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Pharmacological Interventions for the Hemodynamic Management of Deceased Organ Donors

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Résumé

Chaque année, plusieurs milliers de patients aux prises avec une maladie chronique terminale s'ajoutent à la liste d'attente pour une transplantation d'organe, espérant ainsi prolonger leur espérance de vie. Le plus souvent, le don d'organes survient suite au décès neurologique d'un donneur, une condition qui n'est pas sans conséquence sur la qualité des organes. Les traitements pharmacologiques visant à rétablir l'homéostasie et à protéger les organes à transplanter ont été majoritairement étudiés dans des études observationnelles, au début des années 80. Depuis, très peu d'essais randomisés ont évalué l'impact d'interventions chez des donneurs sur des issues cliniques chez des receveurs. Conséquemment, le bénéfice net des traitements pharmacologiques utilisés de routine chez les donneurs d'organes après décès neurologique demeure inconnu et la rationnelle physiopathologique supportant leur utilisation est questionnable.

Cette thèse a pour visée de recenser les évidences supportant les traitements pharmacologiques employés pour la stabilité hémodynamique des donneurs d'organes après décès neurologique et de décrire le niveau d'évidence supportant leur usage. Nous visons également à identifier des cibles de recherche potentielles basées sur de nouvelles observations pathophysiologiques. Pour atteindre ces objectifs, nous avons dressé un large portrait de la prise en charge actuelle des donneurs après décès neurologique, ceci menant ensuite à l'exploration des perceptions des médecins intensivistes canadiens en regard de ces interventions. Nous avons également exploré la présentation clinique cardiaque des donneurs et nous avons identifié des barrières à la recherche clinique dans le domaine. Notre thèse a mené à 4 articles scientifiques.

D'abord, nous avons démontré à l'aide d'une revue systématique des lignes directrices internationales sur la prise en charge des donneurs après décès neurologique que les recommandations actuelles sont incohérentes et que leur faible qualité méthodologique reflète la lenteur de l'émergence de la recherche dans le domaine. Ensuite, nous avons effectué un sondage national auprès de médecins des soins intensifs ayant de l'expérience dans la prise en charge des donneurs. Nous avons ainsi démontré que les perceptions de pratiques sont très variables au pays et avons attribué ces divergences d'opinions au manque de données probantes, et à la possible inexpérience relative des médecins face aux rares cas de don d'organes sur une

unité de soins intensifs. Notre troisième article a démontré que la dysfonction ventriculaire droite est fréquente après un décès neurologique, bien que la littérature actuelle ne mette l'emphase que sur la dysfonction ventriculaire gauche et ses conséquences. Nous émettons l'hypothèse que la description actuelle des conséquences hémodynamique du décès neurologique est incomplète et qu'une meilleure compréhension des mécanismes sous-jacents à la dysfonction ventriculaire droite permettrait d'identifier de nouvelles cibles thérapeutiques. Finalement, en s'appuyant sur nos observations, nous questionnons l'efficacité et la pertinence d'interventions pharmacologiques administrées de routine chez les donneurs telles que l'hormonothérapie de remplacement. Nous avons donc effectué un essai randomisé pilote visant à évaluer la faisabilité d'une étude multicentrique déterminante comparant la levothyroxine au placebo chez des donneurs potentiels. Cette étude pilote a démontré qu'une étude d'envergure était nécessaire afin d'évaluer le bénéfice de l'intervention et a permis d'identifier des barrières à la recherche spécifiques au domaine. Nous proposons que des activités de transfert de connaissances sur le niveau d'évidence supportant les interventions pharmacologiques actuelles soient implantées en préparation d'un essai randomisé contrôlé multicentrique.

Cette thèse a permis de mettre en lumière la validité questionnable du traitement pharmacologique pour la prise en charge de l'instabilité hémodynamique des donneurs d'organes tel qu'il est utilisé présentement. Nous avons fait ressortir que le traitement actuel est historiquement basé sur des données de faible évidence. Nous suggérons que l'avenir de la recherche interventionnelle chez les donneurs d'organes repose sur la capacité des cliniciens et des chercheurs à reconnaitre les zones d'incertitude dans les connaissances actuelle et à accepter des changements dans leur pratique.

Mots-clés : Décès neurologique, don d'organes, hémodynamie, soins intensifs

Abstract

Every year, thousands of chronically ill patients are added to the transplant list, in the hope of an organ transplant that could save their life. Most frequently, organ donation occurs following neurological death of a donor, a clinical pathological condition that can jeopardize the quality and stability of organs. The body of literature on the hemodynamic consequences of neurological death and their treatment exist since the early 80's. Since then, very few randomized trials have been performed on the neurologically deceased donor population. As a consequence, the benefit of routine pharmacological therapies for the hemodynamic management of neurologically deceased donors on recipients' outcomes is still uncertain, and the pathological theory underlying their use remains questionable.

Consequently, this thesis aims at describing the actual body of evidence supporting the pharmacological treatment for the hemodynamic management of neurologically deceased donors and the theoretical rationale for their use. We also aimed at adding to the actual knowledge of brain death physiological hemodynamic consequences. To achieve this goal, we drew a broad portrait of the actual management of hemodynamic instability in organ donors, leading to the exploration of perceptions on these interventions. We then explored physiological consequences of neurological death at the heart level and evaluated the feasibility of conducting a multicentre trial on a pharmacological intervention in donors. Our thesis let to four research articles.

First, we demonstrated through a systematic review of international guidelines for the management of neurologically deceased donors that the existing recommendations are inconsistent and that their poor methodological quality reflects the slow emergence of clinical research in the field. Then, in a national survey of intensive care physicians with experience in organ donor clinical management, we identified varying perceptions of practices in the country. We attributed this difference in opinions to the paucity of research in the field and to the possible relative inexperience of some physicians when managing deceased donors, a relatively rare condition in the intensive care unit. Our third article suggested that right ventricular dysfunction is frequent after neurological death, although existing literature focus mainly on the occurrence and consequences of left ventricular dysfunction. We postulate that the actual description of

hemodynamic consequences of neurological death is incomplete and that a better understanding of the mechanisms underlying right ventricular dysfunction would permit to identify new therapeutic targets. Finally, based on our previous conclusions, we questioned the relevance and efficacy of levothyroxine routine administration in donors and designed a pilot randomized controlled trial to evaluate the feasibility of a multicenter definitive trial. This pilot trial permitted to identify important barriers to interventional research including neurologically deceased donors. We propose that knowledge translation activities on the actual level of evidence supporting routine interventions be implemented in the preparation of a future randomized trial.

This thesis permits to question the validity of the actual pharmacological management of neurologically deceased donors highlighting the paucity of high-evidence literature in the field and the penetrance of historical interventions and concepts. We suggest that the future of research in the field lies on the ability to recognize areas of uncertainties and the acceptance of practice change.

Keywords: neurological death, organ donation, hemodynamics, intensive care unit

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List of acronyms

CONSORT: Consolidated Standards of Reporting Trials

CNTRP: Canadian National Transplant Research Program

KDPI: Kidney Donor Profile Index

IRODat: International Registry on Organ Donation and Transplant

OPTN: Organ Procurement and Transplantation Network

UNOS: United Network for Organ Sharing

List of abbreviations

ACTH: Adrenocorticotrophic Hormone
ADH: Antidiuretic Hormone
ATP: Adenosine Triphosphate
CK: Creatine Kinase
CVP: Central Venous Pressure
ECG: Electrocardiogram
EEG: Electroencephalogram
CPP: Cerebral Perfusion Pressure
DCD: Donation after Cardiocirculatory Death
FSH: Follicle Stimulating Hormone
GIK: Glucose-Insulin-Potassium
ICP: Intracranial Pressure
KDPI: Kidney Donor Profile Index
LDH: Lactate Dehydrogenase
LH: Luteinizing Hormone
LV: Left Ventricle
LVEF: Left Ventricular Ejection Fraction
MAP: Mean arterial pressure
NDD: Neurological Determination of Death
NF-KB: Nuclear Factor-kappa B
ODO: Organ Donation Organization
PCWP: Pulmonary Capillary Wedge Pressure
PVR: Pulmonary Vascular Resistance
RCT: Randomized Controlled Trial
RV: Right Ventricle
SERCA: Sarco/endoplasmic reticulum Ca2+-ATPase
TSH: Thyrotropin Hormone (Thyroid Stimulating Hormone)
T3: Triiodothyronine
T4: Levothyroxine

« 千 里 之 行 始 于 足 下 »

– 老 子

A ma famille et mes amis qui inspirent chacun de ces pas

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Chapter 1: Introduction and theoretical background

1. General introduction

For patients with end organ dysfunction, and with the exception of chronic dialysis for terminal kidney disease, organ donation is often the only option to prolong survival. During the last decades, modern medicine has made progress in the organ donation field, permitting to save thousands of lives.[1] Despite these successes, the disparity between the number of organs available for transplant and the number of patients on the waiting list is growing, and the organ shortage remains a preoccupying social issue.[2] The availability of suitable organs for transplantation rely on a continuum of careful actions along a journey that starts with potential donor identification and ends with organ-recovery surgery.[3] Throughout the process, several limiting factors may impair the ability to successfully transplant organs and contribute to organ wastage. These limiting factors include the inability to identify potential donors, the challenges related to brain death diagnosis, the absence of family or patient consent to donation, the hemodynamic instability of potential donors, and the subjective or objective low quality of retrieved organs.[2-4] Each of these steps warrants improvement through research and education, and should be addressed separately. With this in mind, we have focused on the hemodynamic instability of deceased donors and its pathophysiology, consequences and possible treatments. Specifically, this thesis aims to characterize the actual pharmacological treatment of the hemodynamic instability in potential deceased donors, to add to the actual knowledge on the pathophysiology of brain death-induced cardiomyopathy, and to determine the feasibility of assessing pharmacological interventions for the management of deceased donors' hemodynamic instability in randomized controlled trials.

1.1 Definition of neurological death in the context of organ donation

This thesis focuses on the pharmacological management of organ donors after determination of neurological death. Nowadays, the concept of brain death is largely accepted worldwide and, although specific criteria still vary, institutional protocols for its diagnosis are implemented in the majority of high-income countries.[5,6] However, the lack of recognition of

the cessation of all brain functions as a valid death definition has limited progress in the field for decades.[7] Today, although no religion formally prohibits organ donation, individuals pertaining to specific groups may still have some personal objections due to religious motives, and organ donation knowledge evolves heterogeneously in the world. [8-10] Still, for the majority, the concept of neurological death is well accepted and the debate has mainly moved towards defining specific criteria. The inclusion of broader criteria in the definition of neurological death is now under discussion, and philosophical and religious arguments criticize all avenues, contributing to the ethical debate.[6] In this context, the review of pharmacological interventions, the exploration of brain death pathological consequences and the implementation of research protocols in neurologically deceased donors necessitate a comprehension of the historical views of organ donation. In the next section and as a preamble to the review physiological concepts, we will present the historical perspectives on the concept of brain death as well as the historical hallmarks of organ donation.

1.1.1 Historical perspectives on the concept of death

The concept of breath as a source of life and of vital energy (Qi or prana in oriental cultures) is common to many cultures and times, and is found in ancient texts such as the Bible, the Dao De Jing and the Koran.[6] Traditionally, and as far as ancient Egypt and Greece, death was defined as the irreversible cessation of respiration and heartbeat, but until mid 1800's some advocated that rigor mortis was the only certain criterion of death.[6,11,12] As soon as the Mid-Age period, the Rabbi Moses Maimonides observed and declared that decapitated but still moving victims were indeed dead, but until the late 19th century, the cessation of the heart was still considered as the only admissible diagnosis of death.[11,13,14] Between 1890 and 1905 several observations of the cessation of respiration preceding that of the heart in brain injured patients with elevated intracranial pressure (ICP) led to a progressive shift in paradigm.[15-20]

From these years until the end of the 1950's, several angiographic reports described comatose patients without any passage of contrast in their brain circulation, thus reinforcing a previously evoked idea of a mandatory cerebral blood flow in the maintenance of cerebral function.[21] With the advent of advanced resuscitation and mechanical ventilation in the 1950's, concerns on the maintenance of vital functions in hopelessly brain-injured patients were

raised.[11,22] Comatose patients suffering from severe brain injuries were kept alive on artificial respirators, but their prognosis was more than uncertain.[11] Questions were raised and balanced between the unethical withholding of life-sustaining manoeuvres and the not less unethical extraordinary measures applied to unconscious patients.[11] In 1959, the concept of an "irreversible" death of the nervous system was introduced, and further life supporting manoeuvres were declared futile in patients presenting this condition.[6,23,24] Avoiding the word "dead" to describe this clinical presentation, a physician named Dr Mollaret introduced the historical concept of "*coma dépassé*", adding to the debate.[25] This ultimate form of coma was defined as the absence of consciousness concomitant to a complete loss of vegetative functions. Although the definition of *coma dépassé* does not clearly evoke brain death, the authors recognized the occurrence of death automatically following the cessation of cardiorespiratory support.[25]

In 1968, the Journal of the American Medical Association published a definition for "irreversible coma" that was then considered by the Harvard ad hoc committee as the new criterion for death.[22,26] The Uniform Determination of Death Act resulting from the Harvard committee integrated the whole-brain death in the accepted definition of death and importantly, legally defined the whole-brain death criterion as : "the irreversible cessation of all functions of the brain, including the brain stem".[27] Four conditions were needed at this time to meet the irreversible coma definition: 1) unreceptivity and unresponsiveness 2) absence of movement or breathing 3) no reflexes 4) confirmatory flat electroencephalogram (EEG).[26] Today, although still not uniform in its diagnosis, the concept of neurological death is globally accepted around the world and the vast majority of organ donors are neurologically deceased.[6]

1.1.2 The actual determination of brain death

Although the concept of brain death is broadly accepted, two specific definitions of brain death actually exist: whole brain death and brain stem death.[28] The criteria provided by the 1981 Uniform Determination of Death Act refer to the whole brain death.[29] The whole brain death implies the loss of all brain functions, including and not limited to those of the brain stem.[28] This definition of brain death is the actual standard for the determination of death in Canada, US and a majority of European countries.[6] The diagnosis of brain stem death refers to the loss

of brain stem functions, but does not require the irreversible cessation of all brain functions.[28] However, an irreversible loss of consciousness is still required. The brain stem death definition prevails in the UK.

The clinical determination of brain death lacks sensitivity to differentiate the two definitions, since the patient is declared neurologically deceased on the basis of an irreversible loss of consciousness combined with a clinical loss of all brain stem functions.[28] The clinical exam is not sensitive enough to identify preserved perfusion to specific brain areas and particular functions such as the neuroendocrine response. Over the past years, the use of ancillary tests in the diagnosis of neurological death has gained popularity among the medical community, particularly in cases where confounding factors interfere with the clinical evaluation.[30] Ancillary tests include the assessment of brain function, perfusion or cerebral blood flow, the latter being the preferred one.[30] However, when using ancillary tests, preserved intracranial blood flow or cortical electrical activity in the context of an irreversible loss of consciousness would comply to the definition of brain stem death, but not of whole brain death.[13,31] Moreover, the identification of isolated cell activity of the neuroendocrine axis could be explained by extracranial blood supply.[13] On the opposite, the sensibility of brain stem death diagnosis is criticized in the sense that it cannot exclude a certain level of awareness.[13] In summary, despite a consensus that recognizes brain death as the ultimate end of life, with the advent of sensitive ancillary tests, the debate on the specific definition of brain death was relaunched.[32,33] This particular question of the use of ancillary tests in the diagnosis of neurological death is beyond the scope of this thesis and will not be discussed further.

1.2 History of organ donation after neurological death

The first kidney transplant attempt from a human donor in the modern era was performed by a Russian surgeon, Dr Yu Yu Voronoy, in 1936.[7,14] The donor had died (cessation of heart beat) 6 hours before the transplantation surgery and the recipient survived only 2 days to the surgery, probably due to a blood mismatch.[7,14] Further attempts at kidney transplantations from donors after cardiac death were tried in the following years. In a time before the advent of immunosuppressive drugs, successes were mitigated.[7,14] In 1954, Dr Joseph Murray successfully performed the first kidney transplant from a living donor to his identical twin.[7]

During the following years, transplant centres established themselves throughout the United States and Europe, and kidney, liver, lung, and pancreas transplants were performed one after the other with success.[7] However, all those transplants were from neurologically deceased donors, only after confirming their cardio circulatory arrest.[7,14,34]

The first organ transplantation from a declared neurologically deceased and heart-beating donor was performed in 1963 by the Belgian surgeon Guy Alexandre, 5 years before the Harvard committee criteria were released.[7,34] Alexandre proposed a definition of brain death very similar to the one that would later be adopted by the Harvard committee, but adding the precondition of severe brain injury. His definition incorporated the following: 1) bilateral mydriasis 2) absence of reflexes 3) absence of spontaneous respiration, 5 minutes after mechanical ventilation has been stopped 4) hypotension necessitating vasoactive drugs 5) flat EEG.[7,14] Although the transplant was successful, the concept of organ donation from a neurologically deceased patient was not unanimously accepted by the medical community.

In this context of controversy around the definition of death, in 1964, a single kidney was recovered from a mechanically ventilated comatose Swedish patient for the purpose of transplantation.[7,19] The patient could not be declared neurologically deceased, since no law existed to frame brain death diagnosis.[7] The donor officially died from a cardiac arrest 2 days after the transplant surgery.[7] A strong debate divided the Swedish medical community for years after this case although a new concept of death called "cerebral death" was submitted, based on this experience.[7,19] Even after Alexandre's successful kidney transplant, neurologically deceased donors were still declared cardiorespiratory dead before donation.[7] Since no brain death law existed, transplant surgeons were reluctant to use neurologically deceased donors and were concerned of the potential adverse publicity it could do to further donation surgeries.[7]

Despite all doubts and debates, in 1967, Christiaan Barnard performed the world's first successful human heart transplant in a 54-year-old patient in South Africa.[35] The young female donor and the male recipient were brought to two adjacent theaters, the recipient being prepared while the inevitable death of the donor would occur.[35] Transplantation was performed only after the donor's electrocardiogram (ECG) shown no activity for 5 minutes concomitantly with the absence of spontaneous breathing and reflexes.[35] Already 2 weeks later, Dr Barnard performed a second heart transplant in a male patient, Dr. Philip Blaiberg.[36] The donor suffering from an

unsustainable subarachnoid haemorrhage was declared brain-dead after a mind struggling decision taken by the attending intensive care physician.[37] Still, cardiovascular death was also confirmed before the surgery.[36]

1.3 Epidemiology of organ donation

The majority of organs are transplanted from donors after neurological determination (NDD) of death, but the number of organs transplanted from donors after cardio-circulatory determination of death (DCD) is rapidly rising, and currently reaches around 15% of total deceased donations.[1,38,39] The actual donor rate in Canada is around 15.5-20 donors per million population, and this number has been steadily increasing over the past 20 years.[38,40] In 2016, Canada ranked 19th among 68 countries for deceased donor rate.[40] The highest donor rate in the world is shown by Spain, with 33-46 donors per million population.[1,41] However, statistics on donor and transplant rates need to be interpreted carefully when employed for comparisons, as an inferior donor rate may simply reflect a lower rate of injuries, better healthcare services, or heterogenous definitions of donor rate.[40,42] For example, some countries include in their donor rate donors that were identified, but in whom no organs were recovered or transplanted.[40] In comparison, in Canada, donor rate represents the number of actual donors, referring to donors from whom at least one organ per million population was successfully transplanted.[40] Apart from aforementioned and from differences in organ donor care, disparities in organ procurement statistics between countries could also be attributed to the use of different models of consent to donation, referring here to the existing *opt-out* system (presumed consent) versus the *opt-in* system (explicit consent).[43] However, although the opt-out system was meant to result in increased donor rates, the difference between the performance of the two systems is not obvious, and the impact of these systems on donation rates is still under debate.[43,44] In Canada, an opt-in system in employed for consent to donation, except in Nova Scotia, a province that has recently adopted the opt-out system.[44]

Theoretically, potential donors include all members of the general population.[40] However, not every patient will be considered for organ donation upon its death. In the context of organ donation after NDD, the potential donor pool is limited to identified individuals that fulfill specific diagnosis criteria.[40] Then, every accepted donor has the potential to give up to 8 organs.

However, organ recovery criteria are strict, and organs from donors that do not fulfill *standard* transplant criteria are often rejected.[45] Over the last 10 years, the number of neurological deaths secondary to traumatic brain injury has constantly decreased, thus changing the image of the typical organ donor.[45,46] Patients suffering from fatal strokes and anoxic brain injuries now represent the majority of NDD donors, the consequence being the aging of the potential donor pool.[46] In response to this demographic change, potential donors that were historically excluded from donation are now considered, and donation outcomes from *expanded* criteria donors are presently being studied.[42,47,48] Expanded inclusion criteria for donation typically include an age over 70 years, significant medical history in donors younger than 60 years, high-risk social behaviours or a history of viral exposure.[45,49]

According to the Organ Procurement and Transplantation Network (OPTN), the unified transplantation network in the USA based in Richmond Virginia, the number of organs recovered per donor has stabilized since 2000, with an average of 3.5 organs/donor for standard criteria donors and around 1.8 organ/donor for expanded criteria donors.[39,50] However, numbers vary according to geographical area, donor type (NDD or DCD) and donor's age or characteristics (standard criteria donor or expanded criteria donor).[39,50] Organ donation performance also varies according to the target organ. Although the number of kidneys recovered per donor is high (1.54-2.00), the performance for heart (0 – 0.43) and lung (0.05-0.77) donation remains low.[50]

1.4 Pathophysiology of brain death

Following catastrophic brain injury, an increase in ICP that is not counteracted by a proportional increase in cerebral perfusion pressure (CPP) can lead to neurological death.[51-53] First, the compression of cerebral arteries produces brain tissue infarction.[54] The ischemic pattern then gradually progresses in a rostro-caudal fashion, from mid-brain to pons, to medulla, ultimately reaching the spinal cord. [55,56] Resulting from the injury, mass effect progressively produces venous engorgement.[54] Brain swelling compresses the brain stem which is then forced through the foramen magnum, a phenomenon called "coning".[54,57] Since the cardio-respiratory seat is

located in the reticular formation of the brain stem, respiratory functions are compromised, and death ensues.[57]

1.4.1 Anatomy of the autonomic storm and hormone depletion theory

Following brain injury, and secondary to increased ICP, ischemia within the pons breeds the Cushing reflex, a phenomenon characterized by hypertension, bradycardia and irregular breathing.[18,58,59] The first description of this phenomenon was attributed to the work of Harvey Cushing, in 1901.[18] In a lecture presented before the College of Physicians of Philadelphia in 1902, he described the result of his research on an animal model in which he studied the cerebral vascular adaptation to a generalized increase in ICP.[18] In response to increased ICP and in an attempt to optimize CPP to the ischemic region, the sympathetic system is activated, causing systemic hypertension.[18] Baroreceptors then activate the parasympathetic system to balance the sympathetic system, causing bradycardia.[57] With the increase in systemic blood pressure, perfusion to the ischemic pons is re-established and ICP decreases.[18] However, if the primary cerebral insult is not alleviated, rise in ICP will instore ischemia in the pons again, to a point where the Cushing reflex is no longer sufficient to compensate.[18] While ischemia reaches the most distal midbrain, the vagal motor nucleus is destroyed, and the parasympathetic activity is abolished.[58] With the progression of ischemia to the lower medulla oblongata, an unopposed sympathetic stimulation is responsible for a systemic catecholamine surge.[60] This "autonomic storm" also called "sympathetic storm" or "catecholamine storm" is characterized by hypertension, tachycardia and vasocontriction.[56,61] Ultimately, spinal cord ischemia follows, and hypotension and cardiovascular collapse result from the loss of all sympathetic tone.[57,60]

The acuteness in ICP increment, the speed of neurological death and the extent of the primary injury are probable predictors of the importance of the catecholamine release, and consequently, of the severity and the duration of the autonomic storm.[54,60,62,63] With slower damage progression or with a less severe primary insult, adaptation mechanisms help the brain to autoregulate.[60] However, with an abrupt increase in ICP, autoregulation fails and the adaptation of brain circulation becomes insufficient.[60] Although some authors advocate the opposite, variability between patients' hemodynamic parameters possibly depends on the anatomical structures involved during the brain death process.[60,64] Some viable tissue may

remain despite the global cessation of brain perfusion, and this might explain the variability in hemodynamic and hormonal responses to brain death, thus contributing to the modern controversy around the determination of brain death presented earlier.[54]

In the occurrence of brain death, when ischemia progresses to the medulla, blood supply to the hypothalamus is impaired, causing the gland to cease its production in antidiuretic hormone. As the hypothalamus is responsible for its synthesis, the posterior pituitary lobe, irrigated by the inferior hypophyseal artery, is responsible for the release of anti-diuretic hormone.[57,65] In contrast to the hypothalamus, the pituitary gland, and particularly its posterior lobe, is anatomically protected from the brain-swelling-induced ischemia by the *turcic stella*.[65] Also, blood supply to the posterior lobe is not as affected by ICP as the hypothalamus' because its perfusion comes from the cavernous portion of the internal carotid artery and its branches, which are extradural arteries.[65] The destruction of the hypothalamus, and not of the posterior lobe of the pituitary gland, would be the most probable cause for low antidiuretic hormone levels, and related diabetes insipidus in brain-dead patients.[65]

As the posterior lobe of the pituitary gland remains sometimes completely intact, the anterior lobe of the pituitary gland, on the other hand, often suffers incomplete but important damages.[66] The reason for this difference between the two pituitary gland lobes may be anatomic, since the 2 different lobes are formed from distinct embryologic tissues; anterior (oral ectoderm) and posterior (neuro-ectoderm).[57] In contrast to the posterior pituitary lobe, the anterior pituitary lobe produces hormones (prolactin, adrenocorticotrophic hormone (ACTH), thyrotropin hormone (TSH), follicle stimulating hormone (FSH), and luteinizing hormone (LH)), and their secretion is regulated by hypothalamic hormones. The anterior lobe of the pituitary gland is irrigated by a portal venous system and by the superior and inferior hypophyseal artery. [57,66] The latter originates from the medial side of the carotid siphon, at the level of the ophthalmic artery.[66] Most of its course is intradural and therefore, necrosis of the anterior lobe of the pituitary gland is expected during the brain death process.[66] As a consequence, levels of hormones produced by the anterior lobe should rapidly decrease after brain death, with an expected half-life of 5-34 minutes in normal renal and hepatic function conditions.[66,67] However, the outer layer of the anterior lobe is irrigated by the capsular artery, an extradural vessel.[65] Therefore, anterior pituitary hormones can sometimes be detected in the

peripheral plasma after brain death, and necrosis of the anterior lobe can be incomplete, with preserved peripheral cells.[65,68] These small areas of preserved cells in the pituitary gland and sometimes even in the hypothalamus may be responsible, at least partially, for the blood detection of hormones after brain death diagnosis, and more importantly for the persistence of response to stimulation tests for some days after brain death in some individuals.[67]

In summary, persistence of blood hormone levels and variability in hormonal stimulation tests results in brain-dead patients theoretically depend on the mechanism of the injury, the rapidity of the brain death process, and the timing after brain death, and consequently to the extent of remaining blood supply to the pituitary gland and hypothalamus.[62,69-71] However, the pathophysiology of brain death, the theory of hormone depletion, and consequently, the choice of pharmacological agents employed for donor care mostly rely on animal models, in which such a variability is not evocated. More than 50 years after the first heart transplant from a neurologically deceased donor, the mechanisms responsible for the observed hemodynamic instability after brain death still needed elucidation. The next section will summarize findings on hormone depletion following brain death in both animal models and human studies.

Animal models

In 1984, a group of researcher conducted an experimental Chacma baboon model with the objective of understanding the effects of brain death on the heart and on the circulation.[72] This article would later become one of the most cited in the organ donation field, as it set the basis for ensuing research and, consequently it led to contemporary organ donor pharmacological management.[64,72-78] The experiment consisted in inducing brain death in 10 Chacma baboons by inflating a balloon in the subdural space. The study outcomes were various hemodynamic parameters (e.g., ECG, arterial pressure, pulmonary artery wedge pressure, right atrial pressure, stroke volume, cardiac output, systemic vascular resistance) and hormone blood levels (e.g., circulating catecholamines, thyroid hormones, TSH, cortisol, insulin, antidiuretic hormone (ADH) and glucagon).[72] The investigators also recorded markers of hypoperfusion and of heart damage (e.g., lactate dehydrogenase (LDH), creatine kinase (CK), glycogen, lactates).[72] Amid the 10 animals, 2 also had superimposed bilateral vagotomy, 2 had bilateral

adrenalectomy and 2 received propranolol. Brain death occurred within 20 minutes and the animals were followed for a maximal period of 24 hours.[72] Following brain death, the investigators observed abnormal ECG, described as ventricular arrhythmias, inverted T waves or ST segment elevation. They also described a rapid increase in MAP, PCWP (pulmonary capillary wedge pressure), PVR (pulmonary vascular pressure) and CVP (central venous pressure) followed by a fall in all the observed parameters following brain death.[72] The catecholamine levels variation patterns were similar to that of hemodynamic parameters. Markers of heart ischemia (LDH and CK) rose in some animals, and a group of baboons that were not reanimated with fluids during the experiment also presented an increase in serum lactates and glycogen. Furthermore, the histological analysis of cardiac myocytes revealed the appearance of contraction bands, focal myocardial cell necrosis and interstitial edema. Bilateral vagotomy and propranolol prevented the hemodynamic and ECG changes.[72] Based on these observations, the investigators proposed that the catecholamine surge following brain death was responsible for the hemodynamic changes and for the myocardial damages, and that this phenomenon could be prevented by the administration of beta-blockers.[72,74] The authors also measured pituitary and hypothalamus hormones serum levels. They observed that thyroid hormones (triiodothyronine (T3) and levothyroxine (T4)) levels were decreased to 50% of the baseline values until being undetectable, but that TSH levels remained unchanged.[72] Cortisol levels followed a similar pathway to the thyroid hormones, and insulin levels rapidly declined in the first 5 minutes of the experiment, also reaching undetectable values. Finally, ADH disappeared from the circulating plasma within 6 hours and the animals featured clinical signs of diabetes insipidus.[72]

Although this study was conducted in a limited number of animals, suffered from a lack of control group and presented no statistical plan, the novelty of its findings generated enthusiasm in the scientific community.

Following this first study, the same group of investigators pursued their research with animal experiments in baboons, dogs, pigs and rats. They concluded to 4 major findings: 1) brain death is accompanied by an autonomic storm implying a surge in serum catecholamines 2) due to pituitary gland ischemia, hormone levels (anterior and posterior) are reduced following brain death 3) histologic changes in organs that translate in organ dysfunction occur following brain

death, and these changes are caused by catecholamine toxicity and hormone insufficiency 4) the administration of a hormone cocktail can prevent or treat organ dysfunction.[53,64,76,79,80]

Following these first experiments, other authors have corroborated these conclusions using various animal models (e.g, dogs, rats, pigs): a Cushing reflex occurred immediately after an abrupt increase in ICP, and it was predictably followed by an autonomic storm described as an increase in blood pressure and in vascular resistance. However, some variability was already observed in the presentation and duration of the autonomic storm, with some animals featuring an unexplained biphasic or tardive increase in blood pressure.[71,81,82] The majority of animals presented clinical features of diabetes insipidus, and ADH levels were often decreased to undetectable levels.[63 81-83] Following the induction of brain death, thyroid hormones (T3 and T4) levels were also decreased, reaching undetectable levels in several animal models, but in some animals thyroid hormone levels (T3, T4 and TSH) remained in the normal range.[53,81-84] The pharmacokinetics of cortisol levels was not consistent between studies.[82] In response to increased ICP, some investigators observed an increase in cortisol levels in the first minutes of the experiment followed by a decline, sometimes reaching undetectable levels.[53,71,81] Similarly, insulin levels were described as decreased or normal. [53,84 71,81,82]

Human studies

Although the pathophysiology of the autonomic storm in the period surrounding brain death seems well acknowledged, its epidemiology and diagnostic criteria in potential donors are not reported. Animal models suggest that the autonomic storm is a milestone in the brain death process, and this theory has translated in the common description of human neurological death pathophysiology.[56,64,85] However, the frequency of clinically recognized autonomic storms in potential organ donors could be situated around 60%, depending on clinical definition.[58,86] Also, some potential donors may experience not only one, but repetitive hemodynamic changes corresponding to an autonomic storm in the hours following brain death.[86]

The difference between bench and beside studies may lie in different injury mechanisms leading to brain death. Two main models have been used in animal studies. In the first one, used more

commonly, ICP is rapidly increased with the injection of fluids in the subdural space, through a catheter placed via a trepanation hole in the skull.[53,55,81,87] In this model, brain death predictably occurs in minutes following the intervention (around 20 minutes).[53] The acute increase in ICP and the speed of neurological death are thought to be important predictors of the autonomic storm, thus potentially explaining the reproducibility of the animal study results.[62] In humans suffering from various causes of brain injuries, including not only traumas but also anoxia, strokes or subarachnoid haemorrhages, neurological death rarely occurs in such a predictable and rapid manner. In the second model used in animal studies, brain death is obtained by the ligation of cerebral arteries (carotid and vertebral).[88] The ensuing brain death in animals implies a complete absence of blood flow to the whole brain, which again may not always be the case in humans, where residual flow to specific area, including portions of the pituitary and hypothalamus glands, sometimes remain.[22,27]

A recent narrative review using a systematic search listed 32 studies that evaluated the occurrence of diabetes insipidus as a marker of posterior pituitary failure in brain-dead patients, reporting a mean frequency around 50%.[32] Together, these studies included 1878 adult and pediatric neurologically deceased patients.[32] Thus, not all patients meeting the clinical definition of brain death present with posterior pituitary failure and diabetes insipidus as the animal models suggested. As soon as the first publication on *coma dépassé*, Mollaret et al. observed that some cases, but not all, featured diabetes insipidus criteria.[25] Since then, studies have reported diabetes insipidus frequencies varying from 9% to 100% in humans declared brain dead.[65,89-92] Individual studies reporting a 100% frequency of diabetes insipidus in their sample all have in common small sample sizes and relatively homogeneous mechanisms of traumatic neurological death.[65,91-93] Also, in these studies, describing the epidemiology of diabetes insipidus in brain dead patient was not the primary objective.[65,91-93]

The 2016 narrative review cites 3 studies reporting peripheral levels of hypophysiotropic hormones (luteinizing-releasing hormone, corticotropin-releasing hormone, and growth hormone-releasing hormone) in brain-dead patients.[32] These studies observed detectable levels of these hormones in a majority of patients, but samples were small and showed interindividual variability in results.[32,66,67,70] The anterior pituitary hormones levels were maintained within detectable range up to three days after brain death diagnosis.[67] Six studies cited in the review

used stimulation tests to assess the anterior pituitary function, and the response to insulin-induced hypoglycaemia, thyrotropin-releasing hormone and luteinizing hormone-releasing hormone have been reported as completely blunt or preserved.[65-67,94-96] In the studies reporting negative response to the stimulation test, authors attributed the preserved blood concentration of anterior pituitary hormones to extracranial sources.[94] However, a persistent active secretion could not always be ruled out, since some subjects still had positive stimulation test responses even after brain death declaration.[67]

Following brain death, ACTH levels remained generally in the normal range although random cortisol levels were highly variable and reported as low, normal or high.[32,67,70,97-101] However, in general, healthy humans cortisol reference values have been applied to brain dead patients.[102] No association was observed between hypotension and low random cortisol levels.[70]ACTH stimulation test yielded no increase in cortisol in one study, but did provoke an increase in cortisol in another more recent study, although an attenuated response was commonly observed.[67,102]

Although not universal, but consistent with findings in animal studies, low T3 levels and normal to low T4 levels were observed after brain death.[67,70,97-101,103] However, normal TSH and normal or high reverse T3 levels were interpreted as a euthyroid sick syndrome rather than as a pituitary failure.[32,70,98,99,103] Following a catastrophic cerebral lesion leading to neurological death, inflammatory markers are released, leading to increased intracellular nuclear factor-kappa B (NF-KB).[104] Following its translocation into the cell nucleus, NF-KB induces a reduction in deionidase-1 enzyme expression.[104] A reduction in T4 to T3 conversion ensues, a feature common among various critical care patients.[99] This mechanism is probably adaptive and constitutes a protein saving strategy.[103] Also, the reduction of serum T3 are inversely correlated with plasma levels of norepinephrine and epinephrine, which are increased in brain dead patients, particularly in those presenting an autonomic storm.[103]

1.3.2 Inflammation, cytokine storm and brain death

Following brain injury, a systemic inflammatory response associated with the release of inflammation mediators, the synthesis of radical oxygen species and the recruitment of

leukocytes contribute to vascular permeability and organ damage.[105] A loss of blood-brain-barrier integrity also occurs with local inflammation, contributing to cerebral edema, vasospasm and secondary injury.[105] When local inflammation, edema and ICP lead to an irreversible loss of brain functions, systemic inflammation further increases.[106] In the donor's serum, the marked increase in epinephrine, norepinephrine and dopamine secondary to the autonomic storm surrounding brain death provokes intracellular calcium overload, which then leads to the activation of lipase, proteinase, endonuclease, and nitric oxide synthase, and to the disruption of adenosine triphosphate (ATP) synthesis.[107] As a consequence of the rise in catecholamine levels, a shift towards preferential anaerobic metabolism occurs, causing the activation of NF-KB induced apoptosis, shear stress on the endothelial wall, and gut ischemia with associated bacterial translocation.[106,108] With the following destruction of vagal centres, the anti-inflammatory response normally activated by the parasympathetic nervous system at the cholinergic receptors level is also blunted, resulting in unopposed inflammation.[109]

Independently of the occurrence of an autonomic storm, a central release of inflammatory mediators also occurs following brain death, causing a systemic inflammatory response, metabolic changes and a neuropeptide release from the nervous system.[106] More specifically, an increase in serum type 1 cytokines IL-1beta and TNF-alpha is observed in the hour after brain death.[109] In animal models, the rise in type 1 cytokines was shown to be proportional to the abruptness of brain death and could also be influenced by the mechanism of brain injury. [109] Although type 2 cytokines are probably not involved in post brain death inflammation, type 17 pro-inflammatory cytokine IL-6 is implicated. IL-6 serum levels increase from brain death until organ retrieval, and high concentrations of IL-6 are recovered in multiple organs.[109] Specifically, the production of IL-6 in donors' hearts could be responsible for the induction of nitric oxide synthase in cardiac cells, and explain the early-after-brain-death cardiac failure and hemodynamic instability.[109]

When compared to recipients from living donors, those from brain-dead donors are more prone to allograft dysfunction.[110] For example, liver and kidney recipients from donors featuring high levels of inflammation are repeatedly reported as having worst outcomes.[110] Mainly supported by animal models, research has also shown that increased levels of inflammatory mediators are associated with donors' myocardial dysfunction and with poorer recipients' outcomes.[106,111,112]

High inflammation, demonstrated by increased levels of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6), major histocompatibility complex class II and adhesion molecules (ICAM-1, VCAM-1, E-selectin and P-selectin) are observed not only in donors after brain death, but also in recipients after transplant.[107,112] These mediators could facilitate the ability of the graft vasculature to present antigens to circulating T cells and contribute to graft rejection.[110]

Both antigen-dependant and antigen-independent immune responses influence allografts outcomes in recipients. Occurring before transplant, antigen-independent immune response depends not only on the previously described brain death induced inflammation, but also on ischemia during organ recovery and on reperfusion injury caused by the restoration of blood during organ transfer.[110] The coupling of the two latter mechanisms is defined as the ischemia-reperfusion injury.[110] Ischemia-reperfusion injury thus contributes to inflammation and have known deleterious effects on recipients' allografts.[109] However, recipients of organs from living donors are less prone to rejection episodes and primary graft failure, and have longer survival rates that recipients from brain dead donors, and these differences appear to be independent from ischemic time.[108] In a rat model, heart recipients from living donors only exhibit ischemia-reperfusion injury characteristics, as recipients from brain dead donors featured higher levels of histological inflammation, suggesting an additive interaction between brain death and ischemia-reperfusion injury.[109,112] Complement activation plays a central role in the ischemia-reperfusion injury, and a similar pattern of C3a increase mediated by IgM was also observed following brain death.[108,110] This suggests a common pathophysiology between neurological death induced organ injury and ischemia-reperfusion injury, and the impact of brain death and of typical ischemia-reperfusion injury secondary to organ retrieval and transplant could become additive at the recipient level.[109]

1.4 Hemodynamic consequences of brain death

As brain death is associated with hemodynamic, inflammatory, metabolic, and potentially endocrine changes, organ dysfunction in potential donors is frequent and has direct

consequences on transplant outcomes. Donors' organ dysfunction, not only jeopardizes the possibility of organ recovery, but also threatens recipients' prognosis. After brain death, potential donors can present with hypotension (80%), coagulopathy (29-55%), renal failure (20-35%) and acute respiratory distress syndrome or pulmonary edema (13-18%) and importantly, with heart failure (10-56%).[56,113-115] Since recipients of organs from deceased donors have worst prognosis than recipients from living donors, independently from HLA matching, donors' age, race or cold-ischemia time, consequences of brain death on organ function is obviously concerning.[116]

1.4.1 Brain death induced cardiomyopathy

In the first animal studies, changes in cardiac cells were observed and linked to the hemodynamic instability occurring after brain-death.[72] Histologic changes in cardiac cells have been described on various occasions since then, and comprise contraction bands, apoptosis, myocytolysis, necrosis and massive calcium release.[117-119] When present, contraction bands are most frequently described in subepicardic and sub-endocardic zones.[119] Following brain stem death, increased endogenous catecholamines lead to vasoconstriction, cardiac workload, and myocardial oxygen consumption.[118] In the myocardium, not only inflammation, but also local catecholamine release appears to have direct consequences on cardiomyocytes.[106,112] An observational study evaluated blood levels of endogenous catecholamines in 40 brain-dead donors in which the heart was rejected for transplant because of age, weight or recipient incompatibility.[119] Catecholamines levels were drawn before brain death and up to 4 hours post brain death.[119] Epinephrine and norepinephrine peak levels were 2.36 times and 8.56 times higher than normal, respectively.[119] Local release of noradrenaline from myocardial sympathetic nerve endings could lead to direct cellular cardio toxicity and cause ventricular dysfunction.[53,59,120] Also, an impairment of beta-adrenergic receptor coupling and changes in G-protein function result in a disruption of intracellular signalisation.[117,121] Both mechanisms of beta-receptor desensitization are thought to be adaptative, in response to deleterious beta-adrenergic stimulation, but they ultimately contribute to heart dysfunction.[121]

Although observed consistently in animal models, cardiac lesions are not present in every human donor.[119,122] Around 80% of donors show histologic signs of cardiac damage,

either necrotic, apoptotic or both, at some point between brain death and organ recovery.[119] The difference between animal models and clinical observations may be explained by the difference in beta-adrenergic receptor density in apical myocardia.[118] Experiments often involved dogs, an animal in which the receptor density is greater than in human, suggesting a higher susceptibility to catecholamines toxicity.[118]

Epidemiology of brain death induced cardiomyopathy

In human potential donors, observational studies report that 10 to 56% of brain-dead donors will present clinical cardiac dysfunction following neurological death.[123-135] However, the definition of cardiac dysfunction, the included populations, the timing of the evaluation, the measurement methods and the donors' treatments at the moment of evaluation vary between studies (Table 1). The actual knowledge on the risk factors of reduced left ventricular ejection fraction (LVEF) is scarce, and only age and body mass index have been associated with impaired left heart function in univariate analyses.[123] Longer time from brain death to echocardiography was also identified as a predictor of LVEF improvement, and repeated echocardiography assessment suggests that cardiac dysfunction may be reversible, at least in some donors.[135] One study evaluating the potential impact of beta-adrenergic receptors polymorphism on the occurrence of left ventricular (LV) dysfunction suggested that genetic factors may predispose some individuals.[130] Although several reports have described LV dysfunction in brain-dead donors, right ventricular (RV) function has not been studied as extensively. In an animal model where brain death was induced in 60 mongrel dogs, high pulmonary and right ventricular pressures were observed during the autonomic storm period.[136] Then, RV function decreased during the next several hours. Brain death had a direct impact on the recipient's RV function as well, even in the presence of basal normal pulmonary pressures.[136] It was proposed that RV dysfunction may be induced by inflammation mediators and apoptosis, similarly to LV dysfunction.[137] In a mechanistic study comparting heart donors with and without LV dysfunction, marked decrease in RV maximum contractile response to calcium was observed in heart donors featuring LV dysfunction. Response to beta-stimulation (isoproterenol) was also considerably reduced although no changes in the B1 or B2-adrenergic receptor density was observed.[121]

Table 1. Epidemiology of cardiac dysfunction in neurologically deceased donors

	Study design	Inclusion criteria	N	Study objectives	LV dysfunction definition	LV dysfunction frequency	LV dysfunction predictors
Borbely 2,015,[123]	Cross sectional	Potential heart donors At least 1 TEE post BD declaration	246	Quantify the prevalence of cardiac dysfunction Describe the longitudinal changes in cardiac function Explore organ procurement practices in patients with cardiac dysfunction after BD	EF <50% and/or presence of ≥ 1 RWMAs	74/246 (30.1%)	Age and BMI (univariate analysis)
Krishnamoorthy 2,015,[133]	Cross sectional	Potential pediatric heart donors At least 1 TEE post BD declaration	60	Determine the prevalence and course of cardiac dysfunction	EF <50% and/or presence of ≥ 1 RWMAs	23/60 (38%)	None found

				Examine organ procurement practices			
Kush 2,012,[130]	Retrospective cohort	Consent to donation Stored DNA samples	1407	Describe donors' LV ejection fraction according to genetic polymorphism Describe RWMA and dopamine requirement according to genetic polymorphism	EF <50%	10%	B2Ar46 SNP
Mohamedali 2,012,[131]	Retrospective (?) case series	Organ donors	34	Describe LV dysfunction	N/A	11/34 (32%)	N/A
Godino 2,010,[128]	Retrospective observational	Potential heart donors Age <50 years	100	Identify and quantify the causes for exclusion of potential heart donors Define risk factors for LV dysfunction	EF < 40%	16/97 (16.5%) (3 patients missing)	None
Boudaa 2,003,[126]	Retrospective cohort	Potential heart donors	56	Identify selection criteria for heart procurement	EF < 60%	12/56 (21.4%)	N/A

Paul 2,003,[127]	Retrospective observational	Potential pediatric heart donors Echocardiographic screening before organ donation	23	Define the spectrum of LV dysfunction in pediatric donors	EF <50% or LV shortening fraction <28%	13/23 (56.5%)	N/A
Hutteman 2,002,[129]	Retrospective observational	Patients with brain injury leading to BD	51	Evaluate the impact of TEE on patient management Describe the incidence of LV dysfunction	FAC <50%	7/51 (13.7%)	N/A
Dujardin 2001[124]	Retrospective cohort	BD patient At least one echocardiogram	66	Describe the prevalence and characteristics of myocardial dysfunction	N/A	28/66 (42%)	N/A
Kono 1,999,[132]	Prospective observational	Brain dead patients from non-cardiac cause	30	Describe the course of brain-death induced myocardial dysfunction Assess the ability of dobutamine stress echography to predict	LV shortening fraction <30%	7/30 (23.3%)	Positive stress echocardiography is predictor of LV function normalization

				reversibility of LV dysfunction			
Gilbert 1,998,[125]	Prospective (?) observational	Potential heart donors	74	Evaluate cardiac function in potential heart donors	Abnormal echography results leading to donor exclusion	9/74 (12.2%)	N/A

TEE: Transthoracic echocardiogram; BD: brain death; LV = left ventricle; EF = ejection fraction; RWMAs = Regional wall motion abnormalities; FAC = fractional area change

Transplantation of recovering hearts

Left ventricular dysfunctions account for around 25% of donors' heart rejection.[138,139] Serial echocardiography of potential heart donors demonstrated a temporal improvement of heart function in donors with baseline LV dysfunction.[123,135] However, the potential for allografts to carry stigmas of dysfunction despite apparent recovery remains a concern. This question was studied in a cohort of heart recipients from donors that recovered from initial LV dysfunction compared to heart recipients from donors with normal heart function at baseline.[138] No difference in mortality up to five years after transplant or in acute graft rejection was found, and the results were robust to a propensity score matched analysis.[138] The majority of donors with initial LV dysfunction was treated with inotropes, corticosteroids and thyroid hormones.[138] Another propensity score matched study evaluated the risk of cardiac complications after transplant, one-year survival and LV function in recipients from heart donors with or without a heart dysfunction at the time of the organ transfer.[140] The hypothesis supporting the primary outcome was that impaired LV function hearts would recover after transplant, and that pretransplant LV dysfunction would not affect recipients' survival. In accordance with their hypothesis, the authors did not find any difference on the pre-defined outcomes between recipients from donors with or without heart dysfunction.[140] However, the number of recipients (127) who received a heart with reduced ejection fraction (<40%) was disproportionate compared to the number of recipients who received a heart with normal ejection fraction (30,253), and these two groups largely differed in their clinical characteristics at baseline.[140] Even with the use of a propensity score, residual confounding is possible. Neither the propensity score nor the following logistic regression included interventions during the ICU donor management. We could however expect more aggressive hemodynamic management strategies or team care involvement in donors with lower LV function. If donors with more important LV dysfunction were taken care of more aggressively, then the difference in survival could have been biased towards the null, even though these donors appeared initially sicker. This study also potentially suffers from a lack of power. Although the total cohort includes more than

30,000 donors, only 127 with reduced ejection fraction were matched to donors with normal ejection fraction since the propensity score used 1:1 matching. Despite these limits, the two recipients groups had similar LVEF at one year after transplant, suggesting that heart function may improve after transplant.[140] Similar results were observed in a cohort of pediatric heart recipients.[141]

1.5 Organ donor pharmacological management

The pharmacological management of neurologically deceased donors can arbitrarily be divided in sequential phases corresponding to the autonomic storm and the hemodynamic instability. These treatments are largely derived from the theoretical pathophysiology of brain death, and the rationale for their use relies mainly on the translation of animal model findings to human clinical presentations.

1.5.1 Pharmacological treatment of the autonomic storm

The use of beta blockers to alleviate the consequence of the catecholamine surge following brain stem ischemia was first proposed by Novitzky in his chacma baboon model.[72] Then, the use of beta blockers to prevent heart dysfunction secondary to the autonomic storm was further assessed in preclinical studies.[142-144] In summary, these studies suggest that the administration of a beta blocker could prevent the degradation of myocardial cells after neurological death. However, only one study has evaluated the impact of pharmacologically treating the autonomic storm on human donors' organ function.[58] The retrospective study conducted on a small cohort of 46 potential heart donors evaluated the predictors (including the occurrence or not of an autonomic storm) of a successful cardiac transplantation. Twenty-nine (63%) subjects experienced an autonomic storm, of which, six received esmolol, five received uradipil, one received nicardipine, and 17 received no treatment. A multivariate logistic regression model was used to assess potential predictors of the autonomic storm. The only predictor of the clinical manifestation of a storm was the neurological death cause, being anything but traumatic brain injury. After adjusting for cardiac biomarkers and smoking status, antihypertensive treatment

remained a predictor of preserved LVEF. No distinction among the different storm treatment effects was possible due to the small sample size.

1.5.2 Pharmacological treatment of hemodynamic instability

Almost every potential organ donor will require vasopressors after brain death to overcome profound circulatory instability, mostly hypotension attributed to vasoplegia or insufficient cardiac output. Despite this widely spread use, vasopressors have not been extensively studied in this clinical context. Due to potential cardio toxicity induced by the autonomic storm, the administration of beta-adrenergic vasopressors and inotropes to unstable organ donors is theoretically controversial. On the one hand, some advocate better kidney graft survival with the use of dopamine.[145-147] In theory, dopamine could protect endothelial cells from oxidative stress induced during the cold ischemic time, a mechanism not mediated either by adrenergic or dopamine receptors.[148,149] On the other hand, donors' heart function may be further compromised by the administration of exogenous catecholaminergic vasopressors that mimic the effect of the autonomic storm.[150] These concerns are theoretical and are extrapolated from physiological models.[18,60,72] However, despite being scarcely reported in the literature, the possible link between the administration of catecholamines and heart dysfunction concerns enough clinicians that a dose limit on vasopressors is often recommended.[151,152]

Only one randomized controlled trial (RCT) evaluated the use of a vasopressor in organ donors.[148] This study compared the administration of low dose dopamine to usual care. The study primary outcome was the requirement of dialysis during the first week of kidney transplant. Other measured outcomes were serum creatinine, biopsy proven acute rejection and recipient mortality. A total of 487 kidney recipients were included in the study and demographics were generally well balanced between groups, except for a higher number of suboptimal kidneys in the dopamine group. The authors concluded that dopamine was associated with a significant reduction in need for dialysis (24.7% vs 35.4%; p=0.01). The beneficial effect of dopamine remained after adjustment for demographic imbalances (OR 0.54; 95% CI 0.35-0.83). This study was well powered and adjusted for confounding factors, but was limited by a possible detection bias due to the absence of blinding. Nevertheless, these promising results warrant further attention.

Although the results of this study were positive, concerns on the safety of dopamine in heart transplant remained. The same investigators thus conducted a nested-within-RCT retrospective study of 93 heart transplants (46 dopamine; 47 controls) and compared their LV function.[153] LV dysfunction was defined as an impaired LVEF as per echocardiography, the need for a left ventricular assist device or the need for hemofiltration to handle volume overload. Biopsy-proven acute rejection, graft failure and deaths were also monitored. Despite the retrospective design, demographics were well balanced between the two groups. However, the controls seemed at higher risk for the studied event due to the urgency status of their surgery. Only the requirement for hemofiltration was lower among the dopamine group compared to the control group in the intent-to-treat population (21.7% vs 40.4%; p=0.05). The per protocol population analysis also showed a reduced 3-month mortality in the dopamine group (5.1% vs 21.7%; p=0.03). Based on these results, the authors concluded that dopamine appeared at least safe in heart recipients. However, this study suffers from a lack of power to clearly demonstrate a difference in clinical outcomes related to dopamine administration in heart recipients and bears inherent biases to retrospective designs.

The use of norepinephrine in deceased donors was only evaluated in one retrospective study that compared its administration to dopamine on survival after heart transplant.[154] Because the authors observed a change in practice in the year 2000 implying a switch from dopamine to norepinephrine as the first line vasopressor, they compared patients transplanted before 2000 to patients transplanted after 2000. This study did not demonstrate any difference between groups on recipients' overall survival. However, this study was limited by crossed-contamination of interventions between groups (around 20%), missing data and by the lack of randomization.[154] Based on the limited body of evidence, and despite some data suggesting a possible benefit of dopamine on kidney recipients' outcomes, the controversy concerning the administration of catecholaminergic vasopressors to donors remains.

No study prior to ours existed to evaluate the efficacy or safety of inotrope prescription to potential organ donors.[155] Some inotropes (e.g., dopamine, epinephrine, dobutamine) share with vasopressors catecholaminergic effects, but others (e.g, milrinone) offer different mechanisms. In a retrospective observational cohort nested in a national pilot observational trial, we have analyzed the heart recovery outcome of 99 NDD donors exposed or non-exposed to inotropes.[155]

In this study, we observed that exposed donors tended to have more comorbidities than non-exposed donors, but this finding was not statistically significant, possibility due to a lack of statistical power. However, the proportion of hearts recovered was not different between the two groups.[155] These preliminary data suggest that the use of non-catecholaminergic inotropes may be safe in heart donors, but warrants further investigation.

In summary, in the context of profound hemodynamic instability potentially compromising organ perfusion, the use of vasopressors or inotrope is often inevitable. However, the efficacy and safety of vasopressors and inotropes agents have not been sufficiently studied. Whether their administration has any negative impact on retrieved organs or on recipients' outcomes is still debatable and the preferable agent remains unknown.

1.5.3 Hormone replacement therapy

After the publication of animal studies on the physiology of brain death and hormone deficiency, Novitzky et al. performed in 1987 the first clinical study on combined hormone therapy in humans after brain death.[79] Based on his previous conclusions, 21 consecutive donors were treated with T3, cortisol and insulin with the hope of preventing hemodynamic collapse following the autonomic storm. The hemodynamic parameters (MAP, heart rate, CVP, bicarbonate and inotrope requirements) of the pretreated donors were compared with 26 historical controls. The authors reported significant decrease in the need for inotropes and bicarbonates in the hormone replacement group.[79] Although seemingly promising, the validity of this first study results is limited by the lack of sample size calculation and sound statistical analysis plan, the absence of randomization, and confounding factors such as initial MAP, volemia, vasopressors, fluid replacement strategies, monitoring aggressiveness and team involvement.

Nevertheless, these first results almost immediately triggered practice changes, and hormone cocktails were soon prescribed to potential organ donors.[156] An observational study including 150 multiorgan donors described the use of a hormone cocktail in 52 of them deemed unacceptable for donation, mostly because of hemodynamic instability.[156] The investigators then reported an improvement in organ function in 48 of the initially 52 unacceptable potential

donors with the treatment. They also reported similar survival rate (although no statistical comparison was made) between recipients from initially acceptable and recipients from converted-to-acceptable donors. The intervention encompassed not only a hormone therapy cocktail (e.g, Methylprednisolone 15 mg/kg; insulin minimum 1u/h with dextrose as needed, vasopressin 1 U bolus then 1.5 U/h and T3 4 mcg bolus then 3 mcg/h), but also of the use of invasive hemodynamic monitoring. The results of this study can be criticized for the lack of a control group. Also, in the analyses comparing the two groups, the effect of the hormone cocktail therapy cannot be dissociated from the effect of a change in practice, and the effect of time and aggressive monitoring on the donor.[156] Despite these limits, this study influenced the future of organ donor care and research in organ donation: from then on, hormone therapy was established as a state-of-the-art intervention.

Consequently, in 1999, a standardized management protocol including hormone therapy cocktail was implemented within the United Network for Organ Sharing (UNOS) organization.[157] The impact of the combined hormone therapy (T3 or T4, vasopressin, insulin, methylprednisolone) was then evaluated in 2003, in a large cohort of 10,292 donors from the UNOS database.[157] A total of 701 donors who received hormone therapy was compared with 9591 historical controls managed before the implementation of the protocol. Donors who received hormone therapy were younger, had lower creatinine levels and fewer had a history of diabetes, cancer or cardiovascular events. Despite these clinical differences, hormone therapy was associated with an independent and significant increase in the odds of organ transplant for all organs (ORs between 1.26 (95%CI 1.03-1.54) and 1.82 (85%CI 1.35-2.44)), depending on the organ).

Although the results of this study seemed promising, several limits may have compromised its internal validity. Exposed patients were managed between 2000 and 2001 as non-exposed patients were mostly managed before 1999. Differences in practices other than hormone therapy could explain the observed benefit. More importantly, during these years, interest in organ donation management increased and the 1995 publication definitely raised the interest in donation. As a consequence, teams were probably more aware of donor management issues and all the components of clinical management (monitoring, objectives, treatments) also improved. Although the investigators used a logistic regression model, residual confounding cannot be

excluded. Also, individual components of hormone therapy were not assessed independently precluding from drawing any conclusion on their separate effect.

Later in 2003, investigators published a second study, this time examining the effect of hormone therapy on the early outcome of heart recipients.[158] Patients included in the study were selected from the 10,292 patients of the UNOS database. A total of 4543 heart recipients were further assessed, of which 394 received their heart from a hormone therapy-exposed donor and 4149 from a hormone therapy-unexposed donor. Outcomes of interest as presented by the authors were recipients' death within one month and early graft dysfunction. A multivariate regression model was performed on the mortality at one-month outcome. The authors also performed an unadjusted survival analysis (Kaplan-Meier curves comparison) comparing survival rate between exposed and non-exposed recipients. The investigators reported better survival rate, reduced mortality (OR 0.54; 95%CI 0.31-0.92) and lower risk of graft dysfunction (OR 0.45; 95%CI 0.28-0.72) with hormone therapy. However, exposed and non-exposed donors were again very different at baseline, and residual confounding, principally by co-interventions (monitoring, hemodynamic targets, type of vasopressor, fluid resuscitation), is still probable.

Several other studies using similar designs compared actual donors with historical controls and reported benefits of the use of hormone therapy. Reported positive outcomes included an increase in lung procurement, in the number of donors, in the number of organs yielded and, in thoracic organs recovery[159-162] Common to all those studies are the inherent biases of retrospective designs, and the impossibility of isolating the effect of the studied intervention from that of a change in practice. No RCT has evaluated the use of a hormone therapy bundle including a corticosteroid, thyroid hormone, vasopressin and insulin.

Corticosteroids

Corticosteroids are administered to NDD donors for their potential ability to blunt the inflammatory process secondary to brain death.[101,162] The potential benefit from corticosteroids could include the prevention of organ damage mediated by pro-inflammatory mediators, the stabilization of cellular membranes, the reduction of cell surface adhesion molecules and the avoidance of lipid peroxidation following hypoperfusion.[163,164] Some authors have also

hypothesized that glucocorticoids could alleviate inflammatory neurogenic pulmonary edema or compensate for a relative adrenal insufficiency secondary to brain death, and secondarily reduce the need for vasopressors. However, adrenal insufficiency in brain-dead donors has not been systematically observed, and cortisol levels are reported as low, normal and high.[70,97,101,165]

The efficacy of a corticosteroid prescription to NDD donors compared to placebo or standard treatment was described in two systematic reviews published by our group. [162,166] The first review included 11 RCTs and 14 observational studies.[162] The second review meta-analyzed the pooled results of the 11 RCTs.[166]

Three RCTs included in the meta-analysis evaluated the effect of high-dose corticosteroids on the need for vasopressor in donors, and did not reveal any benefit (pooled RR 0.96; 95%CI 0.89-1.05).[166-168] Similar results were found in the only observational study that compared the effect of corticosteroids to usual care on dopamine doses.[169]In critically ill patients, low-dose corticosteroids can be used to improve hemodynamic stability and reduce the need for vasopressors.[170] In the context of organ donation, only one study, published after our meta-analysis, evaluated the effect of low-dose hydrocortisone on hemodynamic stability.[171] This study reported significantly lower vasopressor doses in the steroid group.[171] However, due to its non-randomized clustered interventional design, this study is considered at serious risk of bias. Further comparisons of high dose methylprednisolone to low dose hydrocortisone did not reveal any difference on patients' or graft survival.[172]

In our meta-analysis, corticosteroids were not associated with any difference on organ donation success, on the risk of acute graft rejection at three months, or on the risk of graft dysfunction.[166] Five of the 11 included studies were published in the 1970's and 1980's and the risk of bias was judged as high, as defined by the Cochrane risk-of-bias- tool for randomized trials.[173-178] Also, cyclophosphamide was administered along with corticosteroids in the intervention group in four studies, limiting the extrapolation of the results in the actual context of practice.[174-177] The isolated effect of corticosteroids was studied in four of the 14 included observational trials of the systematic review.[162] Corticosteroids were associated with an increase in time from brain death until cardiac death, [179] an increase in organs yield and improved oxygenation [169,179,180], and an increase in the number or the probability of lung procurement.[169,181] As previously noted, the effect of corticosteroids was diluted by co-

interventions, including hormonal therapy. Our systematic review highlighted the large heterogeneity in studied regimen, methodological designs and co-interventions, the high risk of methodological bias, and the lack of safety assessment.[162] Potential risks of high dose corticosteroids include hyperglycemia and infections, both associated with detrimental effects in donors[59].

Thyroid hormones

The second component of the initially proposed therapy bundle is thyroid hormones.[156] Acute heart dysfunction following brain death has preoccupied investigators and clinicians since the first experiments in the Chacma baboon.[72,74,79] Although the mechanism for heart dysfunction in donors has not been completely elucidated, a contribution from low level thyroid hormones secondary to anterior pituitary deficiency was initially proposed. However, the pharmacological action, if any exists, of thyroid hormones in this context still needs to be elucidated, and various mechanisms are proposed. Very early in the medical literature, increased heart rate and cardiac contractility were observed in hyperthyroidism.[182] Later, various animal models (rat, cat, baboon) suggested that acute exposition to T3 could increase cardiac contractility through the stimulation of a particular thyroid receptor located in cardiac myocytes.[53,163,183-185] Sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) is the most important protein for calcium sequestration in sarcoplasmic reticulum during heart diastole. It reduces the quantity of calcium available during systole and improves ejection volume by a lusitropic action. SERCA is controlled by a regulatory feedback mediated by a protein called phospholamban.[163,184] *In vitro* studies comparing rat myocytes exposed to T3 to non-exposed myocytes showed an increase in SERCA/phospholamban ratio, increased in calcium influx and a decrease in intracellular sodium. T3 but not T4 has been shown to improve heart rate of pressure change in the ventricle (dp/dt), and this action would be independent of beta-adrenergic pathway.[184] In humans, while some suggest improved heart performance and tolerance to aerobic exercise with the prescription of thyroid hormones to patients suffering from dilated cardiomyopathy, others have failed to demonstrate any difference in cardiac function despite an increase in the expression of the protein SERCA2a.[186-192] However, a lack of statistical power is common to these studies.

Following catastrophic brain injury, inflammatory markers are released and a euthyroid sick syndrome, characterized by a reduction in conversion from T4 to T3, may be responsible for the observed low levels of thyroid hormones in donors. If the euthyroid sick syndrome is indeed the explanation for low thyroid hormones in neurologically deceased donors, the conversion of T4 to the active form T3 would be compromised. In this context, the administration of T4 to donors is questionable and warrants further evaluation.[193] A recent RCT observed no difference between T4 exposed donors and T3 exposed donors on vasopressor weaning.[194,195] In the T3 group, more hearts were transplanted, but the difference did not remain significant after adjusting for baseline imbalances between groups.[194] However, the study included a total of 37 neurologically deceased donors and suffers from a lack of statistical power.[194]

Finally, limitation of the brain-death inflammatory induced cellular apoptosis by thyroid hormones is another proposed mechanism.[196] However, no study has directly assessed this hypothesis in organ donors. Inflammatory markers (IL-6) release in donors has been associated with worst recipients' outcomes.[197] Whether thyroid hormone supplementation in donors could reduce the expression of inflammatory markers and hence, contribute to improved outcomes in recipients is still unknown.

A well-conducted meta-analysis on the efficacy of thyroid hormones in donors was published in 2012.[186] Thirty-seven studies were included in the systematic review, of which 16 were case-series or retrospective audits and seven were RCTs. The review outcomes were hemodynamic stability, dosage of vasoactive drugs and number and retrieved organs quality. Meta-analysis was possible only for the four studies that compared T3 to placebo. No difference on cardiac index, use of vasopressors or any other outcome was found when pooling the study results. This review highlights the large difference between RCTs and observational studies effects and conclusions. Moreover, the body of evidence on thyroid hormone is limited to retrospective studies, as well as open-label RCTs. In observational studies, the observed benefit is probably inflated and biased by residual confusion, due mostly to a change in practice involving more aggressive monitoring, better defined therapeutic targets and better team knowledge, awareness, involvement and interest towards organ donor care. On the other side, open-label RCTs are prone to observer bias and to differences in co-interventions between groups due to the lack of

allocation concealment. In the hemodynamic management of organ donors, significant co-interventions include among others monitoring aggressiveness, individualization of targets, fluid therapy, vasopressors and total management time. The systematic review also highlights clinical and methodological heterogeneity between the publications.

After the publication of this systematic review, Novitzky et al. conducted a retrospective study of 66,629 neurologically deceased donors registered in the UNOS database between 2000 and 2009, evaluating the use of thyroid hormones in NDD donors.[78] This study stated that from these, 30,962 (48.7%) received thyroid hormones (T3 or T4) and the remaining did not receive thyroid hormones, and other components of hormone therapy were used with varying proportions. The investigators reported an unadjusted but statistically significant difference of 12.8% in the number of organs recovered and of 15.3% of organs transplanted in favour of thyroid hormones. The difference persisted in all hormone therapy combination subgroup analyses. However, the subgroup of donors exposed to all four components (thyroid hormones, corticosteroids, antidiuretic hormone and insulin) had the highest number of organs procured. Following their multivariate analysis, the authors concluded that the administration of thyroid hormones was independently associated with an increase in organ procurement (ORs from 0.96 (95%CI 0.91-1.02) to 1.31(95%CI 1.23-1.40), depending on the organ).

Although the administration of thyroid hormones in studies appears unrelated to any worsening of donors or recipients' outcomes, the safety of this practice has not been specifically assessed. Animal models suggest that exogenous thyroid hormones increase oxidative stress and mitochondrial permeability in livers, as shown by increased liver transaminases and oxidize glutathione.[198,199] Increased risk of primary liver malfunction with the use of a hormone therapy cocktail was also suggested. The liver dysfunction was attributed to ATP depletion induced by thyroid hormones, and as a result, a reduction in the adaptive response to the stress caused by the ischemia/reperfusion injury.[200] Also, hypothyroid status is thought to be protective against anoxic ischemia in livers and kidneys, and a small experimental model in rats suggested that the administration of PTU, an antithyroid drug, increases reduced-glutathione, the main liver free radical scavenger.[201,202] Again these findings were not corroborated by clinical studies, but the safety of thyroid donors on recipients' liver function has not been the primary focus. Although

the latest observational study by Novitzky et al. suggested an increase in the number livers recovered from thyroid hormone-exposed donors, this topic warrants further research.[78]

Insulin

In the earliest studies of hormone replacement therapy in donors, insulin was included as the third component of the bundle. The regimen specified a minimum of 1 u/h of insulin, and dextrose was allowed to maintain glycemia within the normal range.[156] In the subsequent retrospective studies, the role of insulin within the cocktail became unclear, and its effect was not analyzed independently.[157,158] Nowadays, it is common to administer insulin to critically ill patients, including to organ donors, to maintain glycemia in the normal range.[151,152] However, the rationale for the administration of insulin to donors as part of a hormone therapy cocktail goes beyond the management of hyperglycemia, and includes possible inotropic effects. High-dose insulin combined with glucose and potassium (GIK) is thought to have beneficial effects on heart function. GIK was first studied in patients suffering from chronic LV dysfunction, acute myocardial infarct and in post cardiac surgery period. These studies suggest a reduction in inotropic support needs and a reduced incidence in low cardiac output.[203,204] A meta-analysis of RCTs comparing GIK with control in heart surgery patients drew similar conclusions.[205] Protection against ischemia-reperfusion injury seems to be independent of glucose, conferring a cardio-protective effect to insulin. Early models hypothesized that the action of insulin implies the promotion of cardiac glycolysis and the inhibition of free fatty acids. Moreover, insulin may activate tyrosine kinase, phosphatidylinositol-3-kinase and Akt cell survival pathways, thus reducing apoptosis.[203]

Only one study has evaluated the effect of GIK on LV dysfunction in NDD donors, and this study compared its effect to dobutamine.[206] This prospective crossover study included 12 subjects with a LVEF equal or less than 30%. Echocardiography was performed at the baseline, after a 30-minute dobutamine infusion, 30 minutes after stopping the dobutamine infusion and after 120 minutes of GIK infusion. Both dobutamine and GIK infusions were associated with an increase in LVEF without any difference between the two strategies. However, GIK resulted in less hypotension and tachycardia than dobutamine. This study concluded that GIK was a least

as efficient as dobutamine at increasing cardiac contractility, and was better tolerated. However, this study suffers from a small sample size, and a time-related improvement cannot be ruled out, this being a major limitation in crossover trials.[207]

Vasopressin (ADH)

The last component of the original hormone therapy bundle was ADH. [156] ADH is a small 9-amino-acid peptide released in the blood after an increase in serum osmolality or a decrease in blood volume.[208] Changes in osmotic pressure are detected by osmoreceptors situated principally in the hypothalamus.[208] Baroreceptors situated in the cardiac atria, the carotid sinus and the aorta detect changes in blood volume.[208] Many stimuli including chemical substances (e.g.; alcohol, opiates, nicotine) and hormones (e.g.; estrogens, progesterone, atrial natriuretic factor) are also responsible for a modification in ADH release.[208] ADH is synthesized in the magnocellular neurons of the hypothalamus and is subsequently released in the blood from the posterior pituitary gland.[208] Then, it binds to three specific receptors from the G-protein coupled receptor family: V1a, V2 and V3.[208] Receptors V1a, specific to ADH, are located on the smooth muscle wall of the blood vessels, the liver, the brain, and the adrenal glands and their stimulation is responsible for the vasopressor effects of ADH analogues.[208,209] Binding to V2 receptors in the apical membranes of the renal collecting duct provokes water reabsorption via the phosphorylation and insertion of aquaporines.[208] Vasopressin is a commercially available synthetic form of ADH. Three other vasopressin analogues are available: desmopressin, lypressin and terlipressin. They differ only by their time of onset and their length of action.[210]

The efficacy of vasopressin at optimizing donors' and recipients' outcome still needs to be evaluated. However, a pharmacologic rationale for its use exists since an autonomic dysfunction is thought to increase the sensitivity to vasoactive effects of vasopressin.[70] Using low dose vasopressin could therefore reduce the need for beta-adrenergic vasopressors.[51,211,212] Preliminary interventional studies comparing vasopressin to placebo or epinephrine in NDD donors suggested an increase in donor survival time and a benefit on hemodynamic parameters. However, these studies were limited by their small sample size, the absence of randomization and/or the absence of blinding.[213,214]

The isolated hormonal replacement potential of vasopressin has been evaluated in two large retrospective studies on data from the OPTN.[215,216] In the first one, donors exposed to vasopressin were compared to non-exposed donors and the number of donors in whom at least four organs were retrieved was evaluated.[215] The incidence of graft refusal due to early dysfunction was also compared. This study found a significant increase in the number of donors of four organs or more after adjustment for age, gender and other risk factors. The analysis also showed reduced refused grafts based on univariate analysis.[215] In the second study, the primary objectives were the incidence of organ retrieval, the pulmonary function in donors and the incidence of pulmonary dysfunction in recipients.[216] In this study, the administration of vasopressin was associated with a benefit on pulmonary function in donors and an increased number of organs retrieved.[216] In both these observational studies, the incidence of vasopressin exposure was high (75% and 62%, respectively).[215,216] Although multivariate regression adjusted the results for confounding factors, residual confounding is still possible.

1.6 Professional knowledge in organ donor management

As we have presented earlier, the body of high-level evidence supporting any pharmacological agent in the organ donor care field is scarce. The vast majority of commonly prescribed pharmacological interventions in the context of an autonomic storm or of hemodynamic instability are supported by observational studies designed after theoretical models of neurological death. However, despite the equivocal role of individual therapies, organ donor care has improved over the past decades, and professional involvement and interest in the field may have played a key role in success. Given the importance of recovering high quality organs in a time fashion manner, standardized processes for organ donation have developed. These processes often include the development of standard drug prescriptions, the involvement of experts in family support and sometimes, the elaboration of research protocols. At the centre heart of all these highly structured and complex process, are the organ donation organizations (ODO). Since these institutions play a crucial role in facilitating the overall course of organ donation, on-site professional knowledge on the best evidence supporting organ donor care directly depends on the quality of ODO's educational programs, and on the ability of their professionals to interpret the evidence.

1.6.1 Organ donation organizations and coordinators

Before the advent of organ donor organizations, few information concerning the availability of organs for transplant was shared between institutions. Often, donors and recipients were brought to the same centre, where transplant surgery occurred.[35,36] If patients needed to be transferred from non-transplant hospitals to transplant hospitals, brain death diagnosis had to be reconfirmed. With the increase in the need for transplant organs and the better recognition of brain death criteria, the necessity for specialized and centralized organizations became obvious.[7] The first roles of these organizations were to organize organ banks and to facilitate organ transfer in broad geographical areas. Nurses and laboratory technicians were the first employees of these new organizations.

The role of ODOs has largely expanded since the 1970's. Today, ODOs interact with healthcare professionals and with the public, as they stand at the centre heart of organ donation and transplantation processes. Roles that have been attributed to ODOs are multiple and include clinical tasks, research, training and education of healthcare professionals, and management.[217] Trained donor coordinators on hospital sites have also been recognized as key players in the identification of potential donors, in the effectiveness of the donation process and in the optimization of the quality of organs.[218] The donor coordinator role, traditionally assumed by a nurse or a physician, implies the ability to provide educational and organizational recommendations to improve donation process within the institution.[218] However, few studies have evaluated these knowledge translation interventions. A systematic review of the impact of critical pathways in the organ donation process highlights the lack of studies on the topic. The review has included only one study after screening 568 entries. The cited study describes an approach where a care pathway is provided by a multidisciplinary team and includes practice guidelines, referral strategy, brain death diagnosis, consent process, and donor management. However, the effect of this care pathway intervention has not been directly evaluated.[218] Since donor coordinator and ODOs play important roles in the donation process, including interventions and education on donor management, not only the implementation of new management strategies needs to be adopted by these key stakeholders, but the quality of intervention depends on their own knowledge and capacity to critically analyze the evidence.

1.6.2 Knowledge assessment

Because of the paucity of primary literature, both the Canadian and the American guidelines' recommendations rely mostly on observational data and expert opinions.[152,219] Few RCTs support the use of recommended pharmacological interventions, and their efficacy and safety remain unknown.[220] Guided by the ODOs, centres have implemented local protocols to assist clinicians in their bedside clinical management of NDD donors. These protocols are more than often a short summary of the guidelines and include the administration of hormone therapy and vasopressors, despite proven efficacy.[221] Multidisciplinary team work and medical involvement in the care for donors have been identified as facilitators to organ donation, but professional beliefs on the utility of these standardized pharmacological interventions have not been studied.[222-225] Despite uncertain physiological rationales, these therapies, first studied in the early 1980, are still extensively recommended and cited in donor management reviews.[220] We can therefore question the actual knowledge of the health professional community on the evidence behind the routine care interventions. Pharmacotherapy knowledge would need to be assessed through validated questionnaires, but none has been developed yet. However, several questionnaires report limited knowledge or self-confidence of healthcare professionals regarding organ donation process. These reports focus on attitudes and beliefs regarding organ donation in general, and on brain death diagnosis criteria, donor acceptability and family consent interventions.[226] Results of the studies generally demonstrate a correlation between personal beliefs, self-perceived competencies or experience and attitude towards organ donation.[227,228] A certain degree of misunderstanding of the concept of neurological death among medical students and nurses is also reported.[226,227,229,230] Again, no questionnaire or survey evaluates healthcare professionals' competencies or self-perceived clinical management of NDD donors.

1.7 Research on organ donor care

Despite obvious growing interest for the topic, few RCTs evaluating any intervention for the management of NDD donors have been published in the last years. Because of a very particular clinical context involving not only hospital centres but also ODOs, research in organ donation faces many challenges that may have impaired interventional research. First, the

context of organ donation is unique in the sense of the multiple partners involved in the care of the donor and the recipients. The management of donors in one centre implies ICU physicians, surgeons, nurses and allied health-care professionals and ODO professionals. Then, organs are transplanted in up to eight different recipients, implying again physicians, surgeons, nurses and other professionals. Conducting interventional research in donors necessarily implies multisite research and ethic committee approval. Consenting neurologically deceased donors' families to research and recipients is also challenging.[231]

Clinicians and investigators may be reluctant to modify any conduct that they judge efficient. Since 1995, improvement in organ donor care and in available organs for transplantation has been attributed, at least in part, to pharmacological interventions such as hormone therapy. Because these commonly used strategies are not perceived to cause any harm, although effects on non-target organs have not been properly evaluated, physicians may wish to pursue their use even in the advent of neutral effects. However, some interventions that are not used widely could benefit donors' organs and recipients, and their proper evaluation is pertinent. As an example, interventions on the prevention or the treatment of the adrenergic storm have not been prospectively studied. Beliefs in the existence or the non-existence of the adrenergic storm or of its consequences may be responsible for the lack of research interest in the topic. No study or survey has evaluated research interests of investigators and clinicians in organ donor management.

At the end, organ donation is a recent field, and interest for research on dead subjects may not appear be as important as in living patients. And finally, determination of the best clinically relevant outcome in organ donor management is still to be determined.[231]

1.7.1 Ethical challenges and outcomes in organ donation research

Research in organ donation share challenges with research pertaining to other fields, but encompasses issues specific to the context. The research model on neurologically deceased donors typically implies the administration of a research intervention to a deceased donor. The goal of research is to measure outcomes either on the donor's organs, on recipients or both. Studies that limit outcome measurement at the donor's level often report the number of organs

recovered/transplanted per donor, specific organ recovery rate, or organ function as study endpoints. Organ function is often evaluated using biological markers or functional tests.

The principal issue with measuring the effect of intervention at the donor level is implicit to the use of surrogate variables. In the context of organ transplant, favourable outcome on a donor's organ does not necessarily translate into a favourable outcome in the recipient. For example, a study aimed at evaluating the relationship between the concentrations of uMCP-1 (a marker of acute kidney injury) in donors and recipients' delayed kidney graft function. The study observed only modest correlation, limiting the clinical utility of this biomarker.[232] Risk index such as the kidney donor profile index (KDPI) calculated on the donor's history profile is better correlated with transplant outcomes. However, the KDPI is not meant to evaluate the effect of an intervention on the donor's organ function and depends solely on donors age, weight and height and pre-existing comorbidities.[233] Acute kidney injury often occurs after neurological death, and although the rise in serum creatinine levels may be only transient in some donors, the discard rate for acute kidney injury kidneys is around 30%, compared with 18% for kidneys from donors with no acute kidney injury.[234] Whether the occurrence of acute kidney injury translates into an increased risk for early graft failure or long-term allograft survival for the recipient is an understandable concern for clinicians. However, recent studies fail to demonstrate any relationship between donors acute kidney injury and recipients risk for graft failure, despite recipients from donors with acute kidney injury being older and having a longer mean cold ischemia time.[234-236]

Similar observations to the lack of clear association between acute renal injury in donors with kidney transplants outcomes can be observed in the heart transplant situation. Because surgeons are reluctant to transplant organs with obvious dysfunctions, the impact of transplanting a heart with reduced LVEF in donors on recipients' outcome is unknown. In heart transplant, reduced LVEF is responsible for 25% of heart non-acceptance, but no difference in recipients' mortality or cardiac allograft dysfunction is observed between recipients from a donor that presented reduced LVEF during their ICU stay than recipients from donors with at all-time normal LVEF.[138] As a consequence, the true importance of achieving normal (>50% in Quebec) LVEF in donors is uncertain.

Extrapolating from the kidney and heart example, actual acceptance criteria for every potentially transplantable organ can be questioned, and optimal outcomes should be studied before conducting any clinical research at the donor level. Then, distinction should be made between recipients of the research-target organs from recipients from research non-target organs. For example, in a study evaluating an intervention on the need for dialysis in kidney recipients (target organ) the impact of the intervention on the liver or heart graft function of other recipients (non-target organs) should be taken into account.[237]

However, since donors and recipients may not be taken care of in the same institution, research becomes a real challenge and this reality probably explains in part the lag in organ donation research. Only a centralized organization that would be responsible for research administration could overcome this issue.[237] ODOs centralized research could permit to allocate research subjects efficiently, especially in wide geographical areas, and facilitate and coordinate multi-centre research through a single institution review and ethics board.

In the US federal regulation "Common Rule," *Human subjects* as designated by the law, refer to living human beings.[238] The FDA defines human subjects as either healthy humans or patients, two definitions that do not encompass neurologically deceased subjects.[239] Consent to research is meant not only to protect the research subject from harm, but also to ensure respect of autonomy and dignity.[240] For obvious reasons, research intervention cannot inflict direct harm to the deceased donor, but it may compromise the donor's and its family's gift wish by affecting organs' quality or suitability. [241] Therefore, controversy among the scientific community concerning these definitions and the need for consenting neurologically deceased donors' families to research remains. Members of the scientific community still identify donor research as human research, and they believe that informed consent is required, even when the investigation is limited to donors' data.[242] A high proportion of the lay population still have inaccurate beliefs and thoughts concerning organ donation, including the idea that a black market for organs exists, that consenting to organ donation will reduce the medical propensity to cure them from sickness, or that a neurologically deceased patient can recover from its terminal injuries. One major concern is that consenting families to research in organ donation

can add a layer to the misunderstanding and result in a decrease in global organ donation consent.

Awareness on the need for an appropriate consent model for recipients from research donors has risen as highlighted by the publication of a complaint by the advocacy group Public Citizen to the Office for Human Research Protections concerning the randomized trial on hypothermia published in the New England Journal of Medicine in 2015.[243,244] The letter claims that not only neurologically deceased donors included in the study were inappropriately designated as human subjects, but also, that it lacked recipients' consent.

Two different aspects of consent need to be distinguished concerning recipients: the clinical consent to receiving an organ from a research donor and the research consent to either provide personal data or to undergo research interventions.[241,244] In the situation where data are collected in recipients that extend beyond the usual follow-up (e.g., biopsy, imaging, blood samples), or when a study intervention is applied directly to the recipient, the need for consenting the recipient to research is unequivocal.[244] However, in the advent of the investigators collecting data pertaining to the usual recipient follow-up (e.g, living status, need for hemodialysis, routine blood work), the need for consent is controversial, and not required if all data are anonymized.[241] The only fact of receiving an organ from a donor included in a study does not by itself imply that the recipient is a human subject of research, under the law.[244]

Obtaining nominal data from recipients is more challenging and needs further assessment. In the advent where investigators are unable (because not allowed as in the province of Quebec) to link information from donors to recipients renders prospective research informed consent of recipients impossible.[244] Therefore, when the recipient does not provide research data beyond usual care, the most efficient way to ensure transplant recipient's protection is to obtain informed *clinical* consent on the organ to be transplanted, and this includes the transparent information of donors' research.[244]

Prospective research, notably RCT design in the organ donation context is complex and needs narrow collaboration between investigators, ODOs, and organ donor and transplant centres.

2. Current gaps in the literature

Gaps in the literature of the management of NDD donors are multiple and pertain to many steps along the way. Rationale for the use of the actual pharmacological arsenal needs to be re-questioned and reinterpreted based on human data. No literature exists actually to describe the beliefs of the medical community towards the interventions in the management of NDD donors. It is also unknown whether the management of NDD donors varies between individual physicians and between countries around the world.

The definition and the impact of the adrenergic storm are not known outside animal models, and the effect of its prevention is not demonstrated. Also, some hemodynamic parameters have not been systematically assessed as potential consequences of neurological death. Specifically, the actual literature describes extensively the impact of neurological death on LV function, but its impact on RV function has not been described. Whether interventions directed on RV pressures could help prevent subsequent hemodynamic instability is unknown.

The actual donor management strategies rely mostly on observational data and extrapolation from animal models. Few RCTs have been published on the topic.

Until now, no RCT has been conducted in Canada in the context of NDD donor research. The ability of recruiting donors, and evaluating pertinent outcomes in recipients is particularly challenging and barriers to the implementation of a study need to be identified, then prevented.

3. Objectives and hypotheses

The general objective of this thesis is to characterize the actual hemodynamic management of NDD donors and its evidence-based level. We also aimed at determining reasons for the use of low-level evidence. To meet our objectives, we designed a systematic review of international guidelines on the management of NDD donors and a survey of Canadian ICU physicians that aimed at describing self-perceived practices on NDD hemodynamic

management. In order to understand gaps in the literature and barriers to research on the heart dysfunction, we described echocardiography results in a population of NDD donors and assessed the use of levothyroxine compared to placebo in NDD donors with LV dysfunction. The objectives of this thesis are achieved through four research protocols that use four different research methodologies. The research was carried out from 2014 to 2018, leading to four research articles:

Articles 1 and 2

The actual hemodynamic interventions for the care of NDD donors rely mostly on animal models and observational data. Therefore, interpretations of the literature and resulting medical decisions may differ between individual physicians and between countries, potentially resulting in variability in transplant organ results. The recommendations drawn from the low-level of evidence body of literature in international guidelines have not been described, nor has been reported the individual ICU physicians' perception of their practice regarding the hemodynamic management of NDD donors within this context. Article 1 aims to identify the published and non-published guidelines and to characterize their recommendations. Our goal is to draw a portrait of the actual management of NDD donors in the world. We also describe the quality of reporting of the guidelines. We hypothesize that the recommendations will vary around the world, will rely on low evidence literature, and that the quality of reporting of the guidelines will be low. Article 2 aims at describing self-perceived practice of Canadian ICU physicians concerning the hemodynamic management of donors, with an emphasis on the diagnosis and treatment of the autonomic storm, and on the prescription of inotropes and hormone therapy. We surveyed ICU physicians working in Canadian centres, which permitted to characterize actual opinions regarding the actual recommendations in donor care. We hypothesize that variability in practice exists in the country, especially on the pre-identified areas of uncertainty, because of the paucity of the literature, and that ODO nurses play an important role at influencing medical decisions.

Article 3

LV dysfunction is frequently reported in NDD donors, and animal models have permitted to generate hypotheses concerning its causes. However, despite advanced general ICU care and the use of potentially useful treatments based on proposed mechanisms, the frequency of LV dysfunction is still preoccupying clinicians and is reported as a limiting factor for heart transplant. We suspect that other mechanisms may be implicated in the observed heart dysfunction and the hemodynamic instability in donors. The right ventricular function has not been described in this population. We used echocardiography results in a population of potential heart donors following neurological death to characterize RV and LV function. We also assessed potential factors that may be associated with heart function. We hypothesize that RV dysfunction will be frequent in NDD donors, and that despite LV and RV dysfunction probably sharing common causes, RV dysfunction may present differently.

Article 4

Given the paucity of literature in NDD donor care, especially of RCTs, and the ethical issues specific to the context of organ donation, Article 4 aimed at evaluating the feasibility of conducting a RCT in a single centre on a population of NDD donors. Therefore, we performed a pilot RCT comparing the administration of a levothyroxine infusion to a placebo in NDD donors to understand and identify barriers to research in organ donation. We hypothesize that limiting factors will include obtaining a waiver of consent for research in donors and identifying the inclusion criteria to represent the target population.

Altogether these articles are the first to investigate the variability of recommendations and medical decisions in the hemodynamic management of NDD donors. These studies lay the foundations for understanding the actual clinical management of donors, for describing mechanisms of RV dysfunction and for identifying future needs for bench to bedside research. This thesis has a direct impact on the insight that clinicians may have on their actual practice. It highlights the importance of identifying predictors of research success, including the

understanding of mechanisms leading to the observed hemodynamic instability in human NDD, and more importantly of their consequences in recipients. Finally, it opens the door to the future possibility of focusing on new interventions to improve donor care and recipients' outcome, thereby abandoning futile treatments.

Chapter II: Methodology and results

1. Overview of the methodology

This thesis is composed of four articles (three published and one submitted) representing four different research methodologies. The method section of individual research projects is described in the published (submitted) articles and therefore, will not be repeated in this section. However, we provide supplementary methodological information relevant to the following articles:

1.1 Worldwide management of donors after neurological death: a systematic review of guidelines

This article was submitted for publication to Critical Care Medicine. The research methods are detailed in the article. In summary, we designed a systematic review of clinical practice guidelines that include recommendations pertaining to the clinical management of neurologically deceased donors. The objective of this systematic review was to identify actual available guidelines for organ donor care, to draw a portrait of the recommendations and to describe their methodological quality. The following sections will present information and rationale for the clinical practice guideline definition used in the review, and will present the AGREE-II validated instrument that was used for the evaluation of the methodological quality.

1.1.1 Clinical practice guideline

For the purpose of this systematic review, we elected to include clinical practice guidelines defined as "*documents endorsed by an ODO, a professional society, or a government*

and that aim at directing the medical management of adult neurologically deceased multi-organ donors". This definition was elaborated and discussed among the investigators, and is the result of a consensus. The Institute of Medicine defines clinical practice guidelines as « systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances».[245,246] To this definition the Institute adds that clinical practice guidelines should be preceded and informed by a systematic review of the evidence, and that recommendations should be the result of the analysis of the balance between benefits and harms.[245] We decided to use a broader definition of clinical practice guideline to include documents lacking rigorous systematic review of the evidence or evaluation of balance and risk to draw a realistic picture of the actual recommendations for the organ donor care. Few randomized controlled trials are available in the field, and we therefore expected recommendations to rely on lower quality of evidence and expert opinions. Since the standards for developing clinical practice guidelines recommends multidisciplinary group of experts and external review, we excluded local protocols in our systematic review.

1.1.2 Evaluation of the quality of reporting for guidelines

The purpose of guidelines is to lead clinicians towards best practice interventions, with the intent of improving patients' outcomes. The AGREE collaboration defines guideline quality as "the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice".[247] In 2005, a systematic review identified 24 appraisal instruments of clinical practice guidelines quality.[248] This number had increased to 40 in 2013.[249] From these 40 instruments, only six, including the AGREE-II instrument, were validated.[249] The comparison between the instruments included a comprehensive literature search and item generation steps. As a result, 24 items covering 13 quality dimensions mandatory to a guideline appraisal instrument were listed.[249] The AGREE-II instrument covers 100% of the quality dimensions and 76% of the selected items and constitutes the best validated instrument to conduct a comprehensive evaluation of guidelines quality.[249] Only one instrument, the DELBI instrument, performs above the AGREE-II instrument, but this tool is only available in German.[249]

Developed in 2013 by a group of researchers from 13 countries, the AGREE-II instrument was designed to evaluate the process of guideline development as well as the quality of its reporting.[247,250] The first edition of the instrument comprised 24 items grouped into five domains (scope and purpose; stakeholder involvement; rigour of development; clarity and presentation; applicability), and a 4-point Likert scale was used to score each item.[250] The instrument was field-tested by 194 appraisers on 100 guidelines from 11 countries. The mean item score was calculated for each of the guidelines and reliability of the instrument was verified using the Cronbach alpha coefficient (internal consistency of each domain) and intraclass correlation (within domain reliability for 1, 2, 3 and 4 appraisers).[250] Several assessments of validity were added to the reliability (face validity, construct validity, criterion validity).[250] The reliability analysis using a varimax rotated factor matrix demonstrated good relevance for the selected items (coefficients varying from 0.589 to 0.804) and suggested the need for the addition of a 6th domain (editorial independence). The inter rater reliability analysis, however, demonstrated that at least 4 appraisers were needed to maintain sufficient intra-domain reliability (ICC varying from 0.57 for domain 4 to 0.91 for domain 3).[250] In the following years, the instrument was modified to introduce a seven-point assessment scale for the items instead of the previous 4-point scale.[251] The instrument was retested by 192 appraisers on 10 guidelines with various known quality. On this new version, reliability was assessed using only exploratory analyses.[251] Intra-domain internal consistency varied from 0.64 (editorial independence) to 0.89 (rigour of development)two to five raters were needed to assure the reliability of 0.7, depending on the domain.[251] The construct validity of the 7-point scale AGREE-II instrument was tested and demonstrated discrimination between low and high quality guidelines.[252]

1.2 A Canadian survey of critical care physician's hemodynamic management of neurologically deceased organ donors

This article was published in the Canadian Journal of Anaesthesia in 2019,[253] The research methods are detailed in the article. In summary, we surveyed Canadian intensive care physicians that work in organ donation high-volume centers with the objective of describing self-perceived practices in the context of knowledge about, and experience with,

neurologically deceased donor care. For this survey, we manually established a list of potential respondents rather than using pre-existing membership lists. A rationale for this decision is provided below. In the following section, we also provide a rationale for surveying the whole target population rather than a sampling.

1.2.1 Listing of survey potential respondents

A survey is meant to represent the opinion of a target population. A selection bias often occurs when the survey potential respondents do not accurately represent the target population. Selection biases in surveys can occur through coverage, nonresponse or voluntary response biases. In the critical care field, surveys are often employed to assess self-perceived physicians' practice, awareness or opinion on a target intervention. [254-257]

Most commonly, when targeting the population of intensive care physicians, survey investigators identify and contact potential respondents through critical care societies membership or critical care meeting lists.[255,256] Although this strategy seems appealing because time and money sparing, the use of membership lists threaten the validity of survey responses by increasing the risk for under coverage and voluntary response. Not all intensive care physicians of the target population are members of societies or attend meetings. We can postulate that these potential respondents are restrained from the possibility of responding to the survey, resulting in a coverage bias. Also, physicians that are members of critical care societies probably differ from non-members in their knowledge, motivations, case exposure and voluntariness. We believe that surveys should be administered to all potential respondents of the target population or that when a sample is used, the probability of receiving the survey be equally distributed (or weighed) between potential respondents. However, lower response rates could be expected from this strategy than from surveys administered to a group of society members or association.[258]

1.2.2 Survey sampling

In survey methodology, two principal types of sampling are generally described: probability sampling and non-probability sampling, the first being the only suitable sampling method when inference to the target population is intended. Non-probability sampling is therefore usually considered inappropriate to statistical quantitative research. However, non-probability sampling may be appropriate in some particular situations.[259] For example, when the whole population of interest is small, and that individuals of the population of interest share uncommon characteristics, total population sampling, a type of purposive sampling, is often used. In this situation, participants are selected based on the investigator's knowledge about the study population, which is considered definite.[259,260] An expert sampling, as used in our survey, is a type of purposive sampling. Whole population sampling reduces the risk of selection bias, but necessitates that the list of potential respondents of the whole population is accurate and exhaustive.[260] Also, the impact of the non-response bias is usually considered more important in whole population sampling that in probability sampling, because non-respondents are not missing at random.

1.3 Right ventricular dysfunction in neurologically deceased organ donors: an observational study in a tertiary-care organ donor referral centre

This article was published in the Journal of Critical Care in 2019.[261] The research methods are fully described in the article.

1.4 A pilot randomized controlled trial comparing levothyroxine to placebo in neurologically deceased donors

This article was published in Progress in Transplantation in 2019.[262]The research methods are detailed in the article and comply to the extended CONSORT statement for randomized and feasibility trials.[263] Criteria for determination of success for the pilot trial were elected by consensus between the investigators based on the primary feasibility objective. In the next section, we comment on the objectives and sample sizes of pilot trials.

1.4.1 Objectives and sample sizes determination in pilot trials

The rationale for conducting a pilot trial can be related to the need to evaluate the process of the study and the feasibility of the needed steps, the needed resources including budget and time, the optimal management or some scientific related issues.[264] It is meant to explore areas of uncertainty about a definitive trial.[263] Because of the emotional nature of the topic and the need to conduct research in a time-sensitive fashion, clinical research on organ donation, although necessary, is expected to bear its load of challenges. Before investing budgets and man power in a definitive RCT, we believed that information on the research process and on potential barriers to research was needed, and we therefore elected to design a pilot trial to evaluate the feasibility of a RCT comparing levothyroxine to placebo in deceased donors.[265]

In the medical literature, the terms "pilot studies" and "feasibility studies" are often confused, used as synonyms or as opposed concepts.[265] We propose to adopt the proposed conceptual framework developed by Eldridge et al. that defines a pilot study as *"a study in which a future study or part of a future study, is conducted on a smaller scale to ask the question whether something can be done, should we proceed with it and if so, how"*.[265] Implicit to the definition of a pilot trial is the concept of a small-scale try-out or the implementation of a research project in a certain setting before the conduct of a full-scale project.[263] Feasibility therefore asks the question whether it is possible to achieve something and evaluates the needed processes. All pilot studies are considered feasibility studies, but all feasibility studies are not pilot studies.[265] In 2016, the Consolidated Standards of Reporting Trials (CONSORT) statement added an extension for pilot trials to its previous checklist for the quality of reporting of randomized trial.[263] This adapted checklist from the most recent version of the randomized controlled trial checklist was developed though a Delphi process and piloted.[263] This report recommends that the primary objective of pilot trials should focus on the assessment of feasibility measures and that the inclusion of outcome measures is facultative.[263] The definition of the study objectives should be clear and explicit and the criteria to determine success based on these objectives be determined *a priori*.[266] However, criteria to determine success of a pilot trial remain undefined and the conclusion to the feasibility or non-feasibility of a definitive trial appears largely subjective.[264] For example, in the Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT), criteria for success included the following: 98.5% of patients received study drug

within 12 hours of randomization; 91.7% of patients received every dose in a blinded manner; 90% or more patient had a lower limb compression ultrasound performed; 90% or more of necessary adjustment doses were performed.[267]

In comparison, the Age of BLood Evaluation (ABLE) trial determined success based on the following: 90% or more compliance to treatment strategies (transfused red blood cell by stored), and the definitive trial was deemed feasible since 73% of patients complied to this criterion.[268]

Similarly, little guidance is published on the sample size justification or on success criteria for pilot trials. Various methods for the justification of a pilot trial sample size have been proposed and these include the confidence interval for a given precision around the anticipated valued, a defined proportion of the planned sample size of the future definitive trial or a convenience sample with proposed sample sizes varying from 12 to 50 subjects per group.[264,269] Given that no clear guidelines are proposed to set a pilot trial sample size, investigators have to weigh the balance between the risk of variance imprecision with the risk of concluding to unfeasibility or to unethically expose subjects to an intervention.[269]

2. Results

Article 1: Worldwide Management of Donors After Neurological Death: a Systematic Review of Guidelines

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Submitted to Critical Care Medicine

Contribution to this article: I designed the protocol, performed and supervised data collection, performed the analysis and interpreted the data, drafted and critically revised the manuscript.

Abstract

Objective:

The aim of this study was to systematically identify and describe guidelines for the care of neurologically deceased donors, highlighting some of their strengths and limitations, and current relevance

Data source: MEDLINE, EMBASE, CisMef, Open Grey, LILACS, SciELO, NICE, Cochrane Database of Systematic Reviews, Global Health, and Base de Données de Santé Publique and grey literature

Study selection: We included any document endorsed by an organ donation organization (ODO), a professional society, or a government, that aims to direct the medical management of adult, neurologically deceased, multi-organ donors, including: clinical goals, therapies, diagnostics or monitoring.

Data extraction: We extracted guidelines details and specific donor management recommendations pertaining to six domains: the autonomic storm, hemodynamic instability, hormone supplementation, ventilation, blood product transfusions, and general ICU care.

Data synthesis: This review includes 27 clinical practice guidelines representing 26 countries over the period 1993 to 2019. Using the AGREE-II validated tool for the evaluation of guidelines quality, documents generally scored well on their scope and clarity of presentation. However, quality was limited in terms of the scientific rigor of guideline development. Recommendations varied substantially across the domains of managing the autonomic storm, subsequent management of hemodynamic instability, hormone therapy, mechanical ventilation, blood product transfusion, and general ICU care. We did find consistent recommendations for

low tidal volume ventilation subsequent to the publication of a landmark clinical trial, one of a limited number of clinical trials in this area.

Conclusion: Highly inconsistent recommendations for deceased donor care summarized in this review likely reflect the relatively slow emergence of high-quality clinical research in this field even while guideline methodology has advanced.

INTRODUCTION

Organ transplantation saves lives and improves quality of life for thousands chronically ill patients, every year.(1, 2) In the United States, in 2018, 113,000 patients were registered on a transplant waiting list, and every day, 20 died before a transplant opportunity materialized.(2) In 2012 the World Health Organization called for research to improve the hospital care of deceased organ donors.(3) While there remains a paucity of research in this field, current findings support the concept that improved organ donor care can improve the quantity and quality of organs for transplantation.(4, 5) Because organ donation is a rare activity in most hospitals, clinicians involved in donor care generally lack experience. Therefore, evidence-based recommendations are an important tool to guide best practices for the care of deceased donors in intensive care units.(6)

Embarking upon new clinical research for the care of neurologically deceased organ donors, we sought to understand the content and variability in current guidelines. We elected, therefore, to systematically identify and describe guidelines for the care of neurologically deceased donors, highlighting some of their strengths and limitations, and current relevance.

METHODS

Literature Search

In collaboration with a senior information specialist, we searched 10 bibliographic databases from their inception: MEDLINE (Supplemental Digital Content 1), EMBASE, CisMef, Open Grey, LILACS, SciELO, NICE, Cochrane Database of Systematic Reviews, Global Health, and Base de Données de Santé Publique. We adapted the search strategy to French and Spanish languages for specific databases. To capture gray literature, we used Google (English, French, Spanish, Portuguese, Italian, Chinese, Japanese, German and Arabic), we searched the TRIP database, and we requested unpublished guidelines from each donation organization represented in the International Registry in Organ Donation and Transplantation (IRODaT) database.(7) Lastly, we examined the references of each guideline included in this review. This literature search is up to date as of March 2019.(7)

Eligibility Criteria

This review includes any document endorsed by an organ donation organization (ODO), a professional society, or a government, that aims to direct the medical management of adult, neurologically deceased, multi-organ donors, including: clinical goals, therapies, diagnostics or monitoring. This review, therefore, excludes recommendations for organ donation following a circulatory determination of death, living organ donation, and paediatric organ donation. We also excluded hospital protocols and checklists, organ-specific recommendations for donor care, and review articles. Except for Table 1 and Table 2, only data pertaining to guidelines released after the 2006 Canadian guideline are presented.

Guidelines Selection

Two independent reviewers (AJF, and one of EC, DRW, KS, FDA, MW, BR, DB, IB) screened titles and abstracts generated from the literature search using Covidence® software (8), and reviewed full text reports for all potentially relevant citations. A third independent reviewer resolved disagreements. Where more than one citation reported a guideline for one organization, this review includes the most recent version.

Quality Assessments

Four reviewers independently assessed the methodological rigour of every guideline using the validated AGREE-II tool.(9-11) AGREE-II evaluates the quality of guidelines on 6 domains: 1) scope and purpose, 2) stakeholder involvement, 3) rigour of development, 4) clarity of presentation, 5) applicability, and 6) editorial independence, with specific items to assess within each domain.(9-11) Based on these item assessments, reviewers rated each domain on a 7-point scale.

Data Extraction

The same reviewers, in duplicate, extracted descriptive information and specific donor management recommendations pertaining to six domains: the autonomic storm, hemodynamic instability, hormone supplementation, ventilation, blood product transfusions, and general ICU care.

Information Synthesis

In reporting the quality of guidelines, we determined the scaled domain score reported as a percentage of the maximum score, across four reviewers for each AGREE-II domain.(12) We elected to transpose these scores to a 3-point classification of 'low quality' (<40%), 'moderate quality' (40-70%), and "high quality" (>70%), as proposed in the AGREE-II manual.(12) We also assessed inter-rater reliability among the four reviewers using two-way random intraclass correlations (ICC), and arbitrarily defined reliability as low (ICC: 0-0.4), moderate (ICC:0.41-0.79), and high (ICC: 0.8-1.0).(9) These analyses were performed with IBM SPSS Statistics v24.0 2018.

This report corresponds with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).(13) We apply the term 'recommend' in this report without distinguishing strong from weak recommendations, since only one of the original guidelines(14-16) clearly distinguished strong from weak using a grading approach.(17)

RESULTS

Description of Guidelines

This review includes 27 clinical practice guidelines representing 26 countries (Figure 1, Table 1). Guidelines were released between 1993 and 2019 (two had no release date (18, 19)) and most were reported in English.(14-16, 20-30) Ten of 27 were published in peer-reviewed journals.(14-16, 23, 25-27, 29-33)

Figure 1. Guidelines selection

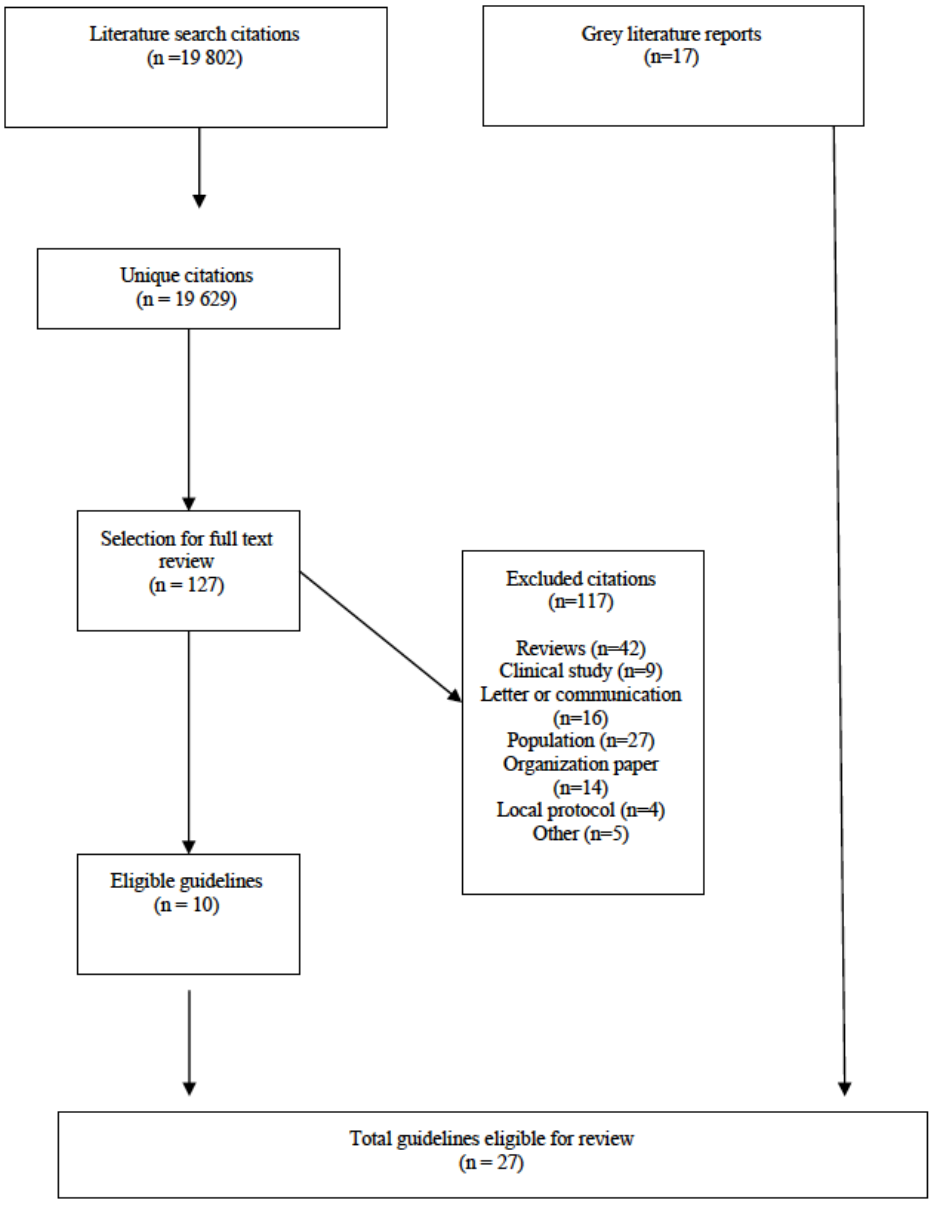

Table 1. Description of the included guidelines

Country, (first author /subcategory) Year (reference number)	Organizations	Language	Source
Ireland (Conrick-Martin) 2019(30)	Intensive Care Society of Ireland	English	Peer review publication
India (Pandit) 2017(29)	Indian Society of Critical Care Medicine	English	Peer review publication
Australia 2016(22)	New South Wales Australia Ministry of Health	English	Website
Austria 2016(34)	Gesundheit Oesterreich	German	Website
Germany 2016(35)	Consul for Organ Donation; German Foundation for Organ Transplantation	German	Website
Norway 2016(41)	Norks Ressursgruppe for Organdonasjon	Norwegian	Website
Denmark 2015(36)	Neuro Anesthesia Committee of the Danish Society of Anesthesia and Intensive Care Medicine; Danish Neurological Society; Danish Transplantation Society	Danish	Website
Europe (Eurotransplant) 2015(24)	Eurotransplant Foundation	English	Website
USA (Kotloff) 2015(27)	Society of Critical Care Medicine; American College of Chest Physicians; Association of Organ Procurement Organizations; Donor Management Task Force	English	Peer review publication
Iran (Firoozifar) 2014(25)		English	Peer review publication
Switzerland (Haberthur) 2014(43)	Fondation Suisse pour le Don d'Organes; Société Suisse de Médecine Intensive; Swisstransplant	French	Website
Oceania (ANZICS) 2013(20)	ANZICS	English	Website
Hungary	Debrecen University;	Hungarian	Website

2013(37)	Hungarian blood services		
Brazil (Westphal) 2011(15,16,17)	Brazilian Association of Intensive Care Medicine; Brazilian Association of Organ Transplants; Transplantation Centre of Santa Catarina	English and Portuguese	Peer review publication
Canada (Bourret) 2010(32)	Transplant Québec	English	Peer review publication (abstract) and website
Chile (Rojas) 2010(38)	Sociedad Chilena de Trasplante	Spanish	Peer review publication
Canada (Trilium) 2010(39)	Trillium Gift of Life Network	English and French	Website
Cuba (Nodal Arruebarrena) 2009(40)		Spanish	Peer review publication
Australasia 2008(21)	Australasian Transplant Coordinators Association	English	Website
Canada (Shemie) 2006(44,46)	Canadian Critical Care Society; Canadian Association of Transplantation; Société canadienne de transplantation; le Conseil Canadien pour le Don et la Transplantation	English and French	Peer review publication
France (Boulard) 2005(31)	Société Francaise d'Anesthésie et de Réanimation; Société de Réanimation de Langue Française; Agence de la biomédecine	French	Peer review publication
United Kingdom 2005(28)	Intensive care society UK; British transplant society	English	Website
USA (Powner) 2004(26)		English	Peer review publication
Slovenia (Avsec-Letonja) 2003(42)		Slovenian	Personal communication
USA(Baldwin) 1993(23)		English	Peer review publication
Argentina ?(19)	Institute Nacional Centre unico Coordinator de Ablacion e Implante; Sociedad Argentina de Terapia Intensiva; Sociedad Argentina de Trasplante; Asociacion Argentina de Procuracion de Organos y Tejidos para Transplante; Ministerio de Salud	Spanish	Website

Spain (Escudero) ?(18)	Red/consejo iberoamericano de donacion y trasplante; Servicio de Medicina Intensiva; Coordinación de Trasplantes Hospital Universitario Central de Asturias	Spanish	Website

Quality of Guidelines

In assessing guideline quality (Table 2), the agreement achieved among four raters was generally moderate. Most guidelines scored moderately well on the clarity of their scope (e.g., specific purpose, target clinicians) (Domain 1),(14-16, 18, 19, 21, 24, 25, 31, 34-40) and the clarity of their recommendations (Domain 4).(14-16, 22, 24-26, 28, 30, 32, 34-37, 39, 41, 42) Most guidelines scored low on other domains. Stakeholder involvement (Domain 2) was limited: many did not appear to involve members of the public, and/or representatives from all target clinician groups.(21, 22, 24, 25, 29-32, 35-37, 39, 40, 43) Almost all guidelines lacked an explicit and research-based approach for formulating their recommendations (Domain 3).(18-26, 28-32, 34-45) For example, only two guidelines mentioned a systematic search of the literature.(14-16, 36) Two guidelines, however, determined the strength of recommendations using a grading approach(14-17, 29), and one reported the agreement between experts on specific recommendations.(31) In terms of applicability (Domain 5), all guidelines but one(44, 46) lacked information on facilitators or barriers to their application and no monitoring or auditing criteria were described (Domain 5). Finally, only three of 27 reported an approach to conflict of interest in guideline development or presentation (Domain 6).(27, 29, 44, 46)

Table 2. Quality assessment with the AGREE-II instrument

Legend: Quality for the criterion on the AGREE-II

Green = high; Yellow = moderate; Reg = low

Country, (first author /subcategory) Year (reference number)	Domain 1: Scope and purpose	Domain 2: Stakeholder involvement	Domain 3: Rigour of development	Domain 4: Clarity of presentation	Domain 5: Applicability	Domain 6: Editorial independence
Ireland (Conrick-Martin) 2019(30)						
India (Pandit) 2017(29)						
Australia 2016(22)						
Austria 2016(34)						
Germany 2016(35)						
Norway 2016(41)						
Denmark 2015(36)						
Europe (Eurotransplant) 2015(24)						
USA (Kotloff) 2015(27)						
Iran (Firoozifar) 2014(25)						
Switzerland (Haberthur) 2014(43)						
Oceania (ANZICS) 2013(20)						
Hungary 2013(37)						
Brazil (Westphal) 2011(15,16,17)						
Canada (Bourret) 2010(32)						
Chile (Rojas) 2010(38)						
Canada (Trilium)						

2010(39)						
Cuba (Nodal Arruebarrena) 2009(40)						
Australasia 2008(21)						
Canada (Shemie) 2006(44,46)						
France (Boulard) 2005(31)						
United Kingdom 2005(28)						
USA (Powner) 2004(26)						
Slovenia (Avsec-Letonja) 2003(42)						
USA(Baldwin) 1993(23)						
Argentina ?(19)						
Spain (Escudero) ?(18)						

Recommendations (Figure 2)

Figure 2. Donor management strategies, displayed as a) hemodynamic therapies, b) hormone therapy components and c) general ICU care.

a) Hemodynamic therapies

b) Hormone therapy components

C) General ICU care

Management of the autonomic storm

Fourteen guidelines described the importance of the autonomic storm(14-16, 18-23, 27-30, 36, 40, 41), but less than half provided recommendations about diagnosis(19, 23, 27-29, 40, 41) or treatment strategies(18, 20, 22, 23, 27-29, 41, 43). Seventeen guidelines recommended specific medications for hypertension and tachycardia;(18-24, 26, 29, 32, 34, 36, 38-40, 42-44, 46) most commonly esmolol(19-22, 29, 34, 36, 38, 40, 43) and nitroprusside, due to the short-acting, titratable effects.(19-22, 29, 36, 43) Alternatives included various classes of anti-hypertensive agents, and even remifentanyl. Due to the transient nature of the autonomic storm, and the risk of subsequent hypotension, four guidelines recommended not treating hypertension or tachycardia in this setting, at all, or limiting treatment to very severe cases.(14-16, 21, 22, 29)

Hemodynamic management after the autonomic storm

Recommended targets for mean arterial pressure ranged from 60 mmHg to 100 mmHg (Supplemental Digital Content 2). (14-16, 18-22, 24-39, 41, 43, 44) As first-line vasopressors, most documents recommended norepinephrine(14-16, 18, 20-22, 31, 35, 37, 43) and/or dopamine(14-16, 18, 19, 23-25, 27, 36, 38, 40, 42) (Table 3). Vasopressin was the preferred agent in Canadian,(32, 33, 39, 44) Irish,(30) Indian,(29) and UK guidelines,(28) potentially because of its additional value in the management of diabetes insipidus. Epinephrine was variably suggested as an alternative agent (14-16), or as a last choice of vasopressors,(19, 29, 32, 33, 39, 42, 44) or it was contraindicated, altogether.(37)

In terms of fluid management, crystalloids were generally recommended as a first-line solution,(14-16, 19, 21-27, 29, 30, 32, 34, 35, 37-39, 43) and some documents recommended

colloids along with crystalloids.(18, 19, 24, 31, 36, 40, 42, 43) Four guidelines recommended intravenous starches,(31, 37, 40) and nine strongly recommended against starch therapy, particularly for donors with renal failure. (19, 21, 22, 27, 29, 32, 34-36, 41, 43) Three recommended a daily negative or neutral fluid balance, to facilitate lung donation.(19, 22, 30)

In terms of inotropic agents, dobutamine(14-16, 18, 19, 22, 26, 30, 31, 34-36, 38, 42, 43), epinephrine(19, 22, 27, 30, 31, 36) and dopamine(19, 26, 33, 35, 36, 44) were all recommended most commonly; other agents included isoproterenol(34), levosimendan(34), milrinone(34) and norepinephrine.(19, 34) The inconsistent indications for each related to various clinical measures of impaired cardiac function.(14-16, 18, 19, 22, 25-27, 29-31, 33, 34, 36-38, 40, 41, 43, 44) Six guidelines made no recommendation on inotropic therapies.(20, 23, 24, 28, 32, 39)

Table 3. Hemodynamic therapies

Country, (first author /subcategory) Year (reference number)	Fluid therapy		Vasopressors	Inotropic support
	Therapy	Contraindicated solutions		
Ireland (Conrick-Martin) 2019(30)	RL, NS or balanced crystalloids 2nd line: colloid solutions		Vasopressin 0.5-2.5 U/h 2nd line: NE or phenylephrine	Dobutamine or adrenaline Limit dobutamine to 10 mcg/kg/min
Australia 2016(22)	½ NS or balanced crystalloids 2nd line: Albumin 20% or 4%	Starches D5%	Vasopressin 2.4 u/h 2nd line: NE, epinephrine, phenylephrine 3rd line: Dopamine	
Australia 2016(22)	Balanced crystalloids 2nd line: Albumin 4%, 20%	Starches Gelatins	NE ad 0.2 mcg/kg/min 2nd line: Add vasopressin 1.2-2.4 u/h	Dobutamine 2nd line: Epinephrine
Austria 2016(34)	1st line: 1/2NS+D5%	Starches	NE, dopamine, phenylephrine, vasopressin	Dobutamine, isoproterenol, levosimendan, milrinone 2nd line : NE
Germany 2016(35)	RL or NS 2nd line: Albumin 5%	Starches	NE 2nd line: Vasopressin 1 U bolus then 0.5-4 u/h	Dobutamine, dopamine
Norway 2016(41)	Ringer acetate, NS, D5%. 2nd line: 2:1 mix crystalloids and colloids (albumin 5% or Dextran)	Starches	Dopamine, NE or vasopressin 1 U bolus then 0.5-2.5 u/h	Dopamine 2-20 mcg/kg/min
Denmark 2015(36)	Balanced crystalloids and consider blood products	Starches Albumin (caution)	Dopamine up to 10 mg/kg/min 2nd line: NE ad 0.1 mcg/kg/min 3nd line: Add vasopressin 0.4-5 u/h	Dobutamine, dopamine or epinephrine

Europe (Eurotransplant) 2015(24)	D5%, NS, D2.5%-0.45 saline, RL 2nd line: 2:1 mix crystalloid/colloid		Dopamine ad 10 mcg/kg/min 2nd line: NE < 0.2 mcg/kg/min	
USA (Kotloff) 2015(27)	NS or RL	Starches	Dopamine up to 10 mcg/kg/min 2nd line: Vasopressin 0.01-0.04 u/min	Dopamine, dobutamine or epinephrine
Iran (Firoozifar) 2014(25)	RL or NS 2nd line: Albumin or gelofusin		Dopamine ad 10 mcg/kg/min 2nd line: NE	Dopamine 2nd line: Epinephrine (congestive heart failure)
Switzerland (Haberthur) 2014(43)	NS or RL 2nd line: HES 130/0.4, gelatin	HES 130/0.4 or gelatin (caution if renal failure)	NE 0.5-3 mcg/kg/min 2nd line: Vasopressin 0.5-2.4 u/h	Dobutamine ≤ 5 mcg/kg/min
Oceania (ANZICS) 2013(20)			NE	
Hungary 2013(37)	Maintenance D5%	HES 0.4/6% (caution)	NE 0.01-2.5 mcg/kg/min 2nd line: Vasopressin 0.01-0.04 u/min alone or in combination with NE	Combination dobutamine/NE ad 10 mcg/kg/min 2nd line: dopamine 4-10 mcg/min
Brazil (Westphal) 2011(15,16,17)	Crystalloid solution		NE, epinephrine or dopamine 2nd line: Vasopressin 1u bolus then 0.5-2.5 u/h	Dobutamine
Canada (Bourret) 2010(32)	D5%-1/2NS maintenance, NS 2nd line: Albumin	Starches (renal failure)	Vasopressin ≤ 2.4 u/h 2nd line : NE <0.2 mcg/kg/min 3rd line: Epinephrine 0.2 mcg/kg/min or phenylephrine 0.2 mcg/kg/min or dopamine ≤10 mcg/kg/min	

Chile (Rojas) 2010(38)	RL or NS 2nd line: gelatin (lung donors)		Dopamine ad 10 mcg/kg/min 2nd line: Add NE	Epinephrine or dobutamine
Canada (Trilium) 2010(39)	Crystalloids		Vasopressin ad to 2.4 u/h 2nd line: Dopamine 5-10 mcg/kg/min 3nd line: NE ad 20 mcg/min, epinephrine up to 20 mcg/min, phenylephrine ad 200 mcg/min	
Cuba (Nodal Arruebarrena) 2009(40)	Mix 65% crystalloids-35% colloids 2nd line: Starches, gelatin		Dopamine ad 3 mcg/kg/min 2nd line: Add noradrenaline 0.1 mcg/kg/min	Dobutamine 5-15 mcg/kg/min
Australasia 2008(21)			NE 2nd line: Vasopressin 0.5-4 u/h	Limit use
Canada (Shemie) 2006(44,46)			Vasopressin 2.4 u/h 2nd line: NE, epinephrine and/or phenylephrine max 0.2 mcg/kg/min	Dopamine ≤ 10 mcg/kg/min

NE = norepinephrine; NS = normal saline; RL = Ringer Lactate; HES = hydroxyethyl starch

Fourteen guidelines recommended “usual care” for arrhythmias,(14-16, 18, 20-22, 27, 29, 35, 37, 38, 40-43) and amiodarone was the most commonly recommended drug.(14-16, 18, 20-22, 29, 41, 43) For bradyarrhythmias, seven reports recommended cardiac pacing (14-16, 18, 22, 37, 41, 43) or beta-agonist agents,(14-16, 18, 22, 29, 35, 37, 41, 43) citing the lack of effect of atropine (14-16, 20, 22, 29, 37, 41-43) or glycopyrrolate (22) after brain death. Seven guidelines addressed cardiac arrest among deceased donors, and recommended routine cardiopulmonary resuscitation.(14-16, 18, 20, 36, 38, 42, 43)

In terms of monitoring, most guidelines recommended central venous pressure (CVP) monitoring, with target ranges from 4 to 15 mmHg.(18, 19, 22, 24-26, 28-30, 32-35, 37-41, 43, 44) Low CVP measures generally triggered fluid administration; however,(14-16, 19, 25, 26, 29, 32, 35, 37, 40, 41, 43) four guidelines, discouraged single CVP measures as unreliable.(14-16, 22, 29, 30, 36)

Guidelines frequently recommended echocardiography to guide hemodynamic therapy, (14-16, 18, 19, 22-36, 39, 43, 44) with minimum targets of left ventricular ejection fraction ranging from 40% to 50%.(14-16, 19, 29, 30, 32, 35, 36, 39, 43) In addition, 19 documents stated various indications for pulmonary artery catheterization, including: young donors,(38) potential heart or lung donors,(19, 25) donors with heart dysfunction or pulmonary hypertension,(14-16, 18, 28, 32, 39, 43, 44, 46) or for all refractory unstable donors.(18, 19, 29, 32, 34, 35, 39, 41, 42, 46)

Ten guidelines recommended non-invasive cardiac output measurement devices.(18, 19, 24, 29, 35-37, 43)

Hormone therapy

Every guideline addressed hormone supplementation (Supplemental Digital Content 3). Nineteen made recommendations about corticosteroid therapy.(14-16, 19-22, 25, 27, 29-32, 36-41, 43, 44, 46) Four recommended steroids for all donors;(27, 35, 36, 41) three recommended steroids for hemodynamically unstable donors,(18, 30, 34) and others recommended steroids only if there was the potential for donation of specific organs: lungs,(18, 19, 22, 32, 37-39, 43, 44, 46) heart,(22) or liver.(43) The most common dosing strategy was high-dose methylprednisolone (14-16, 18-22, 25, 27, 29, 30, 32, 34-39, 41, 43, 44, 46).

Eighteen guidelines recommended thyroid hormone supplementation.(14-16, 19-22, 25, 27, 29-32, 36-40, 43, 44, 46) Indications included: all donors,(29) or those with hemodynamic instability.(22, 26, 30, 36, 43) Suggested agents included triiodothyronine (T3; six guidelines),(20-22, 36-38) thyroxine (T4; four guidelines), (25, 32, 39, 44, 46) or either (six guidelines). (14-16, 19, 27, 29, 35, 43) Three guidelines recommended against routine thyroid supplementation based on the lack of supporting evidence.(18, 23, 42)

Nine guidelines addressed insulin therapy for organ donors.(19, 22, 25, 29, 30, 36, 37, 40) Some recommended insulin for all donors(25, 37, 40), potentially for its possible inotropic effect, while others recommended insulin as needed for glycemic control, similarly to ICU general care practice.(14-16, 18, 20-22, 24, 26-30, 32, 34-39, 43, 44, 46) For the latter, dosing ranges and

glycemic targets varied. One guideline recommended a mixed infusion of glucose, insulin and potassium (GIK) for donors with refractory hemodynamic instability.(43)

Vasopressin was suggested as a component of a hormone therapy bundle in 13 guidelines,(19-21, 29-32, 36-40, 44, 46) in doses ranging from 0.4 to 5 u/h.(14-16, 18-22, 28, 29, 37-39, 44, 46) Desmopressin, a synthetic analogue of vasopressin that lacks the vasopressor properties, was recommended as first line therapy for diabetes insipidus in 23 guidelines, with or without combined vasopressin infusion.(14-16, 18-22, 25-27, 29-32, 34-37, 39-44, 46)

Lung Protective Mechanical Ventilation

All but three (20, 21, 23) reports provided recommendations on ventilation parameters and/or arterial blood gas targets (Supplemental Digital Content 4). Recommended tidal volume ranges included values from 4 ml/kg to 12 ml/kg.(14-16, 19, 22, 24-26, 30, 32, 35-39, 43, 44, 46) Eleven guidelines recommended low tidal volumes (4-8 ml/kg) for all donors,(14-16, 22, 24, 30, 32, 35, 37-39, 41, 43) and four specifically for lung donors(14-16, 18, 19, 36) Recommendations on maximal peak airway pressures ranged from 30 cmH_2O to 47 cmH_2O,(24-26, 32, 35, 37-40, 44, 46) maximal plateau airway pressures ranged from 30 to 35 cmH_2O, (14-16, 18, 19, 22, 26, 30, 35, 43) and 8 guidelines made recommendations about recruitment maneuvers.(14-16, 18, 19, 22, 26, 27, 30-32, 35, 39, 44, 46) Only the Brazilian guideline recommended advanced ventilation strategies in cases of respiratory failure.(14-16)

Blood product transfusions

All but one guideline(20) made recommendations about blood product transfusion. Hemoglobin transfusion thresholds varied from 70 to 100 g/L,(14-16, 18, 19, 21, 22, 24, 25, 27-32, 34, 39-44, 46) and some guidelines provided hematocrit thresholds, which ranged from 20% to 30%.(19, 23-26, 29, 35, 37, 38, 41-43) Few guidelines distinguished stable from unstable donors in making these recommendations.(14-16, 18, 22)

Recommendations for platelet and coagulation factor transfusions appeared in nine guidelines.(14-16, 19, 22, 26, 31, 35, 37, 38, 40, 43) Threshold platelet levels varied from 20 to 150 $x10^9$g/l.(14-16, 19, 22, 26, 31, 37, 38, 43) Recommendations for plasma or fibrinogen transfusions were inconsistent; some required active bleeding,(14-16, 24, 30, 32, 39, 40, 44, 46) while others required only coagulopathy.(14-16, 18-20, 22, 26, 28, 29, 32, 35, 38, 40) Fibrinolytic therapy (with tranexamic acid, aprotinin or aminocaproic acid) was recommended in one guideline(43) and recommended against, due to potential thrombosis risk, in another.(28)

General ICU care

Twenty-three reports addressed body temperature, with recommended ranges falling between 35 to 38 degrees Celsius.(14-16, 18, 21, 22, 24-26, 29-32, 34-40, 43) Recommendations for the management of hyperthermia included antibiotics, (22, 26, 36, 39) antipyretics (acetaminophen), (22, 26, 36) and external cooling.(22, 23, 26, 36, 39) Recommendations for preventing or treating hypothermia included various warming strategies.(14-16, 18, 20, 21, 24-26, 28-30, 32, 34, 35, 37-43)

Most guidelines recommended continuation of previously initiated enteral (14-16, 20, 27, 29, 30, 32, 36, 39, 43, 44, 46) or parenteral nutrition,(27, 30, 32, 39, 43, 44, 46) and five guidelines suggested initiating enteral nutrition.(14-16, 30, 32, 39, 44, 46) One guideline recommended discontinuation of all nutritional support in potential donors, but did not provide the rationale.(41)

Three reports addressed stress ulcer prophylaxis (26, 36, 37), one recommending daily intravenous pantoprazole.(26) Mechanical and/or pharmacological thromboprophylaxis was recommended by two guidelines.(22, 30) Eight guidelines suggested antimicrobial prophylaxis, including 8 different agents or classes.(24, 27, 36, 41) (18, 19, 23, 31) Six other guidelines strongly recommended against routine antimicrobial prophylaxis.(22, 29, 40, 43, 44, 46)

DISCUSSION

This systematic review uniquely summarizes 27 guidelines for the management of neurologically deceased organ donors. It includes the most recent versions of clinical practice guidelines endorsed by organ donation organizations, medical societies, and governments around the world, whether published in peer-reviewed sources, or not. A vast majority originated from Europe, North America and Oceania.

One striking observation from this review is the inconsistency of recommendations across guidelines. With a paucity of clinical research in this field, and particularly randomized trials,(4,

5, 47) medical guidelines tend to emphasize physiologic reasoning and expert opinion,(48, 49) an approach that lends itself to subjectivity and inconsistency.(48, 50) Thus, in a recent joint effort of the *Society of Critical Care Medicine*, the *American College of Chest Physicia*ns, and the American *Association of Organ Procurement Organizations* to produce evidence-based guidelines for deceased donor care, authors reasoned that because "…the available literature was overwhelmingly comprised of observational studies and case series, … a decision was made that the document would assume the form of a consensus statement rather than a formally graded guideline."(27) New standards for guideline development, which predate most of the documents of this review, emphasize the need for an evidence-based approach despite low quality evidence(17) In this review, two guidelines (Brazil 2011; Denmark 2015) incorporated a systematic literature search,(14-16, 36) one described a protocol for reaching consensus (France 2005)(31) and recommendations from Brazil and India partially incorporated GRADE methodology.(14-16, 29)

Another plausible explanation for varied, sometimes conflicting recommendations is the disparate resources available across health systems to support deceased donors.(51-53) Finally, one might expect discernable advances from earlier to later recommendations. We found little evidence of this, with one exception.(5)

Better clinical research to support donor care is slowing emerging, which calls for updates to many of the current guidelines. Examples include two randomized trials, which have evaluated lung-protective ventilation(5), and moderate hypothermia(4), respectively. A ventilation strategy using low tidal volumes and relatively high positive end-expiratory pressure achieved a significant doubling in the number of lung donors.(5) Since the publication of this trial, 10

guidelines included recommendations about mechanical ventilation; 9 of the 10 specifically recommended low tidal volumes(14-16, 22, 24, 30, 35-37, 41, 43) and two of 10 recommended PEEP levels greater than 8 cm H_2O.(14-16, 35) In the more recent trial, moderate hypothermia (34.0-35.0 degrees Celsius) was associated with a significant reduction in terminal creatinine levels, and in delayed renal graft function.(4) In the six guidelines published after 2015, all reported on temperature management but none recommended mild targeted hypothermia.(22, 29, 30, 34, 35, 41)

Strengths of this review include the broad search for relevant guidelines, the systematic assessment of guideline quality using a validated instrument, and duplicate independent data abstraction. This is the only systematic review of guidelines for organ donation, and the findings highlight important opportunities to advance deceased donor care through improved guideline methodology that will incorporate emerging high-quality research. This review also has notable limitations. An assessment of the suitability of current guideline recommendations was beyond the scope of this review. In addition, it is possible that individual hospitals have developed their own documents to supplant the relatively older guidelines included in this review.

Conclusion

The inconsistent recommendations for deceased donor care summarized in this review reflect the slow emergence of high-quality clinical research in this field even while there have been great strides in guideline methodology. In this new age of randomized trials in deceased donor care, we can look forward to more frequent guideline updates, stronger recommendations, and

stronger justification for the standardization of care. An agenda establishing priorities for research could lead to the development of high-quality guidelines to improve transplant outcomes, as demonstrated in other fields of health care. (54-56)

Supplemental Digital Content 1. Medline Search Strategy

1. exp "Tissue and Organ Procurement"/
2. Tissue Donors/
3. Living Donors/
4. Unrelated Donors/
5. ((organ? adj1 dono*) or (organ? adj1 donat*) or (tissue? adj1 dono*) or (tissue? adj1 donat*) or (transplant* adj1 dono*) or (transplant* adj1 donat*) or (organ? adj1 procur*) or (tissue? adj1 procur*) or (transplant* adj1 procur*) or (directed adj1 donation?) or unrelated dono* or (kidney? adj1 dono*) or (kidney? adj1 donat*) or (heart? adj1 dono*) or (heart? adj1 donat*) or (liver? adj1 dono*) or (liver? adj1 donat*) or (lung? adj1 dono*) or (lung? adj1 donat*) or (living adj1 dono*)).mp.
6. 1 or 2 or 3 or 4 or 5
7. brain death/
8. ((brain? adj1 death?) or (brain? adj1 dead*) or irreversible coma? or coma depasse?).mp.
9. 7 or 8
10. exp Practice guidelines as Topic/ or exp Practice Guideline/ or exp Guideline/ or exp Guideline Adherence/ or Guidelines as Topic.mp. or exp Reference Standards/ or exp Evidence-based Medicine/ or exp Evidence-based practice/ or standard of care.mp. or Clinical Protocols/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11. (standard of care or reference standard? or evidence-based practice or evidence-based medicine or evidence-based nursing or (practice adj1 guideline?) or guideline? or handoff? or handover? or (hand adj1 over?) or gold standard or clinical protocol* or (hand adj1 off)).mp.

12. 10 or 11

13. 6 and 9 and 12

14. (6 and 9) not 13

15. (6 and 12) not 14

Supplemental Digital Content 2. Hemodynamic targets

Country, (first author /subcategory) Year (reference number)	Blood pressure targets	Heart rate target	Hemodynamic parameters targets	Echocardiography indication and targets
Ireland (Conrick-Martin) 2019(30)	MAP 60-70 mmHg		CVP 6-10 mmHg PACWP 8-12 mmHg CI >2.4 L/min/m^2	All donors Target: LVEF ≥ 45%
India (Pandit) 2017(29)	SBP >100 mmHg MAP ≥ 60-70 mmHg		CVP 6-8 mmHg PACWP 8-12 mmHg Stroke volume variance <12% CI 2.4 L/min/m^2	All donors (fluid response) Unstable donors Target LVEF ≥ 45%
Australia 2016(22)	SBP >100 mmHg MAP > 60-80 mmHg	60-120 bpm	CVP 6-10 mmHg CI >2.5 L/min/m^2	Unclear
Austria 2016(34)	MAP 65-75 mmHg	60-120 bpm	CVP 6-12 mmHg	Unstable donors
Germany 2016(35)	MAP 70-100 mmHg		Vascular resistance 2000 +/- 500 dynes/sec/cm^5 CVP 7-10 mmHg PACWP <12 mmHg CI 3-5 L/min/m^2 ITBVI >850-1000 ml/m^2 ELWI 3-7 ml/kg Stroke volume index 40-60 ml/m^2	Unstable donors
Norway 2016(41)	MAP >65 mmHg	60-120 bpm	CVP 6-10 mmHg	
Denmark 2015(36)	MAP > 60-70 mmHg		CVP 6-10 mmHg	All donors

Europe (Eurotransplant) 2015(24)	SBP ≥ 90 MAP ≥ 70-90 mmHg		CVP 6-10 mmHg PACWP 10-15 mmHg ITBVI 750-1000 ml/m^2	Heart donor
USA (Kotloff) 2015(27)	MAP ≥ 60 mmHg		CVP and/or PAC	Heart donor Target: > 45%
Iran (Firoozifar) 2014(25)	SBP ≥ 100 mmHg MAP ≥ 60 mmHg, for patients >60 years old aim for MAP equal to age	70-100 bpm	CVP ≥ 12 cmH_2O, up to 15 cmH_2O if donor > 60 years old	Heart donor
Switzerland (Haberthur) 2014(43)	MAP 65-90 mmHg	60-120 bpm	CVP 8-12 mmHg PACWP 10-15 mmHg GEDVI 680-800 ml/m^2 CI >2.5L/min/m^2 EVLWI: < 7 ml/kg PPV: < 10%	All donors (baseline) Unstable donors
Oceania (ANZICS) 2013(20)	MAP >70 mmHg			
Hungary 2013(37)	MAP 65-75 mmHg		Vascular resistance: ≥ 1200 dynes/s/cm^5 CVP 6-12 mmHg PACWP 6-12 mmHg	
Brazil (Westphal) 2011(15,16,17)	SBP > 90 mmHg MAP > 65 mmHg		CI >2.5 l/min/m^2	Unstable donors Target: LVEF >50%

Canada (Bourret) 2010(32)	SBP 100-160 mmHg MAP 65-90 mmHg	60-120 bpm	Vascular resistance 800-1200 dynes/sec/cm^5 CVP 5-10 mmHg,	Heart donors Target: LVEF >50%
Chile (Rojas) 2010(38)	MAP ≥ 60		CVP 6-10 mmHg (if heart or lungs are not considered, CVP > 10 mmHg is acceptable)	
Canada (Trilium) 2010(39)	SBP 100-160 mmHg MAP 70-90 mmHg	60-120 bpm	Vascular resistance 800-1200 dynes/sec/cm^5 CVP 6-10 mmHg	Heart donor Target: LVEF >40%
Cuba (Nodal Arruebarrena) 2009(40)	SBP ≥ 100 mmHg	≤ 100 bpm	CVP 10-12 mmHg PACWP 10-12 mmHg	
Australasia 2008(21)	MAP > 70 mmHg			
Canada (Shemie) 2006(44,46)	SBP ≥ 100 mmHg MAP ≥ 70 mmHg	60-120 bpm	Vascular resistance 800-1200 dynes/sec/cm^5 CVP 6-10 mmHg PACWP 6-10 mmHg CI >2.4L/min/m^2	All donors (baseline) Heart donors

Supplemental Digital Content 3. Hormone therapies

Country, (first author /subcategory) Year (reference number)	Combined hormone therapy		Additional corticosteroids specific details	Additional thyroid hormones details	Additional insulin details	Additional antidiuretic hormone analogues details
	Components	***Indications***				
Ireland (Conrick-Martin) 2019(30)	Vasopressin Insulin Thyroid Corticosteroids	Hemodynamic instability, impaired cardiac function in potential heart donor	**Specific indication:** Shock reversal: MP 1g IV q24h	**Specific indication:** Hemodynamic instability: T3 4 mcg IV then 3 mcg/h	**Specific indication**: Glycemic control: IV insulin for glycemia <10 mmo/l	**Specific indication:** Hemodynamic instability: Vasopressin 1 u IV bolus then 2.4 u/h **Specific indication:** Diabetes insipidus: DDAVP 1-2 mcg IV or SQ PRN or vasopressin 0.5-2.4 u/h
India (Pandit) 2017(29)	Vasopressin Insulin Thyroid Corticosteroids	Refractory hemodynamic instability	MP 15 mg/kg IV q24h or 250 mg IV then 100 mg/h	T4 20 mcg bolus IV then 10 mcg/h infusion or T4 300-400 mcg PO q8h or T3 (if available)	**Specific indication:** Glycemic control: Insulin for glycemia 80-150 mg/dl	Vasopressin 0.5-4 u/h IV infusion **Specific indication**: Diabetes insipidus: DDAVP 10 mcg intranasal, 1-2 puffs q4h or vasopressin 0.5-2 u/h IV infusion
Australia 2016(22)	Unclear	Not formally recommended, consider if LVEF <45% or heart/lung donors	MP 15 mg/kg IV x 1	T3 IV 4 mcg/h	**Specific indication**: Glycemic control: Insulin for glycemia 6-10 mmol/l	**Specific indication**: Diabetes insipidus: DDAVP 1-4 mcg IV q4-8 PRN or vasopressin 0.04-2.4 u/h IV infusion
Austria, 2016			**Specific indication**: Persistent hypotension: Hydrocortisone 200 mg IV then 200 mg/24h		**Specific indication**: Glycemic control: Insulin IV infusion 5u/h and for glycemia 80-150 mg/dl	**Specific indication**: diabetes insipidus: Desmopressin IV 1-4 mcg q6-8h
Austria 2016(34)	Unclear		**Specific indication:**	**Specific indication:**	**Specific indication**: Glycemic control:	**Specific indication:** Diabetes insipidus: DDAVP 1-4 mcg

			All donors: MP 250 mg IV then 100 mg/h	Hemodynamically unstable potential heart donor: T3 IV 4 mcg bolus then 3 mcg/h or T4 20 mcg IV then 10 mcg/h	Insulin for glycemia 6-10 mmol/l	IV bolus PRN or 0.5-2 mcg IV infusion or vasopressin 0.05-0.5 u/h IV infusion
Germany 2016(35)	Unclear	Hemodynamic instability	MP 15 mg/kg **Specific indication:** All donors			**Specific indication: D**iabetes insipidus: DDAVP 1-4 mcg IV PRN
Norway 2016(41)	Unclear	Hemodynamic instability	MP 15 mg/kg **Specific indication:** All donors			**Specific indication:** Diabetes insipidus: DDAVP 1-4 mcg IV PRN
Denmark 2015(36)	Unclear	Hemodynamic instability	MP 15 mg/kg IV q24h	T3 4mcg IV then 3 mcg/h infusion or T4 20 mcg IV bolus, then 10 mcg/h infusion or T4 2 mcg/kg tablets P.O **Specific indication:** Unstable donor with LVEF < 45% Not recommended alone	**Specific indication:** Glycemic control: Insulin for glycemia 6-10 mmol/l	**Specific indication:** Diabetes insipidus: Desmopressin 1-2 mcg IV q6h PRN or nasal spray 10-20 mcg or melting tablet 60-120 mcg
Europe (Eurotransplant) 2015(24)					**Specific indication:** Glycemic control	**Specific indication:** Diabetes insipidus: DDAVP 2-4 mcg IV
USA (Kotloff) 2015(27)	Thyroid hormones, Corticosteroids	LV dysfunction in potential heart donors; Unmet hemodynamic goals and/or LVEF < 45% (unclear)	MP 15 mg/kg, 1g or 250 mg IV then 100 mg/h infusion	T4 20 mcg IV then 10 mcg/h OR T3 4 mcg IV then 3 mcg/h	**Specific indication:** Glycemic control: Insulin for glycemia <180 mg/dl	**Specific indication**: Diabetes insipidus: DDAVP 1-4 mcg IV or vasopressin

Iran (Firoozifar) 2014(25)	Unclear	Hemodynamic instability	MP 15 mg/kg IV q12h	T4 0.6 mg per nasogastric tube x1	Insulin 1u/h and scale adjustment to glycemia <140	**Specific indication**: Diabetes insipidus: Desmopressin 2-4 mcg nasal
Switzerland (Haberthur) 2014(43)	Unclear	Hemodynamic instability or cardiac failure	Hydrocortisone 50 mg IV q6h **Specific indication:** Lung donors: MP 15 mg/kg	T3 4 mcg IV then 3 mcg/h or T4 20 mcg IV then 10 mcg/h or TSH 0.1 mg IV	**Specific indication:** Refractory hemodynamic instability: Glucose 10%-Insulin-Potassium infusion 1ml/kg **Specific indication**: Glycemic control: IV insulin for glycemia 4-8 mmol/l	**Specific indication:** Diabetes insipidus: Desmopressin 0.25-2 mcg IV q6h or vasopressin 0.5-2.0 u/h
Oceania (ANZICS) 2013(20)	Vasopressin Thyroid Corticosteroids	Potential heart donor with LVEF<45%	MP 15 mg/kg IV x1	T3 4 mcg IV bolus then 3 mcg/h	**Specific indication:** Glycemic control	Vasopressin 0.5-4.0 u/h **Specific indication**: Diabetes insipidus: DDAVP 2-4 mcg IV q2-6 h
Hungary 2013(37)	Vasopressin Insulin Thyroid Corticosteroids	Refractory hemodynamic instability	Hydrocortisone 50 mg IV bolus then 50 mg x 4 doses **Specific indication:** All lung donors: MP 15 mg/kg q24h	T3 4 mcg/kg IV bolus then 3 mcg/h	10 u bolus then adjust to target glycemia 4.2-8.3 mmol/l **Specific indication:** Glycemic control: Insulin sliding scale	Vasopressin 1 u bolus then 0.6-2.4 u/h **Specific indication:** Diabetes insipidus: Desmopressin 0.6-2 mcg IV q6-12 h or nasal spray 10-20 mcg q12h or Vasopressin 0.01-0.04 u/min IV
Brazil (Westphal) 2011(15,16,17)	Unclear	All donors	MP 15 mg/kg	T3 4 mcg IV then 3 mcg/h OR T4 20 mcg IV then by 10 mcg/h OR T4 1-2 mcg/kg PO	**Specific indication**: Glycemia control: IV insulin for glycemia <180 mg/dl	**Specific indication**: Diabetes insipidus: DDAVP 1-2 mcg IV q4h PRN to achieve and/or Vasopressin 1 U IV, then 0.5-2.4 u/h
Canada (Bourret) 2010(32)	Vasopressin Thyroid hormones Corticosteroids	Refractory hemodynamic instability	MP 15 mg/kg IV max 1g q24h **Specific indication**: Lung donors	T4 20 mcg then 10 mcg/h OR 100 mcg then 50 mcg IV q12h	**Specific Indication**: Glycemic control **Specific regimen**: IV insulin scale to glycemia 4-8 mmol/l	**Specific indication**: Diabetes insipidus: DDAVP 1-4 mcg IV then 1-2 mcg IV q6h PRN

Chile (Rojas) 2010(38)	Vasopressin Thyroid Corticosteroids	Refractory hemodynamic instability	MP IV 15 mg/kg x1 **Specific indication**: Lung donors	T3 4 mcg bolus than 3 mcg/h	**Specific indication**: Glycemic control: IV c insulin for glycemia 80-150 mg/dl	Vasopressin 1u bolus then 0.5-4 u/h **Specific indication**: Diabetes insipidus: Vasopressin 1u IV then 0.5-4 u/h or DDAVP nasal/IM/SQ 10-20 mcg or DDAVP IV 0.1-0.2 ml q8-12h
Canada (Trilium) 2010(39)	Vasopressin Thyroid Corticosteroids	All donors Hemodynamic instability	MP 15 mg/kg IV bolus (max 1g) q24h **Specific indication:** Lung donors	T4 100 mcg IV then 50 mcg IV q12 or 20 mcg IV then 10 mcg/h	**Specific indication:** Glycemic control: Insulin for glycemia 6-10 mmol/l	Vasopressin ≤ 2.4 u/h **Specific indication:** Diabetes insipidus: DDAVP 4 mcg IV q6h prn or vasopressin 0.5-2.4 u/h
Cuba (Nodal Arruebarrena) 2009(40)	Unclear	Refractory hemodynamic instability			Insulin IV 1u/h adjust to target 120-180 mg/dl **Specific indication**: Glycemic control	**Specific indication:** Diabetes insipidus: DDAVP 0.5-2 mcg IV or nasal drops 10-20 mcg or inhalation 10 mcg q8-12h, or vasopressin
Australasia 2008(21)	Vasopressin Thyroid Corticosteroids	Refractory hemodynamic instability and/or LVEF <45%	MP 15 mg/kg IV x1	T3 4 mcg/IV, then 3 mcg/h	Glycemic control **Specific regimen**: Insulin for glycemia 5-8 mmol/l	Vasopressin 0.5-4 u/h **Specific indication**: Diabetes insipidus: DDAVP 2-4 mcg IV q2-6h or vasopressin 0.5-2 u/h
Canada (Shemie) 2006(44,46)	Vasopressin Thyroid hormones Corticosteroids	All donors LVEF ≤ 40% or hemodynamic instability	MP 15 mg/kg max 1g **Specific indication:** Lung donors	T4 mcg IV then 10 mcg/h OR T4 100 mcg IV then 50 mcg IV q12h	**Specific indication:** Glycemic control: Insulin for glycemia 4-8 mmol/L	Vasopressin ≤ 2.4 u/h **Specific indication:** Diabetes insipidusL DDAVP 1-4 mcg IV then 1-2 mcg IV q6h OR vasopressin ≤ 2.4 u/

Supplemental Digital Content 4. Ventilation strategies

Country, (first author /subcategory) Year (reference number)	Tidal volume	Pressures	PEEP	Recruitment manoeuvres #	Targets
Ireland (Conrick-Martin) 2019(30)	6-8 ml/kg IBW	Plateau <30 cmH2O	5-10 cmH2O	x	PCO2: normocapnia pH 7.35-7.45 PaO2 ≥ 10 kPa
India (Pandit) 2017(29)			Unclear		PCO2: normocapnia pH: 7.35-7.45 SaO2: >95% PaO2: >100 mmHg
Australia 2016(22)	6-8 ml/kg IBW	Plateau <30 cmH2O	5-10 cmH2O >8 cmH2O if lung protective	x	PCO2 35-45 mmHg pH 7.35-7.45 SaO2>95% PaO2 >80-100
Austria 2016(34)					PCO2 35-45 mmHg SaO2 ≥ 95% PaO2 80-150 mmHg
Germany 2016(35)	6-8 ml/kg	Plateau <30 cmH2O or Peak < 35 cmH2O	8-10 cmH2O (up to 15 cmH2O if decreased lung function)	x	Normal blood gas Permissive hypercapnia possible SaO2 ≥92%
Norway 2016(41)	Low tidal volume		5, preferably 10 cmH2O		SaO2 95-100%
Denmark 2015(36)	6-8 ml/kg especially in lung donors		6-8 cmH2O		PaO2/FiO2 >300 (lung donors) PaO2 >12 KPA
Europe (Eurotransplant) 2015(24)	6-8 ml/kg	Peak <35 mmHg	5-10 mmHg		PaCO2 35-45 SaO2 >95% PaO2 >80-100 mmHg
USA (Kotloff) 2015(27)	Unclear			x	PaO2/FiO2 >300 (lung donors)
Iran (Firoozifar) 2014(25)	8-10 ml/kg	Peak < 30 mmHg	5 cmH2O		PaCO2 35-45 mmHg pH 7.35-7.45 SaO2 95-100% PaO2 90-100 mmHg

Switzerland (Haberthur) 2014(43)	4-7.7 ml/kg	Plateau <30 mBar	PEEP minimum 5 mbar		PaO2 min 70 mmHg and SaO2 >88% (except in lung donors)
Oceania (ANZICS) 2013(20)			Unclear	Unclear	
Hungary 2013(37)	6-8 ml/kg IBW	Peak <40 cmH2O; <30 cmH2O (lung donor)	5 cmH2O 8-10 cmH2O (lung donor)		PaCO2 40-45 mmHg pH 7.35-7.45 SaO2 >92% PaO2 >70 mmHg
Brazil (Westphal) 2011(15,16,17)	6-8 ml/kg IBW 5-8 ml/kg IBW if ARDS	Plateau <30 cmH2O	8-10 cmH2O (titrate if ARDS)	x	pH >7.2 SaO2 >90% PaO2 ≥90 mmHg or >60 and/or SaO2 >90% (ARDS)
Canada (Bourret) 2010(32)	6-8 ml/kg IBW	Peak pressure <30 cmH2O	5-10 cmH2O	x	PaCO2 35-45 mmHg pH 7.25-7.45 SaO2 95% PaO2 ≥90 mmHg
Chile (Rojas) 2010(38)	6-8 ml/kg	Plateau <30 cmH2O (lung donor)	5-10 cmH2O		PaO2/FiO2 >200 (lung donors) PaO2 >100 mmHg
Canada (Trilium) 2010(39)	6-8 ml/kg	Plateau ≤30 cmH2O	8-10 cmH2O	x	PaCO2 35-45 mmHg pH 7.35-7.45 SaO2 ≥95 PaO2≥80 mmHg
Cuba (Nodal Arruebarrena) 2009(40)		Peak <30 cmH2O (lung donors)	5 cmH2O; Smallest PEEP for PaO2 >100 mmHg (lung donors)		PaCO2 35-45 mmHg pH 7.35-7.45 SaO2 >90% PaO2 ≥100 mmHg
Australasia 2008(21)			Unclear	Unclear	
Canada (Shemie) 2006(44,46)	8-10 ml/kg	Peak ≤30 cmH2O	5 cmH2O	x	PaCO2 35-45 mmHg pH 7.35-7.45 SaO2 ≥95 PaO2≥80 mmHg

References

1. Burra P, De Bona M. Quality of life following organ transplantation. Transplant international : official journal of the European Society for Organ Transplantation 2007;20(5):397-409.
2. Health Resources & Services Administration. Organ Donation Statistics. 2019 [cited 4-09-2019]Available from: https://www.organdonor.gov/statistics-stories/statistics.html
3. Anonymous. International Guidelines for the Determination of Death - Phase 1. Montreal: Canadian Blood Services, World Health Organization; 2012 May 30-31 2012.
4. Niemann CU, Feiner J, Swain S, et al. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. N Engl J Med 2015;373(5):405-414.
5. 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(23):2620-2627.
6. Hoste P, Vanhaecht K, Ferdinande P, et al. Care pathways for organ donation after brain death: guidance from available literature? J Adv Nurs 2016;72(10):2369-2380.
7. International Registry in Organ Donation and Transplantation (IROdaT). Irodat.org (Internet). 2016 [cited April 2016]Available from: http://www.irodat.org/
8. Elliott J. Covidence(R). [Software] 2010 [cited Available from: https://www.covidence.org/home
9. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. Cmaj 2010;182(10):1045-1052.
10. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. Cmaj 2010;182(10):E472-478.
11. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12(1):18-23.
12. The AGREE Collaboration. The Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. 2001 [cited Available from: www.agreetrust.org
13. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
14. Westphal GA, Caldeira Filho M, Vieira KD, et al. Guidelines for potential multiple organ donors (adult): part II. Mechanical ventilation, endocrine metabolic management, hematological and infectious aspects. Rev 2011;23(3):269-282.
15. Westphal GA, Caldeira Filho M, Vieira KD, et al. Guidelines for potential multiple organ donors (adult). Part III: organ-specific recommendations. Rev 2011;23(4):410-425.
16. Westphal GA, Caldeira Filho M, Vieira KD, et al. Guidelines for potential multiple organ donors (adult): part I. Overview and hemodynamic support. Rev 2011;23(3):255-268.
17. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology 2011;64(4):380-382.
18. Escudero D. Mantenimiento de Donante Multiorganico. [cited 2018 Available from: http://files.sld.cu/trasplante/files/2010/07/mantenimiento.pdf
19. Anonymous. Procurar para Curar; Manual de Tratamiento del Donante a Corazon Batiente. [cited 2016 1-36]. Available from: https://www.incucai.gov.ar/files/docs-incucai/Materiales/profesionales/06-manual_procurar_para_curar.pdf

20. Australian and New Zealand Intensive Care Society. The ANZICS Statement of Death and Organ Donation (Edition 3.2). 2013 [cited 2018 Available from: https://www.anzics.com.au/wp-content/uploads/2018/08/ANZICS_Statement_on_Death_and_Organ_Donation_Edition_3.2.pdf
21. Australasian Transplant Coordinators Association Inc. National Guidelines for Organ and Tissue Donation (4th edition). 2008 [cited 2018 80]. Available from: http://www.atca.org.au/files/F.pdf
22. Office of the Chief Health Officer. Management of the Adult Brain Dead Potential Organ and Tissue Donor. 2016 [cited 2016]1-18]. Available from: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2016_008.pdf
23. Baldwin JC, Anderson JL, Boucek MM, et al. Task force 2: Donor guidelines. Journal of the American College of Cardiology 1993;22(1):15-20.
24. Eurotransplant Foundation. Eurotransplant Manual, version 5.5. 2016 28-07-2016 [cited 2017 6-01]Available from: https://www.eurotransplant.org/cms/index.php?page=et_manual
25. Firoozifar M. Shiraz guideline for the management of patients with brain death. Experimental and Clinical Transplantation 2014;12:193-194.
26. Powner DJ, Darby JM, Kellum JA. Proposed treatment guidelines for donor care. Prog Transplant 2004;14(1):16-26; quiz 27-18.
27. 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. Critical Care Medicine 2015;43(6):1291-1325.
28. Intensive Care Society UK Transplant. Guidelines for Adult Organ and Tissue Donation. 2005 [cited 5-5-2019]50]. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwix5ZmxkYfiAhUjheAKHWNzDRUQFjAAegQIBRAC&url=https%3A%2F%2Fwww.ics.ac.uk%2FAsiCommon%2FControls%2FBSA%2FDownloader.aspx%3FiDocumentStorageKey%3D8b06f7c7-a6b5-4d8b-a852-7e168196b3e9%26iFileTypeCode%3DPDF%26iFileName%3DOrgan%2520and%2520Tissue%2520Donation&usg=AOvVaw0ZpJy1C9JjZjCp9fthkAvQ
29. Pandit RA, Zirpe KG, Gurav SK, et al. Management of Potential Organ Donor: Indian Society of Critical Care Medicine: Position Statement. Indian J Crit Care Med 2017;21(5):303-316.
30. Conrick-Martin I, Gaffney A, Dwyer R, et al. Intensive Care Society of Ireland - Guidelines for management of the potential organ donor (2018-2nd edition). Irish journal of medical science 2019.
31. Boulard G, Guiot P, Pottecher T, et al. Management of subjects in a state of brain death and the preservation of organs. [French]. Annales francaises d'anesthesie et de reanimation 2005;24(7):836-843.
32. Bourret M, Marsolais P, Langevin S. Adults guidelines organ donor assessment and management. Transplantation 2010;90:554.
33. Shemie SD, Baker AJ, Knoll G, et al. National recommendations for donation after cardiocirculatory death in Canada: Donation after cardiocirculatory death in Canada. Cmaj 2006;175(8):S1.

34. Gesundheit Osterreich. Intensivtherapie potenzieller Organspender 2016 [cited 2017 4-01-2017]Available from: http://www.goeg.at/index.php?pid=arbeitsbereichedetail&ab=372&smark=intensivtherapie&noreplace=yes
35. Deutsche Stiftung Organtransplantation. Leitfaden fur die Organspende. 2016 [cited 2019 Available from: https://www.dso.de/uploads/tx_dsodl/Leitfaden.pdf
36. Anonymous. Rekommandation; Benhandling af organdonorer. 2015 [cited 2016]1-25]. Available from: http://e-dok.rm.dk/symfonidms/dco.nsf//UI2/E31BAB9413F4CA38C12577D80034F1B
37. Anonymous. Szervdonacio; Szakmai Kollegiumi Ajanlas. 2013 [cited Available from: http://docplayer.hu/2182569-Szervdonacio-szakmai-kollegiumi-ajanlas.html
38. Rojas JL CE, Buchuk D. Seleccion y Mantenimiento del Donante de Organos para Trasplante. In: Guias Clinicas Sociedad Chilena de Trasplante; 2010. p. 19-26.
39. Trilium Gilft of Life Network. Donation Resource Manual; A Tool to Assist Hospitals with the Process of Organ and Tissue Donation. 2010 [cited 69]. Available from: https://www.giftoflife.on.ca/resources/pdf/Tissue_Donation_Resource_Manual_EN_(final).pdf
40. Nodal Arruebarrena JR MRJ, Quintero Menendez Y, Reyes Perez AM, Jova Duenas J. Guia de Practica Clinica para el Tratamiento del Donante Potencial de Organos. Revista Electronica de la Ciencias Medicas en Cienfuegos 2009;7(Supp 1):249-256.
41. Norsk ressursgruppe for Organdonasjon. Protokoll for Organdonasjon. 2016 [cited 50]. Available from: http://www.norod.no/protokoll-for-organdonasjon/
42. Avsec-Letonja D, Zabavnik, Z, . Vzdrzevanje Moznega Mrtvega Darovalca Organiv in Tkiv V Intenzivni Terapiji. Transplantacijska dejavnost 2003 [cited 2017]87-103]. Available from: Personnal communication
43. Haberthur C, Revelly, J.P., Stocker, R. Recommendations pour le traitement et le monitoring des donneurs d'organes adultes à coeur battant aux soins intensifs. 2014 April 2014 [cited 30-04-2019]; 3.0:[Available from: https://www.swisstransplant.org/fileadmin/user_upload/Infos_und_Material/Swiss_Donation_Pathway/SDP_modul_2_Bhdlg_des_erw_Spenders_FR_2014.pdf
44. Shemie SD, Ross, H., Pagliarello, J. Baker, A.J., Greig, P.D, Brand, T. Cockfield, S. Keshavjee, S., Nickerson, P., Rao, V., Guest, C. Young, K., Doig, C. La prise en charge des donneurs d'organes au Canada: recommendations du forum Optimiser le maintien du donneur afin d'accroitre le nombre d'organes admissibles pour la transplantation. Cmaj 2006;174(6):SF14-SF32.
45. 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(6):e014436.
46. 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(6):S13-32.
47. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. Jama 2009;302(10):1067-1075.
48. Ponce OJ, Alvarez-Villalobos N, Shah R, et al. What does expert opinion in guidelines mean? a meta-epidemiological study. Evid Based Med 2017;22(5):164-169.

49. Cooper DK, Novitzky D, Wicomb WN. The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. Ann R Coll Surg Engl 1989;71(4):261-266.
50. Kennedy PJ, Leathley CM, Hughes CF. Clinical practice variation. The Medical journal of Australia 2010;193(8 Suppl):S97-99.
51. Marsolais P, Durand P, Charbonney E, et al. The First 2 Years of Activity of a Specialized Organ Procurement Center: Report of an Innovative Approach to Improve Organ Donation. Am J Transplant 2017;17(6):1613-1619.
52. Dans AL, Dans LF, Guyatt GH, et al. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. Jama 1998;279(7):545-549.
53. Oczkowski SJW, Durepos P, Centofanti J, et al. A Multidisciplinary Survey to Assess Facilitators and Barriers to Successful Organ Donation in the Intensive Care Unit. Prog Transplant 2019;29(2):179-184.
54. Hubbard IJ, Harris D, Kilkenny MF, et al. Adherence to clinical guidelines improves patient outcomes in Australian audit of stroke rehabilitation practice. Archives of physical medicine and rehabilitation 2012;93(6):965-971.
55. Trogrlic Z, van der Jagt M, Lingsma H, et al. Improved Guideline Adherence and Reduced Brain Dysfunction After a Multicenter Multifaceted Implementation of ICU Delirium Guidelines in 3,930 Patients. Crit Care Med 2019;47(3):419-427.
56. Tullius SG, Rabb H. Improving the Supply and Quality of Deceased-Donor Organs for Transplantation. N Engl J Med 2018;378(20):1920-1929.

Supplementary note: Inter rater reliability of the AGREE-II instrument on included guidelines

Every item of the AGREE-II instrument was scored on the 7-point scale by 4 independent raters. We calculated and report mean item scores and mean domain scores, as well as the inter-rater reliability of the instrument for each 6 domains, using a two-way random intra-class correlation. Inter-rater reliability was generally fair to good, but could not be calculated in a significant number of guidelines domain because of low variance. In all but domain 6, low variance was the result of almost perfect agreement between raters for low-quality guidelines. Domain 6 is comprised of only 2 items, which also fragilizes it’s reliability when some discordance exists between raters. This illustrates certain limits of the AGREE-II instrument. Detailed results of the inter rater agreement is provided in the appendix section of the thesis.

Article 2: A Canadian Survey of Critical Care Physicians' Hemodynamic Management of Deceased Organ Donors

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Contribution to this article: I designed the protocol, manually established the list of potential respondents, designed the survey, supervised data collection, performed the analysis and interpreted the data, drafted and critically revised the manuscript.

Abstract

Objective: We sought to characterize Canadian physicians' perspectives and stated practices regarding their hemodynamic care of deceased organ donors.

Design and Setting: We designed a 24-item electronic survey that 10 critical care clinicians independently pretested for relevance, clarity and intra-rater reliability. With the help of provincial Organ Donation Organizations (ODO), we identified intensive care units (ICUs) with a high volume of adult deceased donors (defined by the management of 5 or more donors per year for 2 consecutive years).

Participants: With direction from the medical directors of these high-volume ICUs, we emailed 448 ICU physicians from 37 centers in 9 provinces: 184/448 (41.1%) responded to one or more survey questions.

Measurements and main results: Respondents identified specialist nurses from ODOs as their primary source of guidance in donor care (107/165; 60%). They typically diagnosed an autonomic storm according to a rise in blood pressure (159/165; 96.4%) and/or of heart rate (135/165; 81.8%), however, their stated management varied substantially. Their preferred first line vasopressors were norepinephrine (93/164; 56.7%) and vasopressin (68/164; 41.5%). Twenty-one respondents (21/162; 13.0%) reported that they never administer inotropes to donors. Corticosteroid and thyroid hormone prescriptions for all donors was reported by 62/161 (37.6%) and 50/161 (31.1%) respondents, respectively. Respondents perceived an influence from ODO nurses or transplant physicians when prescribing corticosteroids (77/161; 47.8%) and/or thyroid hormones (33/161; 20.5%)

Conclusion: We observed important variability in self-perceived practice of ICU physician in the hemodynamic management of deceased donors, particularly in the treatment of the autonomic storm, in the prescription of hormone therapy, and in the administration of inotropes.

Introduction

The main objective for the care of neurologically deceased patients who are potential organ donors in the intensive care unit (ICU) is to optimize the quality and availability of organs for life-saving organ transplantation.(1) In Canada, the vast majority of organs for transplantation stem from brain-injured patients with a neurological determination of death (NDD).(2) Consideration of the unique pathophysiology of brain death and its implications for deceased donor care is, therefore, important to enhance organ transplantability. Animal studies show that intracranial hypertension leading to brain herniation causes ischemia to the vagal motor nucleus; this in turn results in a surge of endogenous catecholamines and a constellation of hemodynamic changes commonly termed the *autonomic storm*.(3) In models, associated tachycardia and hypertension may be abrupt and severe, lasting minutes to hours.(4, 5) Concurrent ischemia of the hypothalamo-pituitary axis leads to vasopressin, adrenal and thyroid hormone depletion, such that termination of the autonomic storm may result in profound vasoplegia and shock.(3, 4, 6, 7) Brain herniation is also associated with a systemic inflammatory response, characterized by elevated circulating levels of interleukin-1, interleukin-6 and TNF-alpha that contribute to distributive shock.(7, 8) Animal models of brain death and clinical research among NDD donors suggest that catecholamine toxicity may lead to heart cell apoptosis and necrosis that limits cardiac transplant suitability.(9-12) Clinical research in NDD donor management is very limited, but supports these observations. (10-12) Moreover, severe inflammation and shock contribute to acute damage of all organs, threatening the transplantability of the kidneys, livers, lungs, hearts and pancreas.(4, 6, 13-15)

Canadian guidelines (2006) for the management of potential NDD donors highlight hemodynamic management and hormone therapy (Table 1).(16) Since then, other groups have

released guidelines on donor care.(17-19) Recommendations on specific interventions (e.g. hormone therapy) vary between guidelines and they still, more than ten years after the Canadian guidelines, rely mostly on animal and retrospective clinical studies, in the context of few published randomized trials.(5, 13, 15, 20) Hemodynamic management is fundamental to the practice of critical care. Most Canadian critical care clinicians, however, have limited exposure to the management of potential NDD donors. Consequently, their approaches likely reflect their hemodynamic management for non-donor populations. While observational studies can elucidate actual practice patterns, we sought to determine self-perceived practices in the context of knowledge about, and experience with, neurologically deceased donor care. We hypothesized that stated knowledge and practices among Canadian critical care physicians are likely to vary, reflecting not only a lack of clinical research to guide practices, but also a potential opportunity for education and knowledge translation initiatives to improve donor care.

Table 1. 2006 Canadian Guidelines recommendations according to survey domains

Survey domains	2006 Canadian guideline recommendations
Autonomic storm management	Hypertension is treated if • SBP > 160 mmHg • MAP > 90 mmHg First line treatment : • Nitroprusside or • Esmolol
Hemodynamic monitoring and treatment	Hemodynamic targets: • MAP ≥ 70 mmHg • SBP ≥ 100 mmHg • Heart rate 60-120 bpm • CVP 6-10 mmHg Agents for hemodynamic support • First line: Vasopressin • Alternatives: norepinephrine, epinephrine, phenylephrine Fluid resuscitation aims at maintaining normovolemia (CVP 6-10 mmHg) and normal urine output (0.5-3 ml/kg/h)
Hormone therapy	Combined hormone therapy (thyroid hormone, vasopressine and methylprednisolone) are recommended in: • Donors with LVEF ≤ 40% • Hemodynamic instability But considered in all donors Corticosteroids are recommended to all donors for lung protection

Materials and Methods

Sampling of Survey Participants and Centers

We surveyed physicians from adult ICUs across Canada characterized by a high volume of adult NDD donors. To facilitate this study, provincial ODOs identified centers that had cared for at least 5 adult organ donors annually for 2 consecutive years (2014 and 2015) in the ICU. In some centers donors are initially managed on-site and then transferred to a designated organ referral center for procurement surgery. This approach to deceased donation is common in the province of Quebec and since management of donors occurs on-site, high-volume centers using this

approach were included. Provincial ODOs provided contact ICU Medical Director information from each center. When authorized by their physician colleagues, the ICU Directors provided an email address for each physician in their ICU. In the situation where ICU physicians declined to share their email addresses, ICU Medical Directors forwarded the survey link to their colleagues. The Research Ethics Board of Hôpital du Sacré-Coeur reviewed and approved this survey (#20141072). All respondent names and email addresses were to remain confidential, as were individual responses.

Survey Development

The development of this electronic self-administered survey followed current standards for item generation, item reduction, pre-testing and administration.(21, 22)

Item Generation and Item Reduction

The principal investigator (A.J.F) generated a preliminary list of survey items within four specific domains of deceased donor care: general support; autonomic storm management; other hemodynamic monitoring and treatment; and hormone therapy. A focus group including ICU donation clinicians and survey methodologists (A.J.F., K.S., P.M., M.M., D.W., E.C., F.DA.) refined the survey and reduced the number of questions. The survey objectives, methods and all survey questions were presented at a scientific meeting of the Canadian Critical Care Trials Group (CCCTG) (Lake Louise, Alberta, February 2015). Members in attendance provided group feedback on the target population, the relevance of survey questions, clarity, and length of the questionnaire. We removed items perceived as redundant, and those perceived as least

relevant to the survey objectives, and we limited the target respondents to intensive care physicians in adult ICUs.

Questionnaire Testing

Five intensive care physicians external to our group, with expertise in survey development reviewed an electronic version of the survey with the objective of evaluating the relevance and comprehensiveness of items (i.e. face-validity). After minor revisions, we assessed test-retest reliability. Ten volunteer ICU physicians from the group of target respondents, with representation from 3 Canadian provinces, completed the questionnaire twice each at a four-week interval. Survey items found to have low intra-rater validity (i.e.: Cohen's kappa < 0.4) were either modified or removed. Since the questionnaire was modified following this pre-testing, questionnaires from those 10 potential respondents were excluded from final analysis, as recommended.(23) Lastly, three ICU resident physicians subsequently tested time required to complete the questionnaire, which ranged from 10 to 13 minutes.

Questionnaire Formatting

We created an electronic English-language survey using SurveyMonkey® (Appendix 1). The final survey included 19 questions pertaining to 4 pre-specified domains and 5 demographic questions, for a total of 24 questions. We used 4-point Likert scales and multiple-choice questions. An option for textual responses was offered after every item. Electronic distribution of the questionnaire to target participants was preceded by a personalized email explaining the study purpose. We also informed potential respondents about the voluntary nature of the survey, our confidentiality policy, and the time required to complete the questionnaire.

Questionnaire administration

We distributed the electronic questionnaire to each target physician by email in September 2016. Two ICU Medical Directors, unable to provide contact information, forwarded an electronic link to the survey to their ICU physician colleagues. Four electronic reminders were sent over a 3 month-period.

Statistical analysis

Completed questionnaires were entered into an SPSS database (IBM SPSS Statistics v24.0 2018). We summarized descriptive data using means (SD) and proportions.

Results

Participants

Provincial ODOs identified 44 centers with the requisite activity in deceased donation. The Medical Director of 4 centers (3 from Ontario and 1 from Saskatchewan) did not respond to email invitations to participate in this survey: therefore, 40 centers are included in this report (40/44; 90.9%). From these centers, we identified 448 potential respondents and contacted them by email. Ultimately, 184/448 (41.1%) participated. We classified the nineteen respondents who answered fewer than 4 of the 19 questions as 'partial respondents' and analyzed their responses separately.(23) Thus, a total of 165/448 (36.8%) potential respondents completed the questionnaire and are included in the final analysis as complete respondents. There was at least one respondent from each participating center, and the number of respondents from each province generally reflects the distribution of organ donation activity in Canada (Table 2). The

majority of responding ICU physicians had specialized training in internal medicine (n=94/165; 57%) and many were responsible for care of 4 to 6 donors per year (n=75/165; 45.5%) (Table 3).

Table 2. Demographics of respondents

Variable	Proportion of Respondents, n (%)
Respondents by province n=165	
British Columbia	14 (8.5)
Alberta	12 (7.3)
Saskatchewan	3 (1.8)
Manitoba	3 (1.8)
Ontario	59 (35.8)
Quebec	55 (33.3)
New Brunswick	4 (2.4)
Nova Scotia	5 (3.0)
Newfoundland	4 (2.4)
No response	6 (3.6)
Medical specialty of respondents n = 165	
Internal medicine	94 (57)
Family medicine	4 (2.4)
Emergency medicine	9 (5.5)
Surgery	17 (10.3)
Anesthesia	33 (20)
No response	8 (4.8)
Teaching hospital	
Yes	138 (83.6)
No	21 (12.7)
No response	6 (3.6)
Transplant center	
Yes	77 (46.7)
No	83 (50.3)
No response	5 (3)
Organ retrieval center *	
Yes	140 (84.8)
No	20 (15.2)
No response	5 (3)

General donor support

More than 60% of respondents (107/165; 64.8%) seek advice from ODO nurse specialists in most or all cases, with further advice occasionally sought from on-call ODO physicians (48/164; 29.1%) or physicians in other centers (34/164; 20.6%). Most reported consulting pharmacists rarely or never (99/164; 60.4%). The majority of respondents always or usually (125/165;

75.8%) rely upon local protocols for donor care, and the 2006 Canadian Guidelines were strongly (84/165; 50.9%) or always (38/165; 23.0%) identified as a reliable source (**Table 3)**

Table 3. Sources of guidance for the medical management of neurologically deceased donors

Variable, n/N (%)	Complete Respondents N = 165*	Partial respondents N =19**
Number of donors managed per year by respondent		
>12	9 (5.5)	0
10-12	13 (7.9)	0
7-9	29 (17.6)	2 (10.5)
4-6	75 (45.5)	7 (36.8)
0-3	39 (23.6)	10 (52.6)
Seeking advice from ODO nurse		
Always	81 (49.1)	8 (47.4)
Most of the time	26 (15.8)	3 (15.8)
Occasionally	22 (13.3)	1 (5.3)
Rarely	26 (15.8)	3 (15.8)
Never	10 (6.1)	3 (15.8)
No response	0	0
Seeking advice from ODO physician[$]		
Always	6 (3.6)	1 (5.3)
Most of the time	12 (7.3)	1 (5.3)
Occasionally	48 (29.1)	4 (21.1)
Rarely	60 (36.4)	9 (47.4)
Never	38 (23)	4 (21.1)
No response	1 (0.6)	0
Seeking advice from physician in another centre[$]		
Always	10 (6.1)	0
Most of the time	21 (12.7)	1 (5.3)
Occasionally	34 (20.6)	3 (15.8)
Rarely	45 (27.3)	5 (26.3)
Never	54 (32.7)	10 (52.6)
No response	1 (0.6)	0
Seeking advice from a pharmacist[$]		
Always	10 (6.1)	3 (15.8)
Most of the time	21 (12.7)	3 (15.8)
Occasionally	34 (20.6)	5 (26.3)
Rarely	45 (27.3)	7 (36.8)
Never	54 (32.7)	1 (5.3)
No response	1 (0.6)	0

Seeking advice in a local protocol***		
Always	80 (48.5)	12 (63.2)
Most of the time	45 (27.3)	3 (15.8)
Occasionally	15 (9.1)	0
Rarely	13 (7.9)	1 (5.3)
Never	12 (7.3)	3 (15.8)
No response	0	0
Seeking advice in online resources[$]		
Always	9 (5.5)	2 (10.5)
Most of the time	16 (5.5)	3 (15.8)
Occasionally	40 (24.2)	7 (36.8)
Rarely	53 (32.1)	1 (5.3)
Never	39 (23.6)	6 (31.6)
No response	8 (4.8)	0
Seeking advice in Canadian guidelines		
Always	38 (23)	6 (31.6)
Strongly	84 (50.9)	7 (36.8)
Fairly	**35** (21.2)	2 (10.5)
Not at all	8 (4.8)	3 (15.8)
No response	0	1 (5.3)

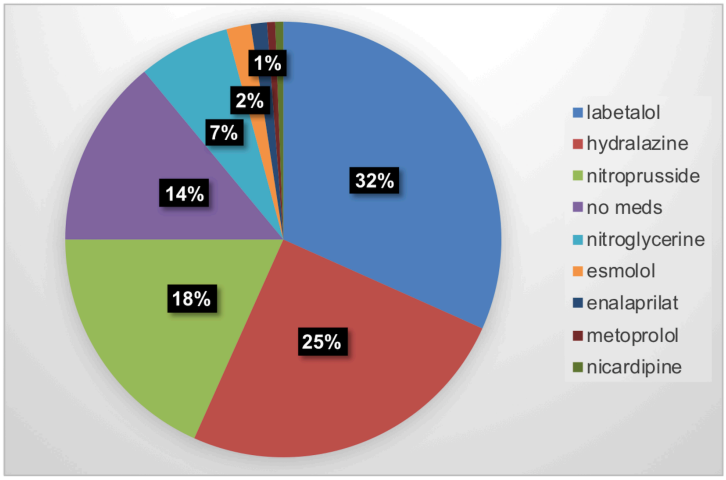
The autonomic storm

Nearly all respondents (159/165; 96.4%) consider a “rise of blood pressure” and most consider a “rise of heart rate” (135/165; 81.8%) as a component criterion for the diagnosis of an autonomic storm. Opinions varied on the importance of the “duration and/or timing” of hypertension or tachycardia in this diagnosis. Most respondents (100/162; 61.7%) stated that they react to isolated hypertension in this setting with the administration of antihypertensive medication, while others stated that they do not treat isolated hypertension (29/162; 17.9%). Preferred medication for the management of symptoms of autonomic storm are presented in Figure 1, showing that beta-blockers were generally a first choice.

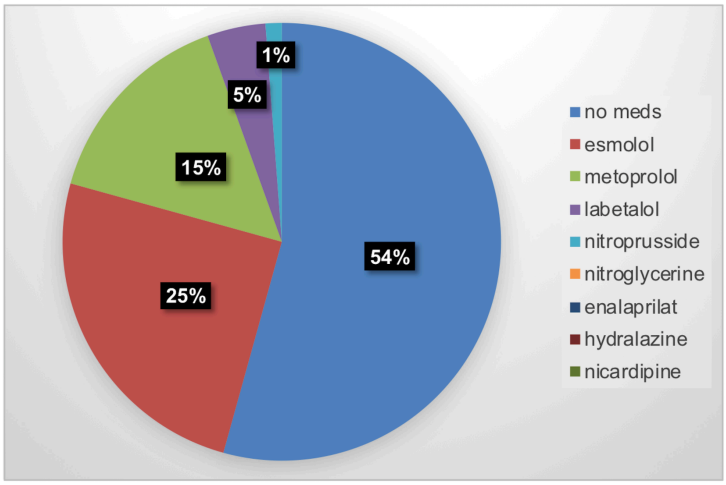
Figure 1. Medication prescribed in the context of an autonomic storm

Drugs used for each diagnosis of an autonomic storm are ranked from the most to the least commonly prescribed

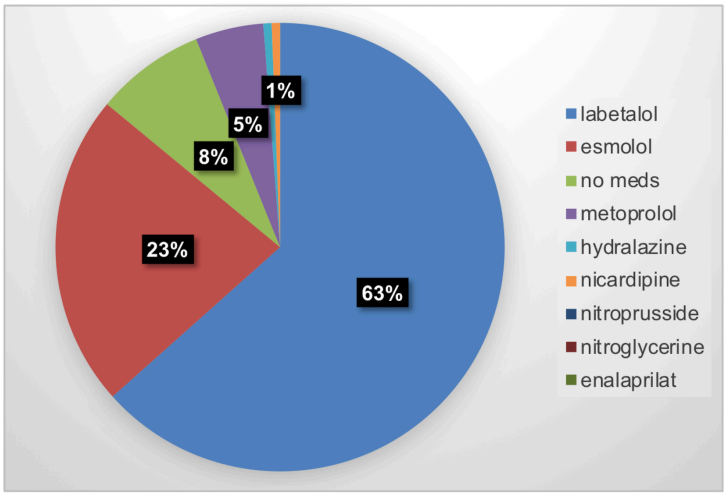
A. High Blood Pressure and Normal Heart Rate



B. High Blood Pressure and Sinus Tachycardia



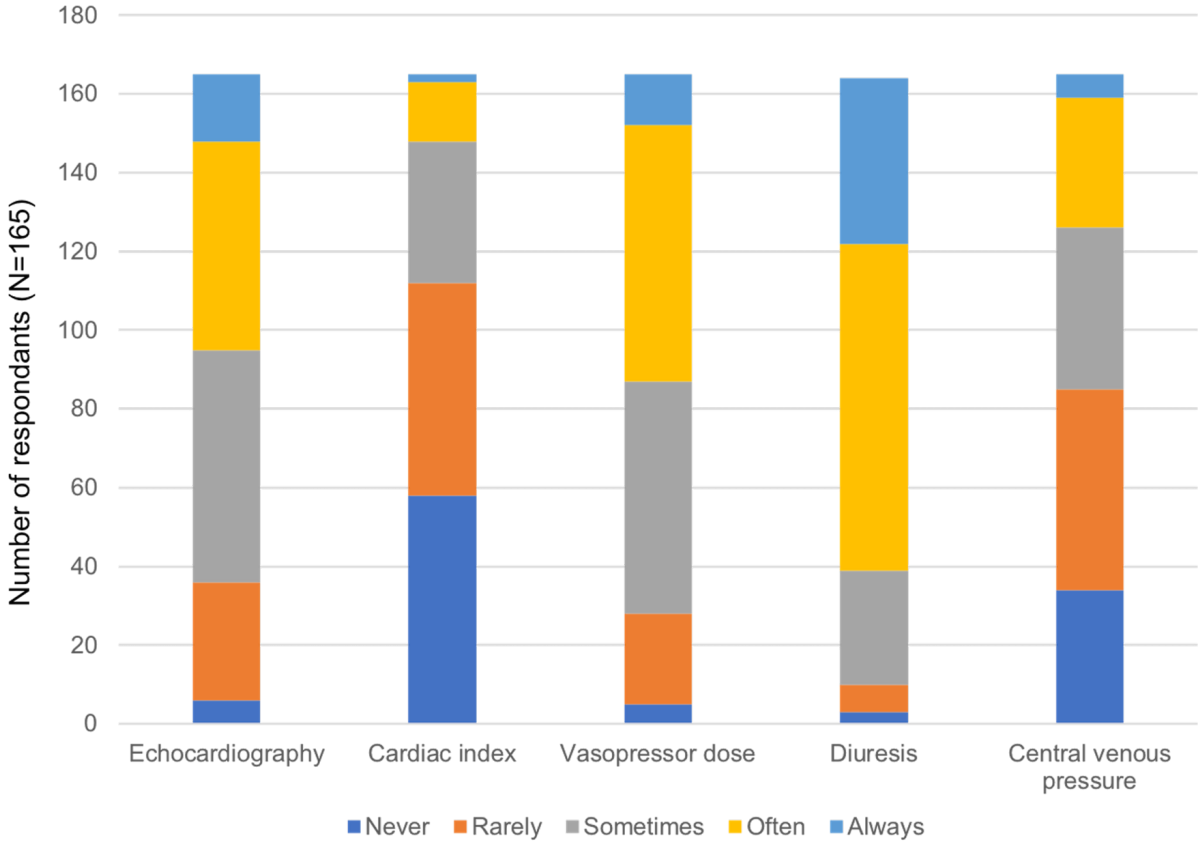
C. Normal Blood Pressure and Sinus Tachycardia



Hemodynamic monitoring and treatment of hypotension

The survey inquired about common triggers for fluid administration and fluid responsiveness prediction in all donors. Results are presented in Figure 2. In the specific situation of a hypotensive multi-organ donor without organ dysfunction and already fluid-resuscitated with 2 liters of crystalloids, the stated preferred resuscitation fluid was Ringer's lactate in 150/164 respondents (94.9%) or normal saline in 98/164 (66.2%). However, 68/164 respondents (47.2%) also perceived that they administer 5% albumin and 27/164 (20.0%) reported use of 25% albumin. Balanced crystalloid solutions (e.g Osmolyte®, Plasmalyte®) were chosen by 47/164 (29.3%) of respondents. No respondents stated that they would administer starch solutions in organ donor resuscitation.

Figure 2. Triggers for fluid administration and fluid responsiveness



Cardiac index measurement includes pulmonary artery catheter and other non-invasive measurements

For a donor evaluated as hypotensive but euvolemic, 118/163 (71.5%) respondents would initiate vasopressor therapy even if no other signs of hypoperfusion were present. This number increased to 131/163 (80.4%) considering a donor with signs of hypoperfusion (e.g., oliguria) and to 134/163 (82.2%) considering a donor with associated hypoperfusion markers (e.g., elevated serum lactate, low central venous oxygen saturation).

When lung donation was considered, the majority of respondents would often or always refrain from additional fluids and, rather, initiate or optimize vasopressors (109/163; 66.9%). However, this number drops to 21/162 (13.0%) when the lungs were not considered for donation.

Mean arterial pressure targets in donors hypotensive and unresponsive to volume varied from 60 mmHg (26/162; 16.1%) to 70 mmHg (20/162; 12.4%) with the majority of respondents identifying 65 mmHg (n=106/162; 65.4%) as their preferred target. For donors with no evidence of diabetes insipidus at the time of hypotension, norepinephrine was the preferred first line vasopressor (93/164; 56.7%). Vasopressin was also frequently reported for this indication (68/164; 41.5%). The use of alternative vasopressors (e.g., epinephrine, dopamine or phenylephrine) appeared rarely (1/164; 0.6%). A minority of respondents 21/162 (13.0%) answered that they would never administrate inotropes (e.g., milrinone, dobutamine) to donors, who are euvolemic and normotensive. Faced with a hypotensive donor with signs of hypoperfusion, use of inotropes appeared to differ according to whether the donor's heart was under consideration for transplantation: for potential cardiac donors, 78/162 respondents (48.2%) would administer an inotrope and for non-heart donors, 94/162 respondents (58.0%) would administer an inotrope.

Hormone therapy

The survey assessed three hormone therapies: corticosteroids, insulin and thyroid hormones. ODO donation and transplant clinicians largely influenced the prescription of both corticosteroids and thyroid hormones. Specifically, 77/161 (47.8%) respondents reported that

they prescribe corticosteroids and 33/161 (20.5%) thyroid hormones to donors specifically when requested by ODO clinicians.

Some respondents stated that they generally order corticosteroids specifically for hemodynamic instability (48/161; 29.8%) and in the setting of potential for transplant of specific organs (43/161; 26.7%). One third (50/161; 31.1%) reported the prescription of corticosteroids to all donors, and few prescribe corticosteroids to no donors (6/161; 3.7%). Methylprednisolone was the preferred corticosteroid in 87/160 of respondents (54.4%). A stress dose of hydrocortisone (200-300 mg/day) was the preferred regimen for 46/160 (28.8%) of respondents.

Thyroid hormones were reported as prescribed to all donors by 62/161 (37.6%) of respondents. Other most frequently reported indications included: left ventricular dysfunction in potential heart donors (40/160; 25%) and hemodynamic instability regardless of heart dysfunction (25/161; 15.5%). Some respondents (64/160; 40.0%) indicated that they were unfamiliar with the administration of insulin as part of a combined infusion of glucose, insulin and potassium (GIK). Still, 20/160 (12.5%) reported using GIK infusion in potential heart donors with left ventricular dysfunction or in donors with depressed left ventricular function regardless of the potential for heart donation (6/160; 3.75%).

Partial respondents

A group of respondents answered only the first 4 questions of the questionnaire (n=19/184). We considered them as partial respondents and their available responses were analyzed separately (**Table 3**). Compared to complete respondents, partial respondents appeared to have less

experience with the management of deceased organ donors. Their responses, however, were generally comparable to those of complete respondents

Discussion

In this survey of self-reported clinical practices in the hemodynamic management of NDD donors, 41% of 448 ICU physicians responded, with a geographical distribution that generally reflects the epidemiology of deceased donation in Canada.(2) Forty of 44 major Canadian donation centers were included and represented in this survey.

The treatment of an autonomic storm in the setting of severe brain injury and potential organ donation is far from uniform. Physicians appear to apply varied diagnostic criteria and hemodynamic strategies, particularly when facing isolated hypertension. Variability in the self-perceived practice on the management of an autonomic storm reflects the paucity of literature, which is limited to animal studies and one small retrospective clinical study.(5, 24, 25) Many respondents demonstrated that they treat an autonomic storm with consideration of the potential for organ donation.**.** Although not evaluated in a clinical study, the administration of a beta-blocker to a potential donor in the context of an autonomic storm could prevent end-organ damage caused by catecholamine-induced direct toxicity.(5)

The use of inotropes in NDD donors also varied, reflecting an existing controversy, particularly in the context of potential heart donation. Many respondents have demonstrated a reluctance to administrate inotropes to deceased donors, highlighting a possible concern to augment the hyperadrenergic state during and following an autonomic storm. Respondents have identified

vasopressin as one of their preferred first line vasoactive medication to treat hypotension in donors, likely reflecting the knowledge of central insufficiency of this hormone and of the 2006 Canadian guideline recommendation on the treatment of hypotension.(16) In animal models, the surge in catecholamines occurring during the autonomic storm was deemed responsible for cardiomyocyte direct damage.(4) The administration of beta-agonist agents could theoretically contribute to further cardiac toxicity. To date, there are no investigations of milrinone or dobutamine in this setting to test this theoretical concern.(26)

The frequent prescription of corticosteroids and/or thyroid hormones appeared largely influenced by ODOs and surgical teams. Since the publication of the guidelines, systematic reviews have concluded in insufficient evidence to support (or refute) corticosteroid or thyroid hormone supplementation.(16, 17) (27-29) Other retrospective studies demonstrating potentially impressive benefits on organ recovery, particularly in lung donors, may be influential in current reported practices.(14, 15, 20, 30-33) Additionally, it is conceivable that the use of low-dose hydrocortisone is largely driven by the general ICU literature.(34, 35) Although the benefit of corticosteroids in general ICU patients with shock remains controversial, they remain frequently prescribed by Canadian intensivists.(36, 37) The use of low dose hydrocortisone might also reflect the impact of the CORTICOME study.(16, 38) In this non-randomized study of deceased potential donors, low dose hydrocortisone was associated with reduced vasopressor doses and duration.(38)

GIK infusions appear to be used infrequently. One observational study suggested an inotropic benefit with the use of GIK in the NDD donor population, specifically among those with severe

heart failure.(39) However, the paucity of confirmatory literature likely explains the lack of apparent uptake on the GIK infusions.

Although ICU physicians indicated by their responses that they see the 2006 Canadian Guidelines as a reliable source of information, self-reported practices suggest otherwise. For example, the Canadian guideline *suggests* combined hormone therapy (vasopressin, corticosteroids, and thyroid hormone) to all donors, but more strongly *recommends* combined hormone therapy to hemodynamically unstable donors, and corticosteroids specifically to lung donors.(16) In contrast, respondents' self-perceived practice on the use of hormone therapy suggested variability in opinions, with about a third of respondents perceiving that they prescribe hormone therapy to all donors. Also, about 20% of respondents report that they do not treat hypertension in the context of an autonomic storm, a practice that does not comply with the 2006 Canadian guideline where a treatment is recommended for a mean arterial pressure over 90 mmHg or a systolic blood pressure over 160 mmHg. (Table 1) (16) Moreover, 9 different pharmacological agents were identified by our respondents as their preferred treatment for an autonomic storm, and yet the guideline recommendation is limited to esmolol or nitroprusside infusions to treat hypertension.

Similar to our findings, a survey on self-reported practice of ODO clinicians when caring for pediatric donors reported variance in compliance to the most recent American guideline recommendations.(17, 40) Varying compliance rates (ranging between 3% and 100%) the American guidelines recommendations was also reported by an observational cross-sectional study in Belgium (17, 41). However, our survey was not designed to compare the self-reported

practices to the Canadian guidelines recommendations. Therefore, we cannot conclude that ICU physicians do not find the guidelines as a reliable source of information. In the context of this survey's objectives, the possible disparity between ICU physicians' self-reported practices in some areas and the guideline recommendations generates hypotheses on the need for knowledge translational educational tools and on the importance of collaborating with stakeholders from transplantation and ODO teams in designing future clinical research.

We surveyed participants about the role of ODO specialists in their care of deceased organ donors. In Canada, on-site ODO nurses are generally responsible for organ compatibility testing and allocation, but their clinical involvement on direct donor care may vary from center to center. Survey results suggest that ODO nurses play a major role in counseling ICU physicians; consequently, their implicit involvement in knowledge translation deserves explicit recognition.(42) Moreover, our findings of varied practices suggest that this is a suitable area for education and knowledge translation interventions and research. Consideration of the implicit or explicit roles of ODO specialists in such initiatives will be essential.(43)

This survey also raised questions about the involvement of ICU pharmacists in deceased donor management since few respondents indicated relying on their expertise when caring for donors.(44) While this survey was not designed to explore specific activities of ICU pharmacists (protocols, counseling, teaching, clinical evaluation), our findings suggest that they may be an underutilized resource for education and knowledge translation.

Strengths and Limitations

This survey meets the objective of exploring the variability in self-perceived practices for the management of NDD donors in Canada. As an ongoing large observational study will describe donor care interventions in Canadian ICUs, this survey helps to understand and generate hypotheses about the rationale for current practices and underlying beliefs.(45) For example, understanding that the prescription of hormone therapy by ICU physicians is largely influenced by ODO and surgery teams, was highly informative in that it suggests the need for more information related to donor care right at the bedside. It also will guide important collaborations with stakeholder ODOs and transplant programs for future clinical trials.

Following current standards for the development of questionnaires to survey health professionals about their stated practices, we used focused groups and extensive pre-testing to ensure relevance, clarity, and ease of completion. Our survey response rate was low (41.1%), limiting generalizability; however, we felt it was important to survey broadly, including physicians across a spectrum of experience with donor care. Also, we successfully obtained information from almost all the major Canadian organ donation centers (40/440; 91.9%), although Alberta physicians appear under-represented. The results, even with low response rate, reveal the variability in management resulting from paucity of evidence. It is likely that survey respondents have a different level of interest and expertise in organ donor management than non-respondents. Corroborating this hypothesis, an analysis among the 19 partial respondents revealed that they had less experience in donor management than complete respondents. Based on empirical evidence, found in unrelated surveys, the characteristics of survey non-respondents are generally similar to those of partial respondents.(46) The response rate in this survey is similar to recent surveys (30-40%) of Canadian ICU clinicians. (47) (48-50) In addition, a recent survey of health professionals on the need for education programs in organ donation reported a

response rate of 15%.(51) One notable difference between our survey and those that have reported higher response rates may be the sampling strategy. Many published surveys have used society membership lists or even research consortia, thus targeting more involved participants. However, we sought to survey a broader sample of critical care physicians.(37, 52)

Conclusion

In a national survey of ICU physicians, we perceived variability in self-perceived practice in the stated management of neurologically deceased organ donors, in a context where the impact of specific interventions on organ suitability or availability is uncertain. Differences in opinions may relate to the paucity of research in this field and to the relative inexperience of many physicians in managing deceased donors, which make up a very small fraction of the clinical case load in most centers. However, the survey also revealed the importance of clinical nurse specialists (from ODOs) in decision-making. Thus, this survey highlights the need for clinical research and education specific to the hemodynamic management of organ donors, and also specific to current models of knowledge dissemination in deceased donor care.

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References

1 *UNOS.* United Network for Organ Sharing 2016 [cited October 5th 2016]. Available from URL; https://www.unos.org/data/transplant-trends/#waitlists_by_organ.

2 *Information CIfH.* e-Statistics on Organ Transplants, Waiting Lists and Donors: 2017 Cumulative Report 2017 [cited 22-07-2018 2018]. Available from URL; https://www.cihi.ca/en/e-statistics-on-organ-transplants-waiting-lists-and-donors.
3 *Smith M.* Physiologic changes during brain stem death--lessons for management of the organ donor. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2004; 23: S217-22.
4 *Novitzky D, Wicomb, W.N., Cooper, D.K.C.* Electrocardiographic, haemodynamic and endocrine changes occuring during experimental brain death in the Chacma baboon. J Heart Transplant 1984; 4: 63-9.
5 *Novitzky D, Wicomb WN, Cooper DK, Rose AG, Reichart B.* Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. The Annals of thoracic surgery 1986; 41: 520-4.
6 *Novitzky D, Cooper DK, Wicomb WN.* Endocrine changes and metabolic responses. Transplantation proceedings 1988; 20: 33-8.
7 The Brain-Dead Organ Donor; pathophysiology and management: Springer; 2012.
8 *Takada M, Nadeau KC, Hancock WW, et al.* Effects of explosive brain death on cytokine activation of peripheral organs in the rat. Transplantation 1998; 65: 1533-42.
9 *D'Amico TA, Meyers CH, Koutlas TC, et al.* Desensitization of myocardial beta-adrenergic receptors and deterioration of left ventricular function after brain death. The Journal of thoracic and cardiovascular surgery 1995; 110: 746-51.
10 *Perez Lopez S, Otero Hernandez J, Vazquez Moreno N, Escudero Augusto D, Alvarez Menendez F, Astudillo Gonzalez A.* Brain death effects on catecholamine levels and subsequent cardiac damage assessed in organ donors. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2009; 28: 815-20.
11 *Dujardin KS, McCully RB, Wijdicks EF, et al.* Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2001; 20: 350-7.
12 *Shivalkar B, Van Loon J, Wieland W, et al.* Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. Circulation 1993; 87: 230-9.
13 *Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR.* Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 1995; 14: 734-42.
14 *Rosendale JD, Kauffman HM, McBride MA, et al.* Hormonal resuscitation yields more transplanted hearts, with improved early function. Transplantation 2003; 75: 1336-41.
15 *Follette DM, Rudich SM, Babcock WD.* Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 1998; 17: 423-9.
16 *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.
17 *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. Critical Care Medicine 2015; 43: 1291-325.
18 *Westphal GA, Caldeira Filho M, Fiorelli A, et al.* Guidelines for maintenance of adult patients with brain death and potential for multiple organ donations: the Task Force of the Brazilian Association of Intensive Medicine the Brazilian Association of Organs Transplantation, and the Transplantation Center of Santa Catarina. Transplantation proceedings 2012; 44: 2260-7.
19 *Pandit RA, Zirpe KG, Gurav SK, et al.* Management of Potential Organ Donor: Indian Society of Critical Care Medicine: Position Statement. Indian J Crit Care Med 2017; 21: 303-16.
20 *Rosendale JD, Kauffman HM, McBride MA, et al.* Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003; 75: 482-7.
21 *Fowler FJ.* Survey research methods, 5th ed. Boston, United States: Sage publications; 2014.
22 *Burns KE, Duffett M, Kho ME, et al.* A guide for the design and conduct of self-administered surveys of clinicians. Cmaj 2008; 179: 245-52.
23 *de Leeuw E.D. HJ, Dillman D.* International Handbook of Survey Methodology; 2012.
24 *Audibert G, Charpentier C, Seguin-Devaux C, et al.* Improvement of donor myocardial function after treatment of autonomic storm during brain death. Transplantation 2006; 82: 1031-6.
25 *Cooper DK, Novitzky D, Wicomb WN.* The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. Ann R Coll Surg Engl 1989; 71: 261-6.
26 *Frenette AJ, Akhtar A., Williams, V., Masse, M.H., Zhou, Q., Hoad, N., Charbonney, E., Serri, K., Meade, M., D'Aragon, F.* Inotrope use in potential heart donors: a prospective cohort analysis. Crit Care Med 2018; 46: 89.
27 *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.
28 *Dupuis S, Amiel JA, Desgroseilliers M, et al.* Corticosteroids in the management of brain-dead potential organ donors: a systematic review. Br J Anaesth 2014; 113: 346-59.
29 *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.
30 *Novitzky D, Cooper DK, Reichart B.* Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. Transplantation 1987; 43: 852-4.
31 *Follette D, Rudich S, Bonacci C, Allen R, Hoso A, Albertson T.* Importance of an aggressive multidisciplinary management approach to optimize lung donor procurement. Transplantation proceedings 1999; 31: 169-70.
32 *McElhinney DB, Khan JH, Babcock WD, Hall TS.* Thoracic organ donor characteristics associated with successful lung procurement. Clin Transplant 2001; 15: 68-71.
33 *Selck FW, Deb P, Grossman EB.* Deceased organ donor characteristics and clinical interventions associated with organ yield. Am J Transplant 2008; 8: 965-74.
34 *Annane D, Sebille V, Charpentier C, et al.* Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288: 862-71.

35 *Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K.* Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358.
36 *Zhu Y, Wen Y, Jiang Q, Guo N, Cai Y, Shen X.* The Effectiveness and Safety of Corticosteroids Therapy in Adult Critical Ill Patients with Septic Shock: A Meta-Analysis of Randomized Controlled Trials. Shock 2018.
37 *Lamontagne F, Quiroz Martinez H, Adhikari NK, et al.* Corticosteroid use in the intensive care unit: a survey of intensivists. Can J Anaesth 2013; 60: 652-9.
38 *Pinsard M, Ragot S, Mertes PM, et al.* Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. Critical care (London, England) 2014; 18: R158.
39 *Nicolas-Robin A, Amour J, Ibanez-Esteve C, Coriat P, Riou B, Langeron O.* Effect of glucose-insulin-potassium in severe acute heart failure after brain death. Crit Care Med 2008; 36: 2740-5.
40 *Ream RS, Armbrecht ES.* Variation in Pediatric Organ Donor Management Practices Among US Organ Procurement Organizations. Prog Transplant 2018; 28: 4-11.
41 *Hoste P, Ferdinande P, Vogelaers D, et al.* Adherence to guidelines for the management of donors after brain death. Journal of critical care 2019; 49: 56-63.
42 *Swain S.* The role of clinical nurse educators in organ procurement organizations. Prog Transplant 2011; 21: 284-7.
43 *Mendes K, de Aguiar Roza, B., Barbosa, S., Shirmer, J., Galvao, C.M.* Trasplante de organos y tejidos: responsabilidades de las enfermeras. Texto contexto - enferm 2012; 21: 945-53.
44 *Thompson DR, Hamilton DK, Cadenhead CD, et al.* Guidelines for intensive care unit design. Crit Care Med 2012; 40: 1586-600.
45 *D'Aragon F, Dhanani S, Lamontagne F, et al.* Canada-DONATE study protocol: a prospective national observational study of the medical management of deceased organ donors. BMJ Open 2017; 7: e018858.
46 *Brick JM, Kalton G.* Handling missing data in survey research. Stat Methods Med Res 1996; 5: 215-38.
47 *Opgenorth D, Stelfox HT, Gilfoyle E, et al.* Perspectives on strained intensive care unit capacity: A survey of critical care professionals. PLoS One 2018; 13: e0201524.
48 *Steinberg M, Dresser LD, Daneman N, et al.* A National Survey of Critical Care Physicians' Knowledge, Attitudes, and Perceptions of Antimicrobial Stewardship Programs. Journal of intensive care medicine 2016; 31: 61-5.
49 *Murthy S, Pathan N, Cuthbertson BH.* Selective digestive decontamination in critically ill children: A survey of Canadian providers. Journal of critical care 2017; 39: 169-71.
50 *Cape D, Fox-Robichaud A, Turgeon AF, et al.* The impact of the Rasouli decision: a Survey of Canadian intensivists. Journal of medical ethics 2016; 42: 180-5.
51 *Hancock J, Shemie SD, Lotherington K, Appleby A, Hall R.* Development of a Canadian deceased donation education program for health professionals: a needs assessment survey. Can J Anaesth 2017; 64: 1037-47.
52 *Shears M, Alhazzani W, Marshall JC, et al.* Stress ulcer prophylaxis in critical illness: a Canadian survey. Can J Anaesth 2016; 63: 718-24.

Supplementary note

Appendix 1. Survey questionnaire

Q1 : How many neurologically deceased donors do you personnally manage in a typical year ? (*0-3 ; 4-6 ; 7-9 ;10-12 ; >12*)

Q2 : When managing a neurologically deceased donor, how often do you seek advice from the following ? (*never ; rare cases, occasional cases ; most cases ; all cases*)

a) A nurse coordinator from the organ donation organization (ODO)
b) Physician experts within the ODO
c) Experts from another centre
d) A pharmacist
e) Local protocol
f) Online resources

Q3 : How strongly do you rely on Canadian guidelines when you are managing a neurologically deceased potential donor ? (*not at all ; fairly ; strongly ; always*)

Q4 : The period of time before, during and after brain death is sometimes associated with an adrenergic storm (also known as cathecolamine storm). In your opinion, what variables should be part of a clinically useful definition of the adrenergic storm ? *(Please check all that apply)*

a) A rise in blood pressure (either as a percentage of a threshold)
b) A rise in heart rate (either as a percentage or a threshold)
c) A duration of the event
d) The timing of onset of the event (relative to declaration of brain death)
e) Other : please specify

Q5 : You are managing a neurologically deceased donor that you perceive is euvolemic. All organs are under consideration for donation and transplantation. You suspect that the donor is in the throes of an adrenergic storm. In which of the following situations would you usually intervene with medication ? (Please check all that apply)

a) A recurrent or persistent rise in blood pressure with no increase in heart rate
b) A recurrent or persistent sinus tachycardia with no associated hypertension or hypotension

c) A recurrent or persistent rise in both blood pressure and heart rate (sinus tachycardia)
d) I would not intervene with medication in this situation

Q6: When you choose to treat an adrenergic storm with medication, what best describes your hemodynamic targets assuming that the donor has no history of hypertension? (*Please select one answer*)

a) I aim for the patient's most recent stable hemodynamic parameters
b) I aim for a percentage reduction in blood pressure and/or heart rate
c) I aim for specific target values of blood pressure and/or heart rate for all donors
d) I do not treat hemodynamic changes in the setting of an adrenergic storm

Q7: In the case of a neurologically deceased donor presenting in an adrenergic storm, for each for the following situations, what would you typically choose as a first line agent, assuming that all the organs are under consideration for transplantation? IF

a) High blood pressure and normal heart rate
b) High blood pressure and sinus tachycardia
c) Normal blood pressure and sinus tachycardia
    a. Metoprolol
    b. Esmolol
    c. Labetalol
    d. Nitroprusside
    e. Nitroglycerine
    f. Enalaprilat
    g. Hydralazine
    h. Nicardipine
    i. I would not typically intervene with medication

Q8: How frequently do you rely upon the following variables (or changes in these variables) to trigger fluid administration and/or monitor fluid response in neurologically deceased donors? (*never, rarely, sometimes, often, always*)

a) Central venous pressure
b) Hourly measured urinary output
c) Catecholamine dose
d) Cardiac output or cardiac index, as measured other than by echography
e) Cardiac echography results

Q9: Neurologically deceased donors often become hypotensive. In which of the following situations would you intervene using vasopressors in a euvolemic donor? (*Please select all that apply*)

a) Hypotension with no other sign of hypoperfusion
b) Hypotension with a decrease in urine output and no other clinical signs of hypoperfusion
c) Hypotension with a significant modification in biological markers of perfusion (e.g.: serum lactate, SVO2)
d) None of these situations
e) Other (please specify)

Q10: A neurologically deceased donor required fluid resuscitation according to your targets. You administered 2 litres of intravenous crystalloid over a short period of time and decided that another fluid bolus is indicated in this patient. Considering only the fluids available in your centre, what would you administer to the donor; assuming that s/he has neither renal failure nor active bleeding and that all organs are under consideration for donation?

a) Ringer's lactate
b) Physiologic saline (0.9%)
c) Osmolyte or Plasma-Lyte or other balanced solutions
d) Albumin 5%
e) Albumin 25%
f) Starches

Q11: You are managing a potential neurologically deceased donor. This donor has reduced PaO2/FiO2 but the lungs are considered for donation if the oxygenation would normalize. All other organs are also considered for donation. Actually the mean arterial pressure is below your target. In similar situations, how often would you refrain from additional fluids and move quickly to initiate (or increase the dose of) vasopressors (norepinephrine, vasopressin, epinephrine, dopamine or phenylephrine)? (*never, rarely, sometimes, often, always*)

Q12: You are managing a potential neurologically deceased donor. This donor has reduced PaO2/FiO2 but the lungs are NOT considered for donation even if the oxygenation would normalize. Only the kidneys are considered for donation in this patient. Actually the mean arterial pressure is below your target. In similar situations, how often would you refrain from

additional fluids and move quickly to initiate (or increase the dose of) vasopressors (norepinephrine, vasopressin, epinephrine, dopamine or phenylephrine)? (*never, rarely, sometimes, often, always*)

Q13: A neurologically deceased donor is admitted to you unit. Very shortly following brain death, s/he develops hypotension that is unresponsive to volume resuscitation. In this situation, what would be your minimum mean arterial pressure (MAP) target? (*Please select one answer)*

a) 60 mmHg or more
b) 65 mmHg or more
c) 70 mmHg or more
d) 75 mmHg or more
e) Other (please specify)

Q14: In a neurologically deceased donor who develops hypotension that is unresponsive to volume resuscitation, what would be your preferred first line pharmacological therapy assuming that this donor has no signs of diabetes insipidus? (*Please select one answer*)

a) Norepinephrine
b) Epinephrine
c) Dopamine
d) Phenylephrine
e) Vasopressin
f) Other (please specify)

Q15: In which of the following situations would you administer pharmacological inotropes (for example dobutamine, milrinone) to neurologically deceased donors? Consider this donor to be euvolemic and with acceptable blood pressure (*Please select all that apply*)

a) In donors with signs of hypoperfusion AND in whom the heart is considered for donation
b) In donors with signs of hypoperfusion BUT in whom the heart is NOT considered for donation
c) In donors with no signs of hypoperfusion BUT with low left ventricular ejection fraction (LVEF) or cardiac index, independent of whether the heart is considered for donation
d) In donors with low LVEF or cardiac index, in whom the heart could be considered for donation if LVEF would normalize
e) Never

Q16: For which of the following situations do you use GIK (a combined infusion of glucose, insulin and potassium) in neurologically deceased donors (Please check all that apply)

a) For low left ventricular ejection fraction (LVEF) (or low cardiac output), in order to optimize heart function for donation
b) For low LVEF (or cardiac output), regardless of the potential for heart donation
c) Every donor receives GIK
d) Only for donors requiring insulin for hyperglycemia
e) None of the situations
f) Unsure (not familiar with GIK administration)
g) Other (please specify)

Q17: In which situation(s) do you prescribe corticosteroids to a neurologically deceased donor (*Please check all that apply*)

a) Neurologically deceased donors featuring any sign of hemodynamic instability (e.g. requiring vasopressors, low left ventricular ejection fraction), regardless of which organs are potentially retrievable
b) Neurologically deceased donors in whom specific organs are considered for transplant (lungs, heart, kidney)
c) I never prescribe corticosteroids in neurologically deceased donors
d) When requested by others (e.g. a transplant surgeon or a member of the organ procurement organization)
e) All neurologically deceased donors regardless of hemodynamic stability and/or potentially retrievable organs
f) Other (please specify)

Q18: Which of the following corticosteroid agent do you typically prescribe for neurologically deceased donors? (*Please select one answer*)

a) Methylprednisolone 25 mg/kg or 1-2 g IV q24h
b) Hydrocortisone 50-100 mg IV q6-8h
c) Hydrocortisone infusion (50 mg bolus and 10 mg/h or any similar regimen)
d) I do not prescribe corticosteroids to donors

Q19: In which situation do you typically prescribe thyroid hormones to neurologically deceased donors? (*Please select all that apply*)

a) Neurologically deceased donors with low left ventricular ejection fraction (LVEF) AND in whom the heart is considered for donation
b) Neurologically deceased donors with low LVEF regardless of if the heart is considered for donation

c) Neurologically deceased donors with hemodynamic instability, regardless of the LVEF and regardless which organs may be donated
d) If requestion by a transplant surgeon, or member of the organ donation organization
e) In none of these situations
f) All neurologically deceased donors regardless of the hemodynamic stability and/or potentially retrievable organs
g) Other (please specify)

Q20: In which province is your hospital situated?

Q21: What best describes your primary medical specialty training?

a) Internal medicine
b) Family medicine (with or without 1 year of emergency medicine)
c) Emergency medicine (5 years)
d) General surgery or surgical subspecialty
e) Anaesthesiology

Q22: Does organ retrieval surgery occur in your hospital? (*yes/no*)

Q23: Does organ transplant occur in your hospital? (*yes/no*)

Q24: Is your centre a university teaching hospital? (*yes/no*)

Article 3: Right ventricular dysfunction in neurologically deceased organ donors: an observational study in a tertiary-care organ donor referral centre.

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Contribution to this article: I designed the protocol, supervised patient recruitment, supervised data collection, performed the analysis and interpreted the data, drafted and critically revised the manuscript.

Abstract

Purpose: Right ventricular RV dysfunction among transplant recipients correlates with transplant outcome**,** but its frequency in donors is unknown. The purpose of this study was to describe the epidemiology of RV dysfunction in potential heart donors."

Methods: In a seven-year retrospective study of potential heart donors, we explored the incidence of RV dysfunction as observed on echocardiography and explored the association of four distinct factors with RV dysfunction: brain injury diagnosis, thoracic trauma, vasopressin infusion and left ventricular (LV) dysfunction.

Results: All 123 potential heart donors underwent echocardiography: 55 had RV dysfunction (44.7%). Fourty-one (33.3%) had LV dysfunction. Isolated RV dysfunction was present in 27 subjects (22%). LV dysfunction was the only factor significantly associated with RV dysfunction (OR = 4.6 (95% CI 1.9-11.4)). We observed no difference in heart acceptance between subjects with or without RV dysfunction.

Conclusion: We observed a high frequency of RV dysfunction in a sample of potential heart donors. However, the temporal evolution of RV dysfunction, the hemodynamic predictors of RV dysfunction, as well the link between donor RV dysfunction and recipient outcomes need to be assessed with further prospective studies.

Introduction

Since the earliest human heart transplantation in 1967, the demand for hearts through deceased organ donation has progressively increased while supply has remained insufficient.[1] In 2016, 4135 candidates were waiting for a heart transplantation in the US.[2] The rate of heart donation from potential neurologically deceased organ donors is relatively low, with study estimates ranging from 29 to 60%.[3, 4] For heart recipients, a longer time spent on the waiting list increases the risk of transplant failure.[5] For these many reasons, careful investigations into opportunities to improve heart donation and transplantation rates are important to the transplant community.

No systematic approach to the assessment of right ventricle function in potential donors exists and the use of monitoring parameters such as cardiac echography, central venous pressure measurement or invasive monitoring is variable.[6] To date, though clinicians caring for deceased organ donors may recognize the importance of the right ventricle and strive to assess its function, clinical studies on heart dysfunction in neurologically deceased donors have been limited to the left ventricle(LV).[4, 7, 8] Current estimates suggest that transplant programs decline hearts 10-42% of potential heart donations based on LV dysfunction.[8-10] Meanwhile, animal models of neurological death and cardiac transplantation suggest that the pathophysiology of brain herniation also induces RV dysfunction.[7] Moreover, RV dysfunction among recipients is an established predictor of transplant failure, but the strength of association between donor and recipient RV dysfunction is unknown.[7, 11, 12]

The primary aim of this study was to describe the epidemiology of RV dysfunction after neurological death among potential heart donors, as assessed by echocardiography in an organ donor referral centre. A secondary aim was to identify potential factors associated with RV dysfunction.

Material and methods

Setting and Study Population

The Hôpital du Sacré-Coeur de Montréal is a tertiary care hospital in Montreal, Canada, and a provincial referral centre for deceased donor management and organ procurement.[13] The hospital Research Ethics Board approved the execution of this research with a waiver of research consent.

In this retrospective cohort study, we identified consecutive potential organ donors admitted to this hospital over the period of January 2009 to July 2016 by cross-referencing the intensive care unit (ICU) admission list to a database of the provincial organ donation organization, Transplant Quebec. Cross-referencing these donors further to the hospital echocardiography

registry, we included every potential heart organ donor that underwent at least one formal transthoracic echocardiogram at the study institution. In keeping with Transplant-Quebec and Hôpital du Sacré-Coeur criteria for potential heart donation, we excluded potential donors that were not potential heart donors with the following exclusion criteria: age of 70 years or more, early termination of the donation process through Transplant-Quebec, known pre-existing cardiac comorbidities (mechanic valve replacement, coronary artery bypass graft, coronary artery disease on angiogram, endocarditis), and extracorporeal membrane oxygenation in the ICU.

At the study institution, all potential donors that do not present one of these explicit heart donation exclusion criteria, even those with risk factors for coronary artery disease (age over 45 years or medical risk factors) are considered as potential heart donors until ruled out by cardiac catheterization, which, occurs after the first echocardiography. Accordingly, these subjects were considered potential heart donors for the purpose of this study. We lastly excluded subjects for whom echocardiography results of the right ventricle were unavailable or uninterpretable. Before 2013, organ recovery surgeries were not performed at the study institution. Potential donors were admitted to the ICU and taken care of until transfer to another facility for organ recovery and organ transplant surgeries. For logistic reasons, potential donors were sometimes transferred before a first echocardiography could be performed at the study institution, explaining unavailable results and exclusion of concerned subjects from the study.

Echocardiography

Study investigators uploaded the digitally-stored, cineloop formal echocardiogram results from the institutional cardiology service echocardiogram database. For study participants with more than one echocardiogram on record, we describe the total number of echocardiograms but include in these analyses only the first echocardiogram after neurological death.

All echocardiograms had been previously analysed by cardiologists with advanced certification in echocardiography. For the purpose of this study, one of these echocardiographers (RL) reviewed each echocardiogram without access to any additional clinical or research data.

Differences between the original report and the study report were resolved by consensus with one of the study investigators (KS).

Echocardiographic images included 5 standard views (parasternal long axis, short axis, and apical 2-, 3- and 4-chamber views). RV function was evaluated by measuring tricuspid annular velocity (S') by tissue Doppler and by calculating the Fractional Area Change (FAC), when feasible.[14] LV dimensions, RV dimensions, left atrial dimensions and the presence of valvular disease were also assessed.[14] RV systolic function was considered abnormal when S' was lower than 10 cm/s and/or FAC was lower than 35%.[14] LV ejection fraction (EF) was assessed visually and measured by the Simpson biplane method, and a LVEF less than 50% was classified as abnormal.[10, 15, 16] LV diastolic function was assessed as recommended by the American Society of Echocardiogram by measuring the early mitral filling wave (E)/atrial contraction wave (A) ratio on pulse-wave Doppler, the tissue-Doppler early mitral filling wave (e') at the lateral mitral annulus, and the E/e' ratio. [17, 18]

Data Collection

Based on literature review and discussion with the investigators, we identified eight variables to test for possible association with RV dysfunction: donor's age, gender, mechanism of brain injury, pre-existing hypertension, LV systolic dysfunction, LV diastolic dysfunction, pulmonary hypertension, and the use of vasopressors.[19]

We developed and pretested a standardized case report form. From medical charts, one study investigator (C.V) recorded demographic data (e.g., age, gender, weight), relevant comorbidities (e.g.,diabetes, dyslipidemia, coronary artery disease, hypertension), and clinical data (e.g., medication at the time of echocardiogram, presence of thoracic trauma and troponin I levels) as well as data relative to the timing and cause of neurological death. We recorded all available troponin levels following neurological death determination and then, classified levels greater than 1.6 mcg/ml as indicative of myocardial injury.[20] We also collected information on the medication administered to the donors (e.g, vasopressor and inotrope infusions, hormone therapy). Thoracic trauma was identified to exclude blunt cardiac injury as a cause of cardiac

dysfunction, as determined by the presence of at least one of the following: rib fracture not related to cardiac compressions, pulmonary contusion, or sternal fracture.

Pulmonary artery pressure measurements were recorded for all potential donors with a pulmonary artery catheter *in situ*. We then classified pulmonary artery pressures greater than 35 mmHg as abnormal. We recorded all available information on LV diastolic function.

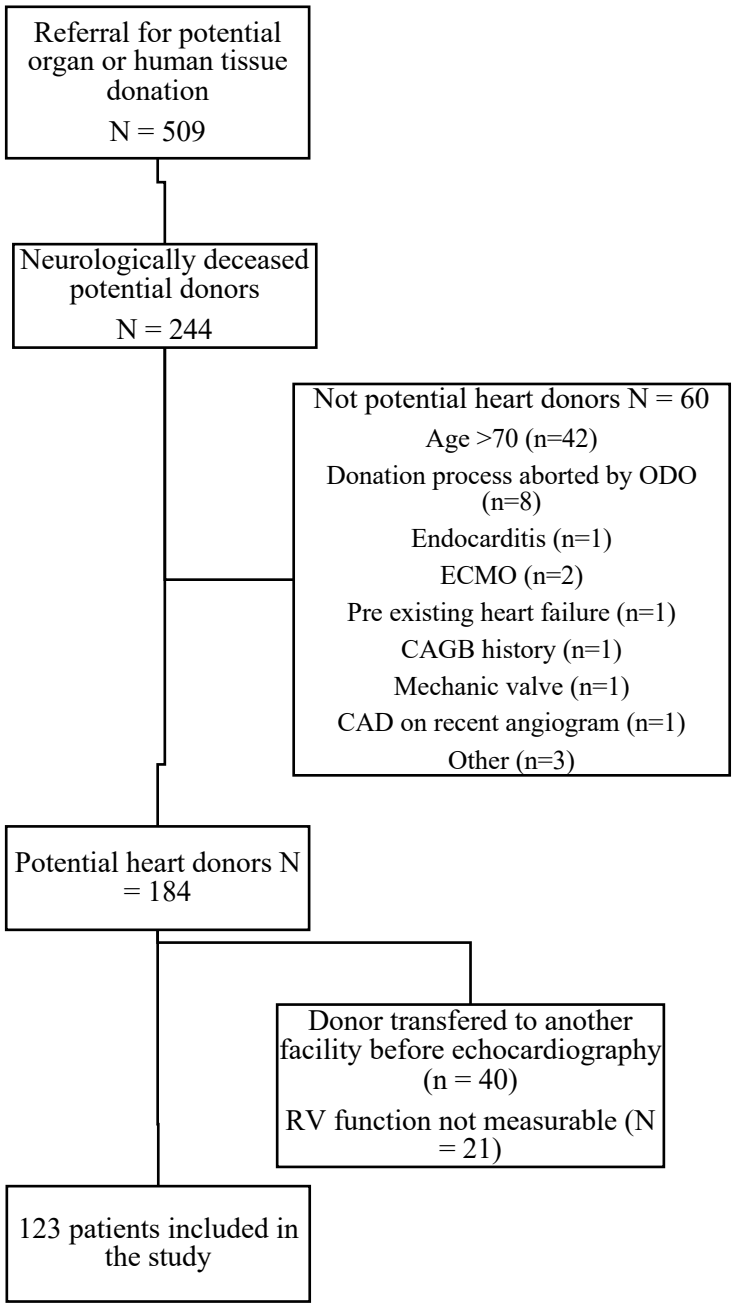
Statistical Analyses

The purpose of this study was to describe the epidemiology of RV dysfunction after neurological death among potential heart donors, as assessed by echocardiography. The primary outcome, was to report the frequency and the incidence of RV dysfunction among potential heart donors**.** We describe characteristics of the study sample using means and proportions with standard deviations (SD), or medians with interquartile ranges (IQR), as appropriate. Incidence are reported in percentage of cases per month. We compared the clinical characteristics of subjects with and without RV dysfunction and of subjects with and without LV dysfunction using Chi-square (or Fisher exact test) and student T-test (or Mann-Whitney U test), as necessary. The secondary objective of the study was to explore potential factors associated with RV dysfunction. To fill the secondary objective of the study, we used multivariate logistic regression and reported the outcome using odds ratio. We selected variables with a nominal statistical significance denoted by a p-value less than or equal to 0.2 in the univariate analysis for the inclusion in the model. Despite a p-value higher than the predefined cut-off, hypertension was forced in the RV dysfunction model because of known associations between pre-existing hypertension and RV functional alterations, hypertension and LV diastolic dysfunction, and LV diastolic dysfunction and RV dysfunction.[21-23] We evaluated goodness of fit using the Hosmer-Lemeshow test. The model was also tested for multicollinearity and residuals and outliers were examined. For all two-sided comparisons, we applied a p value of less than 0.05 to denote statistical significance. One investigator (AJF) performed all of the statistical analyses using IBM SPSS Statistics v24.0 2018 and another investigator (DW) reviewed them.

Results

Over the study period, 244 neurologically deceased potential organ donors, were admitted to our institution. Sixty of them did not meet the specified criteria for heart donation and were excluded from the study. The most frequent reason for heart decline was age over 70 years. From the remaining 184 potential heart donors, 40 were transferred to another facility before the first echocardiography for administrative reasons. The calculated incidence for potential heart donors in the cohort was 5.05%/month**.** For 21 study participants, quantitative parameters of RV function were not measurable due to poor image quality. Table 1 summarizes the characteristics of these 61 excluded subjects. The study cohort, therefore, includes 123 potential heart donors with at least one interpretable echocardiography.

Figure 1. Inclusion of the study subjects



ECMO = exracorporeal membrane oxygenation; CABG = coronary artery bypass graft; CAD = coronary artery disease

The majority of study subjects were males (n = 81; 65.9%), who had suffered a traumatic brain injury (n = 49; 39.8%) (Table 1). Based on charted past medical history, 16 (13.0%) of these subjects had possible pre-existing coronary artery disease at the time of consideration for heart donation.

Table 1. Characteristics of the Study Sample

Variable	All (N=123)	RVD+ (N=55)	RVD – (N=68)
Age, median years (Q1-Q3)	49.0 (28-60)	45 (31-58.8)	53 (28-61)
Male, number (%)	81 (65.9)	39 (70.9)	42 (61.8)
Thoracic trauma, number (%)	31 (25.2)	9 (16.4)	22 (32.4)
Medical history, numbers (%)			
Hypertension	25 (20.3)	13 (23.7)	12 (17.6)
Diabetes mellitus	13 (10.6)	7 (12.7)	6 (8.8)
Coronary artery disease*	16 (13.0)	5 (9.1)	11 (16.2)
Dyslipidemia	17 (13.8)	10 (18.2)	7 (10.2)
Cause of death, numbers (%)			
Traumatic brain injury	49 (39.8)	18 (32.7)	31 (45.6)
Anoxia	27 (21.9)	14 (0.3)	13 (0.2)
Non traumatic subarachnoid haemorrhage	18 (14.6)	9 (0.2)	9 (0.1)
Brain haemorrhage	18 (14.6)	8 (0.2)	10 (0.2)
Ischemic stroke	10 (8.1)	6 (0.1)	4 (0.1)
Methanol poisoning	1 (0.8)	1 (0.02)	0
Medication at the moment of the echocardiography, numbers (%)			
Vasopressin	96 (78.0)	46 (83.6)	50 (73.5)
Noradrenaline	68 (55.3)	32 (58.2)	36 (52.9)
Methylprednisolone	58 (47.2)	27 (49.1)	31 (45.6)
Levothyroxine	17 (13.8)	10 (19.1)	7 (10.3)
Milrinone	4 (0.03)	4 (0.1)	0
LVD +**	41 (33.3)	21 (75.0)	24 (53.3)

Echocardiography Results

The median elapsed time from the declaration of neurological death to the first echocardiogram was 4.6 hours (Q1-Q3 2.0-13.0). Ninety-three subjects (75.6%) had only one echocardiogram performed after neurological death, 21 subjects (17.1%) had 2 echocardiograms and 8 subjects (6.5%) had 3 or more. On the first echocardiogram, mean FAC and S' were respectively 38.8% (SD 10.8) and 11.5 cm/s (SD 3.2). At the time of the first echocardiogram, 21 (17.1%) were receiving vasopressors and 3 (2.4%) had a combined infusion of glucose, insulin and potassium

(GIK). Methylprednisolone was used in 58 subjects (47.2%) and levothyroxine in 17 subjects (13.8%). Twenty-eight (23.8%) subjects had positive troponin I levels. Pulmonary artery pressure results were available for 50 of the 123 included subjects, and 9 (18%) had pulmonary hypertension.

The overall frequency of RV dysfunction either isolated or combined with LV dysfunction was 44.7% (n=55/123), corresponding to an incidence of 6.4%/month for the study period. Mean FAC and S' were respectively 31.0% (SD 8.9) and 10.1 cm/s (SD 3.7) in subjects with RV dysfunction.). LV systolic dysfunction was more frequent in donors with RV dysfunction than in those with normal RV function (51% vs 19%; $p<0.001$). In subject with RV dysfunction, the heart acceptance rate was 47% (26/55). Thirty nine of the 68 subjects (57%) without RV dysfunction became heart donors.

Isolated RV dysfunction was present in 27 of the 123 subjects (22.0%), corresponding to an incidence of 3.14%/month for the study period. FAC measurement results were available for all the 27 subjects with a median of 29.0 % (Q1-Q3: 26.5-35). S' measurement results were available for 11 of the 27 subjects with a median of 12.8 cm/s (Q1-Q3: 4.0-12.8). Characteristics of subjects with isolated RV dysfunction are presented at Table 2. From the 27 subjects with isolated RV dysfunction, none had more than one echocardiography performed. Heart donation was possible for 13 of the 27 subjects (48.1%) with isolated RV dysfunction.

Table 2. Characteristics of subjects with isolated RV dysfunction

Variable	N = 27
Age, median years (Q1-Q3)	58.0 (29.0-63.0)
Male, number (%)	20 (74.1)
Thoracic trauma, number (%)	5 (18.5)
Medical history, numbers (%)	
Hypertension, number (%)	7 (25.9)
Diabetes	4 (14.8)
Coronary artery disease**	4 (14.8)
Dyslipidemia	6 (22.2)
Cause of death, numbers (%)	
Traumatic brain injury	12 (44.4)
Anoxia	3 (11.1)
Non traumatic subarachnoid haemorrhage	3 (11.1)
Brain haemorrhage	7 (25.0)
Ischemic stroke	2 (7.4)
Methanol poisoning	0

** Reported in the medical chart as past medical history

Potential predictors of RV dysfunction

Some pre-selected variables could not be included in the model to identify predictors of RV dysfunction. Only 50 of the 123 subjects had a pulmonary artery catheter *in situ*; 24 in subjects with RV dysfunction (n= 24/55; 43.6%) and 26 in subjects without RV dysfunction (n=26/68; 38.2%). Missing data precluded inclusion of pulmonary artery measurement in the model. Left ventricular diastolic dysfunction was evaluated in 73 of the 123 included subjects and found to be present in 45/73 subjects (61.6%). In the majority (41 of the 45), LV diastolic dysfunction was mild and 4 subjects had moderate dysfunction. Missing data precluded inclusion of LV diastolic dysfunction measurements in the model.

Among the remaining variables, diagnosis of traumatic brain injury, thoracic trauma, current or recent administration of vasopressin, and concomitant LV systolic dysfunction were identified in the univariate analysis as potentially associated with RV dysfunction ($p \leq 0.2$). Comparisons between donors with and without RV dysfunction are shown in Table 1. Only concomitant LV dysfunction was independently associated with RV dysfunction in the multivariate model [OR = 4.6 (95% CI 1.9-11.4); $p < 0.001$] (Table 3). The model was valid based on the analysis of the goodness of fit, residuals and outliers ($R^2 = 0.189$).

Table 3. Multivariate logistic regression models of variables associated with RV dysfunction

Variable	OR	95% CI	P value
LV dysfunction	4.5	1.9-11.1	0.001
Hypertension	1.4	0.5-3.7	0.5
Traumatic brain injury	1.2	0.5-3.1	0.6
Vasopressin	1.2	0.5-3.3	0.7
Thoracic trauma	0.4	0.1-1.1	0.08

*All variables included in the model had a $p<0.2$ in the univariate analysis

Discussion

In this retrospective observational study of consecutive potential heart donors in an organ donor referral centre, we observed a high frequency of RV dysfunction among neurologically deceased potential heart donors. Candidates for heart donor in this cohort was around 5%. The relative frequency of isolated RV dysfunction among potential heart donors is 22%, which is, in our opinion, high, especially if we compare with known frequency of LV dysfunction reported in the literature. While the only apparent predictor of RV dysfunction among these subjects was LV dysfunction, 22% (n=27/123) of the cohort had isolated RV dysfunction.

The specific pathophysiology of RV dysfunction following neurological death has been scarcely described. An increase in pulmonary vascular resistance caused by the catecholamine surge or mediated by neurological death-induced inflammation has been implicated. [24, 25] Moreover, factors associated with increased RV afterload (mechanical ventilation, PEEP) or decreased RV preload (mechanical ventilation, polyuria from diabetes insipidus, or neurological death-associated inflammation) could also play a role in RV dysfunction. If these factors related to the acute process of neurological death or its management are indeed the principal causes for RV dysfunction, reversibility of RV dysfunction is then possible and may be a useful future target for donor management. Repeated echocardiography assessments in potential donors with initial RV dysfunction could further inform on RV dysfunction reversibility and its consequences on

recipients' outcomes. Therefore, further prospective studies should aim at determining factors that lead to RV dysfunction, its optimal diagnosis methods and situations where reversibility of RV dysfunction are possible**.** The strongest predictor of RV dysfunction that we could identify in this study was LV dysfunction. The frequency of LV dysfunction is in accordance with previous published data, and this speaks to the credibility of both LV and RV findings in the current study.[8-10, 15] No predictors of LV dysfunction have been reproducibly identified in published studies, although age, body-mass index and longer management time from neurological death to echocardiogram have been possibly linked with results.[9, 10]

Although RV and LV dysfunction were significantly correlated, isolated RV dysfunction was present in more than 20% of our subjects whereas isolated LV dysfunction was present in 10%. Similarly, in canine models of neurological death, RV dysfunction was found to be more prominent than LV dysfunction.[26, 27]

Following heart transplantation, up to 50% of heart recipients will experience RV dysfunction, and 19% of those experiencing RV dysfunction will die early after transplantation.[28] Although recipient pulmonary hypertension and recipient RV dysfunction are known predictors of graft dysfunction and death, the specific impact of donor RV function on recipient RV function has been absent from reports to date.[29, 30] Careful evaluation of donor RV function and its potential for reversibility may be of outmost importance. In this study, for 15% of the cohort of potential heart donors the echocardiographic parameters of RV function were not measurable due to poor image quality. The routine evaluation of RV function in potential heart donors is, to our opinion, warranted, and because of the potential impact on heart recipients, future studies are needed to determine situations were donors with RV dysfunction should be discarded.

Limitations

This study is limited by its retrospective nature and small sample size. As a result of the necessity to exclude donors with missing or uninterpretable echocardiography results and donors that were transferred to another facility for administrative reasons, the RV frequency reported in this

study needs to be confirmed prospectively. Although reasons for exclusions were not necessarily related to donors' hemodynamic status or potential for heart donation, we cannot exclude residual selection bias on the included sample. Results of the exploratory multivariate analysis should be interpreted with caution since, due to the small sample size, additional potentially relevant variables could not be controlled for. Moreover, data on central venous pressure, fluid status, diastolic function, pulmonary pressures and ventilator parameters, which could potentially have affected RV function, were not retrospectively available. Finally, we did not have access to recipient outcomes. However, a notable strength of this study compared to previous registry-based studies is the standardised conduct and blinded interpretation of all echocardiograms, performed at a single centre.

Conclusion

RV dysfunction is frequent among potential heart donors and LV dysfunction could be one of its predictors. However, the temporal evolution of RV dysfunction, the hemodynamic predictors (diastolic function, fluid status, pulmonary artery pressures) of RV dysfunction, as well the link between donor RV dysfunction and recipient outcomes need to be assessed with further studies. Prospective studies should aim at confirming the incidence of RV dysfunction as well as studying its consequences on transplantation outcomes.

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References

[1] Brink JG, Hassoulas J. The first human heart transplant and further advances in cardiac transplantation at Groote Schuur Hospital and the University of Cape Town - with reference to : the operation. A human cardiac transplant : an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. Cardiovasc J Afr 2009;20(1):31-5.

[2] UNOS. United Network for Organ Sharing, https://www.unos.org/data/transplant-trends/#waitlists_by_organ; 2016 [accessed October 5th.2016].
[3] Apostolakis E, Parissis H, Dougenis D. Brain death and donor heart dysfunction: implications in cardiac transplantation. Journal of cardiac surgery 2010;25(1):98-106.
[4] Khush KK, Menza R, Nguyen J, Zaroff JG, Goldstein BA. Donor predictors of allograft use and recipient outcomes after heart transplantation. Circulation Heart failure 2013;6(2):300-9.
[5] Goldstein BA, Thomas L, Zaroff JG, Nguyen J, Menza R, Khush KK. Assessment of Heart Transplant Waitlist Time and Pre- and Post-transplant Failure: A Mixed Methods Approach. Epidemiology 2016;27(4):469-76.
[6] Frenette AJ, Charbonney, E., D'Aragon, F., Serri, K., Marsolais, P., Chassé, M., Meade, M. Williamson, D.R. . A Canadian Survey of Critical Care Physician's Hemodynamic Management of Neurologically Deceased Organ Donors. Can J Anaesth [Accepted for publication] 2019.
[7] Bittner HB, Chen EP, Biswas SS, Van Trigt P, 3rd, Davis RD. Right ventricular dysfunction after cardiac transplantation: primarily related to status of donor heart. The Annals of thoracic surgery 1999;68(5):1605-11.
[8] Dujardin KS, McCully RB, Wijdicks EF, Tazelaar HD, Seward JB, McGregor CG, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2001;20(3):350-7.
[9] Zaroff JG, Babcock WD, Shiboski SC, Solinger LL, Rosengard BR. Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2003;22(4):383-8.
[10] Borbely XI, Krishnamoorthy V, Modi S, Rowhani-Rahbar A, Gibbons E, Souter MJ, et al. Temporal Changes in Left Ventricular Systolic Function and Use of Echocardiography in Adult Heart Donors. Neurocrit Care 2015;23(1):66-71.
[11] Kirklin JK, Naftel DC, Kirklin JW, Blackstone EH, White-Williams C, Bourge RC. Pulmonary vascular resistance and the risk of heart transplantation. J Heart Transplant 1988;7(5):331-6.
[12] Natale ME, Pina IL. Evaluation of pulmonary hypertension in heart transplant candidates. Curr Opin Cardiol 2003;18(2):136-40.
[13] Marsolais P, Durand P, Charbonney E, Serri K, Lagace AM, Bernard F, et al. The First 2 Years of Activity of a Specialized Organ Procurement Center: Report of an Innovative Approach to Improve Organ Donation. Am J Transplant 2017;17(6):1613-9.
[14] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16(3):233-70.
[15] Nicolas-Robin A, Salvi N, Medimagh S, Amour J, Le Manach Y, Coriat P, et al. Combined measurements of N-terminal pro-brain natriuretic peptide and cardiac troponins in potential organ donors. Intensive Care Med 2007;33(6):986-92.
[16] Zaroff JG, Babcock WD, Shiboski SC. The impact of left ventricular dysfunction on cardiac donor transplant rates. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2003;22(3):334-7.

[17] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18(12):1440-63.
[18] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17(12):1321-60.
[19] Skhiri M, Hunt SA, Denault AY, Haddad F. [Evidence-based management of right heart failure: a systematic review of an empiric field]. Revista espanola de cardiologia 2010;63(4):451-71.
[20] Potapov EV, Ivanitskaia EA, Loebe M, Mockel M, Muller C, Sodian R, et al. Value of cardiac troponin I and T for selection of heart donors and as predictors of early graft failure. Transplantation 2001;71(10):1394-400.
[21] Tumuklu MM, Erkorkmaz U, Ocal A. The impact of hypertension and hypertension-related left ventricle hypertrophy on right ventricle function. Echocardiography (Mount Kisco, NY) 2007;24(4):374-84.
[22] Palmiero P, Zito A, Maiello M, Cameli M, Modesti PA, Muiesan ML, et al. Left ventricular diastolic function in hypertension: methodological considerations and clinical implications. Journal of clinical medicine research 2015;7(3):137-44.
[23] Gorter TM, Verschuuren EAM, van Veldhuisen DJ, Hoendermis ES, Erasmus ME, Bogaard HJ, et al. Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertensiondagger. Interactive cardiovascular and thoracic surgery 2017;24(6):890-7.
[24] Bittner HB, Kendall SW, Chen EP, Craig D, Van Trigt P. The effects of brain death on cardiopulmonary hemodynamics and pulmonary blood flow characteristics. Chest 1995;108(5):1358-63.
[25] Armitage JM, Hardesty RL, Griffith BP. Prostaglandin E1: an effective treatment of right heart failure after orthotopic heart transplantation. J Heart Transplant 1987;6(6):348-51.
[26] Van Trigt P, Bittner HB, Kendall SW, Milano CA. Mechanisms of transplant right ventricular dysfunction. Ann Surg 1995;221(6):666-75; discussion 75-6.
[27] Kendall SW, Bittner HB, Peterseim DS, Campbell KA, Van Trigt P. Right ventricular function in the donor heart. Eur J Cardiothorac Surg 1997;11(4):609-15.
[28] Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001;38(4):923-31.
[29] Bianco JC, Mc Loughlin S, Denault AY, Marenchino RG, Rojas JI, Bonofiglio FC. Heart Transplantation in Patients >60 Years: Importance of Relative Pulmonary Hypertension and Right Ventricular Failure on Midterm Survival. J Cardiothorac Vasc Anesth 2018;32(1):32-40.

[30] Guven G, Brankovic M, Constantinescu AA, Brugts JJ, Hesselink DA, Akin S, et al. Preoperative right heart hemodynamics predict postoperative acute kidney injury after heart transplantation. Intensive Care Med 2018.

Article 4: A Pilot Randomized Controlled Trial Comparing Levothyroxine to Placebo in Neurologically Deceased donors

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Contribution to this article: I designed the protocol, supervised patient recruitment, supervise data collection, performed the analysis and interpreted the data, drafted and critically revised the manuscript.

ABSTRACT

Background: Although commonly prescribed, the efficacy of levothyroxine to improve heart function in neurologically deceased donors is unclear. We evaluated the feasibility of a randomized controlled trial to compare levothyroxine to placebo on the variation of left ventricular ejection fraction, in hemodynamically unstable donors.

Methods: We conducted a pilot, double-blinded, randomized controlled trial. Deceased donors with reduced left ventricular ejection fraction or needing vasopressors were included. We randomized participants to a 20 μg bolus followed by a 20 μg/h infusion of levothyroxine or an identically appearing placebo. We report the proportion of recruited participants, the time to the administration of the study drug, and protocol violations.

Results: Twenty-four participants (N = 24/104; 23.1%) were eligible. Five of them (N = 5/24; 20.8%) were excluded by the attending physician. Four others were not included, due to family refusal for research (n = 2/24;8.3%) and unavailability of research staff (n = 2/24; 8.3%). Fifteen participants were randomized (N = 15/104; 14.4%). Mean time between the echocardiography and the initiation of the drug was 1.73 hours, and14 (93.3%) of 15 of the participants received the drug within 2 hours after the echocardiography. We report no study violation. The study was stopped prematurely because of low recruitment.

Conclusion: This pilot trial suggests that the success of a definitive randomized control trial to assess the efficacy of levothyroxine in deceased donors could benefit from a multicenter recruitment and education on the evidence surrounding the pharmacological management of organ donors. The need for consent to research interventions in deceased donors should also be clarified**.**

Keywords: cardiovascular system; deceased; endocrine system diseases; therapeutics; transplant donor

Introduction

Despite improvements in organ donor care, organ demand remains above supply. In the US, 3769 adult patients were waiting for a heart transplantation in 2017.[1] The potential for heart donation is limited by several factors including the donors' cardiac risk factors as well as acute left heart dysfunction related to neurological death.[2-4] Acute left heart dysfunction, defined as a reduced left ventricular ejection fraction (LVEF), is reported in up to 40% of potential donors.[5] The observed apoptosis and necrosis in cardiac myocytes could be induced by a surge in catecholamines occurring in the period surrounding neurological death.[6-8]

Supportive measures to optimize cardiac function in donors are still limited and poorly studied. Interventions that aim at reducing the impact of neurological death induced inflammation and of the autonomic storm on the heart derive principally from animal and observational studies.[9-11] Among proposed strategies, hormonal resuscitation has been associated with an improvement in organ procurement, particularly of hearts.[11] Historically, hormone therapy has been studied as a bundle not only composed of pharmacological agents (including corticosteroids, insulin, vasopressin and triiodothyronine), but also of medical interventions in the intensive care unit (ICU).[11-13] However, each individual component of the bundle has not been properly evaluated regarding the improvement of heart function. The administration of thyroid hormones represents the only pharmacological intervention specifically targeting the heart.[11] Specifically, thyroid hormones are believed to supply for a deficit in anterior pituitary gland hormones related to neurological death, and improve heart contractility via a specific local receptor.[14.15] Despite being widely used for donor management, the efficacy of thyroid hormones remains controversial, given the low quality of evidence.[16-18] Moreover, the majority of donors included in the randomized controlled studies (RCT) evaluating thyroid hormones were hemodynamically stable, whereas hemodynamic instability in donors is frequent.[18.19] Conflicting data also exists regarding the safety of thyroid hormones in the context of liver donation.[20-22] The efficacy of thyroid hormone administration on the donors' heart function, and ultimately on recipients' heart graft function, and its safety on other transplanted organs, specifically the liver, need to be further assessed in a RCT.[23]

Conducting prospective evaluating research in the context of organ donation is challenging, and many barriers to success have been identified. These limitations include the uncertainty around the need for consent, the difficulty of collecting nominative recipients' data following an intervention on donors, and the ability of enrolling organ donors in a time limited and difficult emotional context.[24.25] For these reasons, we conducted a pilot RCT to assess the feasibility of evaluating the efficacy of levothyroxine infusion compared to placebo, in hemodynamically unstable donors, with the purpose of designing a larger multicenter trial. We also assessed the efficacy of levothyroxine on the improvement of LVEF, as a preliminary analysis.

Methods

Study design

The pilot study was a single centre, parallel, double blinded, RCT comparing the administration of a levothyroxine infusion to a matching placebo infusion, in a 1:1 ratio. Study feasibility was evaluated using the following criteria: 1) Proportion of eligible recruited patients; 2) Time from echocardiography (T0) to study drug administration; 3) Proportion of protocol violations. Feasibility success was defined as: 1) a minimum of 70% of planned study recruitment (50 patients) completed by 2 years; 2) at least 95% of patients receiving the study drug within 6 hours of the first echocardiography; 3) at least 80% of adherence to the study protocol.[26] The preliminary efficacy outcome was the variation in LVEF between baseline and after a 6-hour infusion of the study drug between the 2 groups compared to placebo.

We also described the frequency of donated organs and the frequency of occurrence of *de novo* atrial fibrillation, liver recipients' graft and their survival status at 6 months as safety monitoring. The study protocol was approved by the Ethics Committee of Hôpital du Sacré-Coeur de Montréal (#2014987) and registered on clinicaltrials.gov (NCT02211053).

Consent

In the province of Quebec, when relatives consent to organ donation for a neurologically deceased patient, they can simultaneously consent to research on organs. For this pilot study, the Ethics committee approved the inclusion of subjects of whom relatives had signed both

consent to organ donation and to research on organs. In July 2016, the investigators met with the Ethics committee to discuss the challenges of study recruitment. A waiver of donors' consent to research for this particular study was adopted based on the fact that neurologically deceased donors are not, by definition, designated by the law that aims at protecting Human rights in research.[27] No consent was required from recipients either, since no direct observation was made on recipients and no nominative data on recipients were obtained. Regarding the administration or not of levothyroxine to donors, the prescription usually depends on clinicians' decision, based on the Canadian Guidelines and recent publications, and variation in standard of care is expected.[16-18,28]

Setting and sample

The study was completed at the intensive care unit of Hôpital du Sacré-Coeur in Montréal, Quebec, Canada. This is a tertiary centre with a large experience in the care for organ donors. Data were prospectively collected by an on-site research coordinator (V.W) and a research nurse (AM.L). Given the suggestion for levothyroxine administration in the Canadian guidelines and based on Transplant-Quebec (local organ donation organization) criterion for heart donation, we included neurologically deceased subjects with the following criteria: age of 16 years or more, hemodynamic instability defined as LVEF of less than 50% as per formal echocardiography and/or the need for two vasopressors (at least 0.1 microgram/kilogram/minute noradrenaline and vasopressin) to maintain the target mean arterial pressure.[16] Mean arterial pressure targets were left at the ICU physician discretion. Subjects older than 75 years, with a pre-existing history of heart failure, or with known coronary heart disease were initially excluded. Coronary heart disease (CHD) was defined as a past history of percutaneous coronary intervention or coronary artery bypass graft before admission. Subjects known for a chronic intake of oral T4 or T3 before admission or having received a levothyroxine infusion as a donor management treatment prior to study screening were also excluded.

In June 2015, the study protocol was amended to increase the recruitment capacity. Subjects older than 75 years, with a history of CHD, or a chronic exogenous intake of oral thyroid

hormones prior to admission were then considered admissible. This decision was based on the primary clinical outcome (change in LVEF), considered as a proof of concept in this pilot study. Although the primary outcome of this study was feasibility, we believed that results on the change in LVEF would further inform on the necessity of conducting a multicenter RCT.

Following consent to donation in the ICU, the local organ donation nurse notified the research coordinators. A member of the research team assessed the subject for eligibility and the organ donation nurse informed the family members of the project and verified the consent to research on the organ donation organization form (until July 2016).

Sample size

Forty to sixty donors are admitted every year at our centre and we expected a 40% proportion of hemodynamic unstable subjects, based on local data and literature.[5,29] Although a sample size of 30 is often reported in pilot trials to assess feasibility, a sample size of 50 patients was preferred for this study.[30] This sample size was meant to maximize the representation of the target population and to permit a comparison of the change in LVEF between groups. Considering an anticipated mean baseline LVEF of 35% (variance = 11) in donors with left ventricular dysfunction (local data), 25 patients per arm permitted to detect a 9% difference in LVEF variation between groups ($\alpha = 0.05$; $\beta = 10\%$) in preliminary unadjusted analyses.

Randomization, blinding and allocation concealment

Subjects were randomized to a 20-mcg bolus followed by a 20 mcg/h infusion of levothyroxine or an identically appearing placebo using a simple method (1:1) with an online computer-assisted randomization system (Research randomizer®).[31] The investigators, all attending clinical personnel, and donors' families were blinded to the allocation. Patients were allocated to study groups by retrieving the next allocation number in a series of sequentially numbered list.

Interventions

The research nurse prepared the study drugs immediately after randomization. Levothyroxine 500 mcg/vial, supplied as a commercially available lyophilized powder (PPC), was reconstituted using 10 ml of sterile water according to the manufacturer recommendation. Then, 500 mcg of the reconstituted solution was injected in a commercially available 500 ml 5% dextrose polyolefin bag (final concentration 1 mcg/ml).[32] Placebo consisted of identically appearing 500 ml 5% dextrose in polyolefin bags in which 10 ml of sterile water was added. The ICU nurse was instructed to administer a bolus of 20 ml (20 mcg) of the study drug infusion in 30 minutes followed by a 20-ml/h (20 mcg/h) infusion.[16] Study drugs were delivered in a designated venous line to prevent any potential drug incompatibility. Since levothyroxine was considered as routine care at the time of the study, the study drug was provided from the donor hospital's pharmacy department. In order to isolate the potential action of levothyroxine from other components of the previously reported hormone therapy cocktail, notably of corticosteroids, all donors included in the study received 15 mg/kg methylprednisolone as part of donor management. Also, the use of vasopressin as a primary vasopressor was advised and the use of insulin for glycemic control was recorded.

Management of adverse events

The attending ICU physician was allowed to hold the study drug infusion, according to clinical judgment, if he suspected any adverse event related to the study drug infusion or interference with donor care. We systematically recorded ECG results and reported the number of subjects experiencing *de novo* atrial fibrillation. We also retrieved information about the living status and graft function of liver recipients at 6 months. Anonymous information on the recipients was obtained directly by contacting the provincial organ donation organization. The researchers had no access to recipients' identity or medical chart.

Measurements

We prospectively recorded the time of neurological death, the baseline and follow up echocardiography timing and results, as well as the timing of administration of the study drug. Echocardiographic images included 5 standard views (parasternal long axis, short axis, and

apical 2-, 3- and 4-chamber views). LVEF was assessed visually and measured by the Simpson biplane method.[33.34] Reasons for exclusion or study protocol violation were detailed and the proportion of recruited subjects from those eligible was calculated. Compliance with the study protocol was monitored at bedside by the research coordinator and violations were recorded and detailed.

From the medical chart, we retrieved demographic data (gender, age, cause of brain death) and relevant past medical comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, smoking status, atrial fibrillation, coronary heart disease and dyslipidemia). We also collected the intake of beta blockers, statins, angiotensin converting enzyme inhibitor and angiotensin receptor antagonist prior to admission, and the use of vasopressin, corticosteroids and insulin after neurological death, as part of donor care. Echocardiography was first performed following brain death (baseline) and 6 hours (+/- 4 hours) after. LVEF results were recorded on both echocardiograms. The mean hourly dose of each vasopressor was recorded from baseline (T0) to 6 hours after the onset of the study drug infusion (T6). To facilitate the analysis, the mean hour vasopressin dose was converted and added to the noradrenaline dose in equivalent doses of 0.04 units/h of vasopressin and 8 microgram/minute of noradrenaline.[35] Organ retrieval and transplant status of each donor's organ, and living status and graft rejection in liver recipients were obtained prospectively from the regional organ donation organization. All collected data were reported on a pre-formatted form.

Data analysis

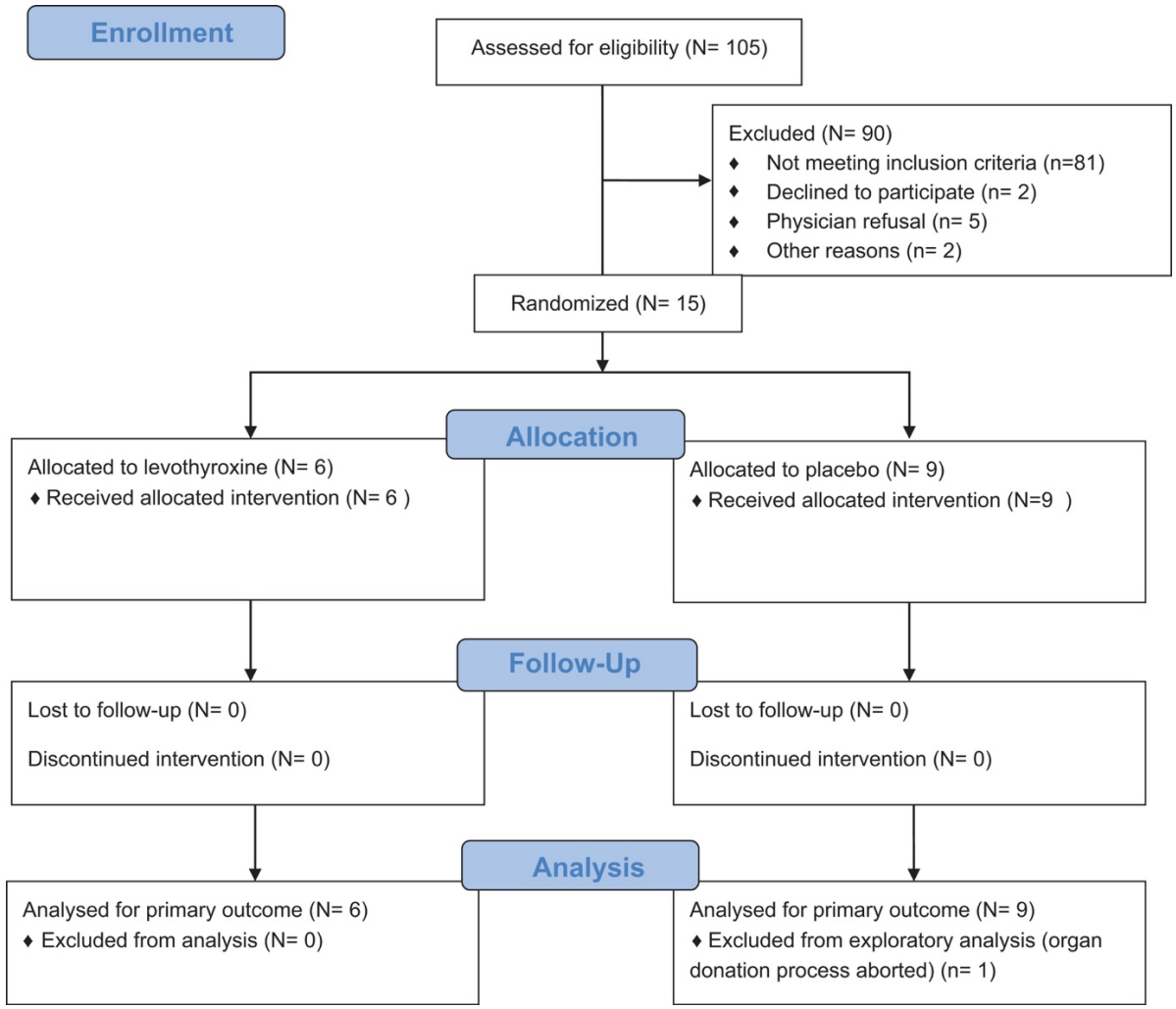
Data were analyzed using SPSS version 25, Chicago, USA. Quantitative data are reported using descriptive statistics (mean or median and proportions). The mean variation in LVEF and in mean hourly vasopressor dose from T0 to T6 was compared between the two groups using the Mann-Whitney test. Data are analyzed according to the intention-to-treat.

Results

Feasibility

We included the first patient in the study in July 2014, and the study was prematurely terminated in December 2016, due to slow recruitment, despite rigorous screening. During the study period, a total of 105 neurologically deceased donors were screened and 81 were considered non-eligible. A total of 24 subjects (22.9%) were considered eligible to the study according to the inclusion criteria. In 5 eligible subjects (n=5/24; 20.8%), the attending physician taking care of the donor refused to include the subject in the study, and administered an open-label levothyroxine infusion. Four others were not included, due to family refusal for research (n=2/24; 8.3%) and unavailability of research personal (n=2/24; 8.3%). Fifteen subjects were effectively randomized in the study (n=15/24; 62.5%) (Figure 1).

Figure 1. Inclusion of the study population



The detailed reasons for exclusion during each study period (before 1st amendment, between 1st and 2nd amendment and after 2nd amendment) are reported in the supplementary material (Appendix 1). In summary, 50 subjects were screened before the 1st amendment and 42 of them (84.0%) were excluded. The main exclusion reasons during this study period were the absence of hemodynamic instability and the lack of consent to research. Thirty-six subjects were screened between the 1st and the 2nd amendment period of the study and 31 of them were excluded (86.1%). Reasons for exclusion were similar than for study period 1. Finally, 19 subjects were screened after the 2nd amendment, and 17 of them were excluded (89.5%), mostly because of the absence of hemodynamic instability.

Six subjects were randomly allocated to the levothyroxine group and 9 to the placebo group. Mean time between the first echocardiography and the initiation of the study drug was 1.73 hours (SD: 3.5 hours), and 14/15 patients (93.3%) of the study subjects were randomized and received the study drug within 2 hours after the echocardiography. Mean time from randomization to the administration of the study drug was 55.9 minutes (SD: 48 min). Follow-up echocardiography occurred at a median of 6 hours (IQR 1-3: 6-7) in the placebo group and at 7.5 hours (IQR 1-3: 5.75-12.5) in the levothyroxine group (p=0.3). The median time of administration was 30 hours (IQR 1-3: 15.8-45.8) for the placebo and 27.5 hours (IQR 1-3: 14.5-35.5) for levothyroxine (p=0.9).

All the included subjects received the appropriate bolus and infusion rate, and no protocol violation was observed. All the included subjects received corticosteroids according to the study protocol. In one subject, a pulmonary cancer was diagnosed before the organ procurement surgery and the donation process was aborted, which precluded the realization of the echocardiography at T6. This subject was included in the feasibility analysis but removed from the preliminary efficacy analysis. He had been randomly assigned to the placebo group.

Clinical characteristics

The patient characteristics are reported in Table 1. The majority (n=9/15; 60%) of the included subjects died from a non-traumatic brain injury. The most common comorbidity prior to admission was hypertension (n=4/15; 26.7%). ICU physicians were specifically asked to indicate if, according to their clinical judgement, the donor had presented an autonomic storm during the period surrounding brain death. ICU physicians diagnosed an autonomic storm in 5/8 (62.5%) subjects in the placebo group and in 1/6 (16.7%) in the levothyroxine group. Three patients in the placebo group received a beta blocker (esmolol for 2 subjects and labetalol for 1 subject) for the treatment of an autonomic storm. No subject in the levothyroxine group was exposed to beta blockers in this context, but one received nitroprussiate. Vasopressin was used in all the placebo group subjects and in 5/6 of the levothyroxine group subjects. Every included subject received insulin for glycemic control.

Table 1. Characteristics of the Study Sample

Characteristics	Placebo (N = 9)	Levothyroxine (N = 6)
Median age, years (IQR 1-3)	29 (27-59)	43 (34-53)
Male gender, n (%)	6 (66.7)	4 (67)
Median LVEF at baseline, %, (IQR 1-3)	36 (30.0-46.0)	36 (32.3-50.8)
Cause of brain death, n (%)		
Traumatic brain injury	3 (33.3)	2 (33.3)
Intracranial bleeding	2 (22.2)	0
Postcardiac arrest	0	3 (50)
Brain anoxia	4 (44.4)	1 (16.7)
Past medical history, n (%)		
Hypertension	3 (33.3)	2 (33.3)
Diabetes	2 (22.2)	1 (16.7)
Chronic pulmonary obstructive disease	1 (11.1)	1 (16.7)
Atrial fibrillation	0	0
Coronary artery disease	0	0
Dyslipidemia	0	1 (16.7)
Smoking	0	3 (50)
Home medications, n (%)		
β-blocker	1 (11.1)	0
Statin	1 (11.1)	2 (33.3)
Angiotensin converting enzyme inhibitor	0	1 (16.7)
Angiotensin receptor antagonist	1 (11.1)	0
Donor management treatments, n (%)		
β-blocker	4 (44.4)	0
Nitroprussiate	0	1 (16.7)
Methylprednisolone	9 (100)	6 (100)
Insulin	9 (100)	6 (100)
Desmopressin	5 (55.6)	3 (50)
Vasopressin	9 (100)	5 (83.3)

Abbreviations: IQR, interquartile range; LVEF, left ventricular ejection fraction.

All but two patients (one in each group) had a baseline LVEF of less than 50%. These 2 patients were considered hemodynamically unstable and included in the study, based on their

vasopressor dose. The median LVEF was similar between the placebo and the levothyroxine groups (36%; IQR 1-3: 30-46 vs 36%; IQR 1-3: 32.3-50.8 (p=1.0)).

In the levothyroxine group, the median increase in LVEF was 11% (IQR: 0-32%) compared to 2% (IQR: 0-12.5%) in the placebo group (p=0.28). Heart procurement was possible in 5/8 (62.5%) subjects in the placebo group and in 3/6 (50%) subjects in the levothyroxine group. From these, 4/5 and 3/3 were successfully transplanted, respectively (Table 2).
Median variation in the dose of vasopressor between T0 and T6 was 0 mcg/min (IQR: -5.3-12.5) and -2 mcg/min (IQR: -5.9-1.9) in the placebo group and the levothyroxine group respectively (p=0.5).

Table 2. Organs Retrieved and Transplanted by Thyroid or Placebo Drug Used During Donor Management

Organs	Placebo (N = 8)[a]	Levothyroxine (N = 6)
Hearts, n (%)		
Retrieved	5 (62.5)	3 (50)
Transplanted	4 (80)	3 (100)
Lungs, n (%)		
Retrieved	7 (87.5)	3 (50)
Transplanted	7 (100)	3 (100)
Liver, n (%)		
Retrieved	7 (87.5)	5 (83.3)
Transplanted	7 (100)	4 (80)
Kidneys, n (%)		
Retrieved	16 (100)	12 (100)
Transplanted	15 (93.4)	10 (83.3)
Pancreas, n (%)		
Retrieved	4 (50)	1 (16.7)
Transplanted	4 (100)	1 (100)

[a]The donation process was not completed in 1 patient.

Safety

One subject in the placebo group developed new onset atrial fibrillation while on the study drug. No atrial fibrillation episodes were recorded in the levothyroxine group.
Mean heart rate before and after 6 hours of the study drug infusion did not change significantly in both groups. Organ procurement and transplant results are presented in Table 2. Six months after the transplant, liver recipients from donors of both groups were alive and free from graft rejection.

Discussion

This pilot study highlights the challenges inherent to the design of a single centre RCT in an organ donor population. First, although the expected number of donors admitted to our centre and the expected proportion of donors with LV dysfunction were correctly anticipated, the study was stopped prematurely because of slow recruitment. The first obstacle to recruitment was the initial need to obtain consent in the donor population. Confusion exists around the need for consent when a clinical study implies the administration of an intervention to organ donors with a potential impact on recipients.[36] In Canada, no legislation encompasses this specific situation. In the US, neurologically deceased donors are not regulated by the law that aims at protecting *Human being* involved in research.[24.25] However, research in donors need to take into account the potential risk for deteriorating organs meant for transplantation, hence precluding to respect donors and their families' wish to give.[25] In our study, the intervention was not considered an additional threat to organ donation since both the administration of levothyroxine and the non-administration of levothyroxine are acceptable.[16-18] Also, the only situation where the transplant recipient's consent is clearly required is in the advent of data collection that extends beyond recipient's routine evaluation, which was not the case here.[37] The decision to waiver consent was obtained following a meeting between the Research and Ethics board and the investigators, at our centre. In Canada, ICU physicians perceive that they prescribe thyroid hormones to 30 to 40% of donors and their decision to prescribe is largely influenced by ODOs and transplant teams.[28] However, a recent survey of ODOs in the US observed that, despite a

possible neutral effect, thyroid hormones are used for all potential heart donors in more than 70% of ODOs.[18,38] Designing a multi-centre clinical trial of levothyroxine in organ donors should therefore include a thorough evaluation of the necessity to consent recipients of organs from donors recruited in the trial. The need for consenting recipients from donors included in a research trial depends on the possible risks of the intervention on the transplanted organs, and on the impact of the recipients consent on his possibility of transplant.[24] The potential risk of not receiving the usual thyroid hormone intervention on any recipients' outcomes and the need for recipients' consent should be further explored.

The second recruitment obstacle encountered in this study was the exclusion of eligible subjects upon physician's decision, with the result open label levothyroxine use. In Canada, around one third of ICU physicians with experience in organ donor management, report prescribing thyroid hormones to all donors, regardless of their heart function.[28] Although the administration of thyroid hormone, and principally of levothyroxine, to donors has not yet been clearly proven beneficial, large observational cohorts demonstrating impressive increase in organ procurement have probably influenced practices.[11-13] The needs for education on the level of evidence supporting this intervention and the clinical equipoise are evident and probably a condition for a successful representation of the target population in a future trial.

No protocol violation were observed in this study and the time from the first echocardiography to the administration of the study drug was less than one hour, despite limited resources and a 24-hours per day and 7 days per week coverage.

In our preliminary analysis, a possibly higher proportion of donors improved their LVEF in the levothyroxine group than in the placebo group. The hourly vasopressor dose also appeared to have been reduced to a greater extent at 6 hours in the levothyroxine group. According to our preliminary results, the administration of levothyroxine also appeared safe. However, the small sample size and the implicit insufficient power precludes from drawing any conclusion regarding a potential benefit of levothyroxine for this indication.

Conclusion

This pilot trial suggests that a definitive RCT comparing the efficacy of levothyroxine to placebo in potential organ donors would benefit from a multicenter recruitment. Restraining the study to potential donors with low LVEF, although mechanistically pertinent, limits the feasibility of the study. Education on the level of evidence surrounding the pharmacological management of organ donors should help to reduce the exclusion of eligible subjects based on individual convictions. The need for consent in a neurologically deceased population should also be clarified. Finally, the possibility to link donors' to recipients' outcomes, in the respect of individual confidentiality, needs to be addressed before conducting future clinical research on organ donation.

References

1. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2017 Annual Data Report: Heart. *Am J Transplant.* 2019;19 Suppl 2:323-403.
2. Khush KK, Menza R, Nguyen J, Zaroff JG, Goldstein BA. Donor predictors of allograft use and recipient outcomes after heart transplantation. *Circulation Heart failure.* 2013;6(2):300-309.
3. Goldstein BA, Thomas L, Zaroff JG, Nguyen J, Menza R, Khush KK. Assessment of Heart Transplant Waitlist Time and Pre- and Post-transplant Failure: A Mixed Methods Approach. *Epidemiology.* 2016;27(4):469-476.
4. Kilic A, Emani S, Sai-Sudhakar CB, Higgins RS, Whitson BA. Donor selection in heart transplantation. *J Thorac Dis.* 2014;6(8):1097-1104.
5. Dujardin KS, McCully RB, Wijdicks EF, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2001;20(3):350-357.
6. Novitzky D, Wicomb WN, Cooper DK, Rose AG, Reichart B. Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. *The Annals of thoracic surgery.* 1986;41(5):520-524.
7. Mertes PM, Carteaux JP, Jaboin Y, et al. Estimation of myocardial interstitial norepinephrine release after brain death using cardiac microdialysis. *Transplantation.* 1994;57(3):371-377.
8. Perez Lopez S, Otero Hernandez J, Vazquez Moreno N, Escudero Augusto D, Alvarez Menendez F, Astudillo Gonzalez A. Brain death effects on catecholamine levels and subsequent cardiac damage assessed in organ donors. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2009;28(8):815-820.
9. Novitzky D, Cooper DK. Thyroid hormone and the stunned myocardium. *Journal of Endocrinology.* 2014;223(1):R1-8.
10. Novitzky D, Mi Z, Sun Q, Collins JF, Cooper DK. Thyroid hormone therapy in the management of 63,593 brain-dead organ donors: a retrospective analysis. *Transplantation.* 2014;98(10):1119-1127.
11. Rosendale JD, Kauffman HM, McBride MA, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation.* 2003;75(8):1336-1341.
12. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 1995;14(4):734-742.
13. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation.* 2003;75(4):482-487.
14. Novitzky D, Cooper DK, Wicomb WN. Endocrine changes and metabolic responses. *Transplantation proceedings.* 1988;20(5 Suppl 7):33-38.

15. Ririe DG, Butterworth JFt, Royster RL, MacGregor DA, Zaloga GP. Triiodothyronine increases contractility independent of beta-adrenergic receptors or stimulation of cyclic-3',5'-adenosine monophosphate. *Anesthesiology.* 1995;82(4):1004-1012.
16. 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(6):S13-32.
17. 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. *Critical Care Medicine.* 2015;43(6):1291-1325.
18. 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(5):1635-1644.
19. Shapiro L.E. B, T. The Efficacy of Thyroid Hormone Therapy in Brain-Dead Heart Donors: A Review of Thyoid Function in Health and Disease. In: Novitzky D, Cooper, D.K.C, ed. *The Brain-Dead Organ Donor: Pathophysiology and Management.* Springer ed. New York, United States2013:91-107.
20. Novitzky D, Mi Z, Videla LA, Collins JF, Cooper DK. Thyroid hormone therapy and procurement of livers from brain-dead donors. *Endocrine Research.* 20,146;41(3):270-273.
21. Castilho RF, Kowaltowski AJ, Vercesi AE. 3,5,3'-triiodothyronine induces mitochondrial permeability transition mediated by reactive oxygen species and membrane protein thiol oxidation. *Arch Biochem Biophys.* 1998;354(1):151-157.
22. Ellett JD, Evans ZP, Fiorini JH, et al. The use of the Papworth cocktail is detrimental to steatotic livers after ischemia-reperfusion injury. *Transplantation.* 2008;86(2):286-292.
23. Economidou F, Douka E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. *Hormones (Athens).* 2011;10(2):117-124.
24. National Academies of Sciences E, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Issues in Organ Donor Intervention Research. Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation. In: Liverman CT DS, Childress JF, ed. Washington DC, USA: National Academies Press (US); 2017: https://www.ncbi.nlm.nih.gov/books/NBK470921/. Accessed 09-07-2018.
25. Abt PL, Marsh CL, Dunn TB, et al. Challenges to research and innovation to optimize deceased donor organ quality and quantity. *Am J Transplant.* 2013;13(6):1400-1404.
26. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC medical research methodology.* 2010;10:1.
27. Conseil de recherches en sciences humaines du Canada CdresneegdC, Instituts en santé du Canada. Enoncé de politique des trois Conseils: Ethique de la recherche avec des êtres humains. In. Ottawa, Canada2014:1-242.
28. Frenette AJ, Charbonney, E., D'Aragon, F., Serri, K., Marsolais, P., Chassé, M., Meade, M. Williamson, D.R. . A Canadian Survey of Critical Care Physician's Hemodynamic Management of Neurologically Deceased Organ Donors. *Can J Anaesth [Manuscript resubmitted after revision].* 2019.

29. Marsolais P, Durand P, Charbonney E, et al. The First 2 Years of Activity of a Specialized Organ Procurement Center: Report of an Innovative Approach to Improve Organ Donation. *Am J Transplant.* 2017;17(6):1613-1619.
30. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC medical research methodology.* 2013;13:104.
31. Urbaniak GC, Plous, S. Research Randomizer (Version 4.0) [Computer software]. 2013; 4.0:www.randomizer.org, 2014.
32. Frenette AJ, MacLean RD, Williamson D, Marsolais P, Donnelly RF. Stability of levothyroxine injection in glass, polyvinyl chloride, and polyolefin containers. *Am J Health Syst Pharm.* 2011;68(18):1723-1728.
33. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16(3):233-270.
34. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18(12):1440-1463.
35. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *Jama.* 2016;316(5):509-518.
36. Rodrigue JR, Feng S, Johansson AC, Glazier AK, Abt PL. Deceased Donor Intervention Research: A Survey of Transplant Surgeons, Organ Procurement Professionals, and Institutional Review Board Members. *Am J Transplant.* 2016;16(1):278-286.
37. Heffernan KG, Glazier AK. Are Transplant Recipients Human Subjects When Research Is Conducted on Organ Donors? *The Hastings Center report.* 2017;47(5):10-14.
38. Cooper LB, Milano CA, Williams M, et al. Thyroid hormone use during cardiac transplant organ procurement. *Clin Transplant.* 2016;30(12):1578-1583.

Supplementary material

Supplemental Table 1. Detailed reasons for exclusion by study period*

Subjects screened before 1st amendment N=50	N (%)
Total number of subjects excluded for the period n = 42 (84.0)	
No hemodynamic instability and normal LVEF	24 (57.1)
No consent to research	12 (28.6)
Exogenous oral levothyroxine before admission	6 (14.3)
Organ donation process cancelled	4 (9.5)
Medical history of coronary heart disease	4 (9.5)
Age > 75 years	4 (9.5)
Echocardiography results unavailable	2 (4.8)
Unavailability of research team	2 (4.8)
Age <16 years	1 (2.4)
Subjects screened between 1st and 2nd amendment N = 36	N (%)
Total number of subjects excluded for the period n = 31 (86.1)	
No hemodynamic instability and normal LVEF	23 (63.9)
No consent to research	12 (33.3)
Exclusion by ICU physician	4 (11.1)
Echocardiography results unavailable	2 (5.6)
Subjects screened after 2nd amendment N=19	N (%)
Total number of subjects excluded for the period n = 17 (89.5)	
No hemodynamic instability and normal LVEF	8 (42.1)
Donation after cardiac death	4 (21.1)
No echocardiography performed or uninterpretable results	2 (10.5)
Extracorporeal membrane oxygenator	1 (5.3)
Exclusion by ICU physician	1 (5.3)
Transferred from another center with levothyroxine infusion for organ donor care	1 (5.3)

*Some subjects had more than 1 exclusion criteria

Chapter III: General Discussion

Overall study conclusions

Since the first successful organ transplant, tremendous efforts have been made by clinicians and by the OPOs community to improve the number and the quality of organs, with the hope that interventions at the donor level would translate in optimized transplant outcomes. However, research on clinical interventions to improve organ donor care is limited and relatively recent. The principal objective of this thesis was to describe the actual state of knowledge on interventions for the hemodynamic management of neurologically deceased organ donors, and to demonstrate that the efficacy of commonly used interventions is questionable. This thesis contributes to the preliminary repositioning of commonly used medication in the context of a better understanding of the pathophysiology of brain death in humans. It also emphasizes the need for rigorous RCTs in this field.

In summary, the first article of this thesis (Article 1) systematically reviewed the worldwide endorsed recommendations for the care of organ donors. It outlined the variability in the focus and in the recommendations between guidelines, and it demonstrated their poor methodological quality. The second article (Article 2) surveyed the Canadian ICU physicians self-perceived hemodynamic management of organ donors. This article showed important variability in the clinical management of deceased donors in the country, particularly regarding the treatment and diagnosis of the autonomic storm, the prescription of hormone therapy and the administration of inotropes. The survey was conducted in a population of intensivists working in high volume centres and considered familiar with the 2006 Canadian guidelines. In this survey, we have also observed that some ICU interventions (corticosteroids and thyroid hormone) are largely influenced by other team members (ODOs and surgical teams).

This work laid the groundwork for understanding the current knowledge gap between the generally recognized pathophysiology of brain death and the management of deceased donors.

In Article 3, we characterized the frequency of RV dysfunction in neurologically deceased donors, which had not been performed before. We observed RV dysfunction, either isolated or combined with LV dysfunction in 44.7% of potential heart donors. Isolated RV dysfunction was present in 22% of the included potential heart donors. A preliminary analysis also suggested that LV dysfunction is an independent predictor of RV dysfunction.

Article 4 was the first Canadian pilot randomized controlled study evaluating a pharmacological intervention in a sample of organ donors. We randomized 24 consented organ donors to a levothyroxine infusion or placebo, and performed echocardiography at baseline and 6 hours after the onset of the study drug. We identified important barriers to intervention research in organ donation and informed future research on the need to clarify the need for consent to research and on the need for education on the level of evidence surrounding the pharmacological management of organ donors.

The next sections will explore potential causes for our findings and summarize the implications of our observations. Measures to improve research in organ donation as well as future research priorities will also be identified and presented.

Why is There Variability in Organ Donor Care Interventions?

Variability in medical practices is not limited to the organ donor care field. In various settings, the gap between research, evidence-based interventions and practice appears to be common, even in the context where clinical practice guidelines are accepted and available.[270-273] Variability can occur at the physician, hospital or organizational level, and cannot always be explained by patients' factors.[270,271] On the opposite, differences in treatments are idiopathic and reflect more often clinician's or institutional subjective preferences rather than patient's objective needs.[270] Adapted from the Australian National Institute of Clinical Studies (NICS), we propose 6 levels of barriers to best practice and to variability in clinical management: guidelines themselves; professional's knowledge, awareness and motivation; professional social context and culture of the network; organisational context; research context.

The Guidelines Themselves

Guidelines are intended to guide clinical decisions in order to improve quality of care and patients outcomes.[274] However, for clinicians to use guidelines appropriately, they need to believe in their usefulness and appropriateness.[270,274] Guideline development should therefore follow a rigorous methodology that includes process planning, question generation, systematic literature search, study risk of bias assessments, summarizing the certainty of the totality of evidence for each question, and peer reviewing.[275] None of the included guidelines in our systematic review respected these steps. As a consequence, guidelines were developed by heterogeneous teams of various experience that focused on different themes. Recommendations appeared to be largely influenced by expert opinions rather than by the result of a systematic literature search and a grading of the evidence level. Neither the country nor the year of publication had an impact on the methodological quality of the guidelines.

A recent epidemiological review of guidelines on various medical topics noted that the proportion of guidelines with expert opinions in their recommendations has increased from 2010 to 2016, despite the use of systematic reviews to select the evidence.[276] The rationales for using expert opinions are many, and include the lack of evidence, the low quality of available evidence including case reports and case series, the evidence in development, and physiological inferences, bench research or clinical experience.[276] Also, expert opinions often result from the extrapolation of evidence from studies that do not answer directly the guidelines' questions (indirect evidence).[276] Randomized controlled trials assessing interventions on organ donor care are few and observational studies carry their intrinsic biases, including residual confounding and information and selection biases. Guidelines recommendations therefore rely mostly on large effect sized observational studies and animal models that have had historical impacts, and possible largely contributed to the shaping of expert opinions.[72,80,156]

Our results are consistent with other systematic reviews of international guidelines that have observed variability in clinical recommendations, heavy reliance on expert opinions, and poor methodological quality.[277-279] These reviews have also concluded that variability between guidelines is more important when the literature supporting the recommendations is of lower

quality.[278,279] Despite the evidence that compliance to guidelines can improve clinical outcomes, barriers to their implementation can limit their applicability and contribute to variability in practices.[270]

The professional's knowledge, awareness and motivation to change practice

In our survey, ICU physicians identified the 2006 Canadian guideline as a reliable source of guidance when caring for organ donors. However, based on their answers, their self-perceived practice differs from guideline's recommendations, and this probably contributes to donor management variability. This gap between self-perceived guidelines adherence and practice may not be exclusive to organ donor management, as similar observations have been described in the context of end-of-life support in the ICU. A questionnaire, sent to 118 ICU physicians in 11 ICUs, aimed at evaluating the correlation between physicians' education on end-of-life support in the ICU and their clinical decisions when treating a patient with a DNR order. This study revealed an important discordancy between self-perceived compliance to recommended management and actual management. Younger physician age, recent attendance to a class, interest in the topic, and literature knowledge were predictors of appropriate clinical compliance to DNR order recommendations.[280] Reasons for gaps between self-perceived adherence to recommendations and actual practices were also assessed in the context of blood transfusion prescription.[270] In this context, the self-perception that the clinician's own practice was already in compliance with the guidelines before their publication, and the idea that guidelines were only meant to reinforce the clinician's own prescribing habits were identified as principal reasons for the gap between self-perceived and actual practices.[270] The feeling that the guidelines were not applicable to one's own specific situations and practices was also common.[270] In summary, the knowledge of the existence of a guideline may differ from the knowledge of the guideline's specific content and from the adherence to its recommendations.[270]

Since the publication of the 2006 Canadian guideline on organ donor management, few but still important RCTs and systematic reviews on the hemodynamic management of organ donors have become available.[148,162,166,186] Physicians' actual level of knowledge on organ donor management interventions and on the evidence level supporting these interventions has not been

studied. We can only postulate that variability in self-reported practices may, at least in part, result from unequal knowledge-updating between respondents. Attitude and knowledge of healthcare professionals on other steps (ex. organ donor identification, brain death diagnosis, family approach) of organ donor care has been evaluated, and these studies seem to corroborate this hypothesis. The attitude and knowledge on organ donation and transplant processes were assessed in 179 physicians and 103 nurses in Hungary.[281] This survey not only revealed that around 40% of the participants had not participated in any educational course on organ donation in the past, but also that from these, more than half were not willing to participate in the future, thus creating inequalities in knowledge uptade.[281] Older respondents, those working in capital city centres or those with less clinical exposure to organ donor management were more negative about participation to educational activities.[281] The need for educational programs on organ donor care in Canada was assessed in a survey of healthcare professionals.[282] However, only 15.3% of the 5424 potential respondents answered the questionnaire.[282] These respondents, probably very different from non-respondents, identified clinical competency in organ donation as a very important topic.[282] Nevertheless, only 50% of participants rated a high or very high level of comfort across all competency domains. ICU physicians indicated a high or very high level of confidence in their competency when managing a potential neurologically deceased donor until transfer to organ procurement centre in 67%. When asked about their level of confidence when managing a potential brain death donor until organ procurement surgery, this number raised to 83%, but only 23.7% of them felt confident in identifying organ transplant outcomes.[282]

Self-confidence in knowledge or competency does not always translate in actual evidence-based knowledge or competency, and we believe that self-confidence influences the motivation to change usual practices and the interest in research.[283,284] Our pilot trial has identified physicians' beliefs has a potential barrier to implementation of a RCT in organ donation and we hypothesize that a in some circumstances, overconfidence has the potential to threaten the updating of outdated practices and the interest in research.[284]

Motivation and interest in the organ donation topic could also influence individual and institutional practices and result in variability in practice. We obtained an answer rate of 41% in our survey, and the answer rate was lower in some provinces (Alberta) than in others (Quebec,

Ontario). Survey respondents are different from non-respondents, often in their motivation and interest, but also sometimes in their competencies and knowledge.[285,286] Variability in individual practices in the country is thus expected to be even more important than what we observed. The province of investigators' origin (Quebec and Ontario) of the survey could potentially have positively influenced the survey response rate in these two provinces. However, medical ICU directors were contacted directly to ensure participation and the survey was pre-tested by representatives of both western and eastern provinces. Variability in response rate between provinces could extend beyond the investigators leadership and suggest variable institutional cultures translating in individual's motivation and variability in self-reported practices.

The professional social context and the culture of the network

Successful organ donation necessitates efforts and collaborative actions from physicians, allied healthcare professionals, organ procurement organizations, and transplant surgeons.[4] Improving the quality and availability of organs in often very unstable patients, and in a timely fashion that respects operating room availability delays can become very challenging.[4,287] The amount of energy, time and effort that a team will invest taking care of a donor is probably proportional to the network's level of commitment to donation.[222,287] We therefore postulate that local mores, educational activities and peer emulation are influenced by the organisation's facilitators, the team's culture and individual beliefs on brain death and organ donation itself.

Literature on the management of organ donors mostly relies on observational trials. In these, although the effect of the studied interventions, including hormone therapy, corticosteroids or hemodynamic measurements, was questionable, a tendency towards an improvement in organ availability was consistently demonstrated after the involvement of a dedicated organ donation team.[156,157,288] For example, hormone therapy has since then been largely incorporated in routine donor management, despite possibly neutral effect on organ donation outcomes.[162,166,186] However, prescription of thyroid hormones and steroids by Canadian intensive care physicians appeared to be largely influenced by other team members for around half of the respondents, depicting potential variable peer pressure. Legal concerns, peer pressure and societal opinion

have been identified as barriers to follow one's beliefs regarding what would be the best treatment for the patient.[280] Hence, stronger peer pressure could influence practice in specific centres or some individuals be more sensitive to peer pressure, both creating variability in donor management.

Finally, individual physicians' cultural and religious influences impact on pharmacological management of organ donors has not been directly studied. We can only postulate that physicians that have some personal barriers to organ donation itself could limit their involvement in organ donor care, and hence have different practice than their colleagues. However, we might extrapolate that religion and culture may be a barrier to self-education, personal interest and professional involvement on clinical management of organ donors from surveys on organ and tissue donation as a broad topic.[289]

The organisational context

In Canada, no less than 9 ODOs are involved in organ donor care. Educational programs provided by these ODOs vary across the country in their content, their pedagogical approaches, their self-assessment and their financial resources.[282] Similarly to ODOs, university programs and classes as well as residency training educational activities on organ donation vary across the country.[282] The impact of educational programs on organ donation has mainly been studied with undergraduate medical students or nurses. Using a pretest-post-test design, these studies have demonstrated that a formal training on organ donation influences attitudes towards donation, including the participant's own will to give his organs, communication with families, and knowledge about donor eligibility and brain death criteria.[290,291] Since education has a direct impact on attitudes, competencies and knowledge on organ donation, variability in educational programs offered by academic institutions and organ donation organizations carries a high potential to result in bedside clinical variability.[290,292]

In Canada, ODOs are involved in organ donor logistic management, educational programs and variably, in direct donor clinical care.[217,218] The influence of an organization such as ODOs on individual physicians' practices depend on both intrinsic factors such as motivation and personal responsibility, and extrinsic factors such as time, structure, leadership, communication and reward system.[293] In our survey, ODOs were identified as a highly reliable source of guidance

for physicians in their management of organ donors. We can therefore assume that ODOs are directly involved in organ donor clinical management, directly or indirectly via standardized protocols. However, the use of a local protocol and consultation of ICU pharmacists were reported by respondents more erratically. Our survey was not meant to investigate the organ donation ICU structure in the country. Based on these preliminary data, we however postulate that differences exist in the organisational structure of organ donation management and in the precise role that ODOs play in the ICUs across the country, thus contributing to clinical variability.

The research context

Factors that have been mostly associated with an evidence-based practice include the clinicians' academic qualification, their own involvement in research and the practitioners' perceptions, attitude and beliefs about research.[294] In our pilot study, we have suggested that the intensive care physicians attitudes and beliefs about individual pharmacological interventions are potential barriers to research in organ donation. Fields in which the quality and quantity of literature are generally poor may be more prone to a low level of evidence-based practice uptake.[295] Since the majority of pharmacological interventions used routinely in organ donor care are based on low methodological quality studies, we can both expect variability in practices due to subjective interpretation of the evidence and increase in the importance attributed to opinion.[296] However, the context of research in organ donation is particular for the importance attributed to historical literature in the field. Therefore, organ donation management may be particularly at risk for reticence to modify practices based on new literature. Medical beliefs have been identified as an important factor affecting the use of evidence-based medicine in other fields. In these researches, the influence of peers, particularly of senior physicians, also appeared to modify individual decisions and attitude towards evidence based-medicine.[295,297]

Is the theory still holding?

As we have previously outlined, the actual management of organ donors is impregnated by animal models in which a predictable autonomic storm, a fall in anterior and posterior pituitary gland hormones and left ventricular damages were observed.[72,74-77,80,298] The evolution of brain

ischemia leading to brain death in a clinical context is undoubtedly different than in animal models, where a severe and abrupt rise in ICP or a complete absence of flow produces a predictable death in 20 minutes.[72] In neurologically deceased humans, causal brain injuries are variable, autonomic storms probably present itself heterogeneously, anterior pituitary gland hormones remain within normal ranges and left ventricular dysfunction is present in a little less than half of donors.[32,86,124] Bearing that in mind, we suggest that the actual pharmacotherapy based on these physiological concepts be re-questioned. The results of our pilot RCT on the use of levothyroxine in organ donors suggest that a definitive multicenter trial is warranted to enlighten the actual understanding of donor management and to evaluate the efficacy and safety of thyroid hormones. We believe that if proven non-efficacious, older treatments should be abandoned and research should turn itself to the discovery of novel therapies that can fulfill pertinent clinical outcomes.

Routine pharmacological interventions for the hemodynamic management of donors

Pharmacological interventions to improve organ donor care have not substantially changed since the first attempts at increasing donor conversion in 1995.[59,156] Hemodynamic pharmacological treatments are meant to support the autonomic storm-induced left heart dysfunction, to prevent end-organ damage, and to replete hormone stocks following brain death.[59,73,157] In patients featuring hypertension and tachycardia, corresponding to an autonomic storm, the proposed pathophysiology of a catecholamine surge supports the rationale for the use of beta blockers. Surprisingly, although the complete theory of brain death induced end-organ damage relies on the existence of the storm, no clear diagnosis exists and none of the proposed interventions for its treatment or prevention has been studied. Treatment of the autonomic storm sometimes includes the prescription of short-acting beta blockers, but only one small retrospective study supports their use.[58] Similarly, none of the pharmacological agents used for the management of hemodynamic instability has been rigorously studied. For example, in the occurrence of hypotension, vasopressin is recommended as a first-line therapy by several guidelines and is largely used in the country, but no study exists evaluating its efficacy.[152,299,300] Although in this case, the rationale strength for its use appears sufficient, the need for a proper scientific

assessment of vasopressin is still present.[211-213] Thyroid hormones and corticosteroids are almost universally prescribed despite systematic reviews suggesting the futility of these treatments.[162,186] However, each of these systematic reviews emphasizes on the low methodological quality of the evidence and on the need for definitive trials. Although the proposed pathophysiological mechanism of anterior pituitary hormone depletion may not be proven accurate, levothyroxine could act directly on cardiomyocytes through specific receptors and result in an inotropic action, independently of endogenous thyroid hormone levels.[183-185] However, in the case of thyroid hormones, the theory needs to be explored again from the beginning. Corticosteroids certainly carry anti-inflammatory effects, but the pathophysiology of the cytokine storm following brain death has been detailed only recently.[109,110] Although this reaction still needs to be characterized more precisely and its predictors be identified, the historical rationale for the use of corticosteroids still make theoretical sense and their efficacy warrants further assessment. Based on this anti-inflammatory mechanism, corticosteroids have been mostly studied and used at high dose.[162] However, our survey respondents also identified the use of low-dose corticosteroids for the hemodynamic management of donors, a practice that we believe mostly extrapolated from general ICU trials, although explored in a non-randomized study.[171,301] This new modality of treatment in organ donors also needs to be specifically assessed, as well as the underlying mechanism of relative adrenal insufficiency in the context of neurological death.

Other routine pharmacological agents for the management of hemodynamic instability of organ donors include adrenergic vasopressors, inotropes, diuretics, and insulin. None of these routinely administered agents has been formally studied. The strength of theoretical rationale for their use or contraindication is variable, but even in the context of a plausible benefit or harm, these interventions should be properly evaluated scientifically.

Right ventricular dysfunction in brain dead organ donors

The results of our observational study suggest that right heart dysfunction may be at least as frequent as left heart dysfunction after brain death and that it warrants further investigation. New interventions targeting RV dysfunction in featuring donors or preventing RV dysfunction in

donors at risk could lead to improvement in organs and recipients' outcomes. The pathophysiology of RV dysfunction may share some common mechanisms and consequences with left ventricular dysfunction. We have indeed shown that LV dysfunction is associated with RV dysfunction. However, in our study, 22% of potential heart donors featured isolated RV dysfunction, also suggesting specific causes and pathophysiological features unique to the right heart after brain death.

Right ventricular dysfunction in donors may directly impact recipients' outcomes. Up to 50% of heart recipients feature RV dysfunction after transplant, and this results in increased premature mortality.[302] However, the relationship between RV dysfunction in donors and recipients outcome has not been studied yet. As a surrogate, animal models suggest that neurological death is not only responsible for left heart dysfunction, but also for right heart dysfunction, both correlating with recipients worse outcome.[136] It was postulated that an increase in pulmonary pre-capillary vascular resistance caused by a surge in catecholamines and inflammation markers could explain brain death induced right heart dysfunction.[137,303,304] In a porcine model of RV dysfunction after brain death, increased levels of IL-6, IL-10, IL-1β, TNF-α and of adhesion molecules were observed, and partly prevented by the administration of methylprednisolone.[137] Right ventricular apoptosis was also confirmed.[137] However, if this may be true, isolated right heart dysfunction is not explained entirely. Following neurological death, donors can present with various pulmonary pathologies including pneumonia, ARDS, atelectasis or neurogenic pulmonary edema (also called brain death induced lung injury).[305,306] Consequently and common to all these pathological entities, pulmonary vasoconstriction could increase right ventricular pressures, leading to right heart failure. However, in the context of neurological death, the pathophysiology linking heart dysfunction, lung injury and neurological death is still debated and the mechanisms leading to brain-death induced lung injury are not yet completely elucidated. Similarly to what has been described in brain death induced heart dysfunction, it has been proposed that the autonomic storm, resulting from a surge of catecholamines, directly affects the pulmonary vascular bed causing vasoconstriction or endothelial disruption with ensuing edema.[307,308] To verify this hypothesis pulmonary and systemic pressures were measured in another porcine model of brain death.[306] This study revealed increased pulmonary venous resistance that persisted until late phase after brain death

and that correlated with oxygenation impairment and increase in inflammation markers, despite normal cardiac output and pulmonary artery wedge pressure.[306] The authors of the model propose that their findings could be explained by pulmonary venous adrenergic hypersensitivity, a phenomenon similarly observed in severe mountain sickness.[306]

Pharmacological strategies aiming at reducing pulmonary pre-capillary pressures in potential donors with neurogenic pulmonary edema have not directly been evaluated. Case reports of nitric oxide administration in these patients have only reported improved oxygenation parameters.[309,310] Other vasodilating pharmacological strategies such as prostacyclin or phosphodiesterase inhibitors have not yet been proposed.

If organ donation is improving anyway, is research still needed?

The number of deceased organ donors in Canada has increased over the last five years, from 486 donors in 2013 to 601 donors in 2017. [311] Since 2008, Canada has sustainably improved his organ donation successes, with a 51% increase in donation. With an average of three organs transplanted per donor, the country is one of the most efficient in the world, along with Australia, Spain, United States and United Kingdom.[311] Despite this improvement and similarly to the rest of the world, Canada still experiences organ shortage. Over 4000 patients are presently waiting for an organ, and 242 of them will not survive the wait.[311] In this context, a national survey conducted by the Canadian National Transplant Research Program (CNTRP) enquired patients, families, caregivers and researchers about research priorities in organ donation. Increasing the number of available organs for transplant was still identified as the number one priority.[312] A systematic approach to the management of hemodynamic instability in neurologically deceased donors could translate into the improvement of organs quality and numbers.[3,4,313] However, the improvement in performance has mostly been attributed to the implementation of donation after circulatory death, creating false comfort towards the success of organ donation after brain death.[314] Until today, only few interventions have been properly evaluated in the context of organ donation after brain death.[243,315] Although some suggest that guidelines adherence and bedside checklists for interventions are wishful, the paucity and the poor methodological quality of the studies evaluating the routinely used interventions are limiting the use of evidence-based

and goal directed therapies.[4,316] Outcomes are influenced by every step of the donation path, from potential donor identification, to brain death diagnosis, organ donor hemodynamic management and organ transplant surgeries.[4] We therefore believe that research should aim at evaluating interventions susceptible of improving transplant outcomes at each of these limiting processes.

How can we improve research in organ donor care?

The necessity of conducting high-quality research in organ donation is unequivocal.[219,312] Improving the quality and quantity of organ donors' organs is one way of achieving a reduction in the gap between organ demand and offer. Because of its unique circumstances involving grieving families and precarious patients on the waiting list, clinical research in organ donation bears its load of significant challenges. This thesis enabled to identify some barriers to research including the uncertainties around the need for consent to research, the self-confidence in the actual pharmacological treatment and the relative rarity of donors, especially of potential heart donors. We here propose what we believe to be milestones on the road to multicenter RCTs in the organ donation field.

Knowledge translation

The success of a RCT relies in part on the buy-in from clinicians working in the studied field.[317] Therefore, relationships between investigators and clinicians should be developed before a study begins in order to engage clinicians and meet their needs.[317] To maximize participation to research, reduce selection bias and optimize efficient communication to research patients, clinicians have to be convinced that improved outcomes are needed, that research does not carry unbounded risks and that clinical equipoise concerning the studied intervention exists. These objectives can be met through knowledge translation educational activities targeting the auditory of clinicians. Key steps to efficient knowledge translation include up-to-date systematic reviews of research findings and the identification of a credible messenger for the transfer of research results to the target auditory.[318] Then successive stages of transfer include the four following steps: *exposure, adoption, implementation, and practice*.[319] This framework was developed for

knowledge transfer in the substance abuse field.[319] We here propose an adaptation and an illustration of this transfer framework to our study of levothyroxine in potential hear donors.

First, at the *exposure* (training) stage, we offered lectures on the literature background, the pharmacological mechanism rationale and the knowledge gaps concerning the studied intervention.[319] The systematic review of the evidence on the efficacy of levothyroxine was presented along with the evaluation of the quality of the evidence.[186] Pharmacological rationale for the use of levothyroxine in organ donors was detailed and the investigators emphasized on the knowledge gap concerning its efficacy and safety.[186,198,199] Clinicians were offered to comment on the proposed study and ask questions during a presentation session. Other proposed strategies to engage clinicians in research design at the *exposure* stage include offering documents for self-study, and planning workshops and discussions about clinical scenarios.[319] Also, at this step, investigators should make efforts to simplify the protocol and reduce clinicians' burden.[317] The next knowledge transfer stage, *adoption*, represents the intention to take action into change.[319] Although a formal decision to take part into the research project is made by the organization, individual clinicians should also engage in the idea of change.[319] Project champions at the institution level can help investigators build bridges with clinicians and facilitate individual commitment.[317] In our study context, clinicians decided as a group to take part in the study, and the study protocol was presented to the institution board and ethics committee for final approval. However, adoption at the individual level means that individual clinicians needed to recognize that clinical equipoise on the efficacy of levothyroxine existed and that research was needed to properly assess the intervention. At this stage, personal beliefs on the efficacy of a specific intervention need to be put aside and clinicians should commit to the unbiased screening of potential donors and to the respect of the study protocol.[319] We believe that individual *adoption* of knowledge transfer probably warrants further assessment and will be discussed in the following section on the readiness for change. The third stage of knowledge transfer is the *implementation* phase defined as a period where clinicians have the opportunity of trying the intervention, and of assessing the feasibility of the research project.[319] In a research context, we believe that this stage directly corresponds to the pilot trial phase of the research program. Our pilot trial permitted to evaluate the feasibility of a definitive trial, allowed clinicians to test the research protocol in a real clinical context and highlighted potential barriers

to success. Finally, the fourth stage of knowledge transfer process is the *practice* stage and it corresponds to the incorporation of a novel action into practice along with continuous reassessment and regular iteration as needed.[319] Informed by the pilot study results, investigators design the definitive trial with the final objective of informing the future practice and the study results trigger a new knowledge transfer process.

Prior to the delivery of knowledge translation, we suggest that the readiness for change be studied in the context of organ donation research and assessed at the individual and institutional levels. [320] Readiness for change, described at the organizational level, is defined as "a comprehensive attitude influenced simultaneously by the nature of the change, the change process, the organization's context and the attributes of individuals."[320] Validated instruments are needed to measure this latent construct. However, the available instruments have limited reliability and validity, and few are adapted to the healthcare or the research contexts.[320] Readiness for change has not been studied in the context of organ donation and validation of the existing instruments should be performed prior to their utilization. Amid the available instruments, the EBP (evidence-based practices) Beliefs Scale is a 16-item instrument that permits to evaluate individual's beliefs about the value of evidence-based practices and the ability to implement it.[321] This scale was validated in a sample of 394 nurses and incorporates constructs of self-reassessment, self-liberation and environmental re-evaluation.[321]

An instrument was developed to measure the readiness for change in the context of technology transfer of evidence-based practices from research to practice, in the alcohol addiction field. The original version of the Organizational Readiness for Change (ORC) instrument included 130 items divided into 6 domains (motivation for change, resources, staff attributes, organizational climate, training exposure and utilization) and was primarily meant to assess organizational readiness for change.[322] A simplified version of the instrument (MORC), adapted to the emergency and primary care settings, also exists.[323] This version containing 45 items grouped into 8 domains (need for external guidance, pressure to change, organizational readiness to change, individual readiness to change, workgroup functioning, work environment, autonomy support, and clinical field focus) was validated in 184 physicians working with patients suffering from alcohol abuse health problems and it demonstrates sufficient reliability.[323] However, the

answer rate was of 45.6% and as discussed previously, respondents generally have different beliefs, demographic profiles, and practices than non-respondents.[323] The readiness for change latent variable is probably very sensitive to the voluntariness characteristic of respondents. Also, the validation process of the instrument was limited to preliminary analysis. This instrument would need to be validated in the organ donation field before it can be applied and utilized for the measurement of readiness for change, but it provides interesting ground for the development of a framework .[323]

Consent model

In our pilot trial, we successfully used a waiver of consent to research in neurologically deceased donors. This was possible for two principal reasons. First, the Institutional Review Board and Research Committee accepted the idea that brain-dead organ donors cannot be considered as human research subjects and therefore, released the need to consenting donors' families. Second, levothyroxine was already part of routine care, but as demonstrated by our survey results, clinical equipoise existed concerning its use. Therefore, neither the placebo nor levothyroxine was expected to carry more risk on donors or recipients' outcomes than the standard of care. Research on interventions in the context of organ donation is especially challenging since the intervention has the potential to influence not only the donor, but also every recipient of the organs. For this reason, every study has to be examined thoroughly and consent models may vary depending on the studied intervention. We believe that the success of future interventional research in the country first relies on the capacity for national stakeholders in organ donation to define clear rules for consent to research in the field. We also propose a centralized research system in the country along with a single Institutional Review Board at the national level specific to organ donation research.[324]Although the development of a consent model to research in organ donation is beyond the scope of this thesis, we propose thoughts to nurture future discussions, based on our research experience.

Donors

For obvious reasons, studied interventions cannot induce any harm to the deceased donor. However, research interventions carry the risk of altering the quality of the organs thus

impairing the donor's and its family's wish to give. Therefore, we believe that donors' families should be informed of research interventions that could impact their possibility to give. Investigators may also be interested in collecting data pertaining to the donors. The need for consent for the utilization of anonymized donor's data is unclear. In our experience, a waiver of consent was allowed to use descriptive data and families were informed of the research project. We propose the implementation of a national research registry that would help investigators to access important donors data and to inform families of research projects on organ donation.[40]

Recipients

Consenting recipients of organs from a donor recruited in interventional research is far more complex and it involves several key institutional players. For example, in 2017, five organs recovered in Canada were sent to the United States for transplant. Also, 313 organs were transplanted to a recipient living in another province than the donor.[311] When an intervention is applied to a donor, both the recipients from the target organs and from the non-target organs may be impacted. This reality may represent a major barrier to research in organ donation and carry significant risk for patients on the waiting list. Transplant candidates need to be able to provide research informed consent rapidly since the viability of organs could soon be compromised. Also, transplant candidates that decline organs exposed to research intervention should be offered alternatives, but given the rarity of donors, organs unexposed to research interventions may not be available.

The clinical consent to receive an organ from a donor included in research should involve a multi-step process. The National Academies of Sciences, Engineering, and Medicine proposes a 2-step process of disclosing information to potential recipients. First, they should be informed of the possibility of being offered an organ exposed to research interventions as soon as they are taken upon the transplant waiting list.[325] Information should include the levels of risks associated with these organs and the risk incurred when declining a research organ.[325] The recipient should be offered the possibility to decline all research organs at this stage.[325] Second, candidates that have not *a priori* declined research organs should be informed upon the availability of an organ, on research-specific information.[325] At this point, the recipient gives

his consent to receiving an organ from a donor included in a study or declines the organ and remains on the waiting list. [237] However, investigators need to realize that the decision to participate in research may be influenced by the anticipated time on the waiting list upon the refusal to receive a research organ, and alternatives should be presented clearly to the potential recipient.[237]

Strengths of the studies presented in this thesis

Research protocol

This thesis contributed to the mapping of the actual practices for the hemodynamic management of organ donors and to the understanding of the pathophysiology of brain death in humans. It also allowed to guide the design of future interventional RCTs in the field and to identify barriers to their success. The research presented in this thesis was the first to describe right ventricular failure in potential heart donors and included the first pilot RCT in a sample of organ donors in Quebec. The interest of this thesis also resides in the inclusion of four different methodological designs creating a longitudinal effect. We drew a portrait of worldwide recommendations for the management of neurologically deceased donors, assessed Canadian intensive care physicians' perceptions of their own practice, described right heart dysfunction in potential heart donors and piloted a RCT to evaluate one of the historical pharmacological therapies to used prevent heart function impairment.

Our systematic review was conducted with rigorous methodology by a group of Canadian clinicians, methodologists and researchers on organ donor care. The review covers the recommendations of 26 countries and draws the portrait of the actual interventions endorsed by governments, organ donor organizations or scientific medical societies in the word. We evaluated the methodological quality of the included guidelines with the validated AGREE-II instrument and measured the inter-rater reliability of the instrument. Our review informed the newly submitted for publication Canadian guideline on the management of neurologically deceased donors. Our systematic review was presented at the methodological meeting for the guideline development and permitted to ensure a rigorous methodological approach.

Intensive care physicians self-perceived practices were assessed using a self-administered questionnaire designed according to the recognized methodology for surveys in critical care.[326] The questionnaire and the manuscript were endorsed by the Canadian Critical Care Trials group. The list of potential respondents was put together manually by contacting ICU medical directors in every centre identified by provincial ODOs. All attending physicians were identified by the ICU medical director and valid email addresses were provided. We thus ensured to include every potential respondent of the target population in the survey distribution and limit the coverage bias.

Our third article describes for the first time the epidemiology of right heart dysfunction in a sample of potential heart donors. We included 123 potential heart donors in the study and we were able to compare donors with or without RV dysfunction. Since potential heart donors are rare, this constitutes a significant sample of donors, representative of the overall population of potential heart donors. We were able to conduct preliminary analysis of variables potentially associated with RV dysfunction and, despite limited data, were able to propose working tracks for future research.

Finally, our pilot RCT was conducted according the CONSORT methodology.[263,327] We were able to randomize donors to levothyroxine or a comparable placebo in one centre in Montréal. Subjects were enrolled within time boundaries and we did not face any protocol violation. This project was innovative by its use of a waiver of consent and permitted to identify barriers to research in the field.

Limits

Article 1 Publication bias

Our systematic review aimed at selecting every clinical practice guideline on the management of neurologically deceased donors in the world. To achieve this goal, we designed a systematic search strategy that we applied to ten databases. We also applied a search strategy in nine

languages to grey literature motor searches and directly contacted by email organ donation organizations in every country listed on the International Registry on Organ Donation and Transplant (IRODaT) website.[1] The majority of guidelines included in the review were not published. This suggests that despite all efforts, we cannot exclude the existence of other guidelines than the ones selected in our review. Practices of some countries might not be represented in our work, especially in underrepresented geographical area such as Asia or Africa. However, we were able to describe the recommendations of 26 countries in the world, this being the largest review conducted so far in this field.

Article 2 Survey biases

Non-response

In our survey, we identified 448 potential respondents that corresponded to our target population of intensive care physicians working in an organ donation high volume centre in Canada. From them, 184 (41.1%) participated to the questionnaire by answering at least one survey question. Non-respondents usually differ from respondents in their interest for the survey topic, their working environment or their practice.[285,286,328] Non-response will not affect the validity of the survey results, but will reduce its external validity.[285] In general, non-response bias can also affect the estimates precision, but since our survey used the whole target population, this does not apply.[286] In our situation, our survey describes the self-perceived practice of intensive care physicians working in a high-volume centre, mostly in the eastern provinces of Canada and who probably have a marked interest for research and/or organ donation. Despite the difficulty to extrapolate our results to all our target population, our survey met his objective of describing variability of practices in the country.

Partial respondents

A total of 165 participants completed the questionnaire (36.8%), leaving 19 partial respondents. In surveys, missing items (complete absence of response or partial responses) are rarely missing at random.[286] Survey partial respondents (defined as respondents who stopped answering the questionnaire after a certain item) are known for being different from respondents.[285] All the 19 partial respondents of our survey stopped answering the questionnaire after the fourth item. This

phenomenon is called *panel mortality,* and it is defined as a situation where potential participants who accepted to participate in the survey abandon at the beginning of the questionnaire.[286] This kind of missing data is described as non-missing at random missing data since non-response is usually related to the survey topic.[286] We can postulate the hypothesis that partial respondents had less interest in organ donation (or in research) than complete respondents, but we cannot exclude that the panel mortality is caused by a time constraint (missing at random). Partial respondents do not compromise the internal validity of the questionnaire but reduce its external validity.[286] In order to reduce the risk of non-response bias or of missing items in the questionnaire we pre-tested the items according to recognized methodology and we explained the project to every potential respondent in a personalized invitation to participate.[326] Finally our response rate is similar to recent published surveys of critical care physicians.

Coverage

In surveys, the coverage bias is present when potential respondents are either non-identified, or non-reached.[328] In both situations, the participant does not have the possibility to participate to the survey, independently of his willingness to participate. We limited the coverage bias by selecting manually the list of potential respondents, specific to the project. Then we used email addresses provided by ICU medical directors to reach individual respondents. However, we cannot exclude that some potential respondents were not reached, due to a change in email addresses, error in the provided address or any technological issue. Limited coverage does not affect the internal validity of our results if questionnaires are missing at random.[328] However, in our survey, we cannot exclude that non-random factors such as geographical area affected the coverage of the questionnaire.

Article 3 Retrospective design

We retrospectively included potential heart donors and reported the frequency of right heart dysfunction in the sample. Subjects that were diagnosed with neurological death at our centre, but were transferred to another facility for organ recovery surgery before the first cardiac echography was performed were excluded from the study. Therefore, we were not able to estimate an incidence for right heart dysfunction, as per epidemiologic definition, in a cohort of potential heart donors. The frequency of right heart dysfunction in the potential heart donor

population could differ from what we have observed. However, subjects that were transferred to another facility did not significantly differ in their characteristic from the included subjects. Amid the studied variables, we have identified left heart dysfunction as the only factor independently associated with right heart dysfunction. However, right ventricular pressure, especially in presence of pulmonary vasoconstriction induced by oxygenation impairment, is strongly affected by PEEP.[329] PEEP permits alveolar recruitment and ensuing pulmonary capillary vasodilation, which improves ventilation-perfusion matching, and reduced right atrial pressure.[52,329] Its measurement necessitates invasive monitoring, which is not always indicated as part of routine donor care. Insertion of a pulmonary artery wedge pressure catheter is a highly variable practice that may depend on donor's presentation, and on physicians preferred practices. Also, the evaluation of left heart diastolic dysfunction was not possible in every included subject. Because of the quantity of missing data, we were not able to include diastolic function in the multivariate regression model that aimed at exploring variables associated with right heart dysfunction. Although every echocardiogram was reviewed by an independent cardiologist, we were not able to obtain diastolic function measurements for every included subject. Characterization of the exact pathophysiological cause of right ventricular dysfunction necessitates invasive monitoring and we were limited by the retrospective design of the study.

Article 4 Small sample and pilot issues

Our pilot trial was stopped prematurely due to slow recruitment. We therefore could not conclude definitely on the feasibility of a larger and definitive RCT comparing the efficacy of levothyroxine to placebo. We however identified barriers to interventional research in organ donors and this has since then contributed to important discussions among groups of ethicists and investigators in the country.

Future research priorities

What is the clinical presentation of brain death in potential donors?

In order to evaluate the efficacy of routine and novel therapies in organ donor care, future research should first aim at better characterizing the clinical presentation, the pathophysiology and the consequences of brain death in human donors. Up to now, some therapies, such as hormone replacement therapies or corticosteroids, have been used and others, such as inotropes, have been avoided based on animal model inferences. However, observational research in humans have demonstrated important variation between brain death presentations depending on clinical causes of death. Given the normal serum concentrations of anterior pituitary hormones in neurologically deceased humans, we can clearly raise doubts concerning the efficacy of hormone replacement therapy. In a multicenter retrospective cohort of neurologically deceased donors, we have observed that some donors feature up to five events of increased blood pressure and heart rate corresponding to an episode of autonomic storm.[86] However, no clear definition exists for the autonomic storm, and this limits the possibility of pursuing research in the field. One priority would be to explore different potential definitions of the autonomic storm based on clinical opinions and physiologic consequences. Then, if the autonomic storm proves to have direct consequences on organ function, particularly on heart function, strategies to counteract or prevent its effect should be studied. For now, only one retrospective study has evaluated the effect of pharmacological therapies on the autonomic storm, but its results are very limited. We have explored the effect of the use of beta blockers on heart dysfunction in a preliminary retrospective study. Results of this study are still underway.

What is the frequency of RV dysfunction in donors and can it be prevented?

Several studies have described the frequency of LV dysfunction in potential heart organ donors as well as its possible pathophysiology related to the autonomic storm. Our study was the first to describe RV dysfunction in this population. The result of our retrospective study should be confirmed in a multicentered prospective observational trial. This future study should aim not only at describing the incidence of RV dysfunction, but also at identifying its predictors. In order to accomplish this, subjects should be monitored to measure pulmonary pressure, potentially with invasive devices such as a pulmonary artery catheter. Then, serial echocardiography could

characterize the evolution of RV dysfunction. Following this observational step, preventive therapies should be studied. Potentially promising pharmacological therapies could include beta blockers, inhaled milrinone, epoprostenol, nitric oxide, or diuretics.

Should levothyroxine (or any of the hormone therapy component) still be used?

In order to answer this question, multicentre definitive RCTs evaluating each of the hormone therapy taken independently and compared to placebo are needed. Prior to conducting these trials, systematic reviews have been published by our group and a national prospective cohort on consented organ donors has been submitted for publication.[330] This study will permit to describe current practices in the country, to assess the effectiveness of interventions and to build a platform for future trials.[330] As discussed previously, conducting clinical research in organ donors bears its load of significant ethical questions. No Canadian consent model exists at the actual time. An initiative was recently undertaken by a Canadian group including ethicists, investigators and patients to determine the ethical conditions to consent donors and recipients to research in organ donation. Future trials will depend on the decisions and work of this team. In the meantime, the vast majority of international guidelines recommend the use of hormone therapy bundle or of its components. Although not supported by high quality evidence these treatments often constitute the standard of care.

Conclusion

Organ donation is the only salvation for many patients on the organ transplant waiting list. Although the capacity of transplanting viable organs in recipients has significantly improved over time, the gap between the offer and the demand is still growing. Different modalities to improve the quality and quantity of organs include a better identification of

potential donors, the optimization of consent to donation and the improvement in the quality of available organs.

In this thesis we have shown that the actual pathophysiological and pharmacological bases for the management of neurologically donors lie on animal models and observational trials. We have observed high variability in international guidelines recommendations and in self-perceived medical practices in Canada, and we have postulated that they are caused by the lack of rigorous methodology in the guidelines' elaboration and the paucity of high evidence literature in the field. We have demonstrated that potential heart donors often present with right heart dysfunction, which has never been reported before. We therefore raise the concern that the extrapolation of brain death pathophysiology from animal models may not represent faithfully the clinical presentation of neurologically deceased donors. We propose that the actual standard pharmacological treatment for the hemodynamic care of organ donor be reassessed in multicentre randomized controlled trials comparing individual treatments to placebo. As a first step, we conducted a pilot trial randomized controlled trial where organ donors were administered levothyroxine or placebo. This trial was stopped prematurely because of slow recruitment, but permitted to identify important barriers to clinical research in organ donation, including the lack of a clear consent model and the need for knowledge translation education programs.

Appendix

Interrater reliability of the AGREE-II instrument on the 26 included guidelines of the systematic review

Guideline	Mean Item score	Scaled domain score (%)	ICC (average of raters)
Domain 1 : Scope and purpose			
Ireland, 2019	1. 6.00	86.1	ND
	2. 6.00		
	3. 6.50		
India, 2017	1. 7.00	100	ND
	2. 7.00		
	3. 7.00		
Australia, 2016	1. 5.50	75.0	0.44
	2. 5.00		
	3 7.75		
Austria, 2016	1. 3.25	55.6	0.81
	2. 4.25		
	3. 5.50		
Germany, 2016	1. 1.75	43.1	0.77
	2. 4.25		
	3. 4.75		
Norway, 2016	1. 5.75	76.4	ND
	2. 5.50		
	3. 5.50		
Denmark, 2015	1. 5.50	69.4	0.69
	2. 5.25		
	3. 5.75		
Europe, 2015	1. 5.00	52.7	0.75
	2. 3.50		
	3. 4.00		
USA, 2015	1. 6.25	87.5	ND
	2. 6.25		
	3. 6.25		
Iran, 2014	1. 5.25	57.7	0.47
	2. 4.50		
	3. 3.00		
Switzerland, 2014	1. 7.00	97.2	ND
	2. 7.00		
	3. 6.50		
Oceania, 2013	1. 6.50	93.1	ND
	2. 6.50		
	3. 6.75		
Hungary, 2013	1. 2.25	41.7	0.77
	2. 3.25		
	3. 5.00		
Brazil, 2011	1. 6.00	65.5	0.89
	2. 5.50		
	3. 5.25		
Canada (Bourret), 2010	1. 3.00	36.1	ND
	2. 3.00		

	3. 3.50		
Chile, 2010	1. 3.75	54.2	ND
	2. 4.25		
	3. 3.25		
Canada (Trilium), 2010	1. 4.25	54.2	0.75
	2. 3.00		
	3. 5.50		
Cuba, 2009	1. 3.25	40.3	ND
	2. 3.50		
	3. 3.50		
Australasia, 2008	1. 4.25	61.1	ND
	2. 4.75		
	3. 5.00		
Canada, 2006	1. 6.00	84.7	ND
	2. 6.00		
	3. 6.25		
France, 2005	1. 5.25	55.6	0.65
	2. 3.00		
	3. 4.00		
United Kingdom, 2005	1. 5.50	73.6	0.83
	2. 4.50		
	3. 6.25		
USA, 2004	1. 2.00	18.1	ND
	2. 2.00		
	3. 2.25		
Slovenia, 2003	1. 3.50	79.2	0.75
	2. 4.25		
	3. 5.00		
USA, 1993	1. 1.50	20.8	0.06
	2. 2.75		
	3. 2.50		
Argentina, ?	1. 3.75	59.7	0.72
	2. 4.50		
	3. 5.50		
Spain, ?	1. 4.50	62.5	0.82
	2. 5.25		
	3. 5.50		
Domain 2 : Stakeholder involvment			
Ireland, 2019	4. 2.00	29.2	0.99
	5. 1.00		
	6. 5.50		
India, 2017	4. 2.75	22.2	0.89
	5. 1.00		
	6. 3.50		
Australia, 2016	4. 1.50	29.1	0.97
	5. 1.50		
	6. 5.25		
Austria, 2016	4. 1.75	48.6	0.70
	5. 1.00		
	6. 2.25		
Germany, 2016	4. 2.50	16.7	0.26
	5. 1.00		

	6. 2.50		
Norway, 2016	4. 5.00	47.2	0.99
	5. 1.00		
	6. 5.50		
Denmark, 2015	4. 2.25	27.8	0.87
	5. 1.50		
	6. 4.25		
Europe, 2015	4. 1.75	16.7	0.75
	5. 1.75		
	6. 2.75		
USA, 2015	4. 4.25	52.8	0.93
	5. 1.50		
	6. 6.00		
Iran, 2014	4. 1.75	12.5	0.89
	5. 1.75		
	6. 2.50		
Switzerland, 2014	4. 2.00	20.8	0.66
	5. 1.25		
	6. 3.50		
Oceania, 2013	4. 2.75	48.6	0.87
	5. 3.00		
	6. 6.00		
Hungary, 2013	4. 1.25	9.7	0.75
	5. 1.25		
	6. 2.25		
Brazil, 2011	4. 3.25	40.3	0.89
	5. 2.25		
	6. 4.75		
Canada (Bourret), 2010	4. 2.25	26.4	0.74
	5. 1.50		
	6. 4.25		
Chile, 2010	4. 6.25	56.9	0.86
	5. 2.50		
	6. 6.00		
Canada (Trilium), 2010	4. 1.00	16.7	0.96
	5. 1.00		
	6. 4.00		
Cuba, 2009	4. 1.00	4.2	0.89
	5. 1.00		
	6. 1.75		
Australasia, 2008	4. 4.00	37.7	0.77
	5. 2.00		
	6. 3.75		
Canada, 2006	4. 5.75	69.4	0.73
	5. 3.75		
	6. 6.00		
France, 2005	4. 2.75	18.1	0.59
	5. 1.00		
	6. 2.50		
United Kingdom, 2005	4. 5.00	59.7	0.75
	5. 2.75		
	6. 6.00		

USA, 2004	4. 4.00	41.7	0.84
	5. 1.25		
	6. 5.25		
Slovenia, 2003	4. 1.50	11.1	0.92
	5. 1.25		
	6. 2.25		
USA, 1993	4. 2.50	20.8	0.79
	5. 1.25		
	6. 3.25		
Argentina, ?	4. 1.75	2.5	0.85
	5. 1.50		
	6. 4.25		
Spain, ?	4. 1.25	22.2	0.21
	5. 1.00		
	6. 2.00		
Domain 3 : Rigour of development			
Ireland, 2019	7. 1.00	13.5	0.66
	8. 1.00		
	9. 1.75		
	10. 1.5		
	11. 3.25		
	12. 3.00		
	13. 2.00		
	14. 1.00		
India, 2017	7. 2.75	30.2	0.86
	8. 1.50		
	9. 2.50		
	10. 3.50		
	11. 4.50		
	12. 5.50		
	13. 1.50		
	14. 1.00		
Australia, 2016	7. 1.25	22.4	0.59
	8. 1.50		
	9. 2.75		
	10. 1.25		
	11. 2.75		
	12. 2.75		
	13. 2.00		
	14. 1.75		
Austria, 2016	7. 1.00	2.1	ND
	8. 1.00		
	9. 1.00		
	10. 1.00		
	11. 1.25		
	12. 1.00		
	13. 1.75		
	14. 1.00		
Germany, 2016	7. 1.00	3.6	0.49
	8. 1.00		
	9. 1.00		
	10. 1.00		

	11. 1.50		
	12. 1.50		
	13. 1.75		
	14. 1.00		
Norway, 2016	7. 1.75	30.7	0.66
	8. 2.00		
	9. 1.75		
	10. 3.50		
	11. 3.50		
	12. 2.25		
	13. 2.50		
	14. 4.25		
Denmark, 2015	7. 4.75	40.0	0.67
	8. 1.75		
	9. 2.25		
	10. 1.75		
	11. 3.25		
	12. 3.50		
	13. 3.50		
	14. 5.50		
Europe, 2015	7. 1.00	8.9	0.49
	8. 1.00		
	9. 1.00		
	10. 1.00		
	11. 2.00		
	12. 1.75		
	13. 2.00		
	14. 2.50		
USA, 2015	7. 3.75	57.3	0.94
	8. 4.00		
	9. 4.50		
	10. 5.00		
	11. 5.00		
	12. 6.25		
	13. 6.00		
	14. 1.00		
Iran, 2014	7. 1.50	7.3	0.70
	8. 1.00		
	9. 1.00		
	10. 1.25		
	11. 1.25		
	12. 1.25		
	13. 3.00		
	14. 1.25		
Switzerland, 2014	7. 1.00	13.5	0.87
	8. 1.00		
	9. 1.25		
	10. 1.75		
	11. 2.00		
	12. 1.75		
	13. 4.00		
	14. 1.00		

Oceania, 2013	7. 2.25	39.1	0.76
	8. 1.50		
	9. 3.00		
	10. 3.25		
	11. 3.25		
	12. 3.50		
	13. 4.50		
	14. 5.75		
Hungary, 2013	7. 1.00	6.3	0.56
	8. 1.25		
	9. 1.25		
	10. 1.50		
	11. 1.75		
	12. 1.50		
	13. 1.25		
	14. 1.25		
Brazil, 2011	7. 5.25	57.8	0.80
	8. 5.25		
	9. 5.00		
	10. 4.50		
	11. 5.25		
	12. 3.25		
	13. 2.25		
	14. 2.25		
Canada (Bourret), 2010	7. 1.25	6.3	ND
	8. 1.25		
	9. 1.50		
	10. 1.75		
	11. 1.25		
	12. 1.25		
	13. 1.50		
	14. 1.25		
Chile, 2010	7. 2.00	24.0	ND
	8. 2.00		
	9. 2.50		
	10. 2.00		
	11. 2.50		
	12. 2.75		
	13. 3.75		
	14. 3.25		
Canada (Trilium), 2010	7. 1.00	1.0	ND
	8. 1.00		
	9. 1.00		
	10. 1.25		
	11. 1.25		
	12. 1.00		
	13. 1.00		
	14. 1.00		
Cuba, 2009	7. 1.25	7.8	0.57
	8. 1.25		
	9. 1.25		
	10. 2.00		

	11. 2.00		
	12. 1.75		
	13. 1.00		
	14. 1.25		
Australasia, 2008	7. 1.50	27.1	0.53
	8. 1.25		
	9. 3.25		
	10. 2.50		
	11. 3.00		
	12. 3.75		
	13. 3.75		
	14. 2.00		
Canada, 2006	7. 3.00	33.3	0.50
	8. 2.00		
	9. 2.75		
	10. 4.50		
	11. 3.75		
	12. 3.25		
	13. 3.25		
	14. 1.50		
France, 2005	7. 2.00	31.8	0.86
	8. 2.25		
	9. 2.75		
	10. 5.50		
	11. 3.25		
	12. 2.75		
	13. 4.75		
	14.1.50		
United Kingdom, 2005	7. 1.50	2.69	0.38
	8. 1.50		
	9. 1.25		
	10. 2.75		
	11. 2.75		
	12. 2.00		
	13. 2.75		
	14. 4.00		
USA, 2004	7. 1.25	24.5	0.28
	8. 1.25		
	9. 1.25		
	10. 1.50		
	11. 2.50		
	12. 2.00		
	13. 2.00		
	14. 1.00		
Slovenia, 2003	7. 1.25	9.9	0.80
	8. 1.00		
	9. 1.25		
	10. 1.25		
	11. 2.75		
	12. 2.75		
	13. 1.50		
	14. 1.25		

USA, 1993	7. 1.00 8. 1.00 9. 1.25 10 1.25 11. 1.25 12. 1.00 13. 2.25 14. 1.00	4.2	ND
Argentina, ?	7. 1.50 8. 1.00 9. 1.75 10. 2.50 11. 3.25 12. 2.50 13. 1.25 14. 1.75	15.6	0.46
Spain, ?	7. 1.50 8. 1.00 9. 1.75 10. 1.25 11. 2.25 12. 2.25 13. 1.00 14. 1.00	8.3	0.38
Domain 4 : Clarity of presentation			
Ireland, 2019	15. 4.50 16. 5.25 17. 5.00	65.3	ND
India, 2017	15. 6.00 16. 5.75 17. 6.50	83.3	ND
Australia, 2016	15. 4.50 16. 4.50 17. 5.00	61.1	0.67
Austria, 2016	15. 3.50 16. 3.75 17. 3.00	40.3	ND
Germany, 2016	15. 3.00 16. 2.75 17. 4.75	41.7	0.09
Norway, 2016	15. 2.25 16. 2.75 17. 4.00	41.7	ND
Denmark, 2015	15. 4.00 16. 4.50 17. 3.25	48.6	0.63
Europe, 2015	15. 3.25 16. 3.25 17. 3.75	40.3	ND
USA, 2015	15. 5.25 16. 6.00 17. 6.25	80.6	ND

Iran, 2014	15. 3.50 16. 3.00 17. 4.25	43.1	0.70
Switzerland, 2014	15. 5.25 16. 5.00 17. 5.50	70.8	ND
Oceania, 2013	15. 4.00 16. 4.75 17. 5.25	61.1	0.70
Hungary, 2013	15. 4.00 16. 3.25 17. 3.75	44.4	ND
Brazil, 2011	15. 6.00 16. 5.50 17. 5.75	79.2	ND
Canada (Bourret), 2010	15. 5.00 16. 3.25 17. 5.25	58.3	0.49
Chile, 2010	15. 5.00 16. 5.00 17. 5.75	70.8	0.89
Canada (Trilium), 2010	15. 4.50 16. 4.50 17. 4.75	59.7	ND
Cuba, 2009	15. 3.25 16. 2.50 17. 3.75	36.1	0.49
Australasia, 2008	15. 4.50 16. 4.75 17. 5.25	63.9	ND
Canada, 2006	15. 5.75 16. 6.25 17. 6.25	84.7	ND
France, 2005	15. 2.75 16. 3.25 17. 2.50	30.6	ND
United Kingdom, 2005	15. 4.00 16. 3.75 17. 4.00	48.6	ND
USA, 2004	15. 4.50 16. 4.25 17. 5.00	59.7	ND
Slovenia, 2003	15. 4.25 16. 3.50 17. 4.75	52.8	ND
USA, 1993	15. 2.25 16. 2.25 17. 2.00	25.0	ND
Argentina, ?	15. 3.50 16. 4.50 17. 5.50	72.2	0.95
Spain, ?	15. 3.50	43.1	ND

	16. 3.75 17. 2.00		
Domain 5 : Applicability			
Ireland, 2019	18. 3.50 19. 2.00 20. 1.00 21. 2.00	18.8	0.26
India, 2017	18. 1.50 19. 3.00 20. 1.25 21. 1.50	13.5	0.54
Australia, 2016	18. 2.25 19. 3.00 20. 2.00 21. 2.00	17.7	ND
Austria, 2016	18. 1.00 19. 1.00 20. 1.00 21. 1.00	0	ND
Germany, 2016	18. 2.75 19. 2.50 20. 1.50 21. 1.00	11.4	0.14
Norway, 2016	18. 1.50 19. 2.50 20. 1.25 21. 1.00	10.4	0.25
Denmark, 2015	18. 1.75 19. 2.75 20. 1.25 21. 3.50	22.9	0.26
Europe, 2015	18. 2.00 19. 2.00 20. 1.25 21. 1.75	9.3	0.21
USA, 2015	18. 4.00 19. 3.50 20. 2.25 21. 1.50	39.6	0.77
Iran, 2014	18. 1.25 19. 1.75 20. 1.25 21. 1.75	8.3	ND
Switzerland, 2014	18. 1.00 19. 1.25 20. 1.00 21. 1.00	1.0	ND
Oceania, 2013	18. 3.00 19. 3.00 20. 3.00 21. 1.75	28.1	ND
Hungary, 2013	18. 1.25	21.9	ND

	19. 1.25		
	20. 1.25		
	21. 1.75		
Brazil, 2011	18. 2.50	29.2	0.27
	19. 3.25		
	20. 2.25		
	21. 3.00		
Canada (Bourret, 2010	18. 1.50	13.5	0.52
	19. 2.25		
	20. 1.25		
	21. 2.25		
Chile, 2010	18. 1.00	4.2	0.33
	19. 1.75		
	20. 1.25		
	21. 1.00		
Canada (Trilium), 2010	18. 1.50	12.5	0.77
	19. 3.50		
	20. 2.25		
	21. 1.00		
Cuba, 2009	18. 1.25	4.2	0.33
	19. 1.50		
	20. 1.00		
	21. 1.00		
Australasia, 2008	18. 2.25	28.1	0.77
	19. 4.25		
	20. 2.00		
	21. 2.25		
Canada, 2006	18. 4.00	41.7	0.48
	19. 4.50		
	20. 3.25		
	21. 2.75		
France, 2005	18. 2.75	12.5	ND
	19. 1.75		
	20. 1.50		
	21. 1.00		
United Kingdom, 2005	18. 3.00	28.1	ND
	19. 3.50		
	20. 2.00		
	21. 2.25		
USA, 2004	18. 1.50	13.5	0.32
	19. 2.75		
	20. 1.25		
	21. 1.75		
Slovenia, 2003	18. 2.00	12.5	ND
	19. 1.75		
	20. 1.25		
	21. 2.00		
USA, 1993	18. 1.25	13.5	0.88
	19. 2.50		
	20. 1.75		
	21. 1.00		
Argentina, ?	18. 1.50	11.5	ND

	19. 1.75 20. 1.50 21. 2.00		
Spain, ?	18. 1.00 19. 1.50 20. 1.25 21. 1.00	3.12	ND
Domain 6 : Editorial independence			
Ireland, 2019	22. 1.75 23. 1.00	5.4	ND
India, 2017	22. 7.00 23. 7.00	100	ND
Australia, 2016	22. 3.50 23. 2.75	28.6	ND
Austria, 2016	22. 2.25 23. 1.00	8.9	0.64
Germany, 2016	22. 1.75 23. 1.00	5.4	ND
Norway, 2016	22. 2.50 23. 1.00	10.7	0.67
Denmark, 2015	22. 1.25 23. 1.25	3.6	ND
Europe, 2015	22. 2.75 23. 1.00	12.5	ND
USA, 2015	22. 5.25 23. 6.75	71.4	0.67
Iran, 2014	22. 1.25 23. 1.25	3.6	ND
Switzerland, 2014	22. 1.25 23. 1.00	1.8	ND
Oceania, 2013	22. 2.50 23. 1.25	12.5	0.32
Hungary, 2013	22. 2.00 23. 1.25	8.9	ND
Brazil, 2011	22. 3.50 23. 2.25	19.6	0.85
Canada (Bourret), 2010	22. 1.50 23. 1.25	5.4	ND
Chile, 2010	22. 1.75 23. 1.75	10.7	ND
Cuba, 2009	22. 2.50 23. 1.00	10.7	0.67
Australasia, 2008	22. 2.25 23. 1.25	10.7	ND no correlation
Canada, 2006	22. 3.75 23. 5.00	48.2	0.75
France, 2005	22. 1.50 23. 2.50	14.3	ND
United Kingdom, 2005	22. 2.00 23. 2.50	19.6	ND
USA, 2004	22. 2.00 23. 1.25	8.9	ND

Slovenia, 2003	22. 2.00 23. 1.25	8.9	ND
USA, 1993	22. 2.00 23. 1.00	7.1	ND
Argentina, ?	22. 4.00 23. 1.00	21.4	0.87
Spain, ?	22. 1.75 23. 1.00	5.4	ND

Bibliography

1. Irodat.org (Internet). 2016. (Accessed April 2016, at http://www.irodat.org/.)
2. Girard M. La difficile décision. La Presse+ 2019 5-07-2019.
3. Tullius SG, Rabb H. Improving the Supply and Quality of Deceased-Donor Organs for Transplantation. N Engl J Med 2018;378:1920-9.
4. Westphal GA, Robinson CC, Biasi A, et al. DONORS (Donation Network to Optimise Organ Recovery Study): Study protocol to evaluate the implementation of an evidence-based checklist for brain-dead potential organ donor management in intensive care units, a cluster randomised trial. BMJ Open 2019;9:e028570.
5. Wahlster S, Wijdicks EFM, Patel PV, et al. Brain death declaration: Practices and perceptions worldwide. Neurology 2015;84:1870-9.
6. Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. Br J Anaesth 2012;108 Suppl 1:i14-28.
7. Howard RJ, Cornell DL, Cochran L. History of deceased organ donation, transplantation, and organ procurement organizations. Prog Transplant 2012;22:6-16; quiz 7.
8. Almohsen SS, Alobaishy SM, Alghammas NI, et al. Attitudes and beliefs on organ donation among students in a university in Central Saudi Arabia. Saudi medical journal 2016;37:591.
9. Bruzzone P. Religious aspects of organ transplantation. Transplantation proceedings 2008;40:1064-7.
10. Lei L, Deng J, Zhang H, Dong H, Luo Y, Luo Y. Level of Organ Donation-Related Knowledge and Attitude and Willingness Toward Organ Donation Among a Group of University Students in Western China. Transplantation proceedings 2018;50:2924-31.
11. De Georgia MA. History of brain death as death: 1968 to the present. Journal of critical care 2014;29:673-8.
12. Laureys S. Science and society: death, unconsciousness and the brain. Nat Rev Neurosci 2005;6:899-909.
13. Baron L, Shemie SD, Teitelbaum J, Doig CJ. Brief review: history, concept and controversies in the neurological determination of death. Can J Anaesth 2006;53:602-8.
14. Machado C, Kerein J, Ferrer Y, Portela L, de la CGM, Manero JM. The concept of brain death did not evolve to benefit organ transplants. Journal of medical ethics 2007;33:197-200.
15. Jalland. Cerebral abscess secondary to ear disease; trephining; death. Lancet 1892:527.
16. Horsley V. On the mode of death in cerebral compression and its prevention. Q Med J 1894;2:306-9.
17. Duckworth D. Some cases of cerebral disease in which the function of respiration entirely ceases for some hours before that of the circulation. Edinburgh Med J 1898;3:145-52.
18. Cushing H. Some experimental and clinical observations concerning states of increased intracranial tension. Am J Med Sci 1902;124:375-400.
19. Settergren G. Brain death: an important paradigm shift in the 20th century. Acta anaesthesiologica Scandinavica 2003;47:1053-8.
20. Cushing H. Some expermimental and clinical observations concerning states of increased intracranial tension. Am J Med Sci 1902;124:375-400.
21. Bergquist E, Bergstrom K. Angiography in cerebral death. Acta radiologica: diagnosis 1972;12:283-8.
22. Halevy A, Brody B. Brain death: reconciling definitions, criteria, and tests. Ann Intern Med 1993;119:519-25.

23. Jouvet M. [Electro-subcorticographic diagnosis of death of the central nervous system during various types of coma]. Electroencephalogr Clin Neurophysiol 1959;11:805-8.
24. Wertheimer P, Jouvet, M., Descotes, J. A propos du diagnostic de la mort du système nerveux. Presse Medicale 1959;67:87-8.
25. Mollaret P, Goulon M. [The depassed coma (preliminary memoir)]. Rev Neurol (Paris) 1959;101:3-15.
26. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA 1968;205:337-40.
27. Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Jama 1981;246:2184-6.
28. Smith M. Brain death: time for an international consensus. Br J Anaesth 2012;108 Suppl 1:i6-9.
29. Uniform Determination of Death Act. (Accessed December 16th 2018, at http://www.lchc.ucsd.edu/cogn_150/Readings/death_act.pdf.)
30. Kramer AH. Ancillary testing in brain death. Seminars in neurology 2015;35:125-38.
31. Dalle Ave AL, Bernat JL. Inconsistencies Between the Criterion and Tests for Brain Death. Journal of intensive care medicine 2018:885066618784268.
32. Nair-Collins M, Northrup J, Olcese J. Hypothalamic-Pituitary Function in Brain Death: A Review. Journal of intensive care medicine 2016;31:41-50.
33. Delimiting death. Nature 2009;461:570.
34. Machado C. The first organ transplant from a brain-dead donor. Neurology 2005;64:1938-42.
35. Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J 1967;41:1271-4.
36. Barnard CN. Human cardiac transplantation. An evaluation of the first two operations performed at the Groote Schuur Hospital, Cape Town. Am J Cardiol 1968;22:584-96.
37. Hoffenberg R. Christiaan Barnard: his first transplants and their impact on concepts of death. Bmj 2001;323:1478-80.
38. Kim SJ, Fenton SS, Kappel J, et al. Organ donation and transplantation in Canada: insights from the Canadian Organ Replacement Register. Canadian journal of kidney health and disease 2014;1:31.
39. Patel MS, Zatarain J, De La Cruz S, et al. The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: a prospective study from the UNOS Region 5 Donor Management Goals Workgroup. JAMA surgery 2014;149:969-75.
40. Norris S. Organ Donation and Transplantation in Canada. In: Service LaSADPIaR, ed. Ottawa, Canada: Library of Parliament; 2018.
41. Matesanz R, Marazuela R, Dominguez-Gil B, Coll E, Mahillo B, de la Rosa G. The 40 donors per million population plan: an action plan for improvement of organ donation and transplantation in Spain. Transplantation proceedings 2009;41:3453-6.
42. Gill JS, Klarenbach S, Cole E, Shemie SD. Deceased organ donation in Canada: an opportunity to heal a fractured system. Am J Transplant 2008;8:1580-7.
43. Arshad A, Anderson B, Sharif A. Comparison of organ donation and transplantation rates between opt-out and opt-in systems. Kidney Int 2019;95:1453-60.

44. Organ and Tissue Donation Act: an overview. 2019. 2019, at https://novascotia.ca/organdonation/.)
45. Deceased Organ Donor Potential in Canada report. 2014. 2019, at https://www.cihi.ca/sites/default/files/organdonorpotential_2014_en_0.pdf.)
46. Kramer AH, Baht R, Doig CJ. Time trends in organ donation after neurologic determination of death: a cohort study. CMAJ Open 2017;5:E19-e27.
47. Young A, Dixon SN, Knoll GA, et al. The Canadian experience using the expanded criteria donor classification for allocating deceased donor kidneys for transplantation. Canadian journal of kidney health and disease 2016;3:15.
48. Kling CE, Perkins JD, Johnson CK, Blosser CD, Leca N, Sibulesky L. Utilization of Standard Criteria Donor and Expanded Criteria Donor Kidneys After Kidney Allocation System Implementation. Ann Transplant 2018;23:691-703.
49. Expanded Criteria Donor (ECD). 2019. 2019, at https://stanfordhealthcare.org/medical-treatments/l/liver-transplant/types/expanded-criteria-donor.html.)
50. Israni AK, Zaun D, Rosendale JD, Schaffhausen C, Snyder JJ, Kasiske BL. OPTN/SRTR 2016 Annual Data Report: Deceased Organ Donation. Am J Transplant 2018;18 Suppl 1:434-63.
51. Shemie SD, Dhanani S. The Physiology of Brain Death and Organ Donor Management. In: Wheeler DS, Wong HR, Shanley TP, eds. Pediatric Critical Care Medicine: Volume 1: Care of the Critically Ill or Injured Child. London: Springer London; 2014:497-518.
52. Guyton AC, Hall, J.E. Textbook of medical physiology. 11th edition ed: Elsevier Saunders; 2006.
53. The Brain-Dead Organ Donor; pathophysiology and management: Springer; 2012.
54. Takada M, Nadeau KC, Hancock WW, et al. Effects of explosive brain death on cytokine activation of peripheral organs in the rat. Transplantation 1998;65:1533-42.
55. Schrader H, Hall C, Zwetnow NN. Effects of prolonged supratentorial mass expansion on regional blood flow and cardiovascular parameters during the Cushing response. Acta neurologica Scandinavica 1985;72:283-94.
56. Smith M. Physiologic changes during brain stem death--lessons for management of the organ donor. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2004;23:S217-22.
57. Ranasinghe AM, Bonser RS. Endocrine changes in brain death and transplantation. Best practice & research Clinical endocrinology & metabolism 2011;25:799-812.
58. Audibert G, Charpentier C, Seguin-Devaux C, et al. Improvement of donor myocardial function after treatment of autonomic storm during brain death. Transplantation 2006;82:1031-6.
59. Korte C, Garber JL, Descourouez JL, Richards KR, Hardinger K. Pharmacists' guide to the management of organ donors after brain death. Am J Health Syst Pharm 2016;73:1829-39.
60. Pratschke J, Wilhelm MJ, Kusaka M, Laskowski I, Tilney NL. A model of gradual onset brain death for transplant-associated studies in rats. Transplantation 2000;69:427-30.
61. Powner DJ, Hendrich A, Nyhuis A, Strate R. Changes in serum catecholamine levels in patients who are brain dead. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 1992;11:1046-53.
62. Shivalkar B, Van Loon J, Wieland W, et al. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. Circulation 1993;87:230-9.

63. Herijgers P, Leunens V, Tjandra-Maga TB, Mubagwa K, Flameng W. Changes in organ perfusion after brain death in the rat and its relation to circulating catecholamines. Transplantation 1996;62:330-5.
64. Cooper DK, Novitzky D, Wicomb WN. The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. Ann R Coll Surg Engl 1989;71:261-6.
65. Sugimoto T, Sakano T, Kinoshita Y, Masui M, Yoshioka T. Morphological and functional alterations of the hypothalamic-pituitary system in brain death with long-term bodily living. Acta neurochirurgica 1992;115:31-6.
66. Schrader H, Krogness K, Aakvaag A, Sortland O, Purvis K. Changes of pituitary hormones in brain death. Acta neurochirurgica 1980;52:239-48.
67. Arita K, Uozumi T, Oki S, Kurisu K, Ohtani M, Mikami T. The function of the hypothalamo-pituitary axis in brain dead patients. Acta neurochirurgica 1993;123:64-75.
68. Ishikawa T, Michiue T, Quan L, et al. Morphological and functional alterations in the adenohypophysis in cases of brain death. Legal medicine (Tokyo, Japan) 2009;11 Suppl 1:S234-7.
69. Fitzgerald RD, Dechtyar I, Templ E, Pernerstorfer T, Hackl W, Lackner FX. Endocrine stress reaction to surgery in brain-dead organ donors. Transplant international : official journal of the European Society for Organ Transplantation 1996;9:102-8.
70. Howlett TA, Keogh AM, Perry L, Touzel R, Rees LH. Anterior and posterior pituitary function in brain-stem-dead donors. A possible role for hormonal replacement therapy. Transplantation 1989;47:828-34.
71. Ferrera R, Ovize M, Claustrat B, Hadour G. Stable myocardial function and endocrine dysfunction during experimental brain death. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2005;24:921-7.
72. Novitzky D, Wicomb, W.N., Cooper, D.K.C. Electrocardiographic, haemodynamic and endocrine changes occuring during experimental brain death in the Chacma baboon. J Heart Transplant 1984;4:63-9.
73. Mi Z, Novitzky D, Collins JF, Cooper DK. The optimal hormonal replacement modality selection for multiple organ procurement from brain-dead organ donors. Clin Epidemiol 2015;7:17-27.
74. Novitzky D, Wicomb WN, Cooper DK, Rose AG, Reichart B. Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. The Annals of thoracic surgery 1986;41:520-4.
75. Novitzky D. Detrimental effects of brain death on the potential organ donor. Transplantation proceedings 1997;29:3770-2.
76. Novitzky D, Cooper DK. Thyroid hormone and the stunned myocardium. The Journal of endocrinology 2014;223:R1-8.
77. Novitzky D, Cooper DK, Muchmore JS, Zuhdi N. Pituitary function in brain-dead patients. Transplantation 1989;48:1078-9.
78. Novitzky D, Mi Z, Sun Q, Collins JF, Cooper DK. Thyroid hormone therapy in the management of 63,593 brain-dead organ donors: a retrospective analysis. Transplantation 2014;98:1119-27.
79. Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. Transplantation 1987;43:852-4.

80. Novitzky D, Cooper DK, Wicomb WN. Endocrine changes and metabolic responses. Transplantation proceedings 1988;20:33-8.
81. Chen EP, Bittner HB, Kendall SW, Van Trigt P. Hormonal and hemodynamic changes in a validated animal model of brain death. Crit Care Med 1996;24:1352-9.
82. Bittner HB, Kendall SW, Chen EP, Van Trigt P. Endocrine changes and metabolic responses in a validated canine brain death model. Journal of critical care 1995;10:56-63.
83. Okamoto S, Corso CO, Nolte D, et al. Impact of brain death on hormonal homeostasis and hepatic microcirculation of transplant organ donors. Transplant international : official journal of the European Society for Organ Transplantation 1998;11 Suppl 1:S404-7.
84. Wicomb WN, Cooper DK, Novitzky D. Impairment of renal slice function following brain death, with reversibility of injury by hormonal therapy. Transplantation 1986;41:29-33.
85. Bugge JF. Brain death and its implications for management of the potential organ donor. Acta anaesthesiologica Scandinavica 2009;53:1239-50.
86. Frenette AJ, Payeur M., Serri, K., Williamson, D., Charbonney, E. Autonomic storm definitions in neurological deceased donor: an multicenter epidemiological study. Unpublished.
87. Spencer W, Horsley, V. On the Changes Produced in the Circulation and Respiration by Increase of the Intracranial Pressure or Tension (Abstract). Proceedings of the Royal Society of London 1890;48:273-5.
88. Shapiro L.E. B, T. The Efficacy of Thyroid Hormone Therapy in Brain-Dead Heart Donors: A Review of Thyoid Function in Health and Disease. In: Novitzky D, Cooper, D.K.C, ed. The Brain-Dead Organ Donor: Pathophysiology and Management. Springer ed. New York, United States2013:91-107.
89. Jastremski M, Powner D, Snyder J, Smith J, Grenvik A. Problems in brain death determination. Forensic science 1978;11:201-12.
90. Kinoshita Y, Yahata K, Yoshioka T, Onishi S, Sugimoto T. Long-term renal preservation after brain death maintained with vasopressin and epinephrine. Transplant international : official journal of the European Society for Organ Transplantation 1990;3:15-8.
91. Kim KA, Wang MY, McNatt SA, et al. Vector analysis correlating bullet trajectory to outcome after civilian through-and-through gunshot wound to the head: using imaging cues to predict fatal outcome. Neurosurgery 2005;57:737-47; discussion -47.
92. Chai CL, Tu YK, Huang SJ. Can cerebral hypoperfusion after sympathetic storm be used to diagnose brain death? A retrospective survey in traumatic brain injury patients. J Trauma 2008;64:688-97.
93. Kinoshita Y, Yahata K, Yoshioka T, Onishi S, Sugimoto T. Long-term renal preservation after brain death maintained with vasopressin and epinephrine. Transplant International 1990;3:15-8.
94. Kinoshita Y, Go K, Yoshioka T, Sugimoto T. Absence of response to hypothalamic stimulation test in brain death. Neurologia medico-chirurgica 1992;32:153-6.
95. Koller J, Wieser C, Gottardis M, et al. Thyroid hormones and their impact on the hemodynamic and metabolic stability of organ donors and on kidney graft function after transplantation. Transplantation proceedings 1990;22:355-7.
96. Imberti R, Filisetti P, Preseglio I, Mapelli A, Spriano P. Confirmation of brain death utilizing thyrotropin-releasing hormone stimulation test. Neurosurgery 1990;27:167.
97. Gramm HJ, Meinhold, H., Bickel, U., et al. Acute endocrine failure after brain death? transplantation 1992;54:851-7.

98. Amado JA, Lopez-Espadas F, Vazquez-Barquero A, et al. Blood levels of cytokines in brain-dead patients: relationship with circulating hormones and acute-phase reactants. Metabolism: clinical and experimental 1995;44:812-6.
99. Robertson KM, Hramiak IM, Gelb AW. Endocrine changes and haemodynamic stability after brain death. Transplantation proceedings 1989;21:1197-8.
100. Taniguchi S, Kitamura S, Kawachi K, Doi Y, Aoyama N. Effects of hormonal supplements on the maintenance of cardiac function in potential donor patients after cerebral death. Eur J Cardiothorac Surg 1992;6:96-101; discussion 2.
101. Lopau K, Mark J, Schramm L, Heidbreder E, Wanner C. Hormonal changes in brain death and immune activation in the donor. Transplant international : official journal of the European Society for Organ Transplantation 2000;13 Suppl 1:S282-5.
102. Dimopoulou I, Tsagarakis S, Anthi A, et al. High prevalence of decreased cortisol reserve in brain-dead potential organ donors. Crit Care Med 2003;31:1113-7.
103. Masson F, Thicoipe M, Latapie MJ, Maurette P. Thyroid function in brain-dead donors. Transplant international : official journal of the European Society for Organ Transplantation 1990;3:226-33.
104. Nagaya T, Fujieda M, Otsuka G, Yang JP, Okamoto T, Seo H. A potential role of activated NF-kappa B in the pathogenesis of euthyroid sick syndrome. The Journal of clinical investigation 2000;106:393-402.
105. Lu J, Goh SJ, Tng PY, Deng YY, Ling EA, Moochhala S. Systemic inflammatory response following acute traumatic brain injury. Frontiers in bioscience (Landmark edition) 2009;14:3795-813.
106. Barklin A. Systemic inflammation in the brain-dead organ donor. Acta anaesthesiologica Scandinavica 2009;53:425-35.
107. Zhang SJ, Wang T. The influence of brain death on donor liver and the potential mechanisms of protective intervention. Front Med 2011;5:8-14.
108. Atkinson C, Varela JC, Tomlinson S. Complement-dependent inflammation and injury in a murine model of brain dead donor hearts. Circulation research 2009;105:1094-101.
109. Watts RP, Thom O, Fraser JF. Inflammatory signalling associated with brain dead organ donation: from brain injury to brain stem death and posttransplant ischaemia reperfusion injury. Journal of transplantation 2013;2013:521369.
110. Mori DN, Kreisel D, Fullerton JN, Gilroy DW, Goldstein DR. Inflammatory triggers of acute rejection of organ allografts. Immunol Rev 2014;258:132-44.
111. Birks EJ, Burton PB, Owen V, et al. Elevated tumor necrosis factor-alpha and interleukin-6 in myocardium and serum of malfunctioning donor hearts. Circulation 2000;102:Iii352-8.
112. Atkinson C, Floerchinger B, Qiao F, et al. Donor brain death exacerbates complement-dependent ischemia/reperfusion injury in transplanted hearts. Circulation 2013;127:1290-9.
113. Hefty TR, Cotterell LW, Fraser SC, Goodnight SH, Hatch TR. Disseminated intravascular coagulation in cadaveric organ donors. Incidence and effect on renal transplantation. Transplantation 1993;55:442-3.
114. Salim A, Martin M, Brown C, Belzberg H, Rhee P, Demetriades D. Complications of brain death: frequency and impact on organ retrieval. The American surgeon 2006;72:377-81.
115. Orban JC, Quintard H, Cassuto E, Jambou P, Samat-Long C, Ichai C. Effect of N-acetylcysteine pretreatment of deceased organ donors on renal allograft function: a randomized controlled trial. Transplantation 2015;99:746-53.

116. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 1995;333:333-6.
117. D'Amico TA, Meyers CH, Koutlas TC, et al. Desensitization of myocardial beta-adrenergic receptors and deterioration of left ventricular function after brain death. The Journal of thoracic and cardiovascular surgery 1995;110:746-51.
118. Berman M, Ali A, Ashley E, et al. Is stress cardiomyopathy the underlying cause of ventricular dysfunction associated with brain death? The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2010;29:957-65.
119. Perez Lopez S, Otero Hernandez J, Vazquez Moreno N, Escudero Augusto D, Alvarez Menendez F, Astudillo Gonzalez A. Brain death effects on catecholamine levels and subsequent cardiac damage assessed in organ donors. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2009;28:815-20.
120. Mertes PM, Carteaux JP, Jaboin Y, et al. Estimation of myocardial interstitial norepinephrine release after brain death using cardiac microdialysis. Transplantation 1994;57:371-7.
121. White M, Wiechmann RJ, Roden RL, et al. Cardiac beta-adrenergic neuroeffector systems in acute myocardial dysfunction related to brain injury. Evidence for catecholamine-mediated myocardial damage. Circulation 1995;92:2183-9.
122. Birks EJ, Yacoub MH, Burton PS, et al. Activation of apoptotic and inflammatory pathways in dysfunctional donor hearts. Transplantation 2000;70:1498-506.
123. Borbely XI, Krishnamoorthy V, Modi S, et al. Temporal Changes in Left Ventricular Systolic Function and Use of Echocardiography in Adult Heart Donors. Neurocrit Care 2015;23:66-71.
124. Dujardin KS, McCully RB, Wijdicks EF, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2001;20:350-7.
125. Gilbert EM, Krueger SK, Murray JL, et al. Echocardiographic evaluation of potential cardiac transplant donors. The Journal of thoracic and cardiovascular surgery 1988;95:1003-7.
126. Boudaa C, Perrier JF, Lalot JM, et al. [Analysis of the criteria that contribute to the decision to harvest the heart in brain-dead organ donors]. Annales francaises d'anesthesie et de reanimation 2003;22:765-72.
127. Paul JJ, Tani LY, Shaddy RE, Minich LL. Spectrum of left ventricular dysfunction in potential pediatric heart transplant donors. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2003;22:548-52.
128. Godino M, Lander M, Cacciatore A, Perez-Protto S, Mizraji R. Ventricular dysfunction associated with brain trauma is cause for exclusion of young heart donors. Transplantation proceedings 2010;42:1507-9.
129. Huttemann E, Schelenz C, Chatzinikolaou K, Reinhart K. Left ventricular dysfunction in lethal severe brain injury: impact of transesophageal echocardiography on patient management. Intensive Care Med 2002;28:1084-8.
130. Khush KK, Pawlikowska L, Menza RL, et al. Beta-adrenergic receptor polymorphisms and cardiac graft function in potential organ donors. Am J Transplant 2012;12:3377-86.

131. Mohamedali B, Bhat G, Zelinger A. Frequency and pattern of left ventricular dysfunction in potential heart donors: implications regarding use of dysfunctional hearts for successful transplantation. J Am Coll Cardiol 2012;60:235-6.
132. Kono T, Nishina T, Morita H, Hirota Y, Kawamura K, Fujiwara A. Usefulness of low-dose dobutamine stress echocardiography for evaluating reversibility of brain death-induced myocardial dysfunction. Am J Cardiol 1999;84:578-82.
133. Krishnamoorthy V, Borbely X, Rowhani-Rahbar A, Souter MJ, Gibbons E, Vavilala MS. Cardiac dysfunction following brain death in children: prevalence, normalization, and transplantation. Pediatr Crit Care Med 2015;16:e107-12.
134. Nicolas-Robin A, Salvi N, Medimagh S, et al. Combined measurements of N-terminal pro-brain natriuretic peptide and cardiac troponins in potential organ donors. Intensive Care Med 2007;33:986-92.
135. Zaroff JG, Babcock WD, Shiboski SC, Solinger LL, Rosengard BR. Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2003;22:383-8.
136. Bittner HB, Chen EP, Biswas SS, Van Trigt P, 3rd, Davis RD. Right ventricular dysfunction after cardiac transplantation: primarily related to status of donor heart. The Annals of thoracic surgery 1999;68:1605-11.
137. Belhaj A, Dewachter L, Rorive S, et al. Roles of inflammation and apoptosis in experimental brain death-induced right ventricular failure. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2016.
138. Madan S, Saeed O, Vlismas P, et al. Outcomes After Transplantation of Donor Hearts With Improving Left Ventricular Systolic Dysfunction. J Am Coll Cardiol 2017;70:1248-58.
139. Zaroff JG, Babcock WD, Shiboski SC. The impact of left ventricular dysfunction on cardiac donor transplant rates. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2003;22:334-7.
140. Chen CW, Sprys MH, Gaffey AC, et al. Low ejection fraction in donor hearts is not directly associated with increased recipient mortality. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2017;36:611-5.
141. Rossano JW, Lin KY, Paridon SM, et al. Pediatric heart transplantation from donors with depressed ventricular function: an analysis of the United Network of Organ Sharing Database. Circulation Heart failure 2013;6:1223-9.
142. McLean KM, Pandalai PK, Pearl JM, et al. Beta-adrenergic receptor antagonism preserves myocardial function after brain death in a porcine model. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2007;26:522-8.
143. Pandalai PK, Lyons JM, Duffy JY, et al. Role of the beta-adrenergic receptor kinase in myocardial dysfunction after brain death. Journal of Thoracic & Cardiovascular Surgery 2005;130:1183-9.
144. Ferrera R, Hadour G, Tamion F, et al. Brain death provokes very acute alteration in myocardial morphology detected by echocardiography: preventive effect of beta-blockers. Transplant international : official journal of the European Society for Organ Transplantation 2011;24:300-6.

145. Schnuelle P, Lorenz D, Mueller A, Trede M, Van Der Woude FJ. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. Kidney Int 1999;56:738-46.
146. Schnuelle P, Berger S, de Boer J, Persijn G, van der Woude FJ. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. Transplantation 2001;72:455-63.
147. Schnuelle P, Berger S, de Boer J, Persijn G, van der Woude FJ. Donor employment of vasopressors and its impact on allograft survival after transplantation. Transplantation proceedings 2001;33:1282-3.
148. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. Jama 2009;302:1067-75.
149. Yard B, Beck G, Schnuelle P, et al. Prevention of cold-preservation injury of cultured endothelial cells by catecholamines and related compounds. Am J Transplant 2004;4:22-30.
150. Stoica SC, Satchithananda DK, White PA, Parameshwar J, Redington AN, Large SR. Noradrenaline use in the human donor and relationship with load-independent right ventricular contractility. Transplantation 2004;78:1193-7.
151. Shemie SD, Ross, H., Pagliarello, J. Baker, A.J., Greig, P.D, Brand, T. Cockfield, S. Keshavjee, S., Nickerson, P., Rao, V., Guest, C. Young, K., Doig, C. La prise en charge des donneurs d'organes au Canada: recommendations du forum Optimiser le maintien du donneur afin d'accroitre le nombre d'organes admissibles pour la transplantation. Cmaj 2006;174:SF14-SF32.
152. 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.
153. Benck U, Hoeger S, Brinkkoetter PT, et al. Effects of donor pre-treatment with dopamine on survival after heart transplantation: a cohort study of heart transplant recipients nested in a randomized controlled multicenter trial. J Am Coll Cardiol 2011;58:1768-77.
154. von Ziegler F, Helbig S, Kreissl N, Meiser B, Becker A, Kaczmarek I. Norepinephrine versus dopamine pretreatment of potential heart donors - impact on long-term outcome. Ann Transplant 2013;18:320-6.
155. Frenette AJ, Akhtar A., Williams, V., Masse, M.H., Zhou, Q., Hoad, N., Charbonney, E., Serri, K., Meade, M., D'Aragon, F. Inotrope use in potential heart donors: a prospective cohort analysis. Crit Care Med 2018;46:89.
156. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 1995;14:734-42.
157. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003;75:482-7.
158. Rosendale JD, Kauffman HM, McBride MA, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. Transplantation 2003;75:1336-41.
159. Follette D, Rudich S, Bonacci C, Allen R, Hoso A, Albertson T. Importance of an aggressive multidisciplinary management approach to optimize lung donor procurement. Transplantation proceedings 1999;31:169-70.

160. Salim A, Velmahos GC, Brown C, Belzberg H, Demetriades D. Aggressive organ donor management significantly increases the number of organs available for transplantation. J Trauma 2005;58:991-4.
161. Nath DS, Ilias Basha H, Liu MH, Moazami N, Ewald GA. Increased recovery of thoracic organs after hormonal resuscitation therapy. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2010;29:594-6.
162. Dupuis S, Amiel JA, Desgroseilliers M, et al. Corticosteroids in the management of brain-dead potential organ donors: a systematic review. Br J Anaesth 2014;113:346-59.
163. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiological reviews 2001;81:1097-142.
164. Michelena JC, Chamorro C, Falcon JA, Garces S. [Hormone modulation of organ donor. Utility of the steroids]. Medicina intensiva 2009;33:251-5.
165. Mariot J, Sadoune, L.O., Jacob, F., Dousset, B., Perrier, J.F., Jacob, C., Strub, P., Voltz, C. Hormone levels, hemodynamics, and metabolism in brain-dead organ donors. Transplantation proceedings 1995;27:793-4.
166. 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.
167. Amatschek S, Wilflingseder J, Pones M, et al. The effect of steroid pretreatment of deceased organ donors on liver allograft function: a blinded randomized placebo-controlled trial. J Hepatol 2012;56:1305-9.
168. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. Ann Surg 2008;248:1042-50.
169. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 1998;17:423-9.
170. Gibbison B, López-López JA, Higgins JPT, et al. Corticosteroids in septic shock: a systematic review and network meta-analysis. Critical Care 2017;21:78.
171. Pinsard M, Ragot S, Mertes PM, et al. Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. Critical care (London, England) 2014;18:R158.
172. Dhar R, Cotton C, Coleman J, et al. Comparison of high- and low-dose corticosteroid regimens for organ donor management. Journal of critical care 2013;28:111 e1-7.
173. Chatterjee SN, Terasaki PI, Fine S, Schulman B, Smith R, Fine RN. Pretreatment of cadaver donors with methylprednisolone in human renal allografts. Surg Gynecol Obstet 1977;145:729-32.
174. Corry RJ, Patel NP, West JC, Schanbacher BA. Pretreatment of cadaver donors with cyclophosphamide and methylprednisolone: effect on renal transplant outcome. Transplantation proceedings 1980;12:348-51.
175. Dienst SG. Statewide donor pretreatment study. Transplantation proceedings 1977;9:1597-9.
176. Jeffery JR, Downs A, Grahame JW, Lye C, Ramsey E, Thomson AE. A randomized prospective study of cadaver donor pretreatment in renal transplantation. Transplantation 1978;25:287-9.

177. Soulillou JP, Baron D, Rouxel A, Guenel J. Steroid-cyclophosphamide pretreatment of kidney allograft donors. A control study. Nephron 1979;24:193-7.
178. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343:d5928.
179. Selck FW, Deb P, Grossman EB. Deceased organ donor characteristics and clinical interventions associated with organ yield. Am J Transplant 2008;8:965-74.
180. Taniguchi S, Kitamura S, Kawachi K, Doi Y, Aoyama N. Effects of hormonal supplements on the maintenance of cardiac function in potential donor patients after cerebral death. Eur J Cardiothorac Surg 1992;6:96-101; discussion 2.
181. McElhinney DB, Khan JH, Babcock WD, Hall TS. Thoracic organ donor characteristics associated with successful lung procurement. Clin Transplant 2001;15:68-71.
182. AMIDI M, LEON DF, DEGROOT WJ, KROETZ FW, LEONARD JJ. Effect of the Thyroid State on Myocardial Contractility and Ventricular Ejection Rate in Man. Circulation 1968;38:229-39.
183. Wang YG, Dedkova EN, Fiening JP, Ojamaa K, Blatter LA, Lipsius SL. Acute exposure to thyroid hormone increases Na+ current and intracellular Ca2+ in cat atrial myocytes. The Journal of physiology 2003;546:491-9.
184. Ririe DG, Butterworth JFt, Royster RL, MacGregor DA, Zaloga GP. Triiodothyronine increases contractility independent of beta-adrenergic receptors or stimulation of cyclic-3',5'-adenosine monophosphate. Anesthesiology 1995;82:1004-12.
185. Kinugawa K, Yonekura K, Ribeiro RC, et al. Regulation of thyroid hormone receptor isoforms in physiological and pathological cardiac hypertrophy. Circulation research 2001;89:591-8.
186. 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.
187. Lu X, Huang J, Zhang X, et al. Effects of thyroxine on cardiac function and lymphocyte beta-adrenoceptors in patients with chronic congestive heart failure. Chinese medical journal 2003;116:1697-700.
188. Moruzzi P, Doria E, Agostoni PG, Capacchione V, Sganzerla P. Usefulness of L-thyroxine to improve cardiac and exercise performance in idiopathic dilated cardiomyopathy. Am J Cardiol 1994;73:374-8.
189. Hamilton MA, Stevenson LW, Fonarow GC, et al. Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. Am J Cardiol 1998;81:443-7.
190. James SR, Ranasinghe AM, Venkateswaran R, McCabe CJ, Franklyn JA, Bonser RS. The effects of acute triiodothyronine therapy on myocardial gene expression in brain stem dead cardiac donors. J Clin Endocrinol Metab 2010;95:1338-43.
191. Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. J Clin Endocrinol Metab 2008;93:1351-8.
192. Hamilton MA, Stevenson LW. Thyroid hormone abnormalities in heart failure: possibilities for therapy. Thyroid 1996;6:527-9.
193. Economidou F, Douka E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. Hormones (Athens) 2011;10:117-24.

194. Dhar R, Stahlschmidt E, Yan Y, Marklin G. A randomized trial comparing triiodothyronine (T3) with thyroxine (T4) for hemodynamically unstable brain-dead organ donors. Clin Transplant 2019;33:e13486.
195. Dhar R, Marklin G. A Randomized Comparison of T3 vs. T4 for Management of Hemodynamically Unstable Brain-dead Organ Donors. The Journal of Heart and Lung Transplantation 2018;37:S342.
196. Sukocheva OA, Carpenter DO. Anti-apoptotic effects of 3,5,3'-tri-iodothyronine in mouse hepatocytes. The Journal of endocrinology 2006;191:447-58.
197. Murugan R, Venkataraman R, Wahed AS, et al. Increased plasma interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation. Crit Care Med 2008;36:1810-6.
198. Castilho RF, Kowaltowski AJ, Vercesi AE. 3,5,3'-triiodothyronine induces mitochondrial permeability transition mediated by reactive oxygen species and membrane protein thiol oxidation. Arch Biochem Biophys 1998;354:151-7.
199. Imberti R, Vairetti M, Gualea MR, et al. The effects of thyroid hormone modulation on rat liver injury associated with ischemia-reperfusion and cold storage. Anesth Analg 1998;86:1187-93.
200. Ellett JD, Evans ZP, Fiorini JH, et al. The use of the Papworth cocktail is detrimental to steatotic livers after ischemia-reperfusion injury. Transplantation 2008;86:286-92.
201. Paller MS. Hypothyroidism protects against free radical damage in ischemic acute renal failure. Kidney Int 1986;29:1162-6.
202. Vairetti M, Ferrigno A, Rizzo V, Richelmi P, Cillo U, Imberti R. Liver damage during ischemia/reperfusion and glutathione: implications for potential organ donors. Transplantation proceedings 2007;39:1768-70.
203. Jonassen AK, Sack MN, Mjøs OD, Yellon DM. Myocardial Protection by Insulin at Reperfusion Requires Early Administration and Is Mediated via Akt and p70s6 Kinase Cell-Survival Signaling. Circulation research 2001;89:1191-8.
204. Howell NJ, Ashrafian H, Drury NE, et al. Glucose-Insulin-Potassium Reduces the Incidence of Low Cardiac Output Episodes After Aortic Valve Replacement for Aortic Stenosis in Patients With Left Ventricular HypertrophyClinical Perspective. Results From the Hypertrophy, Insulin, Glucose, and Electrolytes (HINGE) Trial 2011;123:170-7.
205. Fan Y, Zhang AM, Xiao YB, Weng YG, Hetzer R. Glucose-insulin-potassium therapy in adult patients undergoing cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg 2011;40:192-9.
206. Nicolas-Robin A, Amour J, Ibanez-Esteve C, Coriat P, Riou B, Langeron O. Effect of glucose-insulin-potassium in severe acute heart failure after brain death. Crit Care Med 2008;36:2740-5.
207. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
208. The Hypothalamus and Posterior Pituitary Gland. In: PE M, ed. Endocrine Physiology. New York, USA: McGraw-Hill; 2013.
209. Pharmacology: examination and board review. 11th edition ed: Lange; 2015.
210. Micromedex. Ann Arbor (MI): Truven Health Analytics.

211. Keogh AM, Howlett TA, Perry L, Rees LH. Pituitary function in brain-stem dead organ donors: a prospective survey. Transplantation proceedings 1988;20:729-30.
212. Sharman A, Low, J. Vasopressin and its role in critical care. Contin Educ Anaesth Crit Care Pain 2008;8:134-7.
213. Rech TH, Moraes RB, Crispim D, Czepielewski MA, Leitao CB. Management of the brain-dead organ donor: a systematic review and meta-analysis. Transplantation 2013;95:966-74.
214. Chen JM, Cullinane S, Spanier TB, et al. Vasopressin deficiency and presser hypersensitivity in hemodynamically unstable organ donors. Circulation 1999;100:244-6.
215. Plurad DS, Bricker S, Neville A, Bongard F, Putnam B. Arginine vasopressin significantly increases the rate of successful organ procurement in potential donors. American Journal of Surgery 2012;204:856-60; discussion 60-1.
216. Callahan DS, Neville A, Bricker S, et al. The effect of arginine vasopressin on organ donor procurement and lung function. Journal of Surgical Research 2014;186:452-7.
217. Manyalich M. Organization of organ donation and role of coordinators: transplant procurement management. Saudi J Kidney Dis Transpl 1999;10:175-82.
218. Hoste P, Vanhaecht K, Ferdinande P, et al. Care pathways for organ donation after brain death: guidance from available literature? J Adv Nurs 2016;72:2369-80.
219. 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. Critical Care Medicine 2015;43:1291-325.
220. Chamorro-Jambrina C, Munoz-Ramirez MR, Martinez-Melgar JL, Perez-Cornejo MS. Organ donor management: Eight common recommendations and actions that deserve reflection. Medicina intensiva 2017;41:559-68.
221. Organ Donor Management Recommended Guidelines ADULT Brain Death. 2016. 2019, at http://www.transplant.bc.ca/Documents/Health%20Professionals/NDD/ODHD-ODS.05.011%20Rev07%20Organ%20Donor%20Management%20Guidelines_NDD_08Nov2016.pdf.)
222. Marsolais P, Durand P, Charbonney E, et al. The First 2 Years of Activity of a Specialized Organ Procurement Center: Report of an Innovative Approach to Improve Organ Donation. Am J Transplant 2017;17:1613-9.
223. Guidelines for Adult Organ and Tissue Donation. 2005. (Accessed 5-5-2019, at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwix5ZmxkYfiAhUjheAKHWNzDRUQFjAAegQIBRAC&url=https%3A%2F%2Fwww.ics.ac.uk%2FAsiCommon%2FControls%2FBSA%2FDownloader.aspx%3FiDocumentStorageKey%3D8b06f7c7-a6b5-4d8b-a852-7e168196b3e9%26iFileTypeCode%3DPDF%26iFileName%3DOrgan%2520and%2520Tissue%2520Donation&usg=AOvVaw0ZpJy1C9JjZjCp9fthkAvQ.)
224. Martinez-Soba F, Perez-Villares JM, Martinez-Camarero L, et al. Intensive Care to Facilitate Organ Donation: A Report on the Experience of 2 Spanish Centers with A Common Protocol. Transplantation 2018.
225. Piemonte G, Migliaccio ML, Bambi S, et al. Factors influencing consent to organ donation after brain death certification: a survey of 29 intensive care units. Minerva anestesiologica 2018.

226. Bapat U, Kedlaya PG. Organ donation, awareness, attitudes and beliefs among post graduate medical students. Saudi J Kidney Dis Transpl 2010;21:174-80.
227. Lomero MDM, Jimenez-Herrera MF, Rasero MJ, Sandiumenge A. Nurses' attitudes and knowledge regarding organ and tissue donation and transplantation in a provincial hospital: A descriptive and multivariate analysis. Nursing & health sciences 2017;19:322-30.
228. Meyer K, Bjork IT, Eide H. Intensive care nurses' perceptions of their professional competence in the organ donor process: a national survey. J Adv Nurs 2012;68:104-15.
229. Kocaay AF, Celik SU, Eker T, Oksuz NE, Akyol C, Tuzuner A. Brain Death and Organ Donation: Knowledge, Awareness, and Attitudes of Medical, Law, Divinity, Nursing, and Communication Students. Transplantation proceedings 2015;47:1244-8.
230. Rios A, Lopez-Navas A, Lopez-Lopez A, et al. Do Spanish Medical Students Understand the Concept of Brain Death? Prog Transplant 2018;28:77-82.
231. Feng S. Donor intervention and organ preservation: where is the science and what are the obstacles? Am J Transplant 2010;10:1155-62.
232. Mansour SG, Puthumana J, Reese PP, et al. Associations Between Deceased-Donor Urine MCP-1 and Kidney Transplant Outcomes. Kidney International Reports 2017;2:749-58.
233. Zens TJ, Danobeitia JS, Leverson G, et al. The impact of kidney donor profile index on delayed graft function and transplant outcomes: A single-center analysis. Clin Transplant 2018;32:e13190.
234. Hall IE, Akalin E, Bromberg JS, et al. Deceased-donor acute kidney injury is not associated with kidney allograft failure. Kidney International 2019;95:199-209.
235. Benck U, Schnuelle P, Kruger B, et al. Excellent graft and patient survival after renal transplantation from donors after brain death with acute kidney injury: a case-control study. Int Urol Nephrol 2015;47:2039-46.
236. Rodrigo E, Minambres E, Pinera C, et al. Using RIFLE criteria to evaluate acute kidney injury in brain-deceased kidney donors. Nephrol Dial Transplant 2010;25:1531-7.
237. National Academies of Sciences E, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Issues in Organ Donor Intervention Research. Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation. In: Liverman CT DS, Childress JF, ed. Washington DC, USA: National Academies Press (US); 2017.
238. Protection of Human Subjects. In: Regulations CoF, ed. Title 45; Subtitle A; Subchapter A; Part 462019.
239. Protection of Human Subjects. In: Regulations CoF, ed. Title 21 Volume 1: FDA; 2019.
240. « Department of Health EaW. The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; 1979.
241. Abt PL, Marsh CL, Dunn TB, et al. Challenges to research and innovation to optimize deceased donor organ quality and quantity. Am J Transplant 2013;13:1400-4.
242. Rodrigue JR, Feng S, Johansson AC, Glazier AK, Abt PL. Deceased Donor Intervention Research: A Survey of Transplant Surgeons, Organ Procurement Professionals, and Institutional Review Board Members. Am J Transplant 2016;16:278-86.
243. Niemann CU, Feiner J, Swain S, et al. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. N Engl J Med 2015;373:405-14.
244. Heffernan KG, Glazier AK. Are Transplant Recipients Human Subjects When Research Is Conducted on Organ Donors? The Hastings Center report 2017;47:10-4.

245. guidelines CoSfDTCP. Clinical Practice Guidelines We Can Trust. Washington DC, USA: Institute of Medicine of the National Academies; 2011.
246. Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice G. In: Field MJ, Lohr KN, eds. Clinical Practice Guidelines: Directions for a New Program. Washington (DC): National Academies Press (US)
Copyright (c) National Academy of Sciences.; 1990.
247. The Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. 2001. at www.agreetrust.org.)
248. Vlayen J, Aertgeerts B, Hannes K, Sermeus W, Ramaekers D. A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. International journal for quality in health care : journal of the International Society for Quality in Health Care 2005;17:235-42.
249. Siering U, Eikermann M, Hausner E, Hoffmann-Esser W, Neugebauer EA. Appraisal tools for clinical practice guidelines: a systematic review. PLoS One 2013;8:e82915.
250. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18-23.
251. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. Cmaj 2010;182:1045-52.
252. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. Cmaj 2010;182:E472-8.
253. Frenette AJ, Charbonney E, D'Aragon F, et al. A Canadian survey of critical care physicians' hemodynamic management of deceased organ donors. Can J Anaesth 2019.
254. Dodia NN, Richert ME, Deitchman AR, et al. A Survey of Academic Intensivists' Use of Neuromuscular Blockade in Subjects With ARDS. Respiratory care 2019.
255. Wise R, Rodseth R, Blaser A, et al. Awareness and knowledge of intra-abdominal hypertension and abdominal compartment syndrome: results of a repeat, international, cross-sectional survey. Anaesthesiology intensive therapy 2019;51:186-99.
256. Zhang Z, Xu P, Fang Q, et al. Practice pattern of aerosol therapy among patients undergoing mechanical ventilation in mainland China: A web-based survey involving 447 hospitals. PLoS One 2019;14:e0221577.
257. Mannix R, Zemek R, Yeates KO, et al. Practice Patterns in Pharmacological and Non-Pharmacological Therapies for Children with Mild Traumatic Brain Injury: A Survey of 15 Canadian and United States Centers. J Neurotrauma 2019.
258. Green RS, Fergusson DA, Turgeon AF, et al. Resuscitation Prior to Emergency Endotracheal Intubation: Results of a National Survey. The western journal of emergency medicine 2016;17:542-8.
259. Total Population Sampling. 2012. 2019, at https://www.statisticshowto.datasciencecentral.com/total-population-sampling/.)
260. Etikan I, Musa, S.A, Alkassim R.S, . Comparison of Convenience Sampling and Purposive Sampling. American Journal of Theoretical and Applied Statistics 2016;5:1-4.
261. Frenette AJ, Veillette C, Meade M, et al. Right ventricular dysfunction in neurologically deceased organ donors: An observational study in a tertiary-care organ donor referral centre. Journal of critical care 2019;54:37-41.

262. Frenette AJ, Williamson D, Williams V, Lagace AM, Charbonney E, Serri K. A Pilot Randomized Controlled Trial Comparing Levothyroxine to Placebo in Neurologically Deceased Donors. Prog Transplant 2019;29:261-8.
263. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ 2016;355:i5239.
264. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. BMC medical research methodology 2010;10:1.
265. Eldridge SM, Lancaster GA, Campbell MJ, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PLoS One 2016;11:e0150205.
266. Arnold DM, Burns KE, Adhikari NK, et al. The design and interpretation of pilot trials in clinical research in critical care. Crit Care Med 2009;37:S69-74.
267. Cook DJ, Rocker G, Meade M, et al. Prophylaxis of Thromboembolism in Critical Care (PROTECT) Trial: a pilot study. Journal of critical care 2005;20:364-72.
268. Hebert PC, Chin-Yee I, Fergusson D, et al. A pilot trial evaluating the clinical effects of prolonged storage of red cells. Anesth Analg 2005;100:1433-8, table of contents.
269. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC medical research methodology 2013;13:104.
270. Kennedy PJ, Leathley CM, Hughes CF. Clinical practice variation. The Medical journal of Australia 2010;193:S97-9.
271. Hay MC, Weisner TS, Subramanian S, Duan N, Niedzinski EJ, Kravitz RL. Harnessing experience: exploring the gap between evidence-based medicine and clinical practice. Journal of evaluation in clinical practice 2008;14:707-13.
272. Kitto S, Villanueva EV, Chesters J, Petrovic A, Waxman BP, Smith JA. Surgeons' attitudes towards and usage of evidence-based medicine in surgical practice: a pilot study. ANZ journal of surgery 2007;77:231-6.
273. Chen CY, Huang TW, Kuo KN, Tam KW. Evidence-based health care: A roadmap for knowledge translation. Journal of the Chinese Medical Association : JCMA 2017;80:747-9.
274. Graham ID, Harrison MB. Evaluation and adaptation of clinical practice guidelines. Evidence-based nursing 2005;8:68-72.
275. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology 2011;64:380-2.
276. Ponce OJ, Alvarez-Villalobos N, Shah R, et al. What does expert opinion in guidelines mean? a meta-epidemiological study. Evid Based Med 2017;22:164-9.
277. Abarshi E, Rietjens J, Robijn L, et al. International variations in clinical practice guidelines for palliative sedation: a systematic review. BMJ supportive & palliative care 2017;7:223-9.
278. Hammett S, Youssef NA. Systematic review of recent guidelines for pharmacological treatments of bipolar disorders in adults. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists 2017;29:266-82.
279. Hirsch M, Begum MR, Paniz E, Barker C, Davis CJ, Duffy J. Diagnosis and management of endometriosis: a systematic review of international and national guidelines. BJOG : an international journal of obstetrics and gynaecology 2018;125:556-64.

280. Forte DN, Vincent JL, Velasco IT, Park M. Association between education in EOL care and variability in EOL practice: a survey of ICU physicians. Intensive Care Med 2012;38:404-12.
281. Smudla A, Mihaly S, Okros I, Hegedus K, Fazakas J. The attitude and knowledge of intensive care physicians and nurses regarding organ donation in Hungary--it needs to be changed. Ann Transplant 2012;17:93-102.
282. Hancock J, Shemie SD, Lotherington K, Appleby A, Hall R. Development of a Canadian deceased donation education program for health professionals: a needs assessment survey. Can J Anaesth 2017;64:1037-47.
283. Krautheim V, Schmitz A, Benze G, et al. Self-confidence and knowledge of German ICU physicians in palliative care - a multicentre prospective study. BMC palliative care 2017;16:57.
284. Cassam Q. Diagnostic error, overconfidence and self-knowledge. Palgrave Communications 2017;3:17025.
285. de Leeuw E.D. HJ, Dillman D. International Handbook of Survey Methodology2012.
286. de Leeuw ED HJ, Huisman M. Prevention and Treatment of Item Nonresponse. Journal of Official Statistics 2003;19:153-76.
287. Oczkowski SJW, Durepos P, Centofanti J, et al. A Multidisciplinary Survey to Assess Facilitators and Barriers to Successful Organ Donation in the Intensive Care Unit. Prog Transplant 2019;29:179-84.
288. Wheeldon DR, Potter CD, Ciulli F, et al. Multiorgan donor resuscitation. Perfusion 1992;7:213-6.
289. Weiland TJ, Marck CH, Jelinek GA, Neate SL, Hickey BB. Attitudes of Australian emergency department clinicians toward organ and tissue donation: an analysis of cultural and religious influences. Prog Transplant 2013;23:278-89.
290. McGlade D, Pierscionek B. Can education alter attitudes, behaviour and knowledge about organ donation? A pretest-post-test study. BMJ Open 2013;3:e003961.
291. de Andrade J, Figueiredo KF. Impact of Educational and Organizational Initiatives in Organ Donation in a Southern Brazilian State in the Last Decade. Transplantation proceedings 2019;51:625-31.
292. Murakami M, Fukuma S, Ikezoe M, et al. Effect of an educational program on attitudes towards deceased organ donation. Ann Transplant 2015;20:269-78.
293. Noor A.D HHS, Norashikin A, . Factors Influencing Knowledge Sharing in Organizations: A Literature Review. International Journal of Scienc and Research 2014;3:1314-9.
294. Lizarondo L, Grimmer-Somers K, Kumar S. A systematic review of the individual determinants of research evidence use in allied health. Journal of multidisciplinary healthcare 2011;4:261-72.
295. Sullivan KJ, Wayne C, Patey AM, Nasr A. Barriers and facilitators to the implementation of evidence-based practice by pediatric surgeons. Journal of pediatric surgery 2017;52:1666-73.
296. Irving M, Eramudugolla R, Cherbuin N, Anstey KJ. A Critical Review of Grading Systems: Implications for Public Health Policy. Evaluation & the Health Professions 2017;40:244-62.
297. Rattray M, Roberts S, Desbrow B, et al. A qualitative exploration of factors influencing medical staffs' decision-making around nutrition prescription after colorectal surgery. BMC Health Serv Res 2019;19:178.

298. Novitzky D, Rose AG, Cooper DK. Injury of myocardial conduction tissue and coronary artery smooth muscle following brain death in the baboon. Transplantation 1988;45:964-6.
299. Conrick-Martin I, Gaffney A, Dwyer R, O'Loughlin C, Colreavy F. Intensive Care Society of Ireland - Guidelines for management of the potential organ donor (2018-2nd edition). Irish journal of medical science 2019.
300. Pandit RA, Zirpe KG, Gurav SK, et al. Management of Potential Organ Donor: Indian Society of Critical Care Medicine: Position Statement. Indian J Crit Care Med 2017;21:303-16.
301. Lamontagne F, Quiroz Martinez H, Adhikari NK, et al. Corticosteroid use in the intensive care unit: a survey of intensivists. Can J Anaesth 2013;60:652-9.
302. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001;38:923-31.
303. Bittner HB, Kendall SW, Chen EP, Craig D, Van Trigt P. The effects of brain death on cardiopulmonary hemodynamics and pulmonary blood flow characteristics. Chest 1995;108:1358-63.
304. Armitage JM, Hardesty RL, Griffith BP. Prostaglandin E1: an effective treatment of right heart failure after orthotopic heart transplantation. J Heart Transplant 1987;6:348-51.
305. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. Br J Anaesth 2012;108 Suppl 1:i96-107.
306. Belhaj A, Dewachter L, Rorive S, et al. Mechanical versus humoral determinants of brain death-induced lung injury. PLoS One 2017;12:e0181899.
307. Theodore J, Robin ED. Speculations on neurogenic pulmonary edema (NPE). The American review of respiratory disease 1976;113:405-11.
308. Demling R, Riessen R. Pulmonary dysfunction after cerebral injury. Crit Care Med 1990;18:768-74.
309. Park ES, Son HW, Lee AR, et al. Inhaled nitric oxide for the brain dead donor with neurogenic pulmonary edema during anesthesia for organ donation: a case report. Korean J Anesthesiol 2014;67:133-8.
310. Prodhan P, Casavant D, Medlock MD, Yager P, Kim J, Noviski N. Inhaled nitric oxide in neurogenic cardiopulmonary dysfunction: implications for organ donation. Transplantation proceedings 2004;36:2570-2.
311. e-Statistics on Organ Transplants, Waiting Lists and Donors: 2017 Cumulative Report. 2017. (Accessed 22-07-2018, 2018, at https://www.cihi.ca/en/e-statistics-on-organ-transplants-waiting-lists-and-donors.)
312. Gallego FB MC, Allard J, Anthony SA, Dumez V, Hartell D, Hebert MJ, Knoll G, West LJ, Wright L, Fortin MC. Defining Future Research Priorities in Donation and Organ and Stem Cell Transplantation With Patients, Families, Caregivers, Healthcare Providers and Researchers Within the Canadian National Transplant Research Program. Transplant Direct 2018;4:e360.
313. DuBose J, Salim A. Aggressive organ donor management protocol. Journal of intensive care medicine 2008;23:367-75.
314. Shemie SD. Trends in deceased organ donation in Canada. Cmaj 2017;189:E1204-E5.
315. 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.
316. Hoste P, Ferdinande P, Vogelaers D, et al. Adherence to guidelines for the management of donors after brain death. Journal of critical care 2019;49:56-63.

317. Grieser M, Gurgol, CG., Hildebrandt, MA. Engaging Clinicians in Patient-Centered Research. In: Institute P-COR, ed. Engagement blogs. Washington, DC2016.
318. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implementation science : IS 2012;7:50.
319. Simpson DD. A conceptual framework for transferring research to practice. Journal of substance abuse treatment 2002;22:171-82.
320. Gagnon MP, Attieh R, Ghandour el K, et al. A systematic review of instruments to assess organizational readiness for knowledge translation in health care. PLoS One 2014;9:e114338.
321. Melnyk BM, Fineout-Overholt E, Mays MZ. The Evidence-Based Practice Beliefs and Implementation Scales: Psychometric Properties of Two New Instruments. Worldviews on Evidence-Based Nursing 2008;5:208-16.
322. Lehman WE, Greener JM, Simpson DD. Assessing organizational readiness for change. Journal of substance abuse treatment 2002;22:197-209.
323. Bohman TM, Kulkarni S, Waters V, Spence RT, Murphy-Smith M, McQueen K. Assessing health care organizations' ability to implement screening, brief intervention, and referral to treatment. Journal of addiction medicine 2008;2:151-7.
324. The L. Organ donor research: towards a more effective system. Lancet 2017;390:1928.
325. Childress JF. Organ Donor Research: Overcoming Challenges, Increasing Opportunities. Jama 2017;318:2177-8.
326. Burns KE, Duffett M, Kho ME, et al. A guide for the design and conduct of self-administered surveys of clinicians. Cmaj 2008;179:245-52.
327. Stevanovic A, Schmitz S, Rossaint R, Schurholz T, Coburn M. CONSORT item reporting quality in the top ten ranked journals of critical care medicine in 2011: a retrospective analysis. PLoS One 2015;10:e0128061.
328. Brick JM, Kalton G. Handling missing data in survey research. Stat Methods Med Res 1996;5:215-38.
329. Feihl F, Broccard AF. Interactions between respiration and systemic hemodynamics. Part I: basic concepts. Intensive Care Med 2009;35:45-54.
330. D'Aragon F, Dhanani S, Lamontagne F, et al. Canada-DONATE study protocol: a prospective national observational study of the medical management of deceased organ donors. BMJ Open 2017;7:e018858.