CrossMark

REPORTS OF ORIGINAL INVESTIGATIONS

Hamilton-DONATE: a city-wide pilot observational study of the ICU management of deceased organ donors

Hamilton-DONATE : une étude pilote observationnelle de la gestion en USI des donneurs d'organes décédés à l'échelle d'une ville

Frederick D'Aragon, MD [ORCID] · **Deborah Cook, MD** · **Sony Dhanani, MD** · **Christine Ribic, MD** · **Karen E. A. Burns, MD** · **Aemal Akhtar, MSc** · **Lori Hand, BSc** · **Erika Arseneau, MSc** · **Cynthia Cupido, MD** · **Heather Whittigham, MD** · **Andrew Healey, MD** · **Anne Julie Frenette, BPharm, MSc** · **François Lamontagne, MD** · **Maureen O. Meade, MD** · **for the Canadian Critical Care Trials Group and the Canadian National Transplant Research Program**

Abstract

Purpose *Improving the medical care of deceased organ donors to increase transplant rates and improve allograft function requires an understanding of the current epidemiology and clinical practices of deceased donation within intensive care units (ICUs). Herein, we report the results of our investigation into the feasibility of a multicentre prospective cohort study addressing the afformentioned issues.*

Methods *We conducted a 12-month prospective observational cohort study in six ICUs and one coronary care unit in Hamilton, Canada. We included consecutive children and adults following consent for deceased organ donation (including neurologic determination of death [NDD] or donation after circulatory death [DCD]). Intensive care unit research staff recorded donor management data from hospital records, extending from one day prior to the consent for organ donation up to the time of organ retrieval. The provincial Organ Donation*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12630-018-1179-y) contains supplementary material, which is available to authorized users.

F. D'Aragon, MD
Department of Anesthesiology, Université de Sherbrooke, Sherbrooke, QC, Canada

F. D'Aragon, MD · F. Lamontagne, MD
Research Centre, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada

F. D'Aragon, MD (✉)
Department of Anaesthesia, Université de Sherbrooke, 2001, 12e Avenue Nord, Sherbrooke, QC J1H 5N4, Canada
e-mail: Frederick.DAragon@USherbrooke.ca

D. Cook, MD · C. Ribic, MD · H. Whittigham, MD · A. Healey, MD · M. O. Meade, MD
Department of Medicine, McMaster University, Hamilton, ON, Canada

D. Cook, MD · K. E. A. Burns, MD · A. Akhtar, MSc · L. Hand, BSc · E. Arseneau, MSc · M. O. Meade, MD
Department of Health Research Methods, Evidence & Impact, McMaster University, Hamilton, ON, Canada

S. Dhanani, MD
Division of Critical Care, Department of Pediatrics Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

K. E. A. Burns, MD
Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada

K. E. A. Burns, MD
Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

C. Cupido, MD
Department of Pediatrics, McMaster University, Hamilton, ON, Canada

A. J. Frenette, BPharm, MSc
Pharmacy faculty, Université de Montréal, Montreal, QC, Canada

Organization (ODO) supplemented these data and, additionally, provided data on corresponding organ recipients. We identified, evaluated, and measured three potential obstacles to the feasibility of a national cohort study: obtaining authorization to implement the study with a waiver of research consent, accessibility of transplant recipient data, and the time required to complete very detailed case report forms (CRFs), with valuable lessons learned for implementation in future projects.

Results The local Research Ethics Board and the ODO Privacy Office both authorized the recording of donor and recipient study data with a waiver of research consent. Sixty-seven consecutive consented donors were included (31 NDD and 36 DCD donors); 50 of them provided 144 organs for transplantation to 141 recipients. We identified the age and sex of the recipients as well as the location and date of transplant for all organ recipients in Ontario; however, we obtained no recipient data for six organs transported outside of Ontario. Intensive care unit research staff estimated that future CRF completion will require five to seven hours per patient.

Conclusion The Hamilton-DONATE pilot study supports the feasibility of a larger cohort study to describe the epidemiology and clinical practices related to deceased donor care in Canada.

Trial registration wwwclinicaltrials.gov (NCT02902783). Registered 16 September 2016.

Résumé

Objectif L'amélioration des soins de donneurs d'organes décédés pour augmenter les taux de transplantation et améliorer la fonction des allogreffes nécessite de comprendre l'épidémiologie et les pratiques cliniques actuelles du don d'organe de donneur décédé dans les unités de soins intensifs (USI). Nous présentons ici les résultats de notre enquête sur la faisabilité d'une étude de cohorte prospective multicentrique visant à répondre à ces questions.

Méthodes Nous avons mené une étude de cohorte observationnelle prospective de 12 mois dans six USI et une unité de soins coronariens à Hamilton (Canada). Nous avons inclus les enfants et adultes consécutifs après consentement du don d'organe d'un donneur décédé (incluant la détermination neurologique du décès [DND] ou don après décès cardiocirculatoire [DDC]). Le

personnel de recherche des unités de soins intensifs a consigné les données de la gestion médicale des donneurs à partir des dossiers hospitaliers, commençant une journée avant le consentement au don d'organe jusqu'au moment du prélèvement. L'organisme provincial responsable des dons d'organes (ODO) a complété ces données ainsi que celles des receveurs d'organes correspondants. Nous avons identifié, évalué et mesuré trois obstacles potentiels à la faisabilité d'une étude de cohorte nationale : l'obtention de l'autorisation de mise en place d'une étude avec dérogation de consentement à la recherche, l'accessibilité des données concernant les receveurs de greffes et le temps nécessaire pour remplir des cahiers d'observation très détaillés; nous en avons tiré des points importants pour la mise en œuvre de futurs projets.

Résultats Le Comité local d'éthique de la recherche et le bureau de la protection de la vie privée de l'ODO ont tous deux autorisé l'enregistrement des données d'étude du donneur et du receveur avec une dérogation du consentement à la recherche. Soixante-sept donneurs consentants consécutifs (31 donneurs DND et 36 donneurs DDC) ont été inclus; parmi eux, 50 donneurs ont fourni 144 organes qui ont été greffés chez 141 receveurs. Nous avons identifié l'âge et le sexe des receveurs, ainsi que l'emplacement et la date de la transplantation pour tous les receveurs d'organes en Ontario; toutefois, nous n'avons pas obtenu de données pour six organes transportés hors de la province. Le personnel de recherche des unités de soins intensifs a estimé que le remplissage des cahiers d'observation futurs prendrait de 5 à 7 heures par patient.

Conclusion L'étude pilote Hamilton-DONATE confirme la faisabilité d'une grande étude de cohorte visant à décrire l'épidémiologie et les pratiques cliniques pour les soins aux donneurs décédés au Canada.

Enregistrement de l'essai clinique wwwclinicaltrials.gov (NCT02902783). Enregistré le 16 septembre 2016.

A. J. Frenette, BPharm, MSc
Department of Pharmacy, Hopital Sacre Coeur de Montreal, Montreal, QC, Canada

F. Lamontagne, MD
Department of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada

Organ transplantation is the most effective treatment for patients suffering from end-stage organ failure.[1] In Canada, organ demand consistently exceeds supply as there are three times as many patients on transplant wait lists as there are organs available.[2]

Up to 20% of potentially transplantable organs are not utilized because of suboptimal intensive care unit (ICU) care.[3,4] After consent for deceased donation, the steps to ascertain organ suitability for transplantation, identify potential recipients, and bring in a team of surgeons for organ retrieval typically require 24-48 hr. During this period, ICU clinicians work to resuscitate and maintain

stability of the consented organ donor, striving to prevent and treat common ICU complications (e.g., ventilator-associated pneumonia, episodes of hypotension or hypoxemia) that may compromise organ viability. General and donation-specific therapies to enhance donation and transplant success vary across institutions and focus primarily on fluid repletion, hormone supplementation, and blood glucose management.[5-7] The impact of these and other donor interventions remain largely unknown.[5] While improvements in the standards of deceased donor care are likely to increase the number and quality of transplanted organs,[8-11] research in this field is sparse and provides very limited support for evidence-based guidelines.[5,10,12]

In 2015, the *Canadian Critical Care Trials Group* and *Canadian National Transplant Research Program* together launched a unique program of research in deceased donor care: Canada-DONATE. The first goals are to determine the epidemiology of deceased donation in Canada, identify potentially important variability in donor care strategies and outcomes across Canadian institutions and health systems, and identify and address unique challenges to research in this field. To determine the feasibility of a nationwide prospective study, we conducted a 12-month prospective observational pilot study across seven critical care units in Hamilton, Canada. We perceived three major threats to feasibility: 1) the acceptability of a waiver of research consent, 2) the ability to obtain selected recipient data corresponding to each donor, and 3) the time required for ICU research staff to complete the detailed study case report forms (CRFs).

Methods

This manuscript was drafted in accordance with the STROBE guidelines on the reporting of observational studies.[13]

Design and setting

We conducted a 12-month prospective observational pilot study across all Hamilton, Ontario, ICUs: St. Joseph's Healthcare (one ICU) and the Hamilton Health Sciences Juravinski site (one ICU), General site (two ICUs, one coronary care unit, one cardiac surgical ICU), and McMaster site (one pediatric ICU). At the time of the study, these hospitals employed two ICU physicians with specialized training in deceased donation. Additionally, four ICUs had physician order sets addressing the management of neurologically deceased donors. The provincial Organ Donation Organization (ODO), which is the Trillium Gift of Life Network (TGLN) of Ontario,

employed two organ and tissue donation coordinators (plus an on-call team) within these hospitals to coordinate all deceased donation activity in the city.

Study participants

All potential deceased donors, defined by a legal documentation of consent for donation from a surrogate decision-maker, were eligible for the study. We included donation after a neurologic determination of death (NDD) or a circulatory determination of death (DCD) following a planned withdrawal of life-sustaining therapies. When TGLN staff electronically registered a new consent for deceased donation to activate provincial organ allocation procedures, this triggered an instantaneous email notification to the DONATE study Methods Centre. Methods Centre staff then promptly alerted Hamilton ICU research staff to initiate data collection.

Data collection

Intensive care unit research staff recorded data from ICU clinicians, bedside ICU monitors, and hospital records, starting (retrospectively) from the day prior to consent for organ donation up until (prospectively) the time of organ retrieval or decline of all organs by transplant programs. They recorded the relevant medical history, data related to neurologic and circulatory death determinations, laboratory and radiologic testing, medication and somatic support technologies, cardiopulmonary monitoring, invasive procedures, lung recruitment maneuvers, physicians' suspicion for pneumonia or catecholamine storm, and the time and rationale for declining organs by transplant programs. They also documented each episode of hypoxemia[14] (defined as arterial oxygen saturation $\leq$ 88% for $\geq$ 15 min), hypotension (mean arterial pressure [MAP] < 65 mmHg for > 15 min), and arrhythmia (heart rate < 40 beats·min^{-1} or > 150 beats·min^{-1} with hemodynamic instability). We developed specific procedures, unique to each ICU, that allowed us to collect the more time-sensitive information, including number of bedside ICU echocardiograms, results of these informal echocardiograms, number of recruitment maneuvers, physicians' suspicion of ventilator-associated pneumonia, and data related to acute episodes of hypoxemia, hypotension, and arrhythmias. Intensive care unit research staff received additional training, as needed, on electronic data entry using the iDataFax™ CRFs, which we pre-tested prior to launching the study. They were encouraged to provide real-time feedback on the CRFs with a view to immediate implementation, where appropriate. At study completion, all ICU research staff met together with the principal investigators to formally

debrief about the feasibility of data collection, opportunities to further enhance feasibility, and estimated time required for data collection. Because these data would be essential for future clinical trials in deceased donor care, we also obtained organ recipient data from TGLN including metrics such as age, sex, program and time of transplantation, and the final preoperative calculated panel reactive antigen (CPRA; a measure of immunologic risk).

Study measurements and outcomes

The primary objective of the Hamilton-DONATE pilot study was to determine the feasibility of a national study. To assess the acceptability of a waiver of research consent, we recorded any modifications requested by the Hamilton Integrated Research Ethics Board (HiREB) or the TGLN Privacy Office. To measure our ability to obtain transplant recipient data, we noted any data missing from the six items requested per recipient (i.e., age, sex, latest CPRA, transplant centre, and date and time of transplantation). To estimate the average time required to complete each participant CRF (particularly as we refined the CRF throughout the period of study to enhance clarity and ease of use) ICU research staff estimated, at the end of the study, the average time spent in completing CRFs for each participant.

We also recorded clinical outcomes including: 1) the use of general ICU therapies (i.e., vasopressors; nutrition); 2) organ donation-specific therapies (i.e., thyroid hormone supplementation; intravenous heparin); 3) the conversion of consented donors to actual donors (defined by the surgical retrieval of at least one organ); 4) the total number of organs recovered; 5) the number of organs transplanted; and 6) the number of transplant recipients (since one recipient may receive more than one organ). For the purpose of this study, when two kidneys (or lungs) were transplanted separately we counted them as two organs, and if they were transplanted together we counted them as one organ. If one liver supported two transplants, we counted this as one organ donated and two organs transplanted. We did not include small bowel in this study since it is rarely recovered in deceased donors. At the time of the study, participating centres did not recover hearts from DCD donors.

For each organ that was declined by transplant programs, we determined from TGLN records whether it was ever potentially eligible for transplant and, if so, the reason for declining after it had been offered to specific programs. Two physician investigators independently reviewed the data to make these judgments. When their judgments differed, they reached consensus through discussion.

Statistical analysis

The focus of this pilot study was feasibility; however, we planned to describe selected clinical data. We performed descriptive analyses, reporting continuous data as means and standard deviations (SD) or medians and interquartile ranges [IQR] as appropriate and dichotomous variables as proportions.

We determined clinical adherence to 14 recommendations of current Canadian consensus guidelines for deceased donor care[6] and nine discrete Donor Management Goals of the American United Network for Organ Sharing (UNOS).[7] To do so, we classified donor care as "adherent" on a given day only if all values on that day met specified goals.

To determine agreement on the organ outcome determinations, we used the weighted kappa statistic.[15] Percent adherence was defined as the proportion of total donors that adhered to the recommendations of the Canadian guidelines and UNOS Data Management Goals for the reported day. Based on deceased donation activity in Hamilton over the preceding five years, we expected to enrol 40 consented potential organ donors.

Ethics

We proposed to undertake this study with a waiver of research consent. We posited that the ethical principle of *Respect for Autonomy*, which supports an informed consent, must be considered in light of competing ethical principles of *beneficence* (i.e., an individual who supports deceased donation is likely to support research to improve donation services), *non-maleficence* (which argues against the imposition of time-sensitive research discussions upon decision-makers at particularly difficult times), and *justice* (our long-term goal being to enhance availability of transplantation through research). In keeping with current Tri-Council criteria for a waiver of research consent,[16] this was a very low-risk study for which informed consent for most donors and recipients is impracticable. Moreover, a requirement for research consent has biased the results of prior registry studies.[17] Lastly, institutions participating in this pilot study had previously undertaken observational research with a waiver of research consent.[18,19]

Results

From September 2015 to August 2016, inclusive, TGLN staff obtained consent for 67 potential deceased organ donors (Table 1) in Hamilton, Ontario. Two were children with a neurologic determination of death. Among 65 adults (St. Joseph's Healthcare eight, Juravinski Site, seven;

Table 1 General characteristics of potential consented donors

Characteristic	NDD (n = 31)	DCD (n = 36)
Number of pediatric donors, n	2	0
Age (among adults), mean (SD)	42.5 (19.5)	54.5 (13.4)
Male, n (%)	19 (59.4)	22 (61.1)
BMI, mean (SD)	28.1 (5.1)	32.9 (19.1)
Medication, n (%)		
Thyroid hormone	0	1 (2.8)
Steroid hormone	0	2 (5.5)
Comorbidities, n (%)		
History of smoking	8 (25.0)	10 (27.8)
Hypertension	8 (25.0)	9 (25.0)
Diabetes	5 (15.6)	7 (19.4)
Pulmonary disease	3 (9.4)	3 (8.3)
Coronary artery disease	1 (3.1)	4 (11.1)
Diagnosis leading to organ donation, n (%)		
Global anoxic brain injury	12 (37.5)	14 (38.9)
Intracerebral hemorrhage	7 (21.9)	9 (36.3)
Traumatic brain injury	11 (34.4)	3 (8.3)
Ischemic stroke	1 (3.1)	5 (13.9)
Other*	1 (3.1)	5 (13.9)
Time from donation consent to organ retrieval (hr), mean (SD)	2.3 (0.6)	2.1 (0.5)
Expanded criteria renal donors**, n (%)	8 (25.0)	17 (47.2)

This table reports the characteristics of all donors (pediatrics and adults) in the study

*Brain tumour, central nervous system infection, liver failure

**Deceased donor $\geq$ 60 yr old, or 50-59 yr old with at least two comorbidities (i.e., chronic hypertension, death resulting from cerebral vascular accident, or a serum creatinine level > 132.6 umol·L^{-1})

BMI = body mass index; DCD = donation after circulatory death; NDD = neurologically deceased donor, SD = standard deviation

General Site, 50), 29 had a neurologic determination of death and 36 had plans for the withdrawal of life-sustaining therapies. For these two groups, respectively, the median [IQR] duration of mechanical ventilation prior to consent for organ donation was 2 [2−3] days and 6 [4−10] days. The mean (SD) time from donation consent to organ retrieval was 2.2 (0.5) days [NDD, 2.3 (0.6) days; DCD, 2.1 (0.5) days].

Feasibility outcomes

The HiREB approved the conduct of this study in all participating ICUs without modification to our proposal for a waiver of research consent. The TGLN Privacy Officer similarly approved the sharing of TGLN data on donors and recipients. Organ outcomes and recipient data for six organs transported outside of Ontario were not accessible. For those organs transplanted in Ontario, we obtained complete data on recipient age and sex and on transplant centre, date, and time; however, we obtained the CPRA for 63% of recipients. Intensive care unit research coordinators

provided feedback to support monthly revisions to the CRFs (available as Electronic Supplementary Material). In light of these revisions of the CRF, at the formal end-of-study debriefing, they estimated that future data collection for each will require five to seven hours. Given that some of the data could be reliably abstracted retrospectively, if necessary, they perceived that this time requirement will be manageable in a national study. No participants withdrew from the study.

Practices in deceased donor management

Thirty-one NDD donors (100%) received thyroid hormone supplementation on the day of consent, exclusively in the form of a regularly scheduled intravenous dose of levothyroxine. In addition, five DCD patients (13.9%) received intravenous thyroxine hormone and one received a daily dose of enteral thyroxine (which had been a chronic medication). All NDD and 20 DCD patients (55.6%) received steroid therapy, most often as methylprednisolone (93.8%), starting on the day of consent (96.9%).

Table 2 Mechanical ventilation

	NDD			DCD		
	Consent $n = 32$	Day 1 $n = 29$	Final day $n = 29$	Consent $n = 36$	Day 1 $n = 34$	Final day $N = 34$
Ventilator settings, mean (SD)						
Lowest F_tO_2	0.4 (0.1)	0.4 (0.2)	0.6 (0.2)	0.4 (0.1)	0.4 (0.1)	0.4 (0.2)
Tidal volume (mL·kg^{-1} PBW)	7.9 (1.9)	8.3 (1.2)	8.2 (1.4)	7.5 (4.5)	7.8 (6.1)	7.7 (6.2.)
PEEP (cmH$_2$O)	7.8 (3.0)	8.4 (3.0)	8.4 (2.9)	8.7 (3.1)	9.2 (2.6)	9.3 (2.4)
Plateau pressure (cmH$_2$O)	23.3 (7.4)	22.7 (4.6)	23.9 (6.1)	23.1 (8.1)	23.0 (7.7)	22.2 (7.5)
P/F ratio, mean (SD)						
Highest daily PaO$_2$/F$_t$O$_2$	479 (260)	314 (120)	311 (143)	416 (286)	338 (137)	332 (147)

DCD = Donation after circulatory death, F_tO_2 = fraction of inspired oxygen, NDD = neurologically deceased donor; PBW = predicted body weight; PaO$_2$ = partial pressure of arterial oxygen; P/F = PaO$_2$/F$_t$O$_2$; PEEP = positive end-expiratory pressure; SD = standard deviation

This table reports the ventilator settings and the P/F ratio for the day of consent, one day after consent, and the day of organ recovery (i.e., final day)

Table 3 Supportive therapies

Characteristic	NDD			DCD		
	Consent $n = 32$	Day 1 $n = 30$	Final day $n = 32$	Consent $n = 36$	Day 1 $n = 34$	Final day $n = 36$
Fluids						
Crystalloids, n (%)	22 (68.8)	18 (60.0)	14 (43.8)	8 (22.2)	9 (29.4)	7 (19.4)
Colloids, n (%)	7 (21.9)	6 (20.7)	4 (12.5)	2 (5.6)	1 (2.9)	1 (2.78)
Vasopressin						
Frequency, n (%)	30 (93.8)	27 (93.1)	27 (84.4)	1 (2.8)	4 (11.8)	4 (11.8)
Dose (U·hr^{-1}), mean (SD)	2.0 (1.2)	1.5 (0.7)	1.6 (0.7)	1.92 (0.6)	1.5 (0.7)	2.1 (0.2)
Duration (hr), mean (SD)	13.3 (8.8)	18.1 (6.3)	12.7 (8.3)	24 (8.0)	12.5 (8.4)	6.8 (3.4)
Norepinephrine						
Frequency n (%)	27 (84.4)	21 (70.0)	17 (53.1)	6 (16.7)	7 (20.6)	7 (19.4)
Dose (μg·kg^{-1}·min^{-1}), mean (SD)	0.49 (0.53)	0.25 (0.39)	0.30 (0.60)	0.23 (0.25)	0.4 (0.6)	0.4 (0.6)
Duration (hr), mean (SD)	14.7 (7.8)	8.5 (7.9)	7.2 (6.6)	11.7 (9.0)	10.3 (6.1)	9.1 (6.2)

DCD = donation after circulatory death; NDD = neurologically deceased donor; SD = standard deviation

This table reports the supportive therapies at the day of consent, one day after consent, and the day of organ recovery (i.e., final day). The type of fluids administered corresponds to the fluids given in addition to the maintenance fluid. For vasopressin and noradrenaline we reported the mean dose of drugs administered over 24 hr

Table 2 summarizes donor respiratory data. For NDD patients, the mean (SD) tidal volume was 7.9 (1.9) mL·kg^{-1} predicted body weight (PBW) on the day of consent and increased to 8.3 (1.2) mL·kg^{-1} PBW one day after consent. In contrast, DCD donors received 7.5 (4.5) mL·kg^{-1} tidal volumes at the day of consent and 7.8 (6.1) mL·kg^{-1} during the final day of data collection.

Vasopressors were administered to 31 (100%) NDD donors and seven (19.4%) DCD donors. For NDD donors, vasopressin was the first vasopressor prescribed (93.8%) followed by norepinephrine (84.4%). In contrast, for DCD donors receiving vasopressors, norepinephrine was the most common agent (Table 3) with one DCD donor

receiving dopamine. Clinicians administered crystalloid solutions as a fluid bolus for volume repletion more frequently than colloids for both NDD and DCD donors (Table 3).

Adherence to Canadian and American guidelines

On the day of consent, the Canadian recommendations for NDD donor care that were most frequently met included: 1) indications for thyroid hormone (100%) and systemic steroids (96.9%), 2) vasopressin as a first-line vasopressor (96.9%), and 3) avoidance of empiric antibiotics (90.6%). In general, adherence to current recommendations

Table 4 Adherence to Canadian recommendations for NDD donors

Recommendations	Consent n (%), N	Day 1 n (%), N	Final day n (%), N
Lung protective ventilation			
Tidal volume 8-10 mL·kg^{-1} PBW	5 (15.6), 32	11 (36.7), 30	8 (25.0), 32
Peak inspiratory pressure < 30 cmH$_2$O	25 (78.1), 32	26 (89.7), 29	28 (87.5), 32
Glycemic control			
Glucose level > 8 mmol·L^{-1}	29 (90.6), 32	28 (96.6), 29	24 (96.0), 25
Vasopressin			
First line vasopressor	31 (96.9), 32	30 (100.0), 30	32 (100.0), 32
Dose ≤ 2.4 U·hr^{-1}	24 (90.0), 30	25 (92.6), 27	26 (96.3), 27
Control of systemic arterial hypertension			
Systolic blood pressure ≤ 160 mmHg	24 (75.0), 32	24 (80.0), 30	16 (50.0), 32
Hypernatremia			
Na < 150 mmol·L^{-1}	21 (65.6), 32	21 (72.4), 29	30 (93.8), 32
Transfusion tresholds			
Target hemoglobin level > 70 g·L^{-1}	28 (87.5), 32	25 (86.2), 29	31 (96.9), 32
Broad spectrum antibiotics			
Avoid empirical antibiotics	29 (90.6), 32	27 (90.0), 30	29 (90.6), 32
Pulmonary artery catheter			
Indications	11 (34.5), 32	21 (72.4), 30	27 (84.4), 32
Systemic steroids			
Indications	31 (96.9), 32	29 (96.7), 30	31 (96.9), 32
Methylprednisolone administered	30 (93.8), 32	28 (93.3), 30	30 (93.8), 32
Thyroid hormone			
Indication	32 (100), 32	27 (93.1), 30	28 (87.5), 32
Thyroxine administered	31 (96.9), 32	29 (96.7), 30	31 (96.9), 32

F$_I$O$_2$ = fraction of inspired oxygen; PBW = predicted body weight

This table reports the adherence of physicians to Canadian guidelines on the day of consent, one day after consent, and the day of organ recovery (i.e., final day). n refers to the number of donors meeting the definition of the recommendation and N refers to the total number of donors for which data are available for each recommendation

fluctuated over time (Table 4). Donor management goals from UNOS were infrequently met from the day of consent up to the day of organ recovery for NDD donors (Table 5).

Clinical complications in the ICU

Hypotension was the most common complication during the period of donor management. At least one episode of hypotension occurred in ten of 31 (32.3%) NDD donors, lasting 74.2 (83.5) min, with the lowest mean (SD) MAP recorded of 53.2 (5.8) mmHg. At least one hypotensive episode occurred in four of 36 (11.1%) DCD donors, lasting 105.0 (90.0) min; the lowest MAP recorded was 58.5 (3.1) mmHg. Episodes of arrhythmia causing hemodynamic instability occurred in seven (22.6%) NDD and five (13.9%) DCD donors. The majority of donors experienced just a single episode and two patients experienced two episodes of arrhythmia. Most episodes involved tachycardia (NDD five and DCD three). Acute

desaturation occurred in one (3.2%) NDD and two (5.6%) DCD donors. Importantly, no complication led to the cessation of the organ donation process.

Donation and transplant outcomes

Of the 67 consented donors, 50 (73.5%) successfully donated organs. Ninety-four organs from the original 67 (25.6%) consented donors were determined not suitable for transplantation by TGLN and were therefore not offered to transplant programs. Of those offered to transplant programs, 121 (31.1%) organs were declined. During adjudication, we achieved a high level of agreement on these determinations overall as represented by median [IQR] weighted kappa scores (12 declined hearts, kappa 0.92 [0.77-1.00]; 20 declined pancreas, kappa 0.89 [0.77-1.00]; 18 declined kidneys, kappa 0.88 [0.81-0.91]; 26 livers, kappa 0.83 [0.63-1.00]; 45 declined pairs of lungs, kappa 0.65 [0.23-1.00]). Ultimately, 155 (42.1%) organs

Table 5 UNOS donor management goals for neurologically deceased donors

Variables	Parameters	Consent n (%), N	Day 1 n (%), N	Final day n (%), N
Central venous pressure	4-10 mmHg	13 (40.6), 32	5 (17.0), 30	5 (15.6), 32
Mean arterial pressure	60-100 mmHg	20 (62.5), 32	7 (23.0), 30	12 (37.5), 32
Ejection fraction	> 50%	8 (88.9), 9	10 (83.3), 12	3 (60.0), 5
Vasopressors	< 1 and low dose*	5 (15.6), 32	9 (30.0), 30	20 (62.5), 32
Arterial Ph	7.3-7.45	14 (43.8), 32	20 (83.3), 24	28 (90.3), 31
PaO_2/F_iO_2	> 300	26 (81.3), 32	12 (52.2), 23	10 (50.0), 20
Serum sodium	≤ 155 mg·dL^{-1}	28 (87.5), 32	26 (89.7), 29	31 (96.9), 32
Urine output	0.5-3 mL·kg^{-1}·hr^{-1}	10 (31.3), 32	3 (10.0), 30	7 (21.9), 32
Glucose	4-8 mmol·L^{-1}	14 (46.7), 30	19 (63.3), 30	22 (73.3), 30

F_iO_2 = fraction of inspired oxygen

This table reports the adherence of physicians to the donor management goals from the United Network for Organ Sharing (UNOS) on the day of consent, one day after consent, and the day of organ recovery (i.e., final day). n refers to the number of donors meeting the definition of the variable and N refers to the total number of donors for whom we have data available for each variable. *Low-dose vasopressors were defined as norepinephrine (10 µg·kg^{-1}·min^{-1}), dopamine (10 µg·kg^{-1}·min^{-1}), and neosynephrine (60 µg·kg^{-1}·min^{-1})[7]

Figure Organ outcomes. This table reports the number of organs transplanted, recovered, not recovered (i.e., declined during organ assessment), and not offered by the organ donation organization. The denominator for each organ is 67 with the exception of the heart (n = 31). When two lungs (or kidneys) were transplanted separately, we counted them as two organs, and if they were transplanted together, we counted them as one organ; lungs from five donors were recovered separately (i.e., lung-single). All organs transplanted are also considered recovered
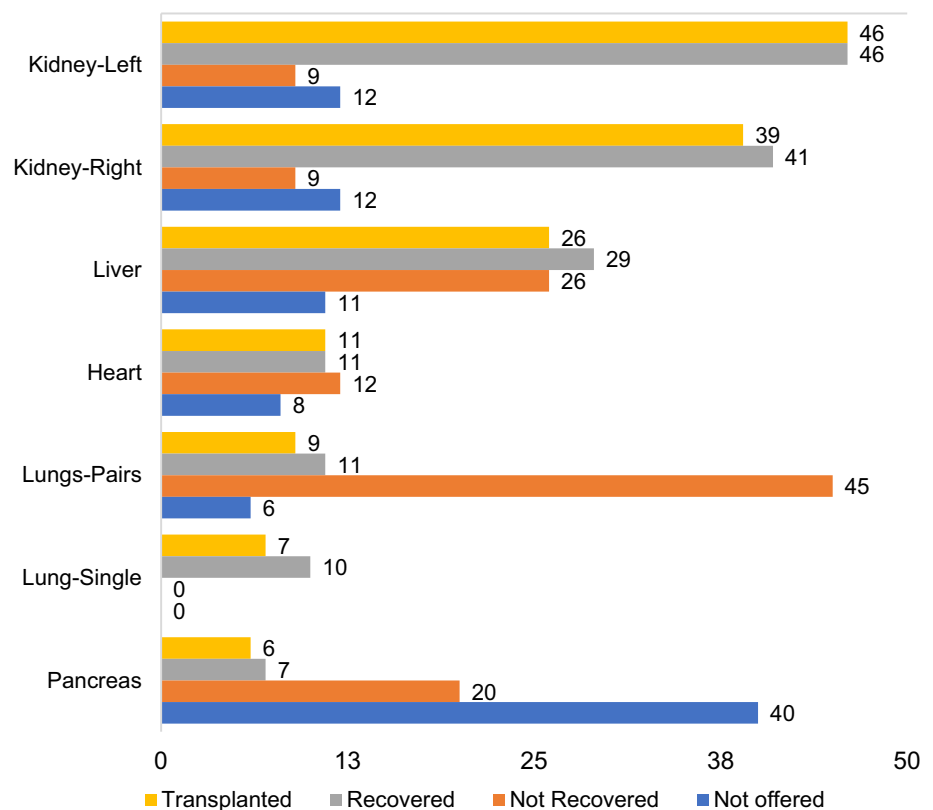
were retrieved from study donors and 144 (39.1%) were transplanted to 141 recipients in Ontario (Figure), with another six transported out of province for anticipated transplantation. Among the five organs that were retrieved but not transplanted, anatomical abnormalities were identified during organ retrieval surgery. Organ donation was accomplished more commonly for NDD donors (n = 29, 93.5%) than DCD donors (n = 21, 58.3%). The mean number of organs transplanted was 3.3 organs per NDD donor and 2.3 organs per DCD donor.

Discussion

This study of deceased organ donation practices across an entire metropolitan area supports the feasibility of a

prospective observational study across the province of Ontario and provides a framework for addressing the challenges to this work at the national level. We observed the clinical care of 67 consented organ donors, 50 of whom donated at least one organ. We addressed and surmounted the three anticipated obstacles to feasibility: 1) authorization for the execution of this study with a waiver of research consent, 2) obtaining complete study data for age, sex, transplant centre, and date and time of transplantation of organs transplanted in Ontario (144 of 150), and 3) the estimated time required for data collection was acceptable.

The most important strength of this study was the partnership with a provincial ODO, TGLN. With hospital REB and TGLN Privacy Office approvals for a waiver of research consent, the instantaneous receipt of an email notification about every consent for donation in the city allowed us to enroll all eligible participants. Retrospective access to TGLN donor data allowed us to supplement data not accessible to ICU research staff and, most importantly, retrieve data about organ outcomes and reasons for organs being declined—data that will be essential for future randomized trials. Finally, the receipt of a small sample of recipient data from TGLN provided a precedent for linking individual donor and recipient data in Canada for the purposes of academic research. The incomplete recording of CPRA levels reflects the completeness of this data within TGLN databases and may reflect the ability of a central clinical service database to support clinical research in general. Nevertheless, close collaboration with TGLN in this Hamilton-DONATE pilot study allowed us to develop a successful model for collaboration with ODO across the country.

Intensive care unit research staff involved in this pilot study had extensive experience in the study procedures and therefore received a level of training that does not reflect what would be required for the national cohort study. Prior to initiating a national study, we plan to conduct a site visit or webinar at each participating centre. This site visit will include training on the study protocol and data collection. Specifically, ICU research personnel will receive a 1.5-hr training on data entry using the CRFs in the electronic data capture in the system: iDataFax[TM]. This training will focus on general aspects of data entry and potential troubleshooting situations and will be supervised by the project manager and central research coordinators.

Limitations of this pilot study point to the challenges we will encounter in a national observational study. One limitation was the inability to obtain data pertaining to the six organs transported outside of Ontario. The exclusion of data related to this small percentage (4.2%) of organs recovered is not enough to deter proceeding to a national study. Moreover, the process of engaging additional provincial ODOs in this research will assist us in identifying out-of-province organ data in the future. Other limitations relate to the observational, feasibility study design. Specifically, the small sample size precludes inferences about associations between specific interventions and organ outcomes; thus, our analyses of clinical data at this stage are purely descriptive.

This city-wide pilot study did, however, provide important data to enhance care in Hamilton. We found variable adherence to donor management goals, which may reflect the acute physiologic derangements in this population or variation in quality of care. Adherence to recommendations for lung-protective ventilation was moderate among NDD donors (Tables 2, 4), where tidal volumes were, on average, slightly lower than the recommended target. This finding likely represents a shift in the ICU toward the adoption of new evidence related to lung-protective ventilation strategies for all ICU patients in general and for neurologically deceased donors in particular. One of a very few rigorous clinical trials that has informed organ donor management is a randomized-controlled trial of a lung-protective ventilation strategy alternative (tidal volume (Vt) 6-8 mL·kg^{-1}; positive end-expiratory pressure [PEEP] 8-10 cm H_2O) *vs* a conventional strategy (Vt 10-12 mL·kg^{-1}; PEEP 3-5 cm H_2O) in 118 organ donors.[20] Lung-protective ventilation was associated with a significantly higher proportion of patients becoming lung donors (54% *vs* 27%; *P* = 0.004).

Adherence to recommendations regarding glycemic control was also low. The use of pulmonary artery catheterization fell far short of recommendations, but reflects the evolution of non-invasive cardiac monitoring in current general ICU practice, and in Hamilton specifically.[21] In contrast, we observed a very high adherence rate to recommendations for hormone therapy supplementation, despite the overall limited existing evidence to support this practice.[12,22,23] Surprisingly, hormone replacement therapy was also administered to DCD donors. While this finding might reflect usual practices in these hospitals outside of the setting of organ donation, the finding may, alternatively, signify an area for increased education of both physicians and organ donation coordinators or a need for specific pre-printed order sets for DCD donors (Table 4).

Conclusion

In summary, the Hamilton-DONATE multicentre pilot study supports the feasibility of a national cohort study on organ donor care. Strong collaboration with provincial ODOs will be essential to conduct a large Canadian

observational study as well as future national or international randomized-controlled trials.

References

1. *Grinyo JM*. Why is organ transplantation clinically important? Cold Spring Harbor Perspect Med 2013. DOI: https://doi.org/10.1101/cshperspect.a014985.

2. *Canadian Institute for Health Information.* Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2004-2013. April 2015. Available from URL: https://secure.cihi.ca/free_products/2015_CORR_AnnualReport_ENweb.pdf (accessed April 2018).

3. *Rosendale JD, Chabalewski FL, McBride MA, et al.* Increased transplanted organs from the use of a standardized donor management protocol. Am J Transplant 2002; 2: 761-8.

4. *Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR.* Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. J Heart Lung Transplant 1995; 14: 734-42.

5. *Kotloff RM, Blosser S, Fulda GJ, et al.* Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. Crit Care Med 2015; 43: 1291-325.

6. *Shemie SD, Ross H, Pagliarello J, et al.* Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. CMAJ 2006; 174: S13-32.

7. *Malinoski DJ, Daly MC, Patel MS, Oley-Graybill C, Foster CE 3rd, Salim A.* Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor. J Trauma 2011; 71: 990-5; discussion 996.

8. *Smith M*. Physiologic changes during brain stem death–lessons for management of the organ donor. J Heart Lung Transplant 2004; 23(9 Suppl): S217-22.

9. *Floerchinger B, Oberhuber R, Tullius SG*. Effects of brain death on organ quality and transplant outcome. Transplant Rev (Orlando) 2012; 26: 54-9.

10. *Dhanani S, Shemie SD*. Advancing the science of organ donor management. Crit Care 2014; 18: 612.

11. *Greer DM, Valenza F, Citerio G*. Improving donor management and transplantation success: more research is needed. Intensive Care Med 2015; 41: 537-40.

12. *D'Aragon F, Belley-Cote E, Agarwal A, et al.* Effect of corticosteroid administration on neurologically deceased organ donors and transplant recipients: a systematic review and meta-analysis. BMJ Open 2017; 7: e014436.

13. *von Elm E, Altman DG, Egger M, et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335: 806-8.

14. *Ferguson ND, Cook DJ, Guyatt GH, et al.* High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013; 368: 795-805.

15. *Higgins JP, Green S*. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration 2011. Available from URL: http://handbook-5-1.cochrane.org/ (accessed April 2018).

16. *Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council of Canada; Social Sciences and Humanities Research Council of Canada*. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Government of Canada; 2014. Available from URL: http://www.frqs.gouv.qc.ca/documents/10191/186009/TCPS2.+pdf/6a8ab915-431b-428d-aa86-b22ca5c78053 (accessed April 2018).

17. *Tu JV, Willison DJ, Silver FL, et al.* Impracticability of informed consent in the Registry of the Canadian Stroke Network. N Engl J Med 2004; 350: 1414-21.

18. *Duan EH, Adhikari NK, D'Aragon F, et al.* Management of acute respiratory distress syndrome and refractory hypoxemia. A multicenter observational study. Ann Am Thorac Soc 2017; 14: 1818-26.

19. *Rabbat CG, Cook DJ, Crowther MA, et al.* Dalteparin thromboprophylaxis for critically ill medical-surgical patients with renal insufficiency. J Crit Care 2005; 20: 357-63.

20. *Mascia L, Pasero D, Slutsky AS, et al.* Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA 2010; 304: 2620-7.

21. *Koo KK, Sun JC, Zhou Q, et al.* Pulmonary artery catheters: evolving rates and reasons for use. Crit Care Med 2011; 39: 1613-8.

22. *Macdonald PS, Aneman A, Bhonagiri D, et al.* A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. Crit Care Med 2012; 40: 1635-44.

23. *Dikdan GS, Mora-Esteves C, Koneru B*. Review of randomized clinical trials of donor management and organ preservation in deceased donors: opportunities and issues. Transplantation 2012; 94: 425-41.