of life support in the intensive care unit. Crit Care Med. 2004;32(5): 1141-1148.

13.0 APPENDIX

APPENDIX A – SEARCH STRATEGIES FOR ELECTRONIC DATABASES

EMBASE (1947 – OCT 2012) using OVID

Search terms used: ("Intensive Care Unit"[Mesh] OR "Intensive Care"[Mesh] OR "critical care" OR "Critical Illness"[Mesh] OR ICU OR "intensive care*" OR "Terminal Care"[Mesh]) AND (Intensivist* OR "Physician"[Mesh] OR "Nurse"[Mesh] OR "Medical Staff"[Mesh] OR "Physician Attitude"[Mesh] OR "critical care physician*" OR "critical care nurs*" OR "intensive care nurs*" OR hospitals OR "Community Hospital"[Mesh] OR clinician*) AND ("life support care" OR "Hypnotic Sedative Agent"[Mesh] OR ("Norepinephrine"[Mesh] OR "Phenylephrine"[Mesh] OR "Vasopressin"[Mesh] OR "Epinephrine"[Mesh] OR "Dopamine"[Mesh]) OR "life support" OR "Renal Replacement Therapy"[Mesh] OR "Vasoconstrictor Agent"[Mesh] OR "Opiate[Mesh]" OR "Analgesic"[Mesh] OR "Artificial Ventilation"[Mesh] OR "mechanical ventilation" OR "end-of-life care" OR "Enteric Feeding"[Mesh] OR "medical futility" OR ("Lorazepam"[Mesh] OR "Midazolam"[Mesh] OR "Morphine"[Mesh] OR "Propofol"[Mesh] OR "Fentanyl"[Mesh]) OR "Deep Sedation"[Mesh] OR "Benzodiazepine"[Mesh]) AND ("Treatment Withdrawal"[Mesh] OR "Passive Euthanasia"[Mesh] OR "withdrawing treatment*" OR "Extubation[Mesh]" OR "terminal extubation" OR "extubat*" OR "ventilator weaning" OR "withdrawal of life support" OR "life support withdrawal" OR "Do-not-resuscitate order*" OR "resuscitation orders" OR "Euthanasia"[Mesh] OR "withdrawing care" OR "Palliative Therapy"[Mesh] OR "withdrawing life support" OR "order of withdrawal" OR "forgo life-sustaining treatment*")

MEDLINE (1946 – OCT 2012, In Process & Other non-Indexed Citations) using OVID

Search terms used: ("Intensive Care Units"[Mesh] OR "Intensive Care"[Mesh] OR "Critical Care"[Mesh] OR "Critical Illness"[Mesh] OR ICU or "intensive care*" OR "Terminal Care"[Mesh]) AND (intensivist OR "Physicians"[Mesh] OR "Nurses"[Mesh] OR "Medical Staff, Hospital"[Mesh] OR "Physician's Role"[Mesh] OR "critical care physician*" OR "critical care nurse*" OR "intensive care physician*" OR "intensive care nurs*" OR "Hospitals, Community"[Mesh]" OR "Hospitals, University"[Mesh] OR "Hospitals"[Mesh] OR "Nursing Staff, Hospital"[Mesh] OR "Professional-Family Relations"[Mesh] OR "Physician's Practice Patterns"[Mesh] OR "Hospitals, Teaching"[Mesh] OR "Attitude of Health Personnel"[Mesh]) AND ("Life Support Care"[Mesh] OR "Hypnotics and Sedatives"[Mesh] OR ("Norepinephrine"[Mesh] OR "Phenylephrine"[Mesh] OR "Vasopressin"[Mesh] OR "Epinephrine"[Mesh] OR "Dopamine"[Mesh]) OR "life support" OR "Renal Replacement Therapy"[Mesh] OR "Vasoconstrictor Agents"[Mesh] OR "Analgesics, Opioid"[Mesh] OR "Analgesics"[Mesh] OR "Respiration, Artificial"[Mesh] OR "Ventilators, Mechanical"[Mesh] OR "end-of-life care" OR "Enteral Nutrition"[Mesh] OR "Medical Futility"[Mesh] OR ("Lorazepam"[Mesh] OR "Midazolam"[Mesh] OR "Morphine"[Mesh] OR "Propofol"[Mesh] OR "Fentanyl"[Mesh]) OR "Deep Sedation"[Mesh] OR "Benzodiazepines"[Mesh]) AND ("Withholding Treatment"[Mesh] OR "Euthanasia, Passive"[Mesh] OR "Withdrawing treatment*" OR "Airway Extubation"[Mesh] OR "terminal extubation" OR "extubation" OR "Ventilator Weaning"[Mesh] OR "Time Factors"[Mesh] OR "withdrawal of life support" OR "life support withdrawal" OR "do-not-resuscitate order*" OR "Resuscitation Orders"[Mesh] OR "Euthanasia"[Mesh] OR "withdrawing care" OR "Palliative Care"[Mesh] OR "withdrawing life support" OR "treatment withdrawal")

EBM Reviews (DARE, Cochrane, HTA, NHS Economic Evaluations) using OVID
Search terms used: ("intensive care unit" OR "intensive care" OR "critical care" OR "critical illness" OR ICU OR "intensive care*" OR "terminal care") AND (intensivist OR physician OR "healthcare worker" OR "physician's role" OR "critical care physician" OR "critical care nurs*" OR "intensive care physician*" OR "intensive care nurs*" OR "care in the ICU") AND ("life support care" OR "hypnotics and sedatives" OR ("norepinephrine" OR "phenylephrine" OR "vasopressin" OR "epinephrine" OR "dopamine") OR "life support" OR "renal replacement therapy" OR vasopressor OR opiods OR analgesic* OR "artificial respiration" OR "mechanical ventilat*" OR "end-of-life care" OR "enteral nutrition" OR "medical futility" OR ("lorazepam" OR "midazolam" OR "morphine" OR "propofol" OR "fentanyl") OR sedation OR benzodiazepine) AND ("withholding treatment" OR "euthanasia, passive" OR "withdrawing treatment*" OR "airway extubation" OR timing OR "extubation" OR "ventilator wean*" OR "time factor" OR "withdrawal of life support" OR "life support withdrawal" OR "do-not-resuscitate order*" OR "resuscitation orders" OR euthanasia OR "withdrawing care" OR "palliative care" OR "withdrawing life support")

APPENDIX B – SAMPLE DATA ABSTRACTION TABLE

Variable	Data Collected
Reference number	Arbitrarily assigned by reference software
General Study Data	
Author(s)	Descriptive
Year of publication	Descriptive
Year study was conducted/data was collected	Descriptive
Sample size of patients who had life support removed	Continuous
Setting of patient care/life support removal (ICU, hospital ward, operating room, etc.)	Descriptive
ICU type (trauma, medical, surgical, mixed)	Descriptive
Hospital characteristics (University, teaching hospital, community hospital, nursing home, etc.)	Descriptive
Study Design (retrospective, chart review, prospective, observational, interventional, use of secondary data, etc.)	Descriptive
Ares of treatment withdrawal process measured (order of withdrawal, drug dosing during withdrawal, timing, description of interventions removed)	Descriptive
Measure of illness severity scoring used (GCS, APACHE II, SOFA, etc.)	Descriptive
Risk of Bias	
Considered illness severity in outcome description?	Binary (Y/N)
Other identified potential biases (problems with data collection, unique population, missing information)	Descriptive

ICU, intensive care unit; GCS, Glasgow Coma Score; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

APPENDIX C – DEFINITIONS OF WITHDRAWAL OF LIFE SUPPORT THERAPY USED IN INCLUDED STUDIES

Study	Definition of Withdrawal of Life Support Therapy	Includes prediction of death
Smedira et al (50)	*No clear pre-defined definition, likely from first intervention withdrawn.*	*NA*
Wilson et al (51)	Withdrawal of MV	No
Wood and Martin (52)	A withdrawal of "a treatment that would have a critical influence on the patient's clinical course" (patient expected to live for minimum of 24 hours if treatment not withdrawn.)	Yes
Keenan et al (53)	A mutual decision (by physician and family) to remove all or some "current life-support modalities"	No
Keenan et al (41)	A mutual decision (by physician and family) to remove all or some "current life support modalities"	No
Hall and Rocker (54)	Removal or no further addition/escalation of "major life support modalities" (including VP, MV, RRT, etc.) with understanding that this would likely result in death	Yes
Esteban et al. (55)	The cessation and removal of an ongoing medical therapy with the explicit intent not to substitute an equivalent, alternative treatment and knowing that the patient will die following the change in therapy.	Yes
Ferrand et al. (40)	Discontinuation of treatments that had been started, including ABX, VP, blood transfusion, nutrition, hydration, inspired oxygen support above 21%, and MV.	No
Rocker et al (56)	Reduction or discontinuation of MV, or continuation of MV while other life support modalities such as VP or RRT are withdrawn	No
Chan et al (39)	Documented withdrawal of MV	No
Gerstel et al (57)	Interventions (RRT, hydration, tube feeding, VP, laboratory tests, MV) withdrawn with the expectation that the patient would die	Yes
White et al (42)	Withdrawal of MV	No
Bloomer et al. (58)	From first therapy withdrawn, including MV, VP, RRT, and nutrition.	No
Wind et al. (29)	*Not overtly stated, likely begins with extubation/disconnect from ventilator.*	*NA*

MV, mechanical ventilation; VP, vasoactive drugs, RRT, renal replacement therapy; ABX, antibiotics

APPENDIX D – LIST OF PILOT STUDY VARIABLES ANALYZED

Category	Variable	Data Collected
Admission & Demographic Data	Admission to intensive care unit	Date & time
	APACHE II score	Score for each category, summary score using validated scale
	Glasgow Coma Score	Score for each category, summary score using validated scale
	Sex	Male/Female
	Chronic Illness	Presence of any chronic illness (Y/N), description
Withdrawal of life sustaining treatments	Start of withdrawal of life sustaining treatment	Date & time
	Declaration of death	Date & time
Respiratory therapies at start of life sustaining therapy withdrawal	Invasive/non-invasive mechanical ventilation, endotracheal tube, nasotracheal tube, nasopharyngeal airway	Presence/absence of each therapy, ventilation settings (rate, positive end expiratory pressure, inhaled oxygen percentage)
Ventilation & Airway management during withdrawal of life support treatment	Extubation	Yes/No, date, time
	Change to T-piece	Yes/No, date, time
	Oxygen wean	Yes/No, date, time and value of each reduction in inspired oxygen percentage
	Suctioning	Whether suctioning was performed, number of times, date and time patient last suctioned

Category	Variable	Data Collected
Administration of vasoactive drugs prior to withdrawal of life sustaining therapies	Administration of vasoactive drugs (epinephrine, norepinephrine, vasopressin, phenylephrine, milrinone, dopamine, dobutamine, nitroglycerin, nitroprusside, labetolol, esmolol, amiodarone, other)	Presence/absence of each medication, dose, date & time of cessation
Administration of vasoactive drugs during withdrawal of life sustaining therapies	Administration of vasoactive drugs (epinephrine, norepinephrine, vasopressin, phenylephrine, milrinone, dopamine, dobutamine, nitroglycerin, nitroprusside, labetolol, esmolol, amiodarone, other)	Yes/No, type of drug, date, time and dose value for each administration of each drug
Administration of analgesics/sedation prior to withdrawal of lie sustaining therapy	Administration of any analgesia/sedation drugs (morphine, fentanyl, hydromorphone, midazolam, lorazepam, diazepam, clonidine, propofol, pentobarbitol, dexmedetomidine)	Presence/absence of each medication, dose, date & time of cessation
Administration of Analgesia/Sedation	Administration of any analgesia/sedation drugs (morphine, fentanyl, hydromorphone, midazolam, lorazepam, diazepam, clonidine, propofol, pentobarbitol, dexmedetomidine)	Yes/No, date, time, and dose value for each administration of each drug
Administration of other drugs during withdrawal of life support therapy	Administration of any other drugs	Yes/No, drug name, date, time, and dose value for each administration of each drug

APACHE II, Acute Physiology and Chronic Health Evaluation II

APPENDIX E – COPY OF RESEARCH ETHICS BOARD APPROVAL LETTER FOR SECONDARY DATA ANALYSIS

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

Friday, February 08, 2013

Dr. Sonny Dhanani
Children's Hospital of Eastern Ontario (CHEO)
401 Smyth Road
Ottawa, ON
K1H8L1

Dear Dr. Dhanani:

Re: Protocol # 20130065-01H **Exploration of DDePICt pilot study data on WLST processes in participating Canadian ICUs**

Protocol approval valid until - Friday, February 07, 2014

I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHREB's review and approval.

Approval is for the following:
- OHREB Electronic Application
- Protocol dated January 7, 2013

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

[redacted]

Francine F-A Sarazin, Ph.D., C. Psych
Vice-Chairman
Ottawa Hospital Research Ethics Board

FFAS/kd

APPENDIX F – DATA ABSTRACTION TOOL USED FOR LIFE SUPPORT THERAPY WITHDRAWAL PROTOCOLS

Characteristic	Data collected
1. Did site provide a protocol for removal of life support for non-organ donor patients?	Binary (Y/N)
2. What was the first "step" in the initiation of life support withdrawal?	Descriptive
3. Was the concept of "no drug limit" clearly stated somewhere in the protocol?	Binary (Y/N)
4. Was the dosing of comfort drugs specifically protocolized (e.g. when each dose could be increased)?	Binary (Y/N)
5. Were there any specific drugs listed? (List)	Binary (Y/N) & description
6. Was the withdrawal of mechanical ventilation explicitly outlined?	Binary (Y/N)
7. If yes, was extubation listed as a step of withdrawal of mechanical ventilation?	Binary (Y/N)
8. Was the weaning or removal of vasoactive drugs outlined?	Binary (Y/N)
9. What was the length of the protocol?	Continuous (number of pages)
10. Was withdrawal of additional interventions (nutrition, dialysis, additional medications) outlined?	Binary (Y/N)
11. Was the decision-making component of life support withdrawal also outlined?	Binary (Y/N)
12. Was there a separation of decision-making at end of life and the actions done as part of the withdrawal process?	Binary (Y/N)
13. How was the protocol presented? (Checklist, paragraphs, lists, etc.)	Descriptive