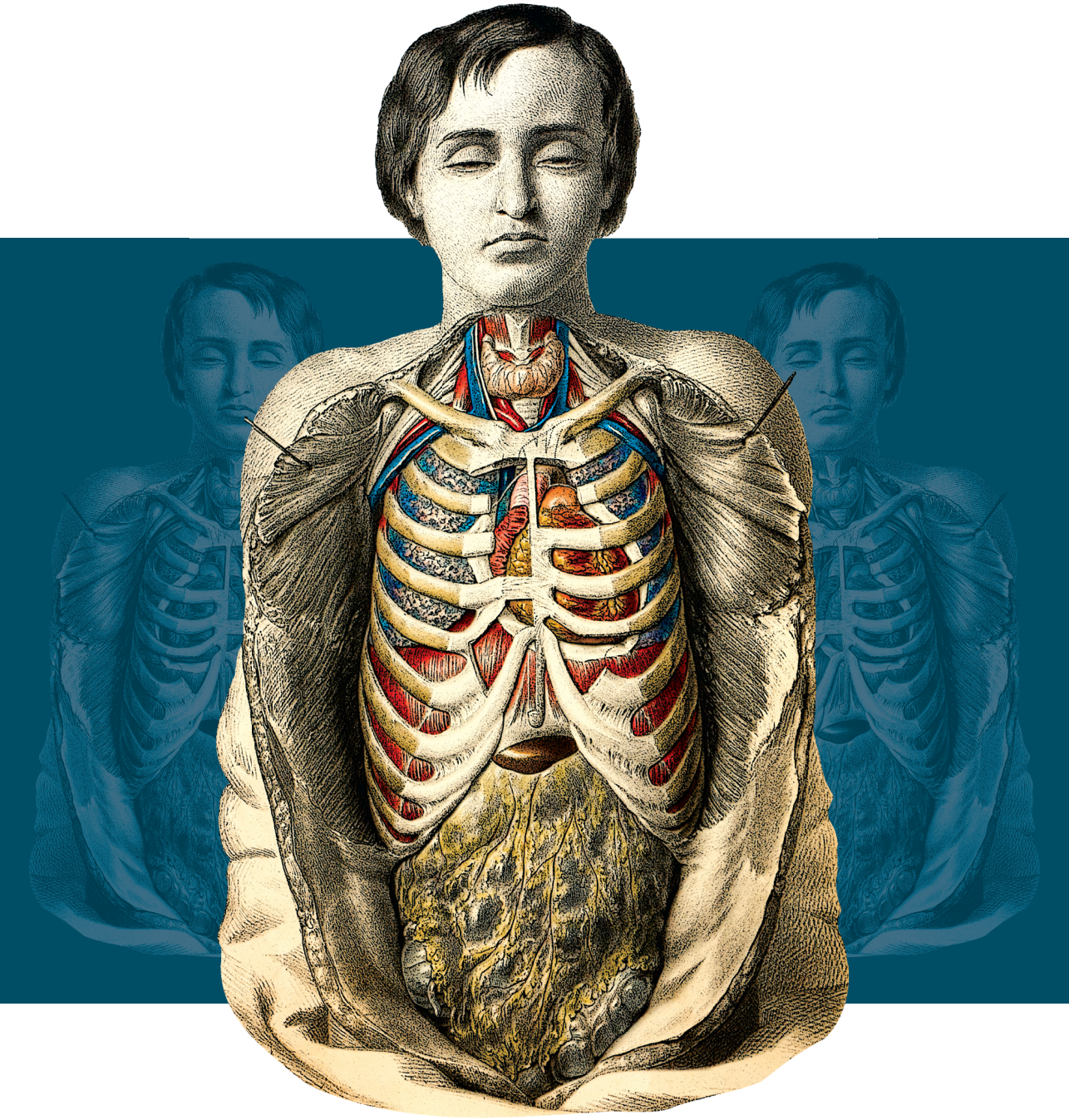

Organ Donor Recognition

Practical and Ethical Considerations

Yorick J. de Groot

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Colophon

Organ donor recognition, practical and ethical considerations

Thesis | Erasmus University Rotterdam | The Netherlands

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"Your time is limited, so don't waste it living someone else's life. Don't be trapped by dogma – which is living with the results of other people's thinking. Don't let the noise of other's opinions drown out your own inner voice. And most important, have the courage to follow your heart and intuition. They somehow already know what you truly want to become. Everything else is secondary."

Steve Jobs at Stanford's Commencement Address in 2005

Voor mijn ouders

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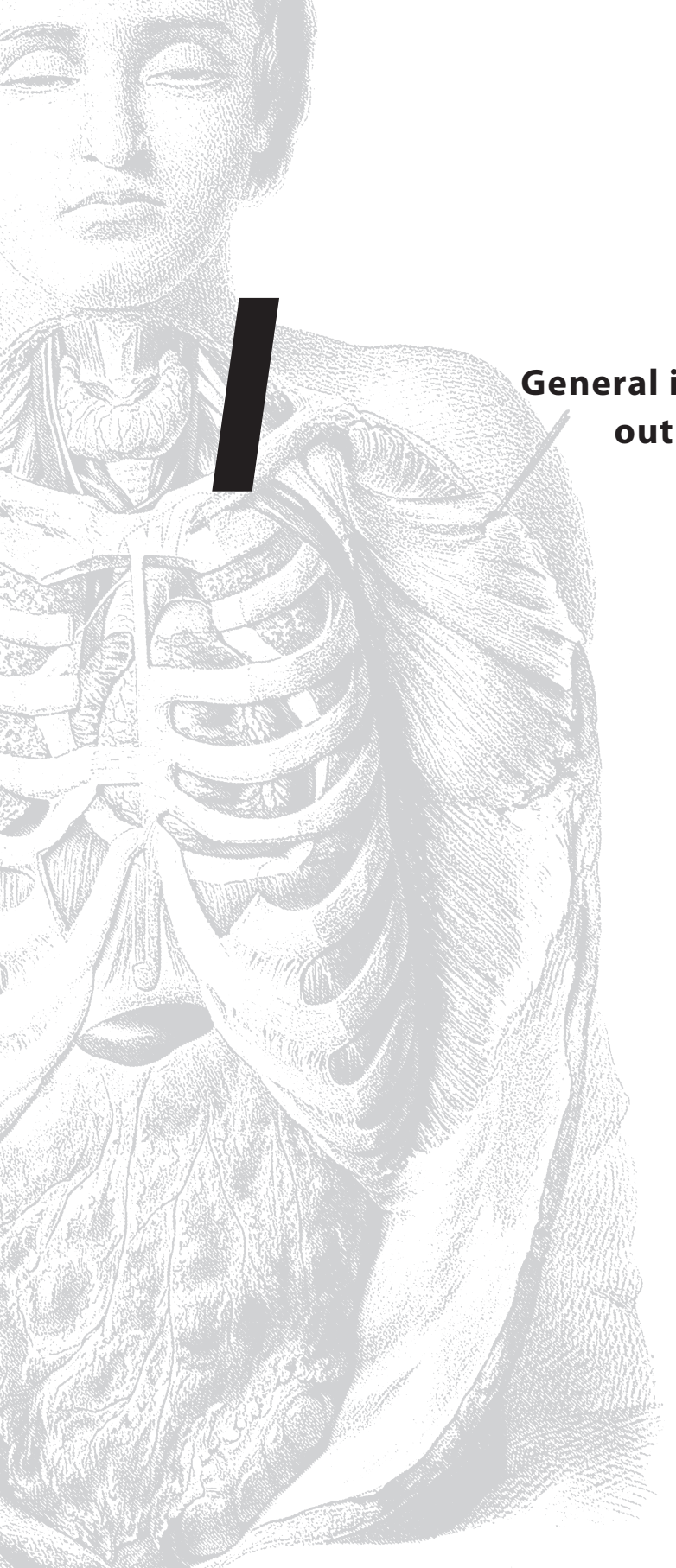
Introduction



1

General introduction and outline of the thesis

"Death is the cure for all diseases"
– Sir Thomas Browne (1605-1682), English author

Solid organ transplantation is one of the most remarkable therapeutic advances in medicine over the past 60 years. What initially began as 'a clinical experiment' gradually developed into a cost effective, lifesaving therapy for patients with end stage organ failure. Organ donation and transplantation has been made possible due to cultural, ethical and political acceptance over time and because of important innovations in organ preservation, surgery, immunosuppression and the management of infectious diseases.[1]

ORGAN DONATION IN A HISTORICAL PERSPECTIVE

The first recorded successful solid organ transplantation between humans was that of a living kidney donation between two identical twin brothers in 1954.[2] Earlier, non-heart-beating donations between humans were attempted but ultimately failed because of the lack of knowledge of organ preservation and immunomodulation at that time. During the 1960s, organ transplantation from unrelated organ donors gained wider acceptance due to the introductions of early generations of immunosuppressive agents. In 1962 Joseph Murray, later a Nobel prize Laureate, performed the first successful cadaveric kidney transplant.[3] This was followed in 1963 by Thomas Starzl who performed the first human liver transplant.[4] It was Christiaan Barnard who performed the very first human heart transplantation in Groote Schuur Hospital in Cape town, South Africa.[5] The recipient, a 54-year-old man, died 18 days later of a double pneumonia. As a result of the strong immunosuppressive medication he received. Noteworthy is that the donor of the heart was not pronounced brain dead. According to the article written by Barnard he states that 'as soon as the donor had been certified dead (when the electrocardiogram had shown no activity for 5 minutes and there was absence of any spontaneous respiratory movements and absence of reflexes)… the donors chest was then opened rapidly, using a median sternotomy.'

The concept of brain death arose as an unanticipated consequence of the advances in medical technology. The introduction of mechanical ventilation using positive pressure ventilation of patients proved to save lives. However this development presented also a new problem. How to deal with patients with devastating neurological injuries who would previously die without mechanical ventilation but now could be kept alive with this new technique. Two landmark articles concerning this topic appeared in 1959. Early 1959, Wertheimer and colleagues published an article called '*A propos du diagnostic de la mort du système nerveux dans les comas avec arrêt respiratoire traites par respiration artificielle*'[6] which translates as 'Diagnosis of death of the nervous system in coma with respiratory arrest treated by artificial respi-

ration'. Later that year Mollaret and colleagues coined the term '*Le Coma Dépassé*',[7] which literally meant 'irreversible coma'. Mollaret et al. described a condition of deep coma without spontaneous respiration, no reflexes, polyuria and low blood pressure (if norepinephrine was not given continuously) and the absence of all electroencephalographic (EEG) activity. They pointed out in their article that if inotropic support was withdrawn that the patient would rapidly die as the result of a cardiac arrest. Schwab et al. were the first who presented a triad for certifying brain death on the 16th annual meeting of the Electroencephalography Society in 1962.[8] They proposed that 'the total absence of EEG activity after 30 minutes of recording is (the) most important evidence of death of the central nervous system'. Schwab et al. incorporated the EEG with other diagnostic criteria in order to determine brain death.'

Henry Beecher, anesthesiologist and established ethicist wrote in 1968 to the Dean of the Harvard Medical School, Robert Ebert, a request to form an Ad Hoc Committee to formulate and establish criteria for the diagnosis of brain death. The Dean complied with this request and the committee was formed with professionals from different areas of expertise. The 13-member Committee consisted of neurologists, ethicists, neurosurgeons, anesthesiologists, transplantation surgeons, public health physicians, one lawyer, one theologian and one historian.[9] The definition of death using neurologic criteria became formalized by the publication in the *Journal of the American Medical Association* on August 5, 1968 in a landmark article 'A definition of irreversible coma, the Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death.'[10] In 1981 the Uniform Determination of Death Act, as published in the *Journal of the American Medical Association*, made no provision for which specific tests should be used to determine brain death. The Act stated that 'an individual who sustained either (1) irreversible cessation of circulatory and respiratory, or (2) irreversible cessation of all function of the entire brain, including the brain stem, is dead. A determination must be made in accordance with the accepted medical standards.'[11] This made clear that there were two medical and legal accepted forms of death. Nowadays the concept of brain death is accepted in all industrialized western countries.[12] The Netherlands accepted brain death in 1974.[13]

THE DEAD DONOR RULE

There are three possible sources of organ donation:

1. Brain dead patients (heart-beating organ donors), these patients can donate every possible transplantable solid organ including the heart.
2. Patients who died after cessation of cardiopulmonary functions (non-heart-beating organ donors; cardiac death donors; circulatory death donors), these patients can donate kidneys, liver, pancreas and lungs.

3. Living organ donors, the donor is usually related to the recipient but this is not a rule of thumb. One kidney and a partial liver are the only possible organs that can be donated.

The main source of organs is post-mortem donors (in some countries, like the Netherlands, for kidneys the living (un)related organ donor is the main source). However post-mortem organ donors have never been sufficient to meet the demand of organs.

One of the most important factors in post-mortem organ donation is the so named 'dead donor rule'. This is the ethical and legal rule that requires that donors are not be killed in order to obtain their organs.[14] Organ retrieval itself may not cause death so the removal of organs necessary for life, like the heart or the lungs, prior to death of the donor would violate the dead donor rule. However the removal of one kidney or a partial liver will not violate the dead donor rule because this will not lead to the death of the patient. The dead donor rule is the ethical axiom for organ donation as it is the ethical linchpin of a voluntary system of organ donation and helps to maintain the public trust in organ donation after death.[14] The dead donor rule results sometimes in a conflict with the ongoing efforts of the transplantation society to procure organs of better quality. A clear example of a violation of the dead donor rule was a study published in the *New England Journal of Medicine* in 2008 by Boucek and colleagues. They performed three heart transplantations from young infant donors with a mean age of 3.2 days.[15] Normally such procedure can only be performed with hearts from brain dead patients because the hearts of donors who died after circulatory death would deteriorate too much as result of warm ischemia. The novelty of this procedure was that they used the hearts from young infants who were declared dead according to cardiopulmonary criteria. The observation time of the first heart transplantation between the declaration of death and organ retrieval was 3 minutes, which was shortened to 1.25 minutes (75 seconds) for the latter two heart transplantations to reduce the risk of warm ischemia. This was based on the recommendations of the local medical ethics committee. According to this committee there was no evidence that autoresuscitation can occur after 60 seconds after cessation of cardiopulmonary functions. In a 2010 systematic review performed by Hornby et al. on autoresuscitation they concluded that there was not a single documented case of true autoresuscitation after life sustaining treatment was withdrawn.[16] However Bernat stated in the accompanying editorial that due to the small database and the empirical nature of the data a conservative observation period of 2-5 minutes as suggested by many scholars and organizations is still prudent.[17] Robert Veatch condemned the short waiting period because he regarded it as a clear violation of the dead donor rule. He stated: "There are controversial implications, however, if the goal is to transplant a heart after cardiac death. It is impossible to transplant a heart successfully after irreversible stoppage: if a heart is restarted, the person from whom it was taken cannot have been dead according to cardiac criteria. Removing organs from a patient whose heart not only can be restarted, but also has been or will be

restarted in another body, is ending a life by organ removal."[19] If one should only look at the neurological criteria for death as stated in the Uniform Determination of Death Act[11] there are also several problems with this adapted form of donation after cardiopulmonary death. According to Plum and Posner[20], "Under clinical circumstances, total ischemic anoxia of the cerebral cortex lasting longer than about 4 minutes starts to kill brain cells, with the neurons of the cerebral cortex and cerebellum dying first." According to the article by Antommaria et al[18], in 7 hospitals pediatric patients were declared dead within 5 minutes, and in 2 hospitals organs were removed within 2 minutes after circulatory arrest. These children were certainly not (brain) dead when their organs were removed, and this is in conflict with the accepted dead donor rule in the Western world.[14,21,22]

THE CURRENT PROBLEMS

Rarity of deceased organ donors

In the last 50 years solid organ transplantation has extended and improved the quality of life of many patients with end stage organ failure. In the United States the gap between the number of patients waiting for a kidney and the number receiving a kidney has widened over the last decade.[23] However the number of patients awaiting heart transplantation decreased over the past 5 years. This is likely a reflection of improvements in medical, interventional (like the left ventricular assisted device[24]) and surgical therapy for end-stage heart failure.[23] In the Eurotransplant area (Austria, Belgium, Croatia, Germany, Luxembourg, Slovenia and the Netherlands) the gap between the number of patients awaiting kidney transplantation and the number of donors slightly decreased over the past 8 years according to the latest annual report of Eurotransplant. The number of deceased donors remained the same and the number of living organ donors grew substantially since 1997.[25] In contrast with the United States the number of heart transplants decreased since 1997 from 759 to 615 in 2010, while the patients on the waiting list grew from 424 patients in 2001 to 1193 patients in 2010.[25] This could have been worse considering the earlier mentioned improvements in medical and surgical therapy for end-stage heart failure. Patients who are awaiting heart transplantation are completely dependent on the availability of brain dead organ donors.

Recognition of a potential organ donor and bottlenecks in the donation process

Timely referral of a potential organ donor to representatives of an organ procurement organization is essential for a smooth donation process. Elementary to achieve this goal is early recognition of a potential organ donor. However, many donors are still not recognized as such and are therefore lost for organ donation.[26-28] Other patients that are identified as a potential organ donor deteriorate too much between the period of recognition and brain death determination. Besides a good assessment tool to identify potential brain death organ donors

it is also of great importance to develop a quality assurance program in order to recognize possible areas of improvement. As such the DOPKI, a European Consortium composed of 13 organizations on behalf of 16 European countries (among which the Eurotransplant International Foundation), which represent 80% of the population and 80% of all the donation and transplantation activity in Europe, funded by the European Commission, tried to develop such a program. The DOPKI project sole purpose is to improve the donation rates and to develop a methodology that can determine the potential for donation and its outcome.[29] They expected that the associated study provides a useful basis for constructing solid programs in European countries targeted to study and monitor the potential of deceased donation and the performance in the deceased donation process, i.e., quality assurance programs. However to this date there is no peer-reviewed report of this methodology.

Dealing with relatives of a potential organ donor

The only realistic improvement, besides optimal donor recognition, that can be made in the current practice of deceased organ donation is to find a way to decrease the family refusals for organ donation.[30] A recent study showed that even non-rational factors like the 'ick factor' or the 'jinx factor' could play an important role in the decision of a family to give consent for organ donation of their deceased loved one.[31] The supply of organ donors will remain the same over the coming decade or will, due to progress in prevention and treatment of conditions leading to brain death, even decrease. Several factors are important to consider if one would want to improve the rate of consent of families of a deceased potential organ donor. First we have to acknowledge the fact that families have some knowledge about organ donation and the concept of brain death. In other words, most families already have some viewpoint about organ donation, which they take in consideration in the decision process. Siminoff and colleagues identified several key improvements.[32] First a good relationship between the family and the requestor could smoothen the way in decision process. Important to add is that seniority of the requestor also plays an essential role. Second, families are more likely to consent to organ donation if they are prepared that a request will be made. Decoupling of the pronouncement of death and requests for organ donation is also a factor to consider.[33]

Presumed consent

Due to the continuing demand for organs and the inadequate supply many countries developed legislative changes in the hope that they have a positive impact on the quantity of organs. Several countries introduced an opt-out system for donor registration. In an opt-out system everyone is considered a donor unless someone explicitly requests to be deleted from the donor registry. Many believe that this initiative will increase the donation rate with 25-30%.[34] Although others have serious doubts about presumed consent and consider it a distraction from the goal to find real solutions in the quest for more organs.[35] Horvat and col-

leagues[36] compared the characteristics and kidney transplantation rates for countries with presumed consent for deceased organ donation with countries with explicit consent. The deceased donor kidney transplantation rates were higher in countries with presumed consent (median, 22.6 transplantations per million populations; interquartile range, 9.3 to 33.8) versus countries with explicit consent (median 13.9 transplantations per million populations; interquartile range, 1.7 to 4.3).

Research Questions

1. Can the shortage of organs, especially hearts, obtained from deceased organ donors be solved?
2. How can a potential organ donor be recognized in daily intensive care practice and how can we identify bottlenecks in the process of organ donation?
3. What is the best moment to contact the relatives of a potential organ donor to request organ donation?
4. Is presumed consent a realistic solution to solve the shortage of organs?

OUTLINE OF THE THESIS

First, we studied the reasons for the ongoing decrease in the number of brain dead patients (**chapter 2**). We evaluate all the possible causes of brain death from an epidemiological viewpoint. Furthermore we looked at the ongoing prevention measures and progress in neurosurgical, neuroradiological and intensive care treatment of conditions potentially leading to brain death with regard to the consequences for organ donation in the nearby future.

In the next section of this thesis we discuss how we could improve potential organ donor recognition and what the possible consequences could be. In **chapter 3** we developed a new definition of a potential brain dead organ donor based on two accepted and validated neurological assessments tools. For our definition we used Glasgow Coma Scale[37] and the FOUR score.[38] The FOUR score, which stands for Full Outline of UnResponsiveness, is developed primarily for critically ill neurological patients admitted to a (neuro)critical care unit. The FOUR score has been validated over the past five years for emergency and intensive care use.[38-40] In this chapter we aimed to make a universally accepted definition that can be used to identify a patient who is in a state of 'imminent brain death'. The criteria for this definition were based on multi-disciplinary consensus among experts in the field. The goal was to propose a definition that could be used for identification and for data analysis.

We put our newly developed definition of imminent brain death to the test concerning the widely used donor conversion rates in **chapter 4**. The donor conversion rate is defined as the

actual number of organ donors divided by the number of patients who were regarded as potential organ donor. Donor conversion rates are used to set a goal for organ procurement agencies in the United States.[41] In this retrospective study we reviewed the medical charts of patients who died on the ICU and were diagnosed with a subarachnoid hemorrhage, a traumatic brain injury or an intracerebral hemorrhage in a two-year period. We applied three different assessment tools on this database. Two definitions of imminent brain death (the Glasgow Coma Scale version and the FOUR score version) and the definition of a potential organ donor used by the Organ Procurement Transplantation Network in the United States.

In **chapter 5** we extended the database to seven Dutch university hospitals. Here we used the old definition of a potential organ donor as used by the Dutch Transplant Foundation. We compared this definition ('severe brain damage': a patient admitted to an intensive care unit, mechanically ventilated, Glasgow Coma Score of $E_1M_1V_t$ and absence of at least one brain stem reflex) with the definition of imminent brain death based on the Glasgow Coma Scale.

In the next section of the thesis we studied the clinical practice for obtaining consent for organ donation and analyzed the practice of brain death determination from a historical perspective. In **chapter 6** we evaluated, in a retrospective fashion, the data of 228 brain dead patients who died in a 24-year period in a large university hospital in the Netherlands. An important factor in obtaining consent for organ donation from the relatives is the timing to discuss organ donation. We therefore compared the practice of brain death determination and obtaining consent for organ donation before 1998 (introduction of the Donor Register) with the standard of care after 1998.

In **chapter 7** we discuss the results of the FABRA study (FAmily presence during BRAin death determination). As already mentioned, the only real improvement possible in order to increase the supply of organ donors is to find a way to decrease refusal rate of families of potential organ donors. The whole process towards the decision of a family is complex. We developed the hypothesis that the presence of family members during the formal brain death determination of their loved one will increase the acceptance of the concept of brain death and hence the consent rate. In other words by demystifying the process of brain death determination we hoped to lessen the reluctance by family members of a potential organ donor. Unfortunately the study did not reach its goal of 50 patients due to several factors. We analyze these factors and make some recommendations.

Chapter 8 is dedicated to our experience concerning patients who are competent and awake but do not want to live anymore. These patients are dependent on life-sustaining intensive care measures however this therapy we provide is no longer improving the quality of life of the patient. We describe two awake patients who asked for the withdrawal of life-sustaining

measures. We discuss in this chapter the central place for autonomous choice of the patient and the care of the patient. Furthermore we analyze the doctrine of double effect in relation to palliative sedation on the intensive care unit.

Derived from chapter 8 we discuss in **chapter 9** why we do not try to obtain consent from patients, who are dependent of life-sustaining treatment but who are competent and awake and do not want to life anymore, for organ donation. We seldom consider these patients as potential organ donors before the withdrawal of mechanical ventilation. There is some experience with organ donation after deliberate termination of life (euthanasia) in Belgium. But we are not aware of documented cases in which ICU physicians ask patients if they are willing to donate their organs after death that occurs after withdrawal of mechanical ventilation on the ICU. In light of the scarcity of organs we discuss, using two scenarios, the pros and cons of obtaining consent from this group of patients in the light of ethical feasibility and practicality.

In the last section (**chapter 10**) of the thesis we externally validate a prognostic model developed by Yee and colleagues.[42] This model uses four easy to obtain neurological parameters to predict time of death after withdrawal of life sustaining measures of patient who have catastrophic brain injury but are not (yet) brain dead. This group of patients is of great importance from a transplantation standpoint because they can donate one or more organs after cardiopulmonary death. With regard to the diminishing supply of organs from brain dead patients this is a group of patients that cannot be missed. Simple prediction models that can identify patients who will die within 60 minutes after cardiopulmonary death do not exist. This is of relevance because a time period of more than 60 minutes could result in organs that are too deteriorated because of the suboptimal levels of oxygen.[43] External validation is essential for creating a clinically applicable prediction model.[44] In chapter 8 we looked at the discriminative properties of the model in a new database of patients. Besides the discriminative properties we also looked at the calibration of the model. Discrimination describes how well a model distinguishes between those who die within 60 minutes and those who survive longer. Calibration indicates how closely predicted outcomes match observed outcomes.

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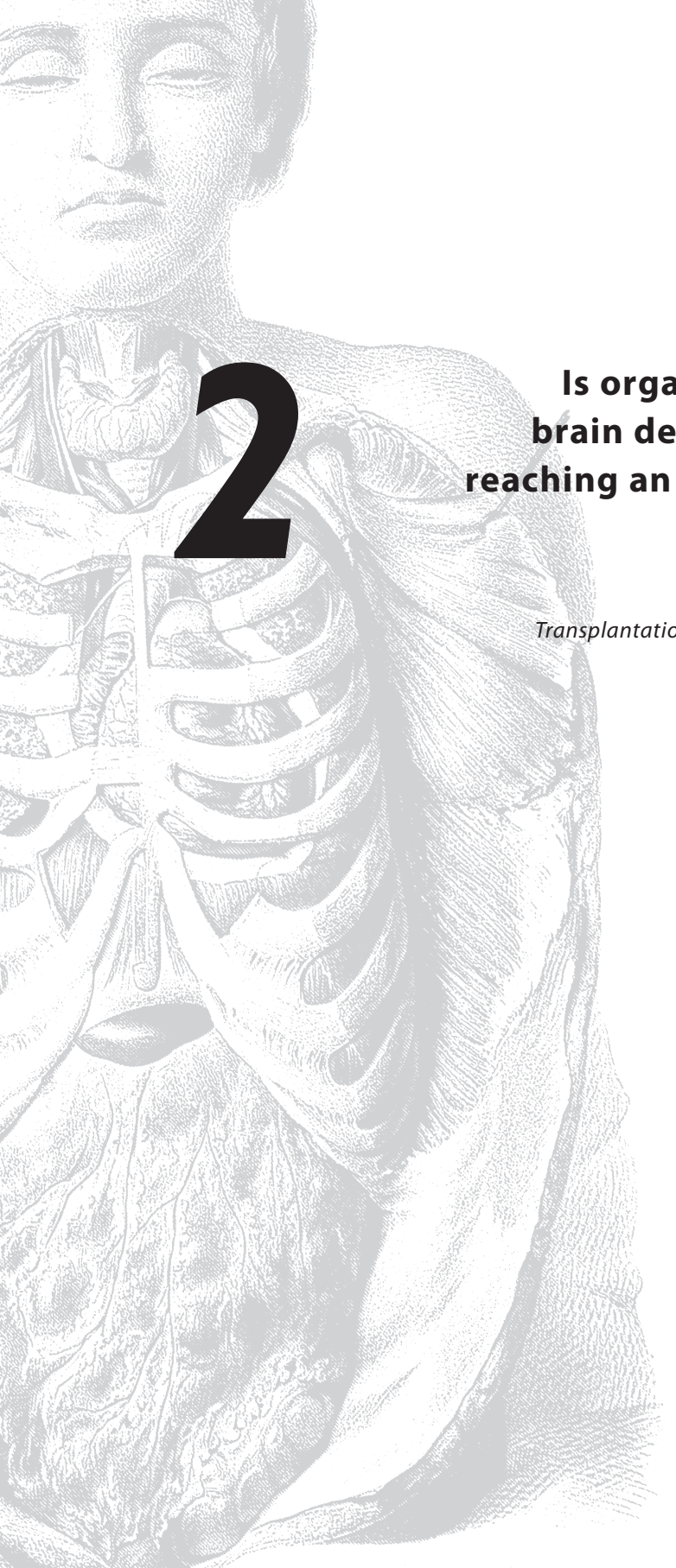
Shortage of organ donors



2

Is organ donation from brain dead organ donors reaching an inescapable and desirable nadir?

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E.J.O. Kompanje
Y.J. de Groot
J. Bakker

ABSTRACT

The brain dead patient is the ideal multiorgan donor. Conversely, brain death (BD) is an undesirable outcome of critical care medicine. Conditions that can lead to the state of BD are limited. An analysis showed that a (aneurysmal) subarachnoid hemorrhage, traumatic brain injury, or intracerebral hemorrhage in 83% precede the state of BD. Because of better prevention and treatment options, we should anticipate on an inescapable and desirable decline of BD. In this article, we offer arguments for this statement and discuss alternatives to maintain a necessary level of donor organs for transplantation.

The brain dead patient is the ideal multiorgan donor for organ transplantation. Conversely, brain death (BD) is an undesirable outcome of critical care medicine and an artifact of nature that results from the ability of medical technology to prolong and distort the process of dying. Conditions that can lead to the state of BD are limited. An analysis of 71 published series of brain dead patients (n=6317) showed that a (aneurysmal) subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), or spontaneous intracerebral hemorrhage (ICH) in 83% precede the state of BD; SAH is the most common BD-associated condition.[1] These findings concur with earlier reports regarding the causes of BD.[2-5] BD is a rare outcome of critical care medicine. Among 4248 patients who died in 1999 to 2000 in European intensive care units, only 330 (7.8%, regional differences between 3.2% [Northern Europe] and 12.4% [Southern Europe]) deaths have been diagnosed as brain dead.[6] BD can be observed exclusively in intensive care units that have policies and facilities to admit and treat patients with SAH, TBI, and ICH. BD is susceptible to changes and differences in its causes and in the location and time of its occurrence. Progress in the prevention and treatment of these conditions that lead to BD can result in a decline in the actual number of brain dead patients in the coming few decades in almost all industrialized countries in the Western world. In The Netherlands, the number of donation after brain death (DBD) declined from 915 patients in the period1995 to 1999 to 637 patients in period 2005 to 2009 (30%; Table 1) according to the annual reports of the Dutch Transplant Foundation (available at http://transplantatiestichting.nl/cms/index.php?page_jaarverslagen). However, the number of donation after cardiac death (DCD) increased from 118 patients in first period to 453 patients in the period of 2005 to 2009 (282%). This is in line with the study of Saidi et al..[7]

The result of this ongoing process can be a further widening gap between the number of donors and the number of recipients. Furthermore, the diminishing role of DBD will have great ramifications for transplantation medicine as a whole. In this article, we will place this in a future perspective. We also mention some possible opportunities, within acceptable legal and ethical frameworks, to maintain a necessary level of organ donors.

Table 1. Comparing effectuated DCD and DBD in different eras in The Netherlands over the past 15 yrs.

	Era 1 (1995-1999)	Era 2 (2000-2004)	Era 3 (2005-2009)	P[a]
No. of donors	1033	1042	1090	0.695
DBD (% of total number of donors)	915 (88.6)	697 (66.9)	637 (58.4)	0.008
DCD (% of total number of donors)	118 (11.4)	345 (33.1)	453 (41.6)	<0.0001

[a] P value from one-way analysis of variance with post hoc Tukey for comparison of multiple groups. P<0.05 was considered significant. DBD, donation after brain death; DCD, donation after cardiac death

SAH is the most common condition that precedes BD. An SAH accounts for approximately 1% to 7% of all cerebral strokes. The incidence is approximately 6 to 7 per 100,000 person-years.[8] Women are at a 1.6 times higher risk of SAH than men.[9] When untreated, an SAH is a life-threatening condition. The case fatality in population-based studies is approximately 50% but have tended to show declining trends in the incidence and case fatality after SAH during the past 3 decades.[10,11] A recent population-based study from the United Kingdom showed that mortality because of SAH decreased by approximately 50% during the past 2 decades; this reduction is mainly due to improved outcome in cases surviving until arrival at hospital. This improvement was consistent with a significant decrease in case fatality during the past 25 years in a pooled analysis of 31 population-based studies, which reflects the improvements in the management of SAH.[12] Endovascular coiling for the treatment of intracranial aneurysms was introduced in 1990. Hospital use of coiling has increased during recent years. The International Subarachnoid Aneurysm Trial demonstrated that coiling was associated with a reduction in the risk of death and dependency at 1 year after SAH.[13] Elective coiling of unruptured intracranial aneurysms and calcium-channel blocker greatly improved outcome.[14-16]

SAH and ICH have two common risk factors: cigarette smoking and untreated hypertension.[17,18] Cigarette smoking is an independent risk factor not only for SAH but also for aneurysm formation.[19,20] In population-based or cohort studies, 70% to 75% of patients with SAH have a history of smoking, and 50% to 60% are current smokers.[21] Regarding the prevention of SAH and ICH, recent studies that examined the impact of antismoking legislation showed that crude rates of admission to hospital because of cardiovascular conditions, including stroke, decreased almost 40% during the ban period that affected restaurant settings; this reinforces the value of smoking bans to public health.[22] Smoking plays a critical role in aneurysm development, especially in younger patients, but physiological mechanisms exist for the repair of the damage that is induced by this toxic insult if cessation is possible.[19]

The pharmacologic treatment of high blood pressure reduces the risk of stroke, including SAH and ICH, which has been confirmed in a large number of randomized controlled trials. Effective delivery of hypertension care in the community requires a rigorous approach in terms of identification, follow-up, and treatment, which could lead to a notable reduction in the incidence of SAH and ICH. Countries with effective delivery of hypertension care show a lower incidence of SAH than other countries.[23] Therefore, cessation of smoking and treatment of hypertension are the most effective prevention measures for SAH and ICH.

Road traffic accidents (RTAs) causing TBI, the second major cause of BD, account for more than 60% of the patients, who become brain dead after TBI.[4] Much societal and political effort is aimed at RTA prevention.[24] Although the total number of road traffic deaths will increase in

the coming decade worldwide, it is declining in most European industrialized countries and in the United States, which reflects effective prevention measures.[25,26] In the United States, in 2009, RTA fatalities were the lowest on record since1954.[25] In 16 European countries, fatalities of vehicle occupants have declined between 1970 and 1999 by 19% to 62%. Pedestrian deaths show an even more significant decline of up to 95%.[26] Belgium is often mentioned as being successful in providing a high number of organ donors; however, BD as a result of TBI declined from 69% to 39% between the period1991 to 1992 and 2006 to 2007 in 26 hospitals in Belgium.[27] In 2009, the absolute number of organ donors was the lowest since 1996, which was linked to the decline in RTAs by the Belgium lay press. RTA-associated deaths have declined in Belgium by 36% in the past decade. In addition to Belgium, Spain is commonly cited as an example of good practice as demonstrated by having the world's highest rate of organ donation. However, this successful Spanish model is likely to be challenged as the number of RTAs has decreased in the past decade. Spain also adopted one of the strictest smoking bans of Europe, which became effective January 2011, which could challenge DBD in Spain and could therefore be reaching a nadir.[28] The decline of RTAs is also observed in many other European countries. In 2006, the United Kingdom reported one of the lowest numbers of RTA deaths in the European Union: 5.4 of 100,000. In 1967, there were 199 casualties per 100 million vehicle kilometers. By 2007, this declined to 48 per 100 million vehicle kilometers.

The ongoing efforts in the prevention of SAH and ICH that result from effective smoking bans and effective delivery of hypertension control and progress in the endovascular treatment of cerebral aneurysms and improvements in road traffic safety in Western industrialized countries can eventually lead to an inescapable and desirable decline in BD as an outcome of neurocritical care. This can have a dramatic effect on the availability of organs, especially hearts, for transplantation. It is clear that no physician or policymakers wants to intervene in this process of prevention and treatment of these causes with the sole reason to increase the number of brain dead organ donors. For this reason, we should anticipate the further decline in the availability of brain dead donor donors and investigate other possible sources as living kidney/liver donors and cardiac death donors, and we may have to consider possible alternatives beyond the more accepted sources.

Currently, donation of hearts is only possible, respecting the "dead donor rule," from brain dead donors. Boucek et al. reported donation of hearts obtained from hopelessly ill infants who were pronounced death according to cardiopulmonary criteria after withdrawal of mechanical ventilation. They transplanted the hearts of two infants after an observation period of less than 2 min after they were declared death.[29] A review confirmed heart transplantation in a pediatric setting after DCD in several hospitals in the United States.[30] Although this form of donation may be a new source of hearts, there are serious ethical and conceptual questions surrounding this practice.[31-35] Extreme solutions as neuro-euthanasia and euthanasia by

surgical heart removal as suggested by Wilkinson and Savulescu[36] face many ethical, practical, and societal concerns. In addition to the actual decline of potential organ donors, we are also confronted with a high family refusal rate. Improvement in communication skills proved to be beneficial in raising the consent rate.[37]

The lungs and lung lobes can be obtained from DCD donors, DBD donors, and living donors.[38] However, living lung lobe transplantation raised many practical and ethical concerns and is therefore not widely accepted. In recent report from the University of Wisconsin concerning the long-term outcomes for all lung transplant recipients who received lungs from DCD donors showed that graft survival rates were equivalent of those who received lungs from DBD donors.[39] Some new lung protective strategies are proposed in brain dead patients to prevent deterioration during the time between the declaration of BD and transplantation suitability. A recently published study showed an increase in the number of eligible and harvested lungs compared with conventional ventilation strategies.[40] Optimal identification and management of controlled DCD could increase the number of donors with 10%.[41] A combination of improved care of the potential organ donors and further improvement of the supply of DCD donors could limit the gap between the numbers of donors and recipients.

The kidneys and livers could be obtained from DCD donors, DBD donors, and living-related or -unrelated organ donation. With the possible decline of BD as an outcome of critical care medicine, we need to further investigate DCD and more importantly living organ donation, which can be seen as the cornerstone of kidney transplantation worldwide. Many incentives have been proposed to remove the barriers for living donors. Because of the concerns of possible exploitation of uninformed and poor donors, the World Health Organization reaffirmed recently their statement "to the principles of human dignity and solidarity which condemn buying of human body parts for transplantation and exploitation of the poorest and most vulnerable populations and the human trafficking that result from such practices".[42] Davis[43] proposes the removal of hurdles such as the lack of funding to cover the loss of wage, travel, and living expenses for potential living organ donors.

The means proposed in this article to improve living kidney and liver donation in addition to the aforementioned are community-specific campaigns, expanding research on the long-term risk of living organ donation and teach patients to tell their stories to the community. DCD, the other major source of kidneys and livers, remains a topic of investigation. Recent studies concerning the long-term graft survival of kidney and liver transplants showed and equivalent survival compared with organs obtained from DBD donors.[44,45]

The transplant community should anticipate on a possible decline of brain dead patients because of better prevention and treatment of the causes leading to BD. This decline is desir-

able and inescapable. Concerning the decline of hearts eligible for transplantation, there is no alternative source without violating the dead donor rule. For obtaining the lungs, kidneys, and livers, there is still potential for further improvement. Better and timely identification and care of the potential organ donor[46] and removal of the hurdles of living organ donation will offer us some time to further investigate more challenging alternative sources that may force us to shift our moral and ethical boundaries.[34,36]

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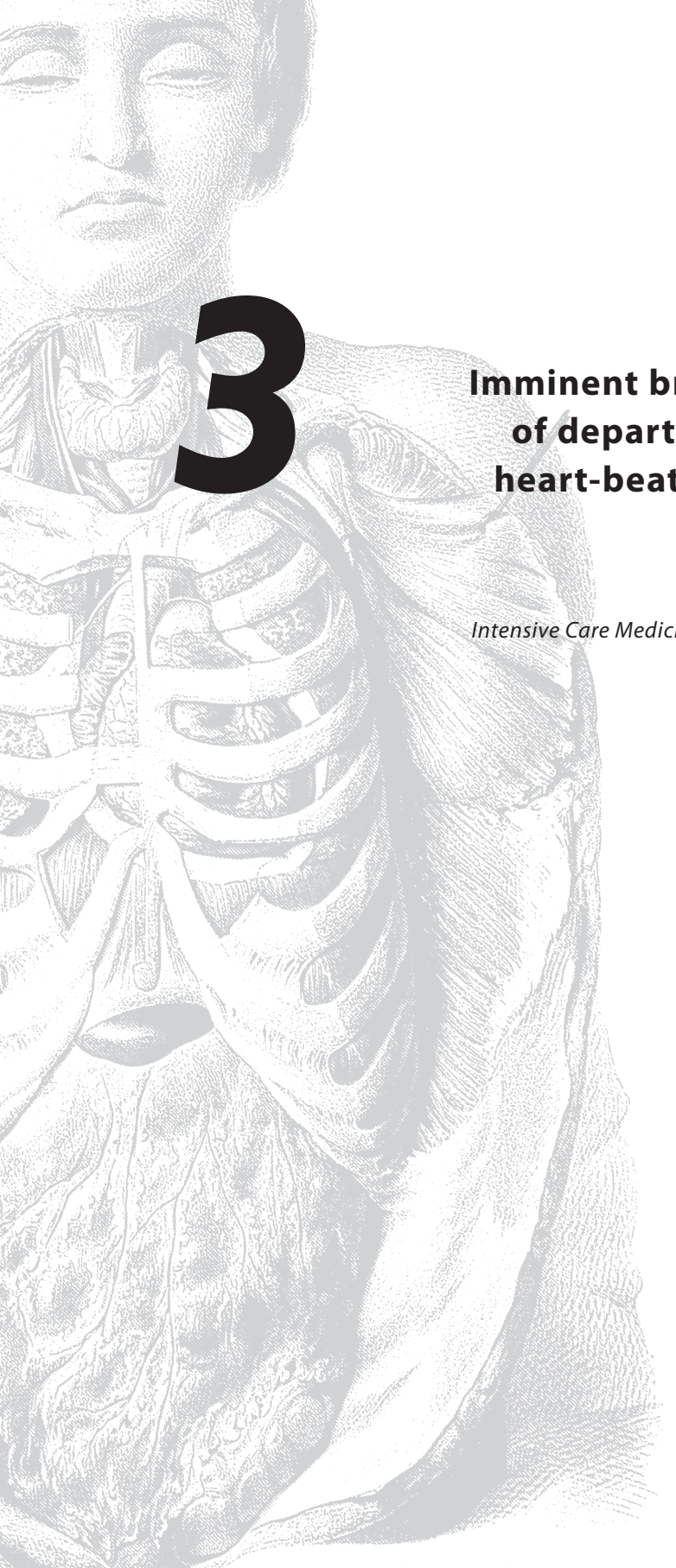
Potential donor recognition and their consequences



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Imminent brain death: point of departure for potential heart-beating organ donor recognition

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ABSTRACT

Purpose: There is, in European countries that conduct medical chart review of intensive care unit (ICU) deaths, no consensus on uniform criteria for defining a potential organ donor. Although the term is increasingly being used in recent literature, it is seldom defined in detail. We searched for criteria for determination of imminent brain death, which can be seen as a precursor for organ donation.

Methods: We organized meetings with representatives from the field of clinical neurology, neurotraumatology, intensive care medicine, transplantation medicine, clinical intensive care ethics, and organ procurement management. During these meetings, all possible criteria were discussed to identify a patient with a reasonable probability to become brain dead (imminent brain death). We focused on the practical usefulness of two validated coma scales (Glasgow Coma Scale and the FOUR Score), brain stem reflexes and respiration to define imminent brain death. Further we discussed criteria to determine irreversibility and futility in acute neurological conditions.

Results: A patient who fulfills the definition of imminent brain death is a mechanically ventilated deeply comatose patient, admitted to an ICU, with irreversible catastrophic brain damage of known origin. A condition of imminent brain death requires either a Glasgow Coma Score of 3 and the progressive absence of at least three out of six brain stem reflexes or a FOUR score of $E_0M_0B_0R_0$.

Conclusion: The definition of imminent brain death can be used as a point of departure for potential heart beating organ donor recognition on the intensive care unit or retrospective medical chart analysis.

INTRODUCTION

Organ transplantation is often the last resort for patients with end-stage organ failure. The number of patients waiting for one or more organ(s) is still increasing in the U.S. and Europe.[1-3] Brain(stem) dead patients provide the major source of solid organs for transplantation.[4,5] Unfortunately, for potential organ recipients, brain(stem) death is a rare form of death. Among 4248 patients who died on European intensive care units (ICUs) in an 18-month period, only 330 patients (7,8%) were diagnosed brain(stem) dead.[6]

Since the first descriptions of brain(stem) death in the late 1950's[7,8], and the first formal definition of brain(stem) death by the Harvard Committee in 1968[9], many thousands of patients are declared dead worldwide each year, based on formal brain(stem) death criteria. Today, brain(stem) death is recognized as legal death in most western countries.[10] The causes of brain(stem) death vary, but approximately 80-90% of patients who develop brain(stem) death are admitted to an ICU with traumatic brain injury (TBI), subarachnoid haemorrhage (SAH) or intracerebral haemorrhage (ICH).[4,11] Other, less frequent, causes are post resuscitation encephalopathy, an intracranial tumor or central nervous system infections.

Current practice in organ donation is based on the "dead-donor-rule" as described by Robertson.[12] As the shortage of organs has become more critical, proposals have been put forth to increase the potential pool of organ donors. Some of these proposals simply abandon the dead donor rule by redefining certain categories of patients (e.g. patients in persistent vegetative state[13] or anencephalic patients) as dead for donations purposes.[10,14] In order to improve the supply of organ donation, but not violate the dead donor rule, we have to look how to increase the conversion rate between potential organ donors and actual organ donors. Many patients with a hopeless neurological prognosis are not identified as possible brain dead organ donor. Other patients deteriorate between the period of possible brain death recognition and formally brain(stem) death diagnosis.[4,15-17] Timely referral of potential organ donors to representatives of an organ procurement organization (OPO) is essential for this reason.[18] The decision whether or not to continue life sustaining treatment of a patient with severe brain damage in the ICU is primarily dependent upon the estimated outcome. A large proportion of these deaths occur in the context of withdrawing life-sustaining treatment, especially when catastrophic neurologic injuries leave little to no chance of meaningful recovery.[19,20] However, when such a patient is identified as a potential organ donor, treatment is generally continued until brain(stem) death has been definitively established. Potential organ donors should therefore be identified as soon as possible and the possible diagnosis of brain(stem) death should never be missed or delayed.

This area of improvement has not been unnoticed by several national procurement organizations and collaborations.[21,22] The Organ Procurement and Transplantation Network (OPTN) in the U.S. developed the term "imminent neurological death" (see www.optn.transplant.hrsa.gov). According to article 7.1.7, as published on their website, a patient with imminent neurological death is defined as "*a patient who is 70 years old or younger with severe neurological injury and requiring ventilator support who, upon clinical evaluation…has an absence of at least three brain stem reflexes*". The Glasgow Coma Scale (GCS) is for unknown reasons not incorporated in this definition. The OPTN definition is solely used for data-submission and analysis and is, to our best knowledge, not used for clinical recognition of potential organ donors. A European Consortium of organ procurement organizations (The DOPKI project) funded by the European Commission tried to find a widely agreed methodology to estimate the potential of deceased organ donors. The goal of the DOPKI-project is develop Quality Assurance Programs that can be used to make international comparisons possible.[21] Until now there is no published peer-reviewed report of this methodology. Nevertheless, we strongly subscribe to the latter argument. Obtaining insight in organ donation performances, the strength and weakness of the donation process and to benchmark donation performance on a hospital, regional and national level is relevant. Early recognition by a clinician of a patient's impending hopeless clinical neurological condition in order to preserve organs[23-25] and to facilitate organ donation is of even greater relevance. The gained extra time can be used to ensure that families are provided with the opportunity to consider organ donation based on correct information. Families have time to understand and accept the fact that their loved one is brain dead. In addition to this, it offers clinicians the opportunity to give information about brain death and the request for organ donation in two separate meetings. Both of which can have a significant impact on the rates of consent.[18,26] However, the identification of a potential organ donor does not discharge a physician to treat the patient in the patients' best interest.

In this article we propose criteria on the definition for a potential organ donor, based on multi-disciplinary consensus among experts. The goal is to propose a definition that can be used for clinical purposes and for retro- and prospective data analysis.

We wish to emphasize that this initiative was undertaken from the perspective of achieving a more consistent and reliable estimation of the number of potential organ donors and an easy to use referral tool for OPOs. In this article, we will give criteria for the determination of, what we will name, 'Imminent Brain Death'. We strongly state that the proposed definition should not be considered equivalent to 'brain(stem) death' and that the designation of a patient with imminent brain death represents no more than a certain risk estimate. Per definition, the assessment of imminent brain death should not lead to withdrawal of treatment. In fact, identifying a patient's situation as imminent brain death may delay or cancel the option to withdraw life support, and add an expressed option to wait for brain death, in order to pre-

serve donor organs. Treatment limiting decisions remain the responsibility of the clinician, who should base his decisions on as much as possible evidence based risk estimates, taking opinions of relatives and autonomy of patients into account.

MATERIAL AND METHODS

We organized expert meetings with representatives from the field of clinical neurology (MAK, HPHK), neurotraumatology (AIRM), intensive care medicine (YJdG; JB, SA, MAK, EFMW, EJOK), transplantation medicine (AJH), clinical intensive care ethics (EJOK), and organ procurement management (NEJ, HAvL). EFMW participated by e-mail.

During these meetings, all possible criteria were discussed to identify a patient with a reasonable probability *to become* brain(stem) dead, in other words to be in a state of imminent brain death. We focused on the practical usefulness of two validated coma scales (Glasgow Coma Scale and the FOUR Score), brainstem reflexes and respiration to define imminent brain death. Further we discussed criteria to determine irreversibility and futility in acute neurological conditions.

RESULTS

First, only ventilator dependent patients admitted to an ICU with a known origin of catastrophic brain damage, and whose condition is considered irreversible and for whom no treatment possibilities are left can fall within the definition of imminent brain death. Establishing irreversibility requires repeated examinations and exclusion of major confounders, such as effects of sedation and hypothermia. This may include multidisciplinary assessment by physicians in intensive care medicine, neurology and neurosurgery.

Imminent brain death implies generalized loss of cortical function and *progressive* brain stem failure. Complete loss of consciousness is thus a prerequisite when considering imminent brain death. The most commonly used scale for assessment of coma is the Glasgow Coma Scale (GCS), which was proposed in 1974 as a practical tool for diagnosis and prognosis of cerebral function of patients with traumatic brain injury.[27] In most countries the GCS is the gold standard for assessing the level of consciousness in patients with acute brain damage. The total GCS is the sum of scores in three categories; eye opening, motor response and verbal response. Using the GCS, the patient with imminent brain death has no eye movement (E_1), no motor response (M_1) and no verbal response (V_1). We recognize that patients in whom a condition of imminent brain death is suspected are mechanically ventilated, thus rendering

reliable estimation of the verbal score nearly impossible. In the absence of any other indication of responsiveness, the verbal reaction can be considered absent in these patients.

Before brain stem failure can be assessed, confounding factors (e.g. hypothermia, metabolic disturbances, sedation) should be excluded. Brain stem failure is determined by the absence of all brain stem reflexes. The most relevant brain stem reflexes to this purpose are: pupillary reactivity to light, corneal reflex, oculocephalic and oculovestibular responses, gag and cough reflex.

First, based on the GCS and examination of brain stem reflexes, imminent brain death can be defined as: *'A state in which a deeply comatose, mechanically ventilated patient, admitted to an ICU, with irreversible catastrophic brain damage of known origin (e.g. TBI, SAH, ICH)), have a GCS of 3 (E_1,M_1,V_1) and with at least 3 or more absent brain stem reflexes.'*

The rationale to choose 3 or more absent brain stem reflexes is to reflect the severity of brain stem lesions.[28] We opted not to establish a hierarchy or ranking of absent brain stem reflexes as in clinical practice different sequences of progressive brain stem reflexes failure may occur.[24,29] In this way every patient with some form of cerebral herniation and brainstem failure which can lead to brain death can be included in this definition and analysis of potential organ donors.

An attractive alternative to the use of the GCS and brain stem reflexes is offered by the FOUR score. [30-35] The FOUR stands for *Full Outline of UnResponsiviness*. The FOUR score has four testable components and the maximal grade in each of the categories is four (Figure 1). It includes the Eye response, Motor response, Brainstem reflexes and Respiration. As the FOUR score includes the essential parts of the GCS, brain stem reflexes and respiration, this coma scale can be very useful for the determination of imminent brain death.

In analogy with the definition of imminent brain death using the GCS, a patient with imminent brain death will have a FOUR score of E_0 (eyelids remain closed with pain), M_0 (no response to pain or generalized myoclonus status), B_0 (pupil -, corneal - and cough reflex absent) and R_0 (breathes at ventilator rate or apnea). The FOUR score includes three brain stem reflexes: pupillary response, corneal and cough reflexes, in the category brainstem reflexes; in B_0 all three reflexes are absent and in B_1 only the pupil and corneal reflex are absent. In the category B_1, patients can have absent pontomesencephalic reflexes but retained cough reflex and some respiratory drive ($E_0M_0B_1R_1$). These patients may or may not progress to full brain death. Loss of the last two points in time will make it likely that these patients will become brain dead. Some patients stop at $E_0M_0B_1R_1$ and do not progress to full brain death. For this reason, we propose, for the definition of imminent brain death, a FOUR score of $E_0M_0B_0R_0$, and not $E_0M_0B_1R_0$ or $E_0M_0B_1R_1$. One patient with a FOUR-score of 0 is described, showing retained isolated medul-

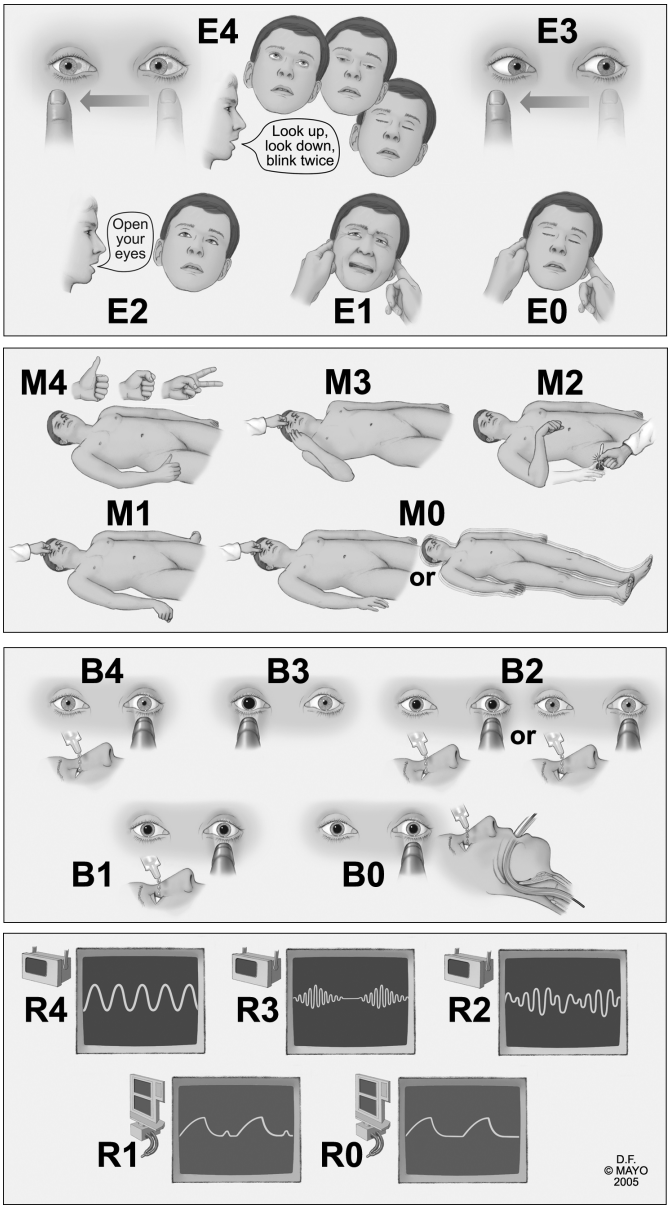

Figure 1 Description of Full Outline of UnResponsivenes (FOUR) score. Eye response: E4 eyelids open or opened, tracking or blinking to command; E3 eyelids open but not tracking; E2 eyelids closed but open to loud voice; E1 eyelids closed but open to pain; E0 eyelids remain closed with pain. Motor response: M4 thumbs up, fist or peace sign; M3 localising to pain; M2 flexion response to pain; M1 extension response to pain; M0 no response to pain or generalised myoclonus status. Brainstem reflexes: B4 pupil and corneal reflexes present; B3 one pupil wide and fixed; B2 pupil or corneal reflexes absent; B1 pupil and corneal reflexes absent; B0 absent pupil, corneal and cough reflex. Respiration pattern: R4 not intubated, regular breathing pattern; R3 not intubated, Cheyne-Stokes breathing pattern; R2 not intubated, irregular breathing; R1 breathes above ventilatory rate; R0 breathes at ventilator rate or apnea

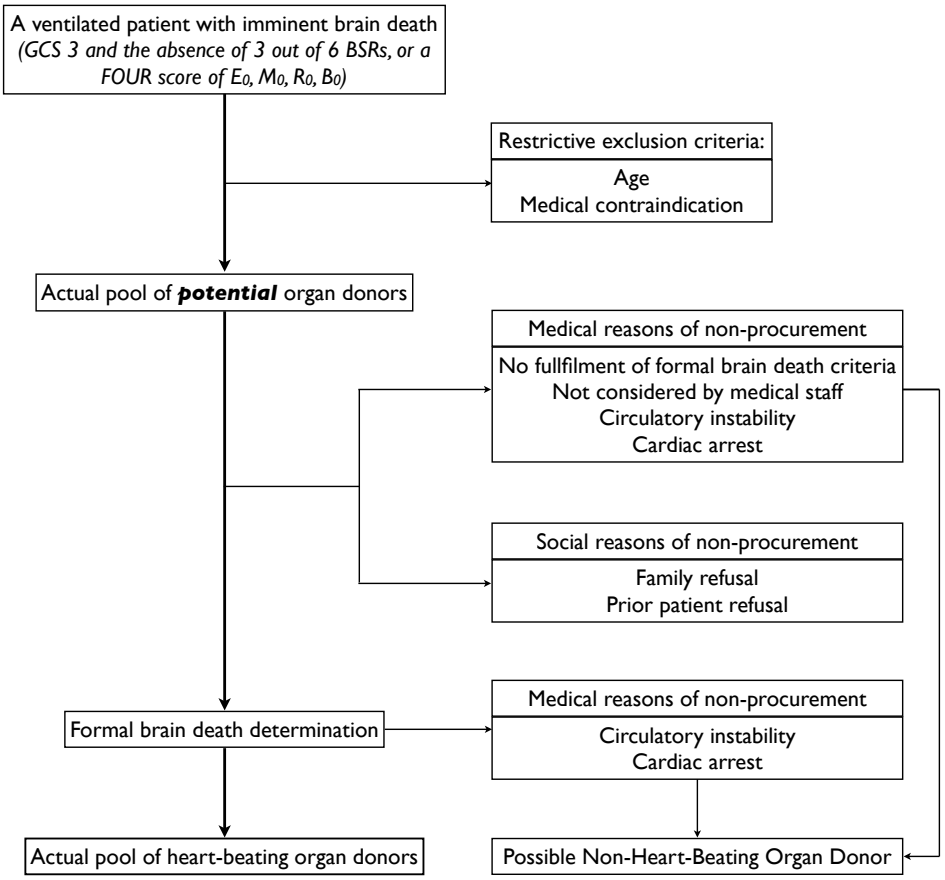

Figure 2. Flowchart of potential organ donors

lary function[36] and who did not progress to loss of all brainstem function. One may conclude that predictive factors for loss of all brainstem function have not yet been identified. Iyer et al showed that patients with a FOUR-score of 0 had a mortality of 89%, 8 out 9 patients died.[37]

As the FOUR score is used in many ICUs and captures information on both levels of consciousness and brain stem reflexes, we consider this score more useful than the GCS alone, when considering a diagnosis of imminent brain death.

As definition for imminent brain death we propose:

'A mechanically ventilated, deeply comatose patient, admitted to an ICU, with irreversible catastrophic brain damage of known origin (e.g. TBI, SAH, ICH). A condition of imminent brain death requires either a GCS of 3 and the progressive absence of at least 3 out of 6 brain stem reflexes, or a FOUR score of $E_0M_0B_0R_0$.'

Formal whole brain death or brain stem death can only be determined after conformation of the absence of all brain stem reflexes and ancillary tests like EEG and apnea test (which are mandatory in several EU countries).

Analysis of the pool of patients, who meet the criteria of imminent brain death, should be conducted in a hierarchical order (Figure 2). Some parameters, such as age and medical condition, are restrictive exclusion criteria. In most countries, a patient fulfilling the definition of imminent brain death, but who is older than e.g. 75 year will not be considered as a potential organ donor. The same holds for some medical reasons for exclusion, such as severe viral, bacterial or fungal infections and malignant neoplasm. These factors cannot be modified. After excluding the patients with these characteristics, the result is the actual pool of potential organ donors who fit every medical criterion to become a heart-beating organ donor.

DISCUSSION

The proposed definition can be used as point of departure for retrospective chart analysis, as recognition for potential organ donors for prospective determination and, derived from this, the estimation of the number of potential organ donors and its conversion rate in actual organ donors. The definition can also be used as a clinical recognition tool.

If a patient, who meets every criterion of a potential heart-beating organ, does not become a donor it is de facto because of factors on a medical level or on a social level. Reasons on a medical level are patients who do not fulfill the formal criteria for complete brain death, are not considered or recognized by physicians and nurses or who suffers from circulatory instability or cardiovascular arrest during the procedure. However these patients could become non-heart beating organ donors, if logistically possible, after they died of circulatory arrest. Optimization of the hemodynamic system and overall physiology of

patients with imminent brain death will decrease the number of donors lost for this reason.[24,25] Education of physicians and nurses has showed to be an improvement for consent rates.[38] Reasons of non-procurement on a social level include family refusal or prior patient refusal. These reasons are modifiable by education of the general population to increase awareness and understanding of brain death.[39,40] Targeting such education campaigns appropriately requires insight into the relative contribution of medical and social attitudes on non-organ procurement.

Simpkin et al. and Siminoff et al. both evaluated the factors that influences relatives' consent for donation of solid organs.[26,40] Families were more willing to give consent for donation

when they had been given enough information about brain death and the donation process to make an informed decision. The time given to families to make the decision was also an important factor in the discussion and consent process of a family. With timely recognition of a potential organ donor and adequate specialized care to preserve the organs for donation, should that be the case, it is possible to offer families information and time for ample discussion.

We choose to make a more strict definition of a potential organ donor then, for example, the OPTN criteria. The reason for this is twofold. First, with a stricter definition, used as clinical recognition tool and referral tool, the sparse resources of an OPO (and ICU) will only be deployed for these patients with the highest chance to become brain(stem) death and eventually, if consent is given, become donor. Second, systematic chart reviews for measuring the actual potential for organ donation has become the gold standard in the US and Europe.[41] With this in mind, we aimed to develop a tool, which measures a realistic pool of potential organ donors and thus a realistic conversion rate that can be widely applied. We think that our proposal is open for debate for the professionals and procurement organizations. One of the aims of this paper is to engage in a discussion about the potential of heart-beating organ donors in a group with a hopeless neurological outcome.

CONCLUSION

In this article we propose criteria for determination of *Imminent Brain Death* and a practical, widely applicable, definition of a potential organ donor based on unambiguous criteria for imminent brain death, which can be seen as a precursor for organ donation. The definition of imminent brain death can be used as a starting point for potential organ donor recognition on the ICU or retrospective medical chart analysis. Further study is needed to determine how many patients fulfilling the definition of imminent brain death will actually become organ donor.

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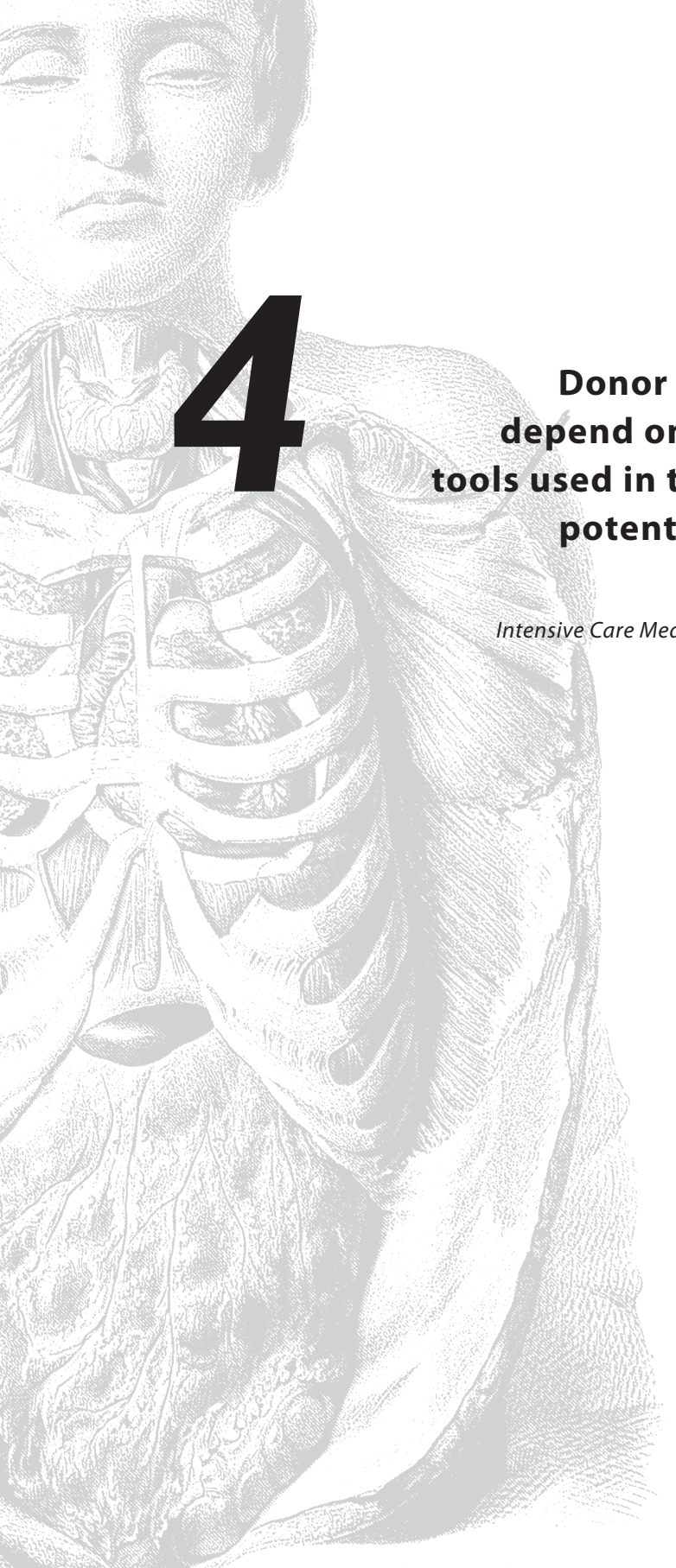

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Donor conversion rates depend on the assessment tools used in the evaluation of potential organ donors

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ABSTRACT

Purpose: It is desirable to identify a potential organ donor (POD) as early as possible to achieve a donor conversion rate (DCR) as high as possible which is defined as the actual number of organ donors divided by the number of patients who are regarded as a potential organ donor. The DCR is calculated with different assessment tools to identify a POD. Obviously, with different assessment tools, one may calculate different DCRs, which make comparison difficult. Our aim was to determine which assessment tool can be used for a realistic estimation of a POD pool and how they compare to each other with regard to DCR.

Methods: Retrospective chart review of patients diagnosed with a subarachnoid haemorrhage, traumatic brain injury or intracerebral haemorrhage. We applied three different assessment tools on this cohort of patients.

Results: We identified a cohort of 564 patients diagnosed with a subarachnoid haemorrhage, traumatic brain injury or intracerebral haemorrhage of whom 179/564 (31.7%) died. After applying the three different assessment tools the number of patients, before exclusion of medical reasons or age, was 76 for the IBD-FOUR definition, 104 patients for the IBD-GCS definition and 107 patients based on the OPTN definition of imminent neurological death. We noted the highest DCR (36.5%) in the IBD-FOUR definition.

Conclusion: The definition of imminent brain death based on the FOUR-score is the most practical tool to identify patients with a realistic chance to become brain dead and therefore to identify the patients most likely to become POD.

INTRODUCTION

In most Western countries, absolute numbers of brain dead patients are declining.[1-3] Approximately 80-90% of these patients suffer from aneurysmal subarachnoid haemorrhage (SAH), traumatic brain injury (TBI) or intracerebral haemorrhage (ICH).[2,4-7] Progress in the prevention and treatment of these three conditions has led to a steady decline in the pool of potential heart-beating organ donors over the past few decades.[8-14]

Organ donation rates in countries are often expressed as the donor rate per million population. This comparison tool is not an appropriate measure because several factors may influence the total number of potential organ donors. For instance, the number of intensive care beds, neurosurgical facilities, road traffic accidents and cerebral hemorrhages differ per country and are not considered in this comparison tool.[1] Another comparison tool that is often used and is not affected by the above-mentioned factors is the donor conversion rate (DCR). The DCR is defined as the actual number of organ donors divided by the number of patients who are regarded as potential organ donors (PODs). Organ procurement organizations in the US aim to achieve a DCR of at least 75%[15], but the actual DCRs in the US, UK and Germany are estimated to be in the range of 42 to 68%.[1,16-18] However, using a DCR has practical limitations. The DCR is calculated with different assessment tools to identify a POD. Using different assessment tools results in different DCRs, which makes comparison difficult.

One of the difficulties associated with the quantification of the number of PODs is the different definitions of a POD.[19,20] To compare groups of PODs between different hospitals or countries, a uniform definition of a POD is needed. This may be hampered by international differences concerning inclusion or exclusion of PODs based on age or medical contraindications to organ donation. With a uniform definition, the causes of non-procurement can be assessed, and ways of improving DCRs can be developed. Recently, we formed an international expert consensus panel and proposed a definition of a POD by defining imminent brain death.[21]

In the present study we investigate the pool of potential heart-beating organ donors in a cohort of patients, who died from SAH, TBI or ICH in the ICU, using three different assessment tools for PODs. Our aims were to determine if these tools could be used for an accurate estimation of a potential donor pool and to ascertain how they compare to each other with regard to the DCRs, by using a cohort of PODs.

MATERIAL AND METHODS

We conducted a retrospective chart review of patients who were admitted to a 32-bed medical/surgical ICU in a university hospital between 1 January 2006, and 31 December 2008, and died from SAH, TBI or ICH. Lists of these patients were obtained from three independent sources: the patient-data management system of the ICU (Critical Care Manager 8.1; Picis, Inc. Wakefield, MA, USA), the central hospital patient registry and the medical chart review database of the Dutch Transplant Foundation. These three lists were then crosschecked. Patient age, sex, dates of admission and death, definitive diagnosis based on computed tomography, cerebral angiography, clinical examination and outcome on ICU discharge were extracted from the medical records. From the patients who died in the ICU from SAH, TBI or ICH, we extracted the last known absent brain stem reflexes and the reason for non-procurement, if applicable. After identifying this cohort of patients, we applied the following three different assessment tools, which included two definitions of Imminent Brain Death (IBD) that we recently proposed in this journal [21] and a definition used in the United States:

1. Imminent Brain Death, GCS based (IBD-GCS): defined by a GCS score of 3 and at least 3 out of 6 absent brain stem reflexes.[21]
2. Imminent Brain Death, based on a FOUR score[22-24] of $E_0M_0B_0R_0$(IBD-FOUR), which represents eyelids remaining closed with pain (E_0), no response to pain or generalized myoclonus status (M_0), absent pupillary, corneal and cough reflex (B_0) and absence of spontaneous ventilation or apnea (R_0).[21]
3. Imminent Neurological Death (IND) as defined by the Organ Procurement Transplantation Network (OPTN) in the US and published on their website (see http://www.optn.transplant.hrsa.gov). The OPTN defined imminent neurological death *as a patient … with severe neurological injury and requiring ventilator support, who upon clinical evaluation … has an absence of at least three brain stem reflexes.* Age, which is part of this definition, is excluded from our statistical analysis to prevent its influence on the comparison.

All patients in our cohort underwent regular neurological evaluations by a neurologist during their stay in the ICU because of their deteriorating neurological condition. This resulted in an accurate record of neurological examinations in the medical charts that could be used for retrospective analysis of the defined neurological assessment tools.

Statistics

Normally distributed continuous variables are described as means with standard deviations, and skewed continuous variables are described as medians with inter-quartile ranges. Binary variables are described as proportions. Differences between the three sub-groups were tested with ANOVA with the Tukey post-hoc test for normal continuous distributed variables;

the Kruskal-Wallis test was used for skewed continuous variables. All binary variables were analyzed using the chi-square test.

RESULTS

Demographics

Between 1 January 2006, and 31 December 2008, 3429 patients were admitted to the ICU, where the overall mortality was 647/3429 (18.9%). We identified a cohort of 564/3429 (16.4%) patients who were diagnosed with SAH, TBI or ICH, of whom 179/564 (31.7%) died. These 179 patients comprised 27.6% of the overall ICU mortality. The medical charts of two patients, who died as a result of SAH, could not be retrieved and were therefore excluded from the analysis.

Table 1 shows the demographics of the non-survivors divided into three subgroups. Between the period from 2006-2008, 25 patients became heart-beating organ donors, 23 of whom died from SAH, ICH or TBI; one patient became brain dead as a result of post-anoxic encephalopathy after cardiac arrest and one patient with TBI, who was transferred directly from the emergency department to the operating theatre for multi-organ donation, was excluded from the analysis. A total of 36 patients, who were admitted to the ICU with SAH, ICH or TBI, donated one or more organs; 13 of these patients were non-heart-beating (NHB) organ donors.

Table 1. Demographics of patients died from SAH, ICH or TBI (n=179)

	SAH	ICH	TBI	P[a]
No. of donors	73 (40.8)	45 (25.1)	61 (34.1)	
Age, year (±SD)	56.7 (10.3)	58.7 (14.1)	49.8 (20.5)	<0.05
Female sex, no. (%)	48 (55.7)	19 (42.2)	15 (24.6)	<0.001
Length of stay, no. days (IQR)	2 (1-9)	2 (1-6)	1 (1-6)	0.318
Mortality at day 2, no. (%)	35 (47.9)	21 (46.7)	32 (52.5)	0.810
Year of admission, no. (%)				
2006	32 (43.8)	12 (26.6)	16 (26.3)	
2007	22 (30.1)	15 (33.3)	29 (47.5)	
2008	19 (26.0)	18 (40.0)	16 (26.2)	

[a] P value from one-way analysis of variance with post hoc Tukey for comparison of multiple groups. P<0.05 was considered significant.

Potential organ donors

After applying the three different assessment tools, the numbers of patients who fulfilled the criteria for IBD or IND, before exclusion due to medical reasons or age, and were regarded as PODs were as follows: 76 per the IBD-FOUR definition, 104 patients according to the IBD-GCS definition and 107 patients based on the OPTN definition of imminent neurological death (Figure 1). Examining the detection rates of the different assessment tools before exclusion for medical reasons or age, revealed incremental increases in the percentages of detection of PODs as a result of the broadening of the selection criteria (see table 2). The highest detection of PODs was noted in the SAH admission group.

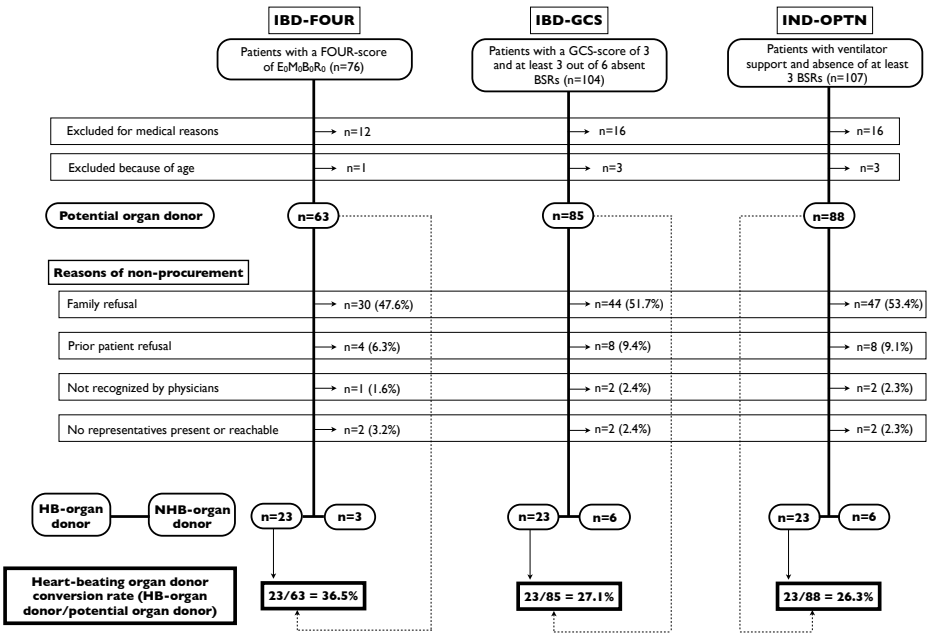

Figure 1. Flowchart of the assessment tools. *IBD-FOUR* imminent brain death based on the FOUR criteria, *IBD-GCS* imminent brain death based on GCS criteria, *IND-OPTN* imminent neurological death used by the OPTN, *BSRs* brain stem reflexes, *HB-organ donor* heart-beating organ donor, *NHB-donor*, non-heart-beating organ donor

Table 2. Detection rates of the different assessment tools per admission diagnosis before exclusion of medical reasons or age greater than 76 years

	SAH	ICH	TBI	Total
IBD-FOUR (%)	58.9	31.1	31.1	42.5
IBD-GCS (%)	72.6	53.3	44.2	58.1
IND-OPTN (%)	75.3	55.5	44.2	59.8

Imminent Brain Death – FOUR score

Of the 179 patients who died from SAH, TBI or ICH, 76 (42,5%) were eligible for organ donation after applying the IBD-definition based on the FOUR score. After exclusion due to age (1 patient) and medical reasons, such as malignancy, sepsis or viral infections (12 patients), 63 patients (35.1%) were identified as PODs. Of this cohort, 26 patients donated one or more organs: 23 were heart-beating organ donors and 3 were non-heart-beating organ donors. The majority of the patients (56.6%) who were identified as PODs by this definition were admitted to the ICU after an SAH, followed by 25.0% after TBI and 18.4% after ICH.

Imminent Brain Death - GCS

Of the 179 patients who died from SAH, TBI or ICH, 104 (58.1%) were eligible for organ donation, after applying the IBD- GCS definition. After exclusion due to age (3 patients) and medical reasons, such as malignancy, sepsis or viral infections (16 patients), 85 patients (47.5%) were identified as PODs. Of this cohort, 29 patients donated one or more organs; 23 were heart-beating organ donors and 6 were non-heart-beating organ donors. The majority of the patients (51.0%) who were identified as PODs by this definition were admitted to the ICU after an SAH, followed by 26.0% after TBI and 23.1% after ICH.

Imminent Neurological Death – (OPTN definition)

Of the 179 patients who died from SAH, TBI or ICH, 107 (59.8%) were eligible for organ donation, after applying the IND-OPTN-definition. After exclusion due to age (3 patients) and medical reasons, such as malignancy, sepsis or viral infections (16 patients), 88 patients were identified as PODs. Of this cohort, 29 patients donated one or more organs; 23 were heart-beating organ donors and 6 were non-heart-beating organ donors. The majority of the patients (51.4%) who were identified as PODs by this definition were admitted to the ICU after an SAH, followed by 25.2% after TBI and 23.4% after ICH.

Reasons for non-procurement

After applying the assessment tools to define a POD, family refusal accounted for more than 50% of the non-procurements in two of the three definitions. Comparison between the three assessment tools showed a family refusal rate of approximately 75% in the ICH group and approximately 40-50% in the SAH and TBI groups. Other reasons for non-procurement included malignancy, sepsis, age, prior patient refusal, no representative who could give consent to organ donation and in two cases, failure of the treating physicians to recognize a POD.

DISCUSSION

In this retrospective study, we used three different assessment tools for PODs to calculate the DCR and to analyze the reasons for non-procurement. Resulting from restrictions that are incorporated into the IBD-FOUR definitions, three NHB-donors were not identified as potential heart-beating organ donors. These patients sustained serious neurological damage but retained one or more brainstem reflexes (one patient was ventilated on pressure support settings and two patients had positive cornea reflexes) and were excluded by the application of the IBD-FOUR definition. The IBD-FOUR definition showed the highest DCR of 36.5%, which is still low when compared to other published DCRs.[1,16,17] As stated before, comparison is difficult with different definitions of a POD. An additional 7 potential NHB-donors were not identified in our cohort by using the three assessment tools, reflecting the high sensitivity of these tools for potential heart-beating organ donors.

Regardless of the definitions of a POD, we identified a considerably substantial group of patients with a high risk of becoming brain dead. However, most of the patients, who we considered to be PODs, did not proceed to fulfill official brain death criteria. Before the formal brain death determination, relatives were often informed about the poor prognosis and the possibility of organ or tissue donation. If relatives of a patient declined organ donation, mechanical ventilation was withdrawn and the patient subsequently died after cardio-pulmonary arrest. Some patients, when treatment was withdrawn, had some remaining positive brain stem reflexes and hypothetically, were not identified by using one of the assessment tools. It is possible that some of these patients would have deteriorated into a state of imminent brain death after continuation of treatment, probably resulting in an underestimation of the full potential of PODs.

A POD, as defined in this study, is considered a risk estimate of a possible outcome for a patient. This risk estimate has to be realistic to provide health care professionals with accurate data. For instance, if every patient admitted to an ICU was considered a POD, a DCR will never achieve a goal of 75% or higher. The OPTN definition is illustrative of this because it is the only definition that does not include any formal and validated neurological assessment tool for the level of consciousness. This results in the largest group of patients who could be regarded as PODs before exclusion due to medical reasons and age; this did not increase the identification of PODs who actually proceeded to organ donation. The result of this definition is a low donor conversion rate. The use of a less specific definition of a potential organ donor, such as the OPTN, results in a low DCR and a high estimate of the reasons for non-procurement if we examine heart-beating organ donation. The high estimate of reasons for non-procurement is the result of the inclusion of a large group of patients who are ineligible for heart-beating organ donation. Regardless of the definitions used, the patients who died from SAH were

most likely to become heart-beating organ donors. After reviewing our data, we conclude that using the definition of imminent brain death, based on the FOUR score[23], offers the most accurate estimation of a pool of PODs, due to a more detailed neurological assessment of critically ill neurological patients in the ICU. One should keep in mind that although a high DCR correlates with a higher specificity of the assessment tools used in our study, it does not necessarily translate into an increased rate of organ procurement. Therefore, a prospective validation of the different assessment tools is necessary.

Limitations

Our study has some limitations. First, it is a single center study, and data were obtained by retrospective medical chart review. As is the case for all observational studies, some cases may have been missed in a non-random manner. Second, the neurologists who assessed the patients did not record the data regarding the GCS-score and the last known absent brain stem reflexes at a pre-defined moment, resulting in data recorded at different stages during treatment. This is a troublesome limitation of the retrospective nature of this study. Third, to illustrate the use of the different assessment tools, we selected patients based on their diagnosis and outcome. We used this cohort to apply three different definitions to analyze our ICU-population to determine the donor potential and the reasons for non-procurement in a transparent way.

CONCLUSION

Brain dead patients are a scarce, but important, source of organs. This report shows that the assessment tools used are easy to apply and easy to report in a comprehensive way. The definition of imminent brain death based on the FOUR score appears to be the more neurologically practical tool for identifying patients with a realistic chance of becoming brain dead. A prospective study is necessary to validate these assessment tools.

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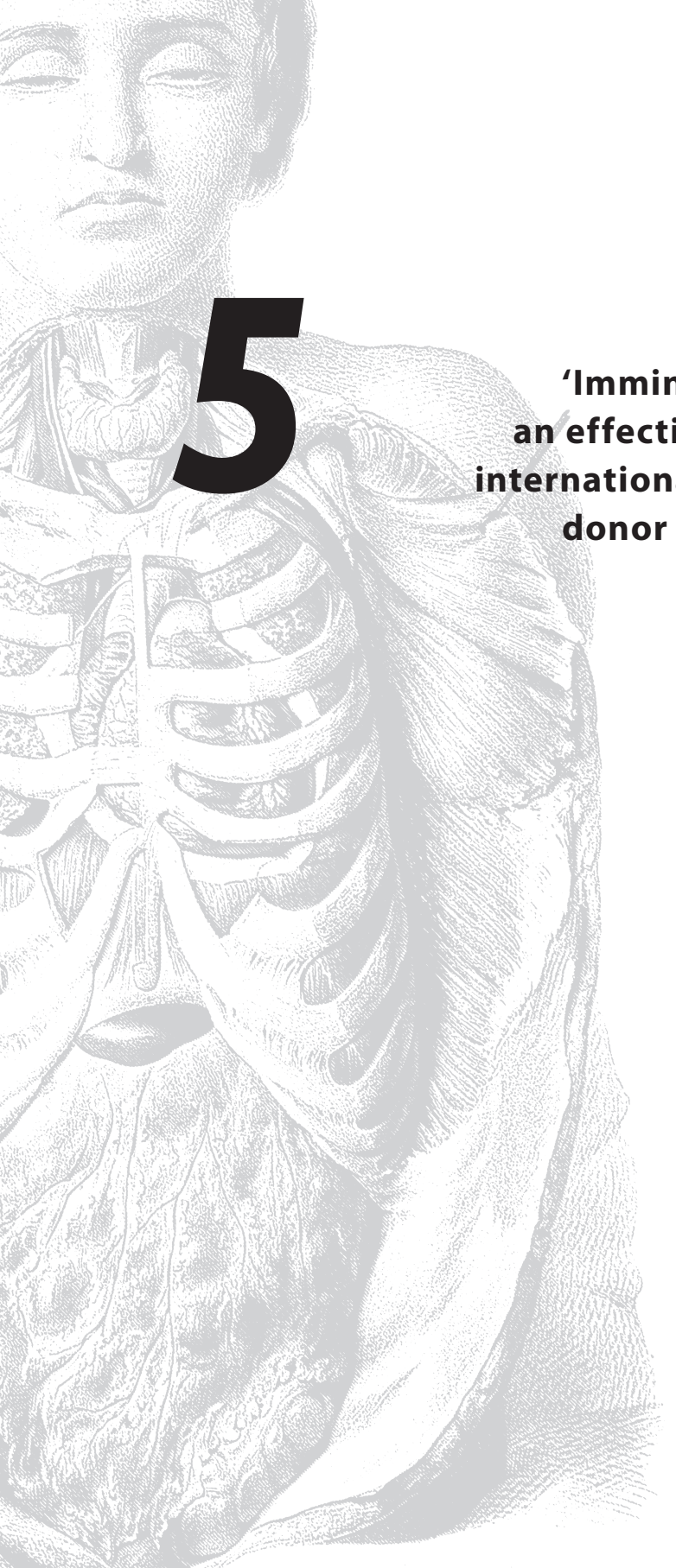

5

‘Imminent brain death’ an effective definition for international comparison of donor conversion rates

Submitted

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ABSTRACT

Background: International donor conversion rates (DCRs) vary, but a uniform starting point for defining a potential heart-beating donor is lacking. To establish a universal definition we proposed 'Imminent Brain Death' (IBD). We analyzed a dataset of ICU deaths on a national level to illustrate the impact of donor potential definitions on the DCR.

Methods: Medical charts of 4814 patients who died on an ICU in Dutch university hospitals between January 2007 and December 2009 were reviewed for potential heart-beating donors. We compared two different tools: 'Severe Brain Damage' (SBD) (old definition) and IBD (new definition), which differ in the number of absent brainstem reflexes.

Results: The number of potential donors in the IBD group was lower than in the SBD group, but 45.6% of the potential donors in the IBD group fulfilled formal brain death criteria, compared to 33.6% in the SBD group. This results in a higher DCR in the IBD group (40% versus 29.5%).

Conclusions: It is necessary to use a universal starting point for reviewing donor potential. We showed, when using two definitions, significant differences in DCRs even in one country. To compare countries and hospitals, one universal definition of a potential organ donor should be used.

INTRODUCTION

Measuring the pool of potential organ donors is important for policymaking and (inter)national comparison of efficiency of hospitals and countries in an international landscape of low donor supply and a high demand for donor organs for transplantation. The efficiency of organ procurement is often expressed by the number of actual donors divided by the number of potential donors; the donor conversion rate (DCR). For example, three large studies in the US, the UK, and four European countries revealed a DCR of 42%, 45%, and 43.2% respectively.[1-3] The Netherlands has lower DCR figures reaching 30%.[4,5] The question is however, if these rates can be used for a sound comparison among countries. A review published previously, showed that no uniform definition for a potential organ donor was used in studies from different European countries.[6] The starting points for analyzing the pool of potential heart-beating organ donors that were found ranged from patients confirmed with brain death, to severe brain damage with a Glasgow Coma Scale (GCS) of E_1M_1V-intubated without any absent brainstem reflexes.[1-3,7-10]

A methodology to estimate the pool of potential heart-beating donors and to evaluate the performance in the deceased donation process was recommended by the DOPKI consortium in 2009.[11] Although this was an important first step in the effort to come to a universal definition, there was no consensus on criteria for the exact starting point like the GCS and the number of absent brainstem reflexes. This same phenomenon is seen in a recent review article in this journal of Dominquez-Gil et al., where a critical pathway for organ donation was introduced.[12] Although the pathway looks very complete, including donation after brain death *and* after circulatory death, there is no exact starting point formulated. They used as a definition of a potential brain death donor 'a person whose clinical condition is suspected to fulfill brain death criteria', but this is not specific enough.

Because DCR is widely used as a performance indicator in international comparisons for organ procurement, achievement of a more consistent and reliable estimation of the pool of potential heart-beating donors by establishing a universal starting point in is important. For this reason, in 2010, we proposed the use of 'Imminent Brain Death' (IBD), as a reasonable probability to become brain dead.[13] A patient who fulfills the IBD definition is admitted to an ICU, mechanically ventilated, has an irreversible catastrophic brain damage of known origin and either a GCS of E_1M_1V-intubated (no eye movement, no motor response, no verbal response) with a progressive absence of at least 3 out of 6 brainstem reflexes (pupillary reaction, corneal reflex, oculocephalic and oculovestibular responses, gag and cough reflex), or a FOUR Score of $E_0M_0B_0R_0$ (Eye response, Motor response, Brainstem reflexes, Respiration).[13] The FOUR Score stands for Full Outline of UnResponsiveness.[14,15] A hierarchy in absent brainstem reflexes was not established, because in clinical practice different sequences of progressive

brainstem reflexes failure may occur. Therefore, every patient with some form of cerebral herniation and brainstem failure that can lead to brain death is included. The rationale for three or more absent brainstem reflexes for the definition of IBD is to reflect the severity of brainstem failure.[13] A recent study has shown that the definition of IBD appears to be a more appropriate and practical tool to identify potential heart-beating organ donors[16], compared to 'imminent neurological death' as defined by the Organ Procurement Transplantation Network in the USA (see http://optn.transplant.hrsa.gov). From the universal applicable starting point IBD, restrictive exclusion criteria, like age and absolute contraindications to organ donation, are adjusted in a hierarchical order to obtain the pool of potential heart-beating donors. Subsequently, the DCR and the reasons for non-procurement can be analyzed from this pool of potential donors. This study[16] was conducted in a single university hospital, and did not include the, in the Netherlands, commonly used starting point for heart-beating donation defined by 'Severe Brain Damage' SBD. The definition of SBD is based on a GCS of E_1M_1V-tube and at least one absent brainstem reflex.[4,5] The IBD definition is stricter than the SBD definition and differs in the number of absent brainstem reflexes (minimal one for SBD and minimal three for IBD). In the present study we illustrate the impact of different starting points in measuring the pool of potential heart-beating organ donors on the DCR. Therefore, we applied IBD and SBD on a data set of ICU deaths on a national level.

MATERIAL AND METHODS

We used data of patients who died on an ICU in seven of the eight university hospitals in the Netherlands during the years 2007 until 2009. These data were collected from the medical records and entered in a web-based application of the Dutch Transplant Foundation by in-house transplant coordinators. One university hospital was excluded from our study because there was incompleteness of data. The last known medical information before death of the patient was leading for reviewing potential organ donors. This included the GCS and the number of absent brainstem reflexes, if applicable. When confounding factors for brainstem failure were found (e.g. hypothermia, metabolic disturbances and sedation), the case was excluded for the potential donor pool. Only medical records of deceased patients until 75 years of age were reviewed, the upper age limit for organ donation during the study period. Therefore, insight in all patients fulfilling the criteria of SBD or IBD (without age limit) is not possible. Our selection continued with patients who were medically ventilated, and had no restrictive exclusion criteria / 'medical contraindication' for organ donation (e.g. unknown cause of death, unknown identity, non treatable sepsis, malignancy except some brain tumors, active viral infections, active tuberculosis and anencephaly). We then retrospectively applied the two different definitions SBD and IBD separately to determine the pool of potential heart-beating organ donors (see box):

Two conditions of heart-beating organ donor potential that were compared:

1. Potential heart-beating organ donors according to 'Severe Brain Damage' (SBD: old definition). A patient in this definition is admitted to an ICU, is mechanically ventilated, suffered severe and irreversible brain damage, as defined by a GCS of E_1M_1V-intubated and has absence of at least one brainstem reflex. These patients have no medical contraindication to organ donation, and are under the age of 76 years [5].

2. Potential heart-beating organ donors according to 'Imminent Brain Death' (IBD: new definition). A patient in this definition is admitted to an ICU, is mechanically ventilated, and suffered irreversible catastrophic brain damage of known origin and has a GCS of E_1M_1V-intubated and thus far the same condition as SBD, but the absence of at least 3 out of 6 brainstem reflexes. These patients have no medical contraindication to organ donation, and are under the age of 76 years.

From these defined pools of potential heart-beating organ donors we analyzed the admission diagnosis and compared the percentage of donors who were subsequently diagnosed brain death, defined by an iso-electric electroencephalogram and a positive apnea test. We also compared the DCR and the distribution of reasons that were recorded when brain death was not determined, which could be divided in medical reasons (e.g. circulatory instability, cardiac arrest) and social reasons of non-procurement (e.g. early family refusal, prior patient refusal).

This study is based on a retrospective review of medical records of deceased patients, therefore, according to Dutch law; no approval of legal representatives or a medical ethical review board was necessary. The board of directors of all centers formally agreed on collecting data of deceased patients from the ICU to identify potential organ donors.

RESULTS

Severe Brain Damage

In total 4814 patients died in the study period of whom 3792 were aged 75 years or younger and 3719 were mechanically ventilated as well. After excluding patients who were not suitable for heart-beating organ donation because of restrictive exclusion criteria 559 patients were regarded as potential heart-beating organ donors applying the SBD definition. Table 1 shows the demographics of this group divided over the years 2007-2009. Of this cohort the admission diagnosis was in majority stroke (subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction) (57.4%, 321/559) and traumatic brain injury (TBI) (19.3%, 108/559).

The admission diagnosis 'other' consists of multiple diagnoses, such as 'intoxication', 'gun shot / stab wound', 'drowning', and 'suicide'.

In 188 patients, 33.6% of all 559 potential heart-beating donors, formal brain death was determined, leading to165 actual heart-beating organ donations. The DCR of potential heart-beating donors based on SBD was 29.5% (165/559). In 11 cases families objected to heart-beating but not to non-heart-beating donation and organs of all of these donors were procured in a non-heart-beating procedure.

Imminent Brain Death

Of our cohort of 559 potential heart-beating donors according to the SBD definition, 412 patients met the more strict IBD-GCS criteria and were regarded as potential heart-beating organ donors after applying the IBD definition (Figure 1). The admission diagnosis of these patients was in majority stroke (58.5%, 241/412) and TBI (18%, 74/412). In 45.6% (188/412) of the potential donors formal brain death was determined leading to 165 actual heart-beating donors. The DCR based on IBD-GCS was 40% (165/412). In 7 cases families objected to heart-beating donation but not to non-heart-beating donation and organs of these donors were procured (data not shown).

Table 1. Demographics and admission diagnosis of deceased patients in the group 'severe brain damage' (SBD) and 'imminent brain death' (IBD)

	2007		2008		2009		Total	
	SBD	**IBD**	**SBD**	**IBD**	**SBD**	**IBD**	**SBD**	**IBD**
Total	192	140	181	135	186	137	559	412
Age, year (±SD)	46.6 (17.2)	46.2 (17.3)	46.5 (17.6)	46.1 (18.5)	47.2 (17.7)	45.9 (17.8)	46.7 (17.5)	46.0 (17.8)
Female sex, no. (%)	90 (46.9)	71 (50.7)	90 (48.4)	58 (42.9)	79 (43.6)	64 (46.7)	259 (46.3)	193 (46.8)
Admission diagnosis	**2007**		**2008**		**2009**		**Total**	
Stroke	118	88	93	67	110	86	321	241
Traumatic brain injury	33	25	36	24	39	25	108	74
Multi-trauma	21	13	16	12	10	7	47	32
Post-anoxic encephalopathy	3	2	15	13	13	9	31	24
Other	17	12	21	19	14	10	52	41

GCS= Glasgow Coma Scale

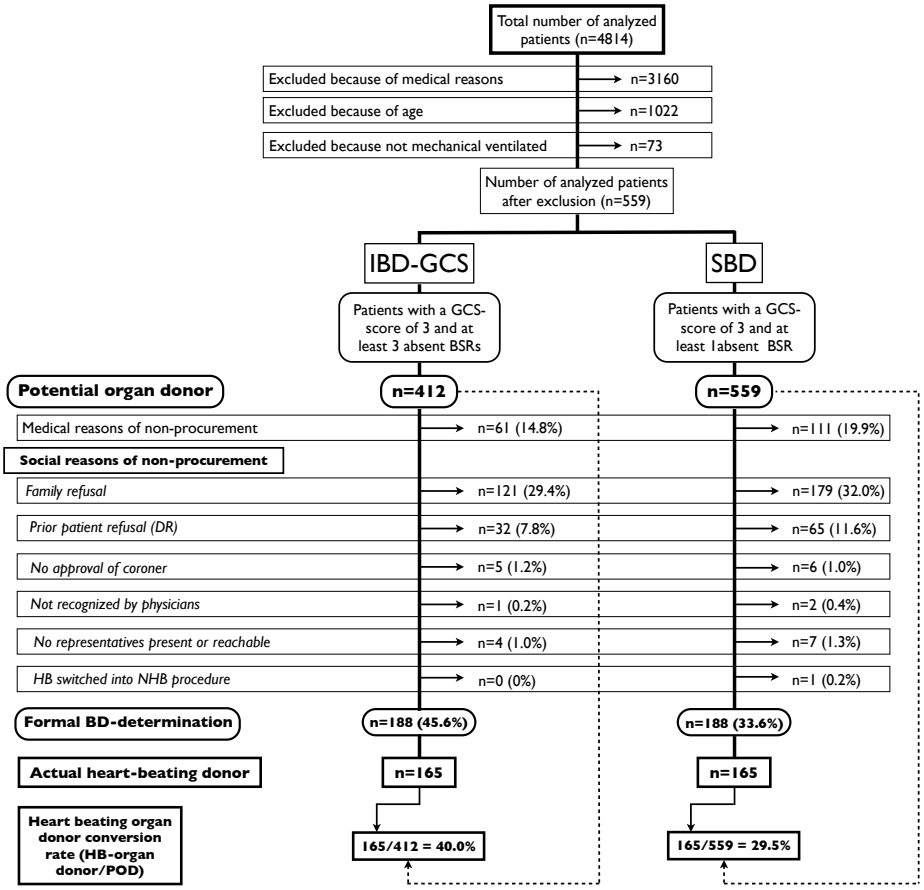

Figure 1. Flowchart of the assessment tools SBD and IBD for identifying potential heart-beating organ donors

Although table 1 shows differences per year in the SBD group compared to the IBD group for the variables age, sex and admission diagnosis, no significantly differences were seen in the total numbers for the years 2007-2009.

Reasons for non-procurement before and after brain death

After analyzing the reasons for non-procurement of the potential donor pool before formal brain death determination, according to the two assessment tools (SBD and IBD), family refusal was the most important reason in both groups (32% and 29.4% respectively) (Figure 1). Medical reasons of non-procurement before formal brain death were: no fulfillment of all formal brain death criteria, circulatory instability, cardiac arrest, and legal incapacity (in total 19.9% (111/559) in the SBD-group and 14.8% (61/412) in the IBD-group)).

Reasons for non-procurement after formal brain dead were; family refusal (n=11), eventually medically unsuitable donors (n=6), patient refusal as registered in the Donor Register (n=2), sudden cardiac/circulatory arrest (n=2), refusal by coroner (n=1), and no medical suitable recipient (n=1).

DISCUSSION

In this study we illustrated the practical consequences of applying two assessment tools with different starting points for identifying the pool of potential heart-beating donors; SBD and IBD. We analyzed data obtained on a national level, in seven Dutch university hospitals, which form an addition to the single center study where IBD was applied as described earlier [16]. The outcome is revealing, the DCRs are significant different (40% versus 29.4%). When these differences occur within one study, caused by inclusion of 2 extra brainstem reflexes, what does this imply for DCRs from international data that depend on different definitions for heart-beating potential? The large numbers of published articles world wide on reviews of medical records from ICU deaths indicates the interest in identifying numbers of potential of organ donors.[1-4,7-10,16-23]

Our study showed that IBD as a starting point to determine the donor conversion rate leads to a more consistent and reliable estimation of the pool of potential heart-beating donors compared to SBD. As explained in our article[13] the pool of potential heart-beating donors can be derived from the total group of patients who meet the criteria of IBD after adjusting restrictive exclusion criteria in a hierarchical order (age and medical contraindication). The observation that in the IBD group 45.6% of the potential heart-beating donors were determined brain death, compared to 33.6% in the SBD group is related to the fact that for the IBD definition more brainstem reflexes must be absent, and therefore reflects more severe brain failure. The main reason for non-procurement was the high proportion of families who refused consent for donation in both the IBD and SBD group. As visible in figure 1, a great number of families were requested for organ donation early in the clinical course, even before formal brain death. As published in a number of articles the high numbers of family refusals is a bottleneck in the donation performance of the Netherlands.[4-6] Thus far, these rates could not be compared to other countries because of differences in the definition of a potential donor. After applying IBD as a universal starting point, the family refusal rate can be determined in an internationally better comparable way. The possible differences between countries in the moment of approaching families for donation are wiped-out when using IBD.

The stricter IBD definition proved to be a better precursor for heart-beating organ donation than SBD, and is therefore a more realistic estimation of the pool of potential heart-beating

organ donors. However, using a more stringent definition like IBD has a small risk. It is conceivable that a few potential donors can be missed using this more stringent definition for retrospective chart review. That raises the question what is the best strategy for screening potential heart-beating donors. Taking the chance of loosing a few potential donors, or including a number of patients to the potential pool who would never become a heart-beating donor. In our opinion the more realistic the pool of potential heart-beating donors the better data can be used for international comparison.

Looking at the DCR for heart-beating donation, the IBD-definition shows a significant higher rate (40%) than the SBD definition (29.5%).

Potential non-heart-beating donors can also occur in the remaining cases where the medical treatment was futile.[24] After withdrawal of life-sustaining treatment and mechanical ventilation, circulatory arrest is expected. When death occurs in a hospital within a certain amount of time, the kidneys, liver, lungs and pancreas can be donated. These are the so-called Maastricht category III controlled non-heart-beating organ donors. During the study period in the 7 university hospitals, organs were procured from in total 99 non-heart-beating donors. Therefore, a uniform definition for the additional pool of potential non-heart-beating should be proposed, which is necessary to evaluate DCR and family refusal for the total group of potential organ donors between hospitals and countries.

Limitations of this study

First, the medical charts of patients in this study were reviewed by ten in-hospital transplant coordinators. It is conceivable that not everyone assessed the medical information in the exact same way, although data entry into the application was conform one standardized format. There is no information if the GCS and brainstem reflexes were recorded at the same time. This could be a confounder, although only the last medical information before death of the patient is leading for data entry. Furthermore, the medical records did not always give detailed information on the neurological assessment, so the full number of potential heart-beating organ donors could be underestimated. To limit this possibility, an external audit was performed which led to some corrections.

The FOUR-Score, as an alternative to determine IBD[13], is not (yet) used (on a large scale) in ICUs in the Netherlands, so we only reviewed the data on IBD based on the GCS.

We considered analyzing differences in the numbers of potential donors in seven Dutch university hospitals, because of the small numbers per center this appeared to be not useful. Furthermore, in the Netherlands a national policy for organ donation is used, this eliminates possible differences in practice between the centers.

CONCLUSION

This study shows that it is necessary and effective to use a uniform starting point for reviewing medical records of patients who died on an intensive care unit for analyzing the potential of heart-beating organ donors. The initiatives taken so far are not enough to allow international comparison of DCRs between countries.[11,12] The results of our study suggest that Imminent Brain Death (IBD) forms a more reliable estimation of the pool of potential heart-beating donors compared to the Severe Brain Damage (SBD) definition. We would like to encourage other countries to use IBD, which in our opinion is an internationally better comparable assessment tool to identify the potential heart-beating donor pool. Only with one universally used uniform definition of a potential organ donor, comparison between hospitals and countries is meaningful. Therefore, further work is needed to test IBD in different settings in various countries with the ultimate goal to achieve reliable DCRs.

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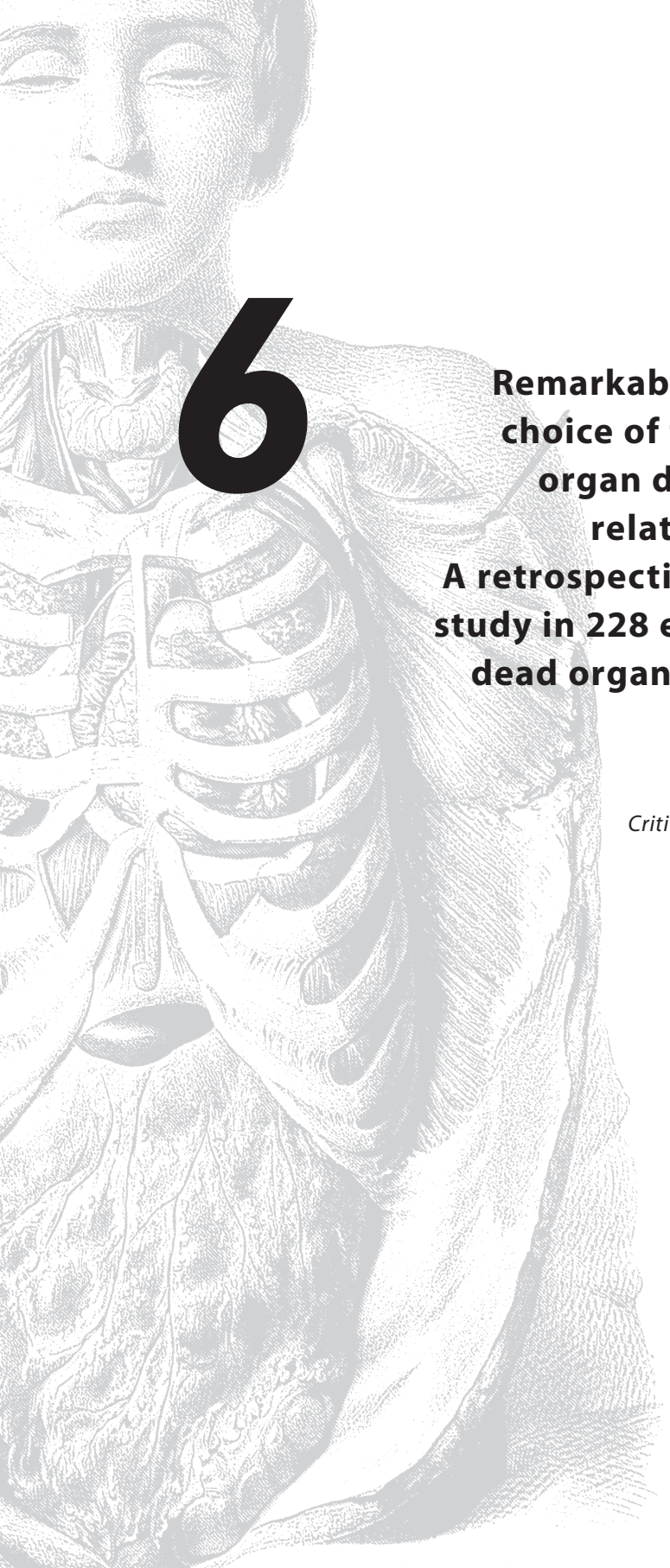
Clinical practice for obtaining consent for organ donation



6

Remarkable changes in the choice of timing to discuss organ donation with the relatives of a patient. A retrospective observational study in 228 effectuated brain dead organ donors between 1987 and 2009

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ABSTRACT

Introduction: We aimed to study whether the choice of timing of discussing organ donation for the first time with the relatives of a patient with catastrophic brain injury in the Netherlands has changed over time and explore its possible consequences. Secondly, we investigated how thorough the process of brain death determination was over time by studying the number of medical specialists involved. Thirdly, we studied the possible influence of the donor register on the consent rate.

Methods: Retrospective chart review of all effectuated brain dead organ donors between 1987 and 2009 in one Dutch university hospital with a large neurosurgical serving area.

Results: A total of 271 medical charts were collected, of which 228 brain dead patients were included. In the first period, organ donation was discussed for the first time after brain death determination (87%). In 13% of the cases, the issue of organ donation was raised before the first EEG. After 1998, we observed a shift in this practice. Discussing organ donation for the first time after brain death determination occurred in only 18% of the cases. In 58% of the cases, the issue of organ donation was discussed before the first EEG but after confirming the absence of all brain stem reflexes, and in 24% of the cases, the issue of organ donation was discussed after the prognosis was deemed catastrophic but before a neurologist or neurosurgeon assessed and determined the absence of all brain stem reflexes as required by the Dutch brain death determination protocol.

Conclusions: The phases in the process of brain death determination and the time at which organ donation is first discussed with relatives have changed over time. Possible causes of this change are the introduction of the Donor Register, the reintroduction of donation after circulatory death and other logistical factors. It is unclear whether the observed shift contributed to the high refusal rate in the Netherlands and the increase in family refusal in our hospital in the second studied period. Taking published literature on this subject into account, it is possible that this may have a counterproductive effect.

INTRODUCTION

Background

In the Netherlands, the concept of brain death was accepted in the 1970s.[1-4] In addition, in 1996, the Dutch Organ Donation Act (DODA)[5] became effective. The DODA was drawn up with four objectives in mind: (a) to clarify the legal position of organ donation, (b) to increase the supply of organs and tissues, (c) to ensure the fair distribution of organs and tissues and (d) to prevent trade in organs and tissues. In line with the DODA, in 1997, the Dutch government legally established the brain death criteria described by the Dutch Health Council.

A second initiative integrated with the DODA was the establishment of a national Donor Register (DR) in 1998. The DR, designed as an opt-in system, allows people to register their preferences regarding organ, bone and tissue donation, including their refusal to donate. Those who are not registered in the DR can donate with explicit consent from the patient's next of kin.[5]

If the patient has registered his or her consent or objection, the physician is expected to inform the family about the patient's wishes and explain the steps involved in the donation process if applicable. Consent given by the patient in the DR for organ donation permits the physician to begin organ-preserving treatment. Before 1998, individuals in the Netherlands could register their will concerning organ donation in a handwritten donor card. A third development in the 1990s was reintroduction of donation after circulatory death (DCD) in the Netherlands.

After the establishment of the brain death criteria, brain dead (BD) donors became the most important source of organs due to the superior organ quality and because these donors are the only source of hearts for transplantation. However, due to the declining availability of BD donors in the Netherlands, DCD became a reasonable and necessary alternative and was therefore reintroduced, first only for allocation of kidneys, and later for liver and lungs. In the past 15 years in the Netherlands, there has been a decline of donation after brain death (DBD) from 915 donors, 88.6% of the total number of donors, to 697 donors (58.4%), whereas DCD increased accordingly from 118 donors (11.4%) to 453 donors (41.6%). The decline in the number of DBD is completely compensated by an increase in the number of DCD.[6] This trend is consistent with literature from outside of Europe [7]. Due to the nature of DCD, permission for organ donation is requested prior to patient death. This sequence of consent is in contrast with obtaining consent for DBD, which is founded in the brain death protocol, in which consent can only be obtained after the formal determination of brain death.[5] Some believe that the issue of organ donation in case of a catastrophic brain injury is nowadays discussed with

relatives earlier in the process (before formal determination of brain death) than it was before the year 2000. This may have a negative effect on the consent rate.

Study aims

We aimed to study whether the choice of timing of discussing organ donation for the first time with the relatives of a patient with catastrophic brain injury in the Netherlands has changed through time and explore the possible consequences of such change. Secondly, we investigated how thoroughly the process of brain death determination was performed over time by studying the number of medical specialists involved. Thirdly, we studied the possible influence of a hand-written donor card (before 1998) and registration in the DR (after 1998) on consent rate.

MATERIAL AND METHODS

We conducted a retrospective chart review of all patients who became brain dead during their stay in the intensive care unit of the Erasmus MC University Medical Center between 1987 and 2009 and who donated organs for transplantation. This study was exempt from review and approval by the institutional Ethics Committee due to the retrospective, observational nature. We obtained a list of patients from the in-house transplant coordinator and crosschecked this with the central hospital patient registry. The following data were extracted: patient age, sex, cause of death, the moment of neurological examination of brain stem reflexes, the moment of confirmatory testing for brain death, the time at which organ donation was first discussed with the relatives of the patient, permission for organ donation by family or patient as documented in the patient's medical chart, the time at which consent was requested during the process and the number and specialty of the reviewing independent medical specialists. Exclusion criteria were age <12 years, insufficient data or failure to retrieve the medical chart from the hospital archive and BD patients who were converted to DCD. The age limit of 12 years was selected because in the Netherlands an individual may only register his or her will in the DR after this age.

Timing of discussing organ donation with the relatives

To analyze the time at which organ donation was first discussed with the relatives of the patient, we identified three events surrounding the process of determination of brain death:

1. The determination of the absence of consciousness (Glasgow Coma Score of 3), the absence of all brain stem reflexes as assessed by a neurologist or neurosurgeon as described by the Dutch brain death protocol.[4]

2. Performing the confirmatory tests. In the Netherlands, an electroencephalogram (EEG) followed by an apnea test is mandatory to declare brain death and to proceed with organ donation.[4]
3. The time at which organ donation was first discussed with the relatives of the patient in relation to the first two events or the time at which consent for the organ donation procedure was obtained from the next of kin, or in the case of consent by a patient in the DR, assent of the next of kin.

We determined three possible scenarios for the process of brain death determination and the time at which the issue of organ donation was first discussed with the relatives of a BD patient (Fig. 1), which could lead to consent or objection to organ donation. The ICU physician approaches the family with the issue of organ donation. Consent for organ donation by the relatives in the Netherlands is a verbal agreement between the ICU physician and the relatives of the patient. This is not further formalized by a signed agreement by the relatives. The decision about organ donation by the relatives or the patient is documented in the patient's medical chart, which, under Dutch law, serves as a legal document.

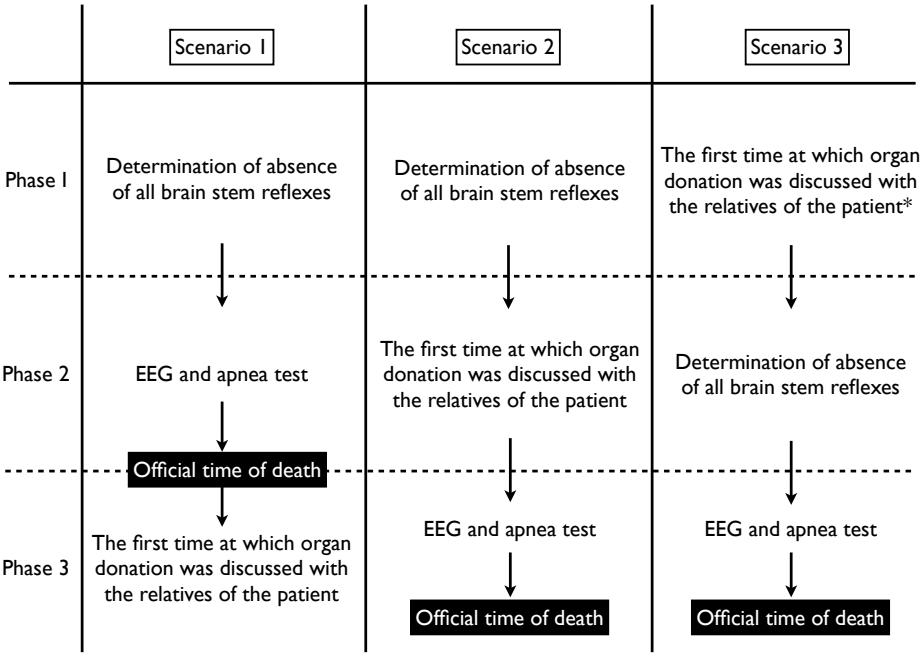

Figure 1. Flowchart of three possible scenarios concerning the moment of requesting organ donation consent from the relatives of a patient.
(* patients who were regarded as potential brain dead organ donors and for whom further treatment was deemed futile)

Consultation by independent medical experts

We investigated how thoroughly the process of brain death determination was performed over time by studying the number of independent medical specialists involved by reviewing the medical charts on written statements of brain death confirmation.

Influence of hand-written donor card and registration in donor register on consent rate

We studied the possible influence of the DR on the consent rate by searching for documentation in the medical charts on the presence of a written donor card or print-out of the DR.

Because changes in legislation were introduced in 1998 in the Netherlands, we divided the study cohort into two periods to study the changes over time. Period 1 consisted of the patients who died between 1987 and 1998, and period 2 consisted of the patients who died between 1999 and 2009.

Statistics

Normally distributed continuous variables are described using their means and standard deviations. Skewed continuous variables are described using medians and inter-quartile ranges. Binary variables are described using proportions. Differences between the two subgroups were tested using Student's *t*-test for normally distributed continuous variables, and the Mann-Whitney U test was used for skewed continuous variables. All binary variables were analyzed using the Chi-square test. Differences between three or more subgroups were tested with ANOVA using the post-hoc Tukey test for normally distributed continuous variables and the Kruskal-Wallis test for skewed continuous variables.

Results

Between 1987 and 2009, 271 patients were declared brain dead and donated one or more organs; 19 patients in this cohort were excluded due to fact that relevant data for analysis could not be extracted from the medical chart, and 24 patients younger than 12 years were excluded due to the minimal age requirement. Therefore, 228 patients were included in the study for further analysis. In this cohort, the most frequent fatal conditions of effectuated

Table 1: Causes of brain death in 228 effectuated organ donors age ≥12 yrs (1987–2009) n=228

	1987–1998 (n=123)	1999–2009 (n=105)	Total	p-value
Age, yr (±SD)	43.9 (15.2)	47.3 (15.7)	45.5 (15.5)	0.867
Sex (M/F)	71/52	47/58	118/110	0.051
Consent no. (%)				
Family	116 (94.3)	62 (59.0)	178 (78.1)	<0.001
Patient	7 (5.7)	43 (41.0)	50 (21.9)	

brain-dead organ donors were subarachnoid haemorrhage (SAH) (50.0%), traumatic brain injury (TBI) (28.9%) and intracerebral haemorrhage (ICH) (12.7%) (Table 1).

Timing of discussing organ donation with the relatives

Figure 2 shows the sequence of events surrounding the formal determination of brain death and the timing of the first discussion of organ donation with the patients' relatives. In the first period, Scenario 1 was the most common practice, occurring in 87% of the cases. In 13% of the cases, the issue of organ donation was raised before the first EEG (Scenario 2, Figure 2).

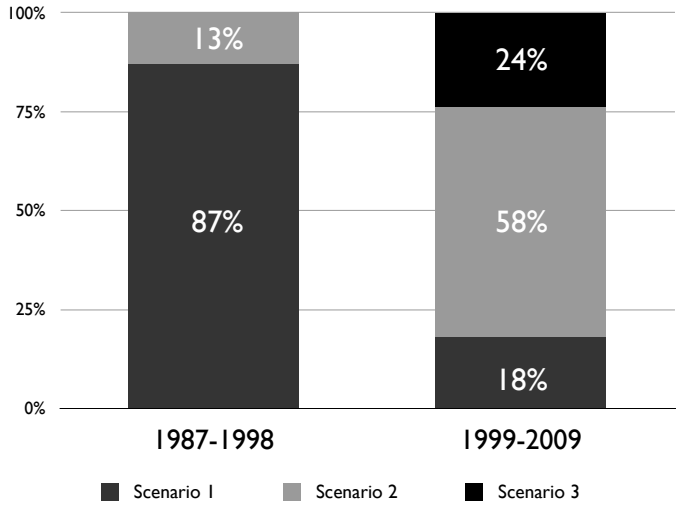

Figure 2. Sequence of brain death determination.

After 1998, we observed a shift in this practice. Scenario 1 occurred in only 18% of the cases. In 58% of the cases, the issue of organ donation was discussed before the first EEG, but after confirming the absence of all brain stem reflexes (Scenario 2), and in 24% of the cases, the issue of organ donation was discussed after the prognosis was deemed catastrophic but before a neurologist or neurosurgeon assessed and determined the absence of all brain stem reflexes as required by the Dutch brain death determination protocol (Scenario 3).

Consultation by independent medical experts

Before 1998, it was the custom in our ICU that two or more independent medical specialists from different departments (neurosurgery, neurology, surgery and/or internal medicine) confirmed the results of the completed brain death determination process. Before 1998, two or more experts reviewed the medical chart and the obtained results of neurological examination and confirmatory tests, examined the patient and finally confirmed brain death determination, with 'no objection to organ donation' in 78.4% of the cases. This time-consuming but careful practice was gradually abolished after 1998 (Figure 3). We found no remaining

record of an independent specialist confirming the brain death determination process after 2002. We must stress that there is a difference between the neurologist and neurosurgeon who assesses the absence of brainstem reflexes as described as step 1 in the Material and methods section of this article and the review of an independent specialist of the whole process.

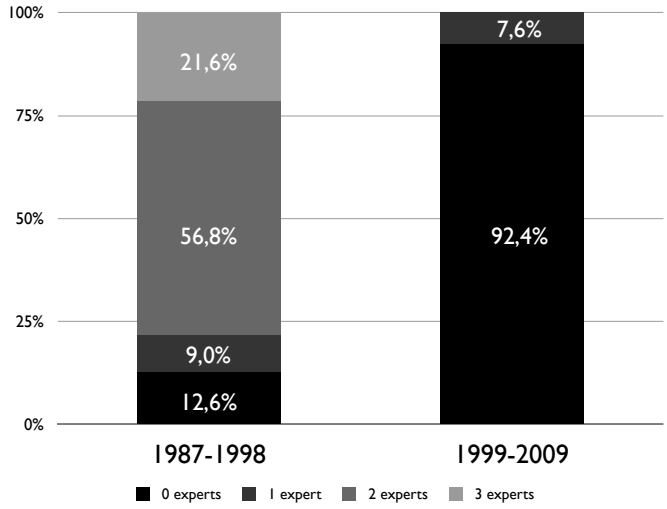

Figure 3. The number of experts who independently reviewed the process of brain death determination between the two study periods.

Influence of hand-written donor card and registration in donor register on consent rate

Before the introduction of the DR in 1998, patients could provide their consent for organ donation via a signed and dated hand-written donor card. In this period, we found a written donor card in 5.7% of the cases of effectuated organ donation. However, after the introduction of the DR, this form of consent was no longer tenable, and none was found after 1999. Before 1998, consent for organ donation was obtained from the next of kin of the deceased in the majority of the cases (94.3%, Table 2). Even in case of a donor card, consent for organ dona-

Table 2 Demographics of effectuated brain-dead organ donors who gave consent for organ donation in the two study periods (n=228)

Cause n (%)	1987–1998	1999–2009	Total	p-value
SAH	51 (41.5)	63 (60.0)	114 (50.0)	0.049
ICH	18 (14.6)	11 (10.5)	29 (12.7)	
TBI	44 (35.8)	22 (21.0)	66 (28.9)	
Other	10 (8.1)	9 (8.5)	19 (8.4)	
Total	123	105	228	

tion was asked from the next of kin of a brain dead patient. In case of legitimate objections of the relatives, the physician was not constrained to proceed to organ donation. Following the introduction of the DR in the second period, a considerable fraction of the study population provided their own consent and preferences for organ donation through the DR. We found a positive registration in no less than 41.0% of the cases of effectuated organ donation.

DISCUSSION

Timing of discussing organ donation with the relatives

We observed remarkable changes in the sequence of brain death determination in terms of the time at which organ donation was first discussed or consent for organ donation was first requested in relation to the sequence of brain death determination. A possible explanation for the changes in the sequence of the clinical and confirmatory tests with respect to the discussion of organ donation with the patients' relatives (Figure 2) is the introduction of the DR, which allowed the physician to consider the possibility of organ donation at an earlier time than was required before its introduction 1998. If the physical condition of a patient made organ donation a plausible outcome, then the physician was expected to consult the DR to determine the registered wishes of the patient, leading to a possible decision about organ donation, which was made earlier in the whole process of organ donation.

In addition, DCD was reintroduced at our hospital in 1998. This required physicians to discuss organ donation and seek official consent before the withdrawal of life support in patients with catastrophic brain injury (but not (yet) brain-dead), and the practice may have extended to the pool of potential BD patients. A significant decline in DBD and an increase in DCD is observed in the Netherlands in the last 15 years.[6] The final explanation for the observed changes is that the physicians may have anticipated the possible adverse outcomes at an earlier stage due to the higher demand for ICU beds. If organ donation was refused and further treatment of the patient was judged to be futile, then withdrawal of life support was selected. The determination of an isoelectric EEG is not required for the decision to withdraw treatment in case of catastrophic brain injury. Continued treatment of a possible organ donor to keep vital organs in good condition is seen as a service for transplant medicine. The primary responsibility of the ICU physician is to provide good end-of-life care to patients with no hope of survival. Some will say that the continuation of futile treatment in the context of organ donation can be seen as the use of patients as a means rather than an end, but in case of a positive record in the DR and consent of the relatives of the patient who act in the conviction of the will of the patient, continued treatment can also be seen as an end and not as a means.

Refusal by relatives is the step in the donation process at which most donors are lost. Some studies have found that families are more willing to provide consent if they are given adequate information about brain death and the donation process.[8,9] An adequate understanding of brain death has been considered essential for obtaining donation consent. Rates of donation are higher when a timely brain death explanation is provided.[10] In a study from a European country with a high donor conversion rate (Spain), Andres et al.[11] state that relatives must correctly understand brain death of the deceased before they are interviewed to request donation. The timing of the request is an important factor that can influence the rate of consent. The most important factor is a clear separation ('decoupling') in time between the notification and acceptance of brain death and the request for organ donation. An analysis of a series of nine published reports by Simpkin et al.[9] suggested that there is an improved rate of consent when there is decoupling between notification and acceptance of brain death and the request for organ donation. Only one older study, by Niles and Mattice[12], found that consent was similar regardless of whether relatives were approached before (62%) or after (57%) death. Commonly mentioned reasons for the relatives to decline organ donation are concerns about disfigurement, emotionally overwhelmed feeling, inappropriate notification of brain death by physicians, and surprise at being asked for consent to donate.[13,14] Rodrigue et al.[10] found that for relatives who thought that the timing of the donation discussion was appropriate, 68% donated, whereas only 18% consented to donation if they considered the timing poor. Simpkin et al.[9] concluded after reviewing a series of published studies that the main and modifiable factors associated with consent or refusal for organ donation by relatives are perceived quality of care of the donor, understanding of brain death, timing of the request, the setting in which the request is made and the approach and skill of the individual making the request. The current standard in our hospital and many other Dutch hospitals of informing the patients' relatives and asking consent for organ donation prior to formal brain death determination does not address the above-mentioned issues. In the Netherlands, the refusal rate by relatives approached for a family member's organ donation were 65% in 2005, 71% in 2006, 59% in 2007 and 69% in 2008.[15] Taking the literature on this subject into account, it is possible that we shoot ourselves in the foot on this subject.

Besides the aforementioned study by Niles and Mattice[12], we were unable to find any evidence that requesting organ donation before or after death has a positive or negative effect on the consent rate. However, the results of many published studies on the effect of decoupling the announcement of brain death and the request for organ donation, and the positive impact of a clear explanation of brain death, suggest that a pre-BD request may have a negative effect on the relatives' consent rate. The continuing gap between the need and demand for organs for transplantation forces us to perform such an emotional and delicate process as brain death determination and notification with the highest ethical and medical standards.

Consequently, and based on the results of many studies, we believe that consent for organ donation should only be requested and obtained after the full formal brain death determination.

Consultation by independent medical experts

The number of medical experts who reviewed the whole process of brain death determination declined after 2002 to zero. It was not compulsory but was permitted in the national brain death protocol to invite an independent medical expert to review the completed BD determination process. This was an extra safeguard in our hospital that nothing be overlooked or missed that could make the conclusion that a patient was brain dead invalid. Why this practice is not continued remains unclear. It was comforting for relatives that an elusive state such as brain death was confirmed by independent medical specialists. Certain states in the US still require independent confirmation by another physician of the declaration of brain death.[16] In European countries, there are no requirements of an independent review of the brain death process, although the number of physicians that should be involved varies per country from zero to four.

Influence of hand-written donor card and registration in donor register on consent rate

The introduction of the DR formalized the process of organ donation. One of the aims of the DR was to provide individuals with the option of registering their preferences. Physicians could easily locate the registration of the potential organ donor in the DR and act according to the patient's wishes. Our data suggest that the DR has been beneficial over the past decade. Families are no longer obligated to make an ad hoc decision about organ donation if a positive (consent) or negative (objection) registration is available. A potential disadvantage is that families seem to be more reluctant to consent to organ donation if the patient is not registered. If someone believes that being an organ donor is important to him or her, then registration would be expected. Although we have no scientific proof on this matter, this is the common experience of health care professionals in the Netherlands. The mean refusal rate in our hospital in the first study period was 31% but increased in the second period to 45% (unpublished data, Erasmus MC Rotterdam). The reason for this rise in refusal rate is complex and difficult to determine, but reluctance of relatives in cases of non-registration could be a major factor.

According to the latest report (August 2011) of the Dutch DR[17], 33.5% of the Dutch population had registered their decision for organ donation, amongst whom 58.8% stated that they wished to donate one or more organs, whereas 28.7% refused to donate, 10.7% left the decision to donate to their relatives and 1.8% to an appointed person. Debate has raged in the Netherlands about the advantages and disadvantages of the opt-in and opt-out systems.[18]

Study limitations

Our study has some limitations. First, the study was performed in a single center, and data were obtained through a retrospective review of medical charts. However, our hospital is one of the largest university hospitals in the Netherlands, with a large neurosurgical service area, and hence, the results may be exemplary for other large hospitals in the country. As with all observational studies, some cases may have been missed in a non-random manner. Due to the retrospective nature of our study, we could not obtain the charts of all potential brain-dead organ donors or of all brain-dead patients who did not donate organs because there was no formal listing of this group of patients. However, the data obtained from this study are valuable for the study of the influence of the DR on the moment of consent. Further studies should be conducted to determine whether requesting consent for organ donation before neurological examination or before confirmatory testing in possible BD patients has a positive, neutral or negative influence on the consent rate.

CONCLUSION

The sequence of brain death determination and the time at which organ donation is first discussed with relatives have changed over time. Currently, in most cases, the issue of organ donation is first discussed after the clinical-neurological assessment as described in the brain death determination protocol but before the required confirmatory tests. Possible causes of this change are the introduction of the DR, the reintroduction of donation after cardiac death and other logistical factors. It is unclear whether the observed shift contributed to the high refusal rate in the Netherlands and the increase in family refusal in our hospital in the second studied period. Taking the published literature on this subject into account, it is possible that this may have a counterproductive effect on the matter. After the introduction of a national DR, donation by patient consent has increased from 5.7% to 41.0%.

KEY MESSAGES:

- Over the past 15 years in the Netherlands, there has been a decline in donation after brain death from 89% to 58%, while donation after circulatory death increased from 11% to 42% in the same period.
- After introduction of the Donor Register in the Netherlands, the rate of organ donation by patient consent in our hospital increased from 5.7% to 41.0%.
- Before 2002, independent medical experts reviewed and confirmed the outcome of the whole process of brain death determination of a potential brain-dead organ donor and

documented their findings in the medical chart. After 2002, this careful procedure is no longer conducted.

- The time at which organ donation is first discussed with relatives has changed over time in our hospital. Initially, between 1987 and 1998, organ donation was mentioned for the first time after completion of ancillary tests conforming to the national brain death protocol. After 1998, in most cases, organ donation was discussed after determination of loss of consciousness and the absence of brainstem reflexes but before completion of the confirmatory tests.

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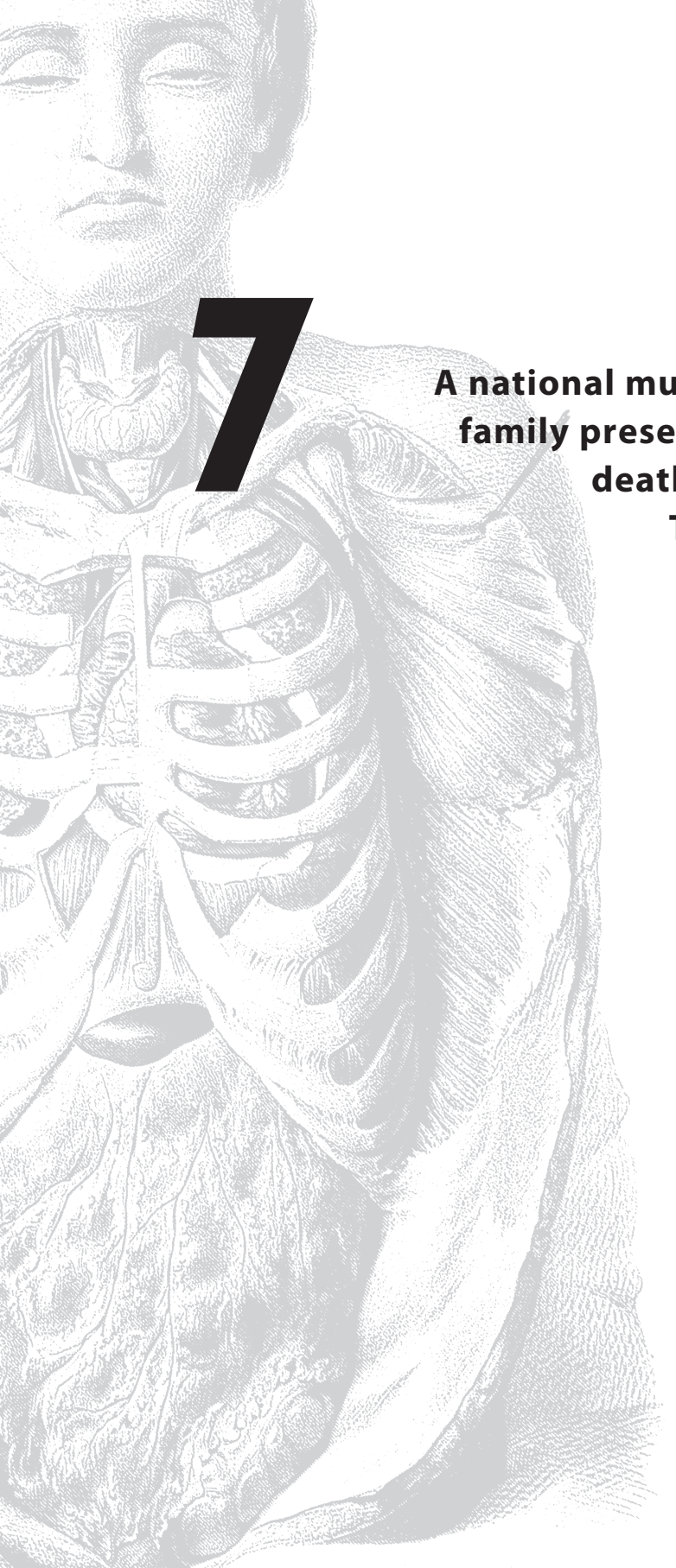

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A national multicenter trial on family presence during brain death determination: The FABRA study

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ABSTRACT

Purpose: As brain death is a difficult concept for the lay public to understand, we hypothesized that allowing relatives of the patient to be present during brain death determination would improve their understanding of this condition and would eventually lead to an increased consent rate for organ donation.

Methods: A prospective multicenter trial was conducted in five Dutch hospitals. Relatives were given the opportunity to be present during brain death testing. The family consent rate for organ donation was the primary endpoint examined, and the degree of the relatives' understanding of brain death was the secondary endpoint.

Results: Between April 2010 and July 2011, we included the relatives of 8 patients in this study. The relatives witnessed brain death testing during this time. This sample size was too small to draw valid statistical conclusions. However, we have documented some noteworthy experiences of the relatives.

Conclusions: Although, the hypothesis behind this study had promise, we were unable to reach our predefined goal. The possible causes for this shortcoming included the rarity of patients with brain death, the common practice in the Netherlands of obtaining consent for organ donation before brain death testing and the uneasiness of the staff in the presence of the patients' relatives during brain death determination. Although, we cannot draw a conclusion from statistical evidence, we would recommend that relatives be given the opportunity to be present during brain death testing and, specifically, during the apnea test.

INTRODUCTION

Brain death is an undesirable outcome of critical care medicine and is an artifact of nature that results from the ability of medical technology to prolong and disrupt the process of dying. However, the brain dead patient is the ideal multi-organ donor for organ transplantation. Progress that has been made in the prevention and treatment of conditions leading to brain death (especially subarachnoid hemorrhage and traumatic brain injury) has resulted in a decline in the actual number of brain dead patients in almost all industrialized countries of the Western world.[1] In the USA and Europe, another factor that has led to the decreased number of brain dead organ donors is that patients with severe brain injuries have been allowed to die by the discontinuation of life-sustaining treatments before their progression into brain death and as soon as the family has understood the futility of these treatments. This phenomenon also helps to explain the concomitant increase in organ donors after circulatory death. These trends in organ donation may result in the further widening of the gap between the number of heart-beating organ donors and the number of recipients.

In the Netherlands, the concept of brain death was accepted in the 1970s. In addition, in 1996, the Dutch Organ Donation Act (subsequently referred to as "the Act") came into effect. The Act was created with the following four objectives in mind: (a) to clarify the legal position on organ donation, (b) to increase the supply of organs and tissues, (c) to ensure the fair distribution of organs and tissues, and (d) to prevent trade in organs and tissues.[2] In 1997, and in line with the Act, the Dutch government legally established the brain death criteria that were proposed by the Dutch Health Council. The committee of the Health Council endorsed the most stringent definition of brain death, or the "whole-brain death" concept. Since then, brain death has been determined according to the national Brain Death Protocol.[3,4]

In the Netherlands, the determination of brain death consists of three phases (Fig. 1). In phase 1, the cause of the coma is established, and the ascertainment of the irreversibility of the coma as well as the identification of such possible confounding factors as metabolic disturbances, hypothermia, neuromuscular blocking agents, and hypotension are made. If this phase of the analysis has been completed, a clinical neurological examination is performed (phase 2) and consists of the determination of the absence of consciousness (Glasgow Coma Score of 3) and the absence of all brain stem reflexes (as assessed by a neurologist or neurosurgeon). The third phase consists of two confirmatory tests: an electroencephalogram (EEG) and a subsequent apnea test. Both tests are mandatory under Dutch law to declare a patient brain dead and to proceed with organ donation. This requirement is in contrast with the brain death guidelines in the USA (which also have interstate variability)[5] and in other European countries, where the EEG is used less frequently as a confirmatory test.[6] The phases of the determination of brain death need to be done by a medical professional within this particular

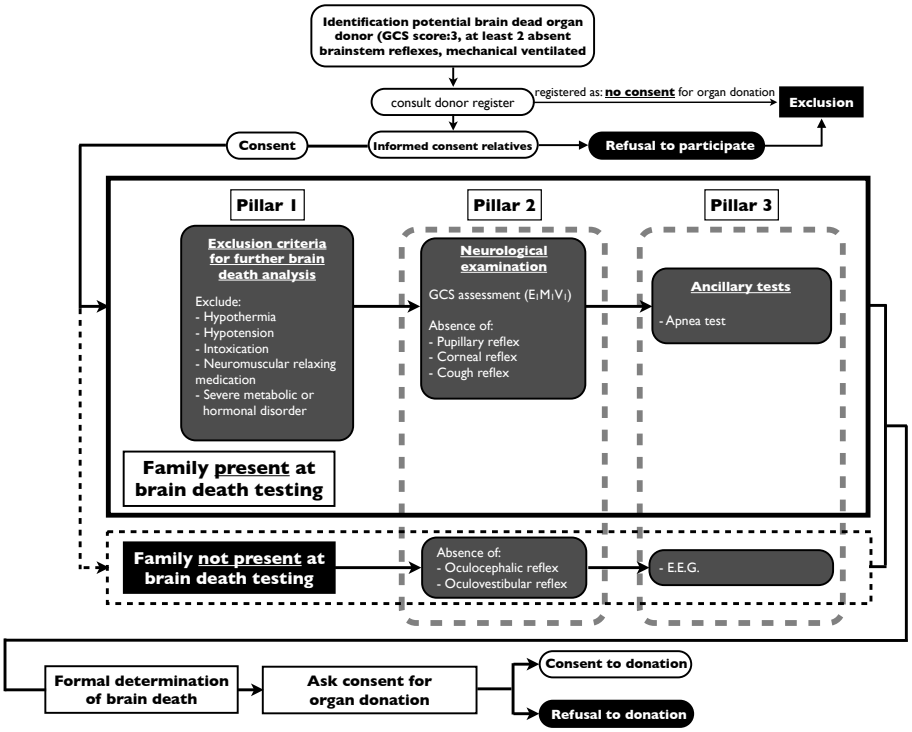

Figure 1. Flowchart of the study

field of expertise, a neurologist or a neurosurgeon must test for brain stem reflexes, a neurologist with a registration in neurophysiology should assess the electroencephalogram and an intensivist or anesthesiologist must perform the apnea test.

A second initiative, which was integrated into the Act in 1998, established a national Donor Register (DR). The DR, which was designed as an opt-in system, allows individuals to register their preferences regarding organ, bone, and tissue donation and also their refusal to donate. Those who are not registered in the DR can still donate with the explicit consent of their next of kin. If the patient has registered his or her consent or objection, the physician is expected to inform the family of these wishes and to explain the steps that are involved in the donation process, if applicable. The donation consent that is given by the patient according to the DR permits the physician to initiate organ-preserving treatment. A consenting registration in the DR is generally respected, but it is uncommon that organs are removed against the will of the relatives. In other words, the family generally retains the right in all scenarios to veto the patient's previous consent.

For the general public, the concept of "brain death as death" is often difficult to understand. The body of the brain dead patient is warm and pink, the chest rises and falls due to mechanical ventilation, there is visible evidence of a heartbeat and there is production of urine. For the relatives, the brain dead patient can be perceived as a comatose, but alive, patient.

It is an established practice in most intensive care units for relatives to not be present for the brain death testing.[7] However, some authors have suggested that the witnessing of brain death testing by relatives may be helpful for their understanding of the concept of brain death before organ donation[7-12], although, there is little evidence that this would work in daily practice. A study by Pugh et al.[12] contacted 28 neurotrauma intensive care units in the United Kingdom by telephone to identify the senior staff member who is generally involved in the testing for brain stem death. Next, they sent a questionnaire to 147 consultants and 167 senior nurses who had been identified in the telephone survey, and 79% of the consultants and 77% of the senior nurses returned the questionnaire. Overall, 32% of the consultants and 42% of the nurses had experience with the presence of patients' relatives during brain death testing, and 69% felt that this was helpful for the relatives. Nurses were more likely than physicians (84% versus 53%) to believe that witnessing the tests would help the relatives to accept that the idea that the patient had died, and 48% of nurses thought that the relatives would gain comfort from being present during the testing.

A study by Bell et al.[8] created a questionnaire for members of the Neuroanaesthesia Society of the United Kingdom that concerned brainstem death testing. Twenty-two percent of the respondents stated that they would allow the family to observe these tests if the relatives asked to be present.

A study from Ormrod et al.[11], which was also from the United Kingdom, examined the experiences of the relatives of brain dead patients. In this series (27 relatives of 23 patients), thirteen individuals were given the opportunity to witness brain death testing, but only five (including 2 members of one family) relatives observed the tests.

It will be difficult to alter the current trend of the decrease in brain dead organ donors in many Western countries that has resulted from improved preventative and therapeutic treatment options. Upon analyzing the possible ways to improve donor rates, family refusal is the one factor that could be modified.[13,14] For this reason, we initiated a national multicenter trial in April 2010, focused on family presence during brain death determination, which was termed the FABRA (FAmily presence during BRAin death determination) study. However, the trial was not successfully conducted over an 18-month period because a sufficient number of relatives were not included (we aimed to include relatives of at least 50 brain dead patients to achieve a statistically valid number). Although, the anecdotal results concern a small number

of individuals and valid statistical conclusions cannot be drawn, we believe that this type of study is worth reporting because the hypothesis holds great potential. In this article, we have provided the results of this study and have attempted to determine the reasons behind the failure to include a sufficient number of subjects.

MATERIALS AND METHODS

This trial was set up as a prospective multi-center trial at five Dutch hospitals. The study was initiated between April 2010 and August 2010 at the intensive care units of three university hospitals and two large non-university hospitals. The institutional review boards at the participating hospitals approved the study protocol. After reviewing the study protocol, the boards chose to make informed consent of the relative's mandatory before their participation in the study, due to the possible psychological stress involved for the relatives of the patients.

For inclusion in the study, we selected patients with severe and irreversible brain injury who had been admitted to intensive care and for whom brain death was suspected (as determined by evidence of severe brain injury on CT scan, by relevant information provided by relatives concerning the medical condition of the patient and by a GCS of 3 with absent pupillary and corneal reflexes and controlled mechanical ventilation) (Fig. 1). In addition to this, inclusion criteria patients needed to be medically suitable for organ donation and their family members (legal representatives) should be present at the hospital. The relatives that were included in the study were asked if they would be willing to be present during the testing of the brain stem reflexes and during the apnea test. This conversation took place at the time when the physician announced to the relatives that the patient had severe and irreversible brain damage and that further treatment would be futile. Important to add here is that in the Netherlands, when the multidisciplinary ICU team decide that prolonging life-sustaining measures, like mechanical ventilation, is not in the patient's interest anymore, the decision will be made to withdraw these measures to let the patient die. Further life-sustaining measures are judged futile, the palliative care of course not. The relatives of the patient will be informed about the decision to withdraw life-sustaining measures, but have no legal right to stop this. If the patient is suitable for organ donation, relatives are asked for consent, and life-sustaining measures will be continued to preserve vital organ function. If they refuse consent, mechanical ventilation will be withdrawn, administration of vasopressors will be stopped, and the patient will die after circulatory arrest.

After brain death was confirmed, the relatives were asked to provide consent for organ donation. The relatives were present for the scoring of the GCS, the tests for pupillary, corneal and cough reflexes, and the administration of the apnea test.

The family consent rate for organ donation was appointed the primary endpoint for this study, and the degree to which brain death was understood as the death of the individual was made the secondary endpoint. To test this secondary endpoint, we contacted by telephone the relatives who had witnessed the brain death tests three and six months after the death of their relative.

RESULTS

Between April 1, 2010 and July 1, 2011, we screened 27 relatives of patients for eligibility (Fig. 2) of which 8 relatives eventually consented to participate in the study. Twenty-one patients' relatives were screened in the primary hospital (Erasmus MC University Medical Center, Rotterdam, The Netherlands), 6 were screened in the participating hospitals. None of the participating hospitals included a patient for the study. Reasons for exclusion in the participating hospitals were refusal to participate (n = 2), already obtained consent for organ donation on the emergency room (n = 3) and one patient that retained a ventilatory drive. Of the eight relatives that witnessed the brain death testing 7 consented for organ donation, one relative declined organ donation. The reasons of admission for the patients whose relatives participated in the study were a subarachnoid hemorrhage (n = 5) and a traumatic brain injury (n = 3). The overall major reasons of exclusion were a prior registration in the Donor Register stating refusal to donate (n = 6) and refusal to participate (n = 9).

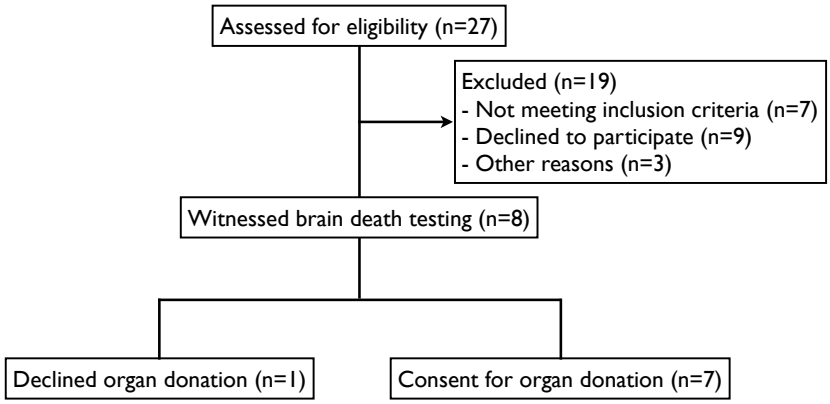

Figure 2. Flowchart of the results

The sample size of this study was too small to make a valid statistical conclusion or to reach a conclusion concerning the primary endpoint. However, regarding the secondary endpoint, we recorded noteworthy, though anecdotal, experiences from the patients' relatives.

Experiences of Relatives

The relatives who had witnessed brain death tests were contacted by telephone between three and 6 months after the death of their loved ones, and these anecdotal personal experiences provided information regarding the effect of a family presence during brain death determination.

"We knew that my mom had died when the intensivist stopped the respirator and when we saw an absence of breathing." (son of a brain dead patient after witnessing the apnea test)

"The fact that she had no response to pain was not considered to be a sign of death for us, as we saw the nurses test the motor response many times before she was declared brain dead (and she didn't respond at these times either); at this particular moment, she was comatose and not brain dead." (son of a brain dead patient)

"We were shocked when the nurse reconnected the respirator after the apnea test had been performed. For us, she was dead when she was not breathing, but then she breathed again." (spouse and son of a brain dead patient)

"When we observed that she was not reacting to the painful stimulus on her fingers, we knew that she was not suffering anymore." (spouse of a brain dead woman)

"When I saw the hemorrhage in her head on the CT scan, it was clear to me that she would not survive." (spouse of a brain dead woman)

"Those tests were a type of theater for me. I understand that they need to be done, but they did not convince me." (spouse of a brain dead woman)

"We also witnessed the electroencephalography test. We did not understand what was going on, and the woman who made the recording was not very helpful at explaining this test." (daughter of a brain dead woman)

"I knew that she was dead and that the tests were just a formality. (spouse of a brain dead woman)

"It was reassuring that the ventilator had been turned off and that I didn't see her gasping for breath." (daughter of a brain dead woman).

DISCUSSION

We had hypothesized that the observation of the testing process would help relatives to understand that the patient had died when brain death was established. The relatives who observed the testing were pleased that it had been offered and said that it had helped their understanding of brain death. It was striking that the relatives were surprised about the thoroughness of the testing. In this small sample of participants, the apnea testing was the most convincing test for the relatives in terms of the realization that the patient had died. Some relatives were disturbed to see that the respirator was reconnected after they and the medical team had observed a lack of breathing by the patient. The relatives saw the moment during the apnea test as the moment of death and questioned why resuscitation was necessary when death seemed so obvious. None of the relatives who observed the tests and none who we have spoken to subsequently indicated any reservations regarding their attendance during the testing. The FABRA study failed to include a sufficient number of patients and, therefore, could not conclude that family presence during brain death determination was an efficient tool to provide a better understanding of 'brain death as death' or to raise the consent rate for organ donation. However, we have examined what may have caused this and have suggested the following five possible reasons for this failure:

1. The rarity of brain death as an outcome of neurocritical care

In the Netherlands, brain death is a rare outcome of neurocritical care. Over the past 15 years in the Netherlands, there has been a decline in the number of organ donors following brain death; the number has dropped from 915 donors (88.6% of the total number of donors) to 637 donors (58.4% of the total). However, the number of donors following circulatory arrest has increased accordingly from 118 donors (11.4% of the total number of donors) to 453 donors (41.6% of the total).[1,15] Therefore, the decline in the number of brain dead donors has been completely compensated for by the increase in the number of circulatory arrest donors.[1] The recognition of certified donors is the goal in the Netherlands[16], although, the refusal rate from relatives of the patients is high. In the Netherlands, this refusal rate was 65% in 2005, 71% in 2006, 59% in 2007, and 69% in 2008. At the Erasmus MC University Hospital in Rotterdam, the refusal rate is approximately 45%. At one of the participating centers (VU Medical center in Amsterdam), only two brain dead patients were evaluated during the FABRA study period (personal communication, Dr. A. Beishuizen).

2. The common practice of asking relatives before brain death testing

In the Netherlands, the current practice is to ask for organ donation permission before the formal brain death testing, although the Act states otherwise. In our opinion, this was the most significant reason behind the failure of this trial to include a sufficient number of subjects. From a retrospective medical chart review of all effectuated brain dead organ donors be-

tween 1987 and 2009 at our hospital, we found a remarkable shift of the time at which organ donation was first discussed with a patient's relatives.[17] For this article, we divided the data from 228 brain dead patients into two time periods (1987–1998 and 1999–2009). In the first period, organ donation was first discussed with relatives after formal brain death determination in 87% of the cases. In 13% of the cases, the issue of organ donation was raised before the first EEG. After 1998, we observed a shift in this practice, as the first discussion of organ donation occurred after formal brain death determination in only 18% of the cases. In 58% of the cases, organ donation was discussed before the first EEG but after the confirmation of an absence of all brain stem reflexes. Furthermore, in 24% of the cases, organ donation was discussed after the prognosis was deemed poor but before a neurologist or neurosurgeon assessed and determined the absence of brain stem reflexes, as is required by the Dutch brain death determination protocol. One possible explanation for these changes in the sequence of the clinical and confirmatory tests with respect to the discussion of organ donation with the patients' relatives is the introduction of the DR, which allowed the physician to consider the possibility of organ donation sooner than was required prior to its introduction in 1998. If the physical condition of the patient rendered organ donation possible, the physician was expected to consult the DR to determine the registered wishes of the patient and to make a more informed, faster decision regarding this process. According to the FABRA study protocol, relatives should have been asked to witness brain death testing before the request for organ donation (as was stated as mandatory by the medical ethical review boards). Although it is stated in the Dutch Organ Donation Act[4] that consent must be sought after declaration of death, this is contrary to the common practice at most hospitals in the Netherlands, as was discovered by our retrospective analysis.[17] When we developed this study we used the Act as point of departure to formulate our inclusion and exclusion criteria. We have not anticipated on the fact that only a few hospitals were willing to divert from their routine to seek consent after the formal determination of brain death to make the study possible. The determination of brain death according to the Act was and is followed in every hospital to the letter only the moment to seek consent has changed over time. We already described this practice in an earlier report[17] but from an analytic point of view we think it can be considered as one of the major reasons why we failed to include a sufficient number of patients for this study.

3. Electroencephalography

During the study period, various neurologists refused to conduct an electroencephalography when the relatives had not given their consent for organ donation. The reason for this refusal was that this test is only necessary in the context of organ donation. Prolongation of life-sustaining measures like mechanical ventilation or the administration of vasopressors is already judged as futile and not any more in the interest of the patient. Conducting an electroencephalography will not change that conclusion and the decision to withdraw life-sustaining measures. Neurologists are reluctant to perform the electroencephalography

when the need for this (confirmation of brain death for organ donation after relatives have consented) remained uncertain.

4. Uneasiness of medical, nursing, and technical staff with having relatives present

To our surprise, we were confronted with opposition from medical and technical staff (not from the nursing staff) in regards to their participation in the FABRA study. A technician from the department of electroneurophysiology was quoted as saying: "It was very confrontational when the family of the patient was present when I came to perform the EEG. I was not used to seeing the grieving children of a young dying woman present at the bedside. The son of the patient began to ask questions about the EEG and what it measured that I could not answer. Afterwards, I was very upset." A fellow intensive care doctor (anesthesiologist) said the following: "This is the most difficult study that I have ever participated in. It made me very uneasy when the relatives of the patient were present during the brain stem testing." The medical specialists had fewer objections. A senior neurologist was quoted as saying: "I have no problem with family members observing the brain stem reflex testing, as I have nothing to hide." A senior intensivist said the following: "I think it is good that relatives observe the apnea testing. It can be reassuring to see that the patient is not breathing anymore." Members of the technical staff from the department of electroneurophysiology are rarely confronted by grieving relatives during their work. Thus, we can understand the uneasiness of these health care workers during this study.

The family presence during brain death determination is comparable to the presence of family during resuscitation. Traditionally, when a patient has suffered a circulatory arrest in a hospital, the family is taken into the waiting room while the resuscitation is initiated. However, this scene has been changing since the 1980s. Many countries and many hospitals, including those in the Netherlands, have debated whether family members should be allowed at the patient's bedside at the time of resuscitation. However, this has become common practice. Early reports demonstrated that three-quarters of relatives felt as if their adjustment to the death of their loved one was made easier by their presence, and 64% felt that their presence was beneficial to the dying person. If given the opportunity, 94% would again choose to be present in this situation.[18,19] Family members with no medical background have reported that being at a loved one's side during resuscitation and that saying goodbye during the final moments of life was comforting.[20] Nowadays, family presence during resuscitation is seen as a normal in family centered care and has given rise to the declaration of position statements from many international medical societies.[21-24] The American Heart Association stated in their 2010 guidelines that "in the absence of data documenting harm and in light of data suggesting that it may be helpful, offering select family members the opportunity to be present during a resuscitation seems reasonable and desirable (assuming that the adult patient has not

raised prior objection)."[25] Public opinion polls in the USA have shown a strong majority sentiment in favor of relatives being able to be present during resuscitation. Several studies have indicated that the majority of nurses endorse family presence during resuscitation, and this endorsement can be compared with between 50 and 70% of physicians and only about 20% of residents who endorse family presence.[26] These results are in line with our experiences in family presence during brain death determination. We have not experienced any objections from ICU nurses or from staff ICU physicians, but we have received objections from residents and fellows from intensive care.

LIMITATIONS

During the time of this study, we were confronted with several setbacks. First and foremost, there was a low supply of potential organ donors who were brain dead. As reported earlier, an intensivist in this study only evaluated two brain dead potential organ donors in a one-year period. At our hospital, we were confronted with problems regarding the consent of patients' relatives. Many intensivists had difficulty introducing the study in the same conversation as the discussion of the patient's grave condition. Aside from this observation, there was no clear indication as to the proper time to seek consent for organ donation. As per the protocol, we wanted to ask for consent after the complete and formal determination of brain death.

However, this approach was received with much resistance because the common practice was different than the formal brain death protocol. This common routine was difficult to change, and this resistance made the fulfillment of the primary endpoint not feasible. The reasons why the participating hospitals failed to include a patient for this study are difficult to grasp. The already mentioned absolute low number of potential brain dead patients certainly plays an important role but is not a reasonable answer. Sometimes, they were confronted with patients with devastating neurological injury that were admitted from the emergency room with already obtained consent for organ donation. But overall, we think that the participating hospitals failed to include any patient seen the ingrained and common practice to ask for organ donation before official brain death determination. However, the documented experiences of the relatives who witnessed the brain death assessment were very helpful for our understanding how they have experienced to witness some of the tests. These anecdotal experiences provided insight into the psyche of the mourning relatives and were helpful for the revision of the brain death protocol at a national level.

CONCLUSIONS

Although, the hypothesis behind our study was promising, it was difficult in practice to conduct. Unfortunately, we were only able to include the few relatives who were willing to observe the brain death determination testing. One of the reasons for this scarcity of study subjects was the extreme rarity of brain death as an outcome of neurocritical care in the Netherlands. It is possible that the FABRA study could be repeated in a different country with more brain dead patients. To conduct a study similar to the FABRA study, it is important to note that is the common practice in most hospitals in the Netherlands to inquire about organ donation before a formal brain death determination. Allowing relatives who had already given consent for organ donation to be present for the brain death testing would be helpful for their understanding of "brain death as death", but this would do little to alter the organ donation viewpoint of those attending. For these cases, there is a strong parallel between family presence during brain death testing and family presence during resuscitation. When resuscitation was introduced in the 1980s, there was resistance from the residents to let family members be present, and this level of resistance is similar to what we experienced during the FABRA study. However, it is now common practice in many hospitals throughout the world, and it has been judged to be beneficial, for family members to be present during this procedure.

For this reason, although we cannot conclude with statistical evidence that family presence during brain death determination was beneficial, we would recommend that relatives be given the opportunity to be present. Specifically, the observation of the apnea test may serve as a reassuring experience enabling the relatives to come to terms with the patient's death.

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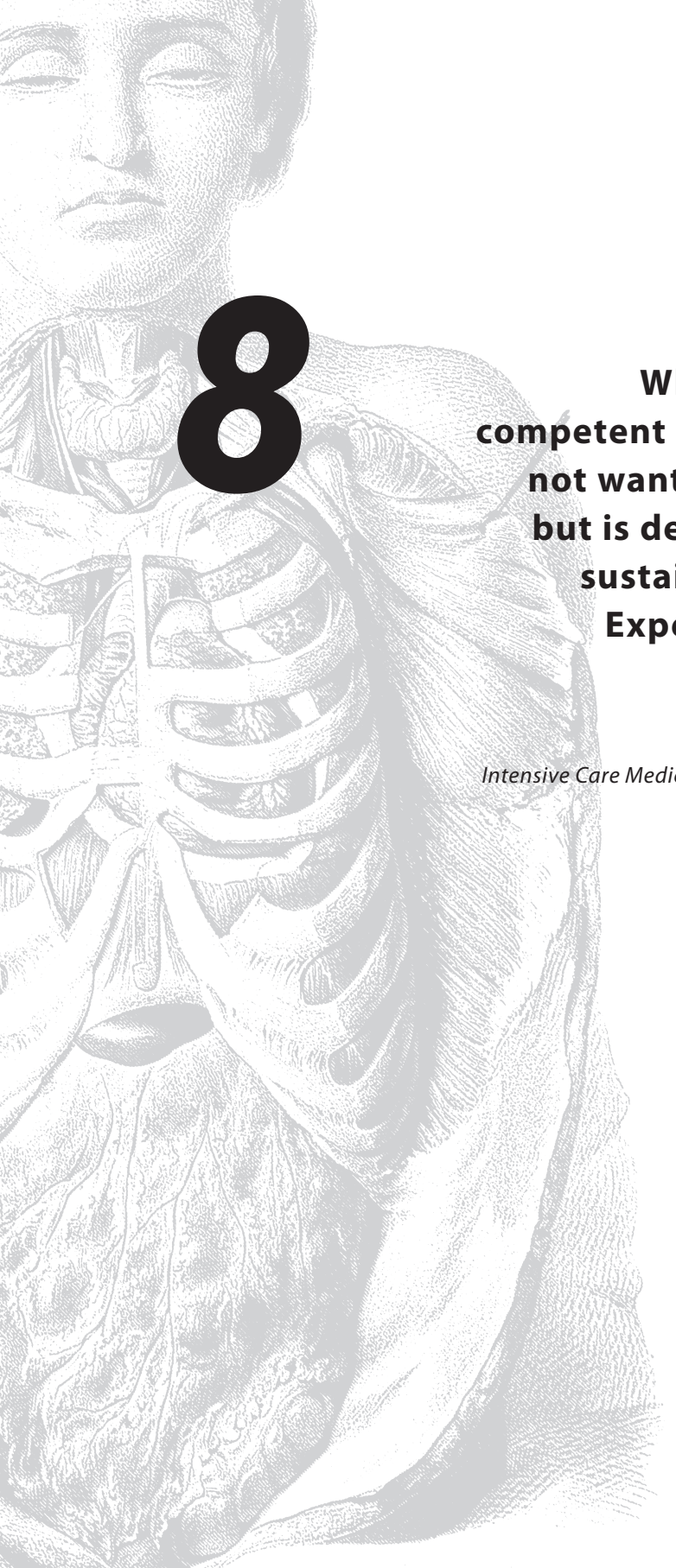

8

What to do when a competent ICU patient does not want to live anymore but is dependent on life-sustaining treatment? Experience from The Netherlands

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ABSTRACT

If patients on the intensive care unit (ICU) are awake and life-sustaining treatment is suspended because of the patients' request, because of recovering from the disease, or because independence from organ function supportive or replacement therapy outside the ICU can no longer be achieved, these patients can suffer before they inevitably die. In The Netherlands, two scenarios are possible for these patients: (1) deep palliative (terminal) sedation through ongoing administration of barbiturates or benzodiazepines before withdrawal of treatment, or (2) deliberate termination of life (euthanasia) before termination of treatment. In this article we describe two awake patients who asked for withdrawal of life-sustaining measures, but who were dependent on mechanical ventilation. We discuss the doctrine of double effect in relation to palliative sedation on the ICU. Administration of sedatives and analgesics before withdrawal of treatment is seen as normal palliative care. We conclude that the doctrine of the double effect is not applicable in this situation, and mentioning it criminalized the practice unnecessarily and wrongfully.

INTRODUCTION

Some awake patients on the ICU request for withdrawal of life sustaining treatment in order to die. In the Netherlands two scenarios can be offered: a. deep palliative sedation through administration of barbiturates or benzodiazepines before withdrawal of treatment or b. we can offer deliberate termination of life (euthanasia) before termination of treatment. The aim of palliative sedation is to prevent suffering by lowering consciousness as a means to achieve this. In this context, it is important to understand that withdrawal of treatment, consequently allowing the patient to die, after intentional lowering of consciousness, is not equivalent with euthanasia, or deliberate termination of life.[1,2] Euthanasia is the intentional termination of life of an adult patient on his or her request. This presupposes voluntariness and a deliberate act and excludes every form of intentional non-voluntary termination of life. Usually the patient is sedated to unconsciousness and then given a barbiturate and muscle-paralyzing agent. In the Termination of Life on Request and Assisted Suicide Act[3], the requirements of due care are described. Deliberate termination of life is illegal in most countries in the world.

Recently, two of our conscious ICU patients asked for discontinuation of life-sustaining measures. We want to emphasize the central place for the autonomous choice of the patient and the care of the patient and his or her benefits and interests.

Patient A

A 61-year old ventilator dependent patient on our ICU requested to withdraw life-sustaining treatment and if necessary to deliberately terminate her life. In a series of extensive deliberations with the patient and after consulting an independent physician, we agreed to comply with her will. We offered deep palliative sedation followed by withdrawal of life-sustaining treatment. In presence of her relatives, intravenous administration of midazolam (starting dose 5 mg, thereafter 10 mg/hour) and fentanyl (100 µgr starting dose, with 50 µgr/hour to follow) was started. Within 15 minutes she was unconscious. Subsequently the inotropes, other life-sustaining medication and mechanical ventilation were withdrawn. She died quietly from heart failure and circulatory collapse.

Patient B

Patient B, a 58-year old building constructor, was admitted to the general ICU with a traumatic spinal cord injury at the C6-C7 level. In the following weeks, we were unable to wean the patient off the ventilator. Furthermore he showed no improvements of his spinal cord injury and remained tetraplegic. Several weeks after admission, he repeatedly expressed a clear wish to withdraw treatment and asked the ICU team to take him off the mechanical ventilator. Because of the anticipated anguish, he further wished to be deeply sedated beforehand. After consulting two independent physicians, the nursing staff and a clinical ethicist, the

patient was granted his wish. A combination of intravenously administration of midazolam (starting with a dose of 5 mg/hour, thereafter 10 mg/hour). and a low dose of fentanyl (100 µgr starting dose, with 50 µgr/hour to follow) was started and after entering a deep sleep, the mechanical ventilation was withdrawn. Shortly thereafter he died peacefully and surrounded by his family.

DISCUSSION

Approximately 80% of patients, who die in an ICU in the Netherlands, die after organ function supportive care or organ function replacement therapy is withdrawn (Unpublished data, Erasmus MC, department of Intensive care). Those surviving for a number of hours after discontinuation of treatment, can develop symptoms such as dyspnea associated respiratory distress, terminal restlessness and death rattle. The majority of terminal patients in the ICU are however unconscious due to the severity of their disease or multiple organ failure and are not or only superficially aware of the distressing symptoms. The burden of terminal distress in such cases rests predominantly with the relatives.[4] Most symptoms however, can be successfully prevented or treated.[5] A national guideline in the Netherlands on withdrawal of futile intensive care measures focuses on anticipation of distressing symptoms. Even in The Netherlands, deliberate termination of life of ICU patients is extremely rare.[1]

Palliative sedation is initiated in the ICU in the terminal phase of life to prevent or relieve aggravating symptoms such as terminal restlessness, delirium or anxiety. Sedatives are administered aiming to induce a deep unconscious sleep in anticipation of death. In principle, the national guideline palliative sedation of the Dutch Royal Society of Medicine (KNMG)[6] is adhered to, based on the understanding that in ICU practice, only midazolam and propofol are used for sedation. Morphine is not an effective sedative and is not used in the ICU as such.[7] In the ICU, the transition from sedation with mechanical ventilation to palliative sedation is usually imperceptible. As a rule, the sedative regime the patient received while being treated with mechanical ventilation will be continued in the palliative phase until death. The dose required in ICU patients can be significantly higher than mentioned in the recommendations in the guideline. If the patient is adequately sedated before withdrawal of treatment, then this dose is adhered to. It serves no purpose to adjust an adequate sedative dose either to a lower level or to increase it to abide by the guideline recommended starting dose. After publication of the guideline in 2005, palliative sedation was recognized by the Public Prosecutor to be normal medical practice. There is, however, a directive to prosecute and bring before a court anyone who performs an act, not stated as such in the professional guidelines, and treating this as a life-terminating act without the consent of the patient. In the ICU, we deviate from the precise statements in the guideline, but with good reason. During the documented fol-

low up of the use of sedatives in patients in the ICU it is important to judge whether one has acted according to the professional standards. Comparing palliative sedation in the ICU with other non-ICU settings is not realistic.

Crucial in the decision-making process in the described cases is respect for the autonomy of the patient. Based on the law, Dutch caregivers have to respect the wishes of the patient if these are understandable and within the accepted possibilities of medical care and also if the patient is judged to be competent to make these judgments. In the cases, caregivers had no reasons to doubt the cognitive functioning and competency of the patients.

One cannot always predict with certainty whether or not aggravating symptoms will arise after stopping treatment in the ICU. Patients who are awake may prefer to be unconscious during dying with failing organ functions after seizure of therapy. It is our moral duty as caregivers in the ICU to acknowledge this request, and instilling palliative sedation prior to withdrawing active treatment offers a righteous means.[5] But with this, we digress from the Dutch Guideline, in which is stated that administering sedatives to patients for the sole reason of the patient's wish to be free of suspected suffering at the end of life is not permitted. There must be objective proof that there is untreatable suffering, which only can be treated by lowering consciousness of the patient.

Many published ethical analyses on palliative sedation use the doctrine of double effect (DDE), mentioning that palliative sedation may hasten or induce death, and therefore morally questionable. When evaluating an action, the DDE distinguishes between intended effects and the consequences that are foreseen but unintended. As long as intentions are good, it is permissible to perform actions with foreseen consequences that it would be wrong to intend. In this line of thought, deliberately causing death is morally wrong, even if desired by a competent patient whose suffering cannot be relieved in another way. If the patient dies unintentionally as a consequence of another ethically justified intervention (e.g. withdrawal of futile treatment), the action is morally acceptable. The unintended but foreseen effect must also be proportional to the intended good effects. The DDE is often mentioned in justifying the use of opiates and sedatives at the end of life to relieve suffering. There is a growing body of evidence that administration of normal doses of sedatives and opiates at the end of life does not shorten life, but prolong it[8-12], and only scarce anecdotal data mention that opioids can hasten death[13], making the DDE in end-of-life care a myth.[14] It is concluded that "Clinical studies and decades of experience by experts in pain management and palliative care have shown that the double effect of pain medication has little basis in medical fact.' and that '...the myth of the double effect of pain medication, directly contributing to the undertreatment of suffering at the end of life. It is ironic that an ethical principle that is used to justify adequate opioid analgesics contributes to the undertreatment of pain'.[14] The same could be said about

palliative sedation with barbiturates and benzodiazepines. DDE in end-of-life care is nothing more than a myth and using it to label palliative sedation and administration of opiates at the end of life questionable and only defendable from the perspective of the DDE, unsound.

When a competent patient on the ICU asks for termination of treatment we should seriously take this request in deliberation. The principle of respecting autonomy is a strong guidance in bioethics.

The American Academy of Neurology published a position paper concerning the care of conscious, competent patients with profound paralysis.[15,16] They concluded that such patients have the right to make health-care decisions about their own lives, including acceptance or refusal of life-sustaining treatment. Once patients have decided to forego life-sustaining treatment, physicians have an ethical obligation to minimize their subsequent suffering. This is particularly true of profoundly paralyzed patients, because cognition and sensation may be intact, and they are capable of great suffering.

CONCLUSION

In competent ICU patients in the Netherlands who are dependent on life-sustaining measures, as mechanical ventilation and administration of vasoactive agents, withdrawal of these measures is ethically good care when they ask for withdrawal. This is not to be seen as deliberate termination of life, even if they die after the withdrawal of life-sustaining measures. Administration of sedatives and analgetics before withdrawal of treatment is normal palliative care. The DDE is not applicable on this situation.

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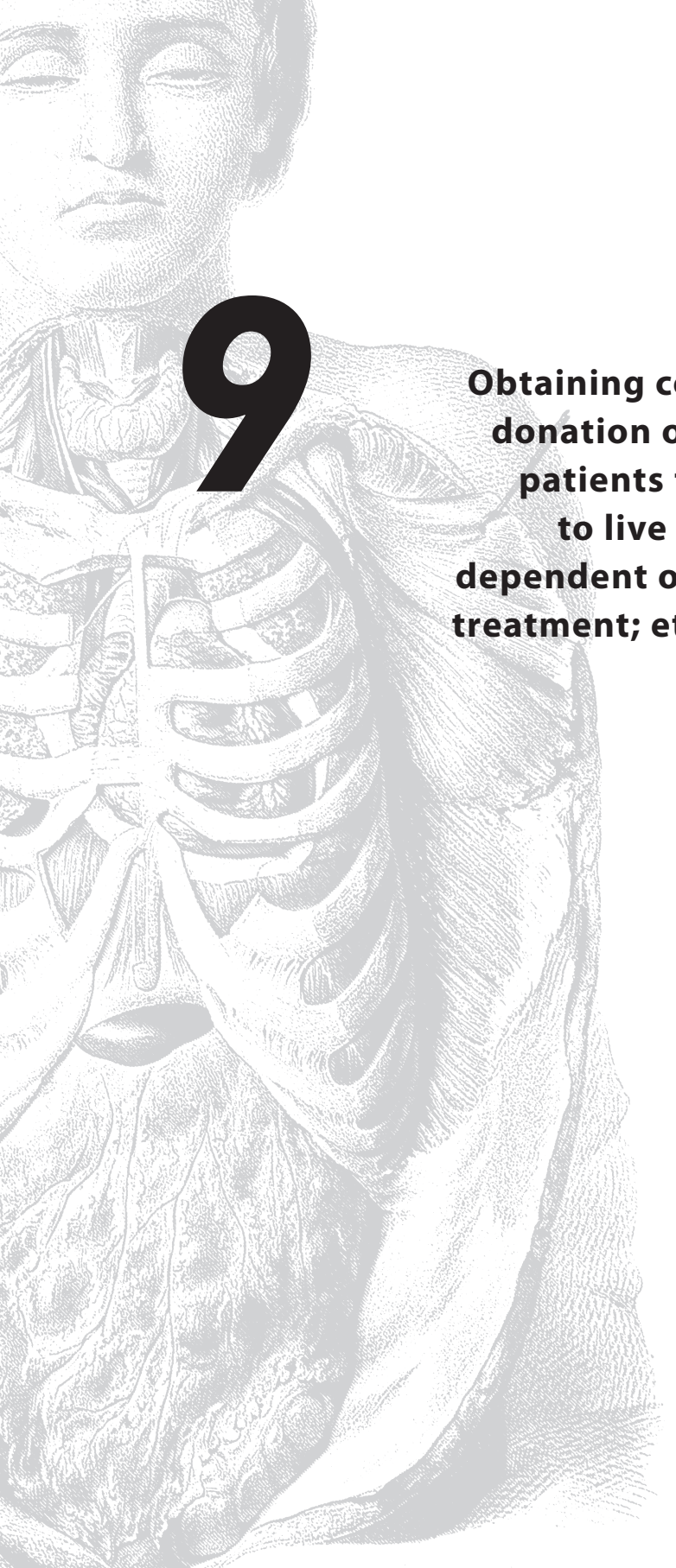

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Obtaining consent for organ donation of competent ICU patients that do not want to live anymore but are dependent on life-sustaining treatment; ethically feasible?

Submitted

Y.J. de Groot
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ABSTRACT

We anticipate a further decline of patients that eventually will become brain dead. The ICU is considered a last resort for many patients with severe and multiple organ dysfunction. Patients with primary CNS failure constitute the largest group of patients in which life-sustaining treatment was withdrawn. Almost all these patients are unconscious on the moment physicians decide to withhold and withdraw life-sustaining measures. But sometimes competent ICU patients state that they do not want to live anymore because of the severity of their illness and the poor prognosis and ask for withdrawal of life-sustaining measures like mechanical ventilation. Do we consider the unconscious patients as potential organ donors before withdrawal of mechanical ventilation? This is rarely the case in conscious patients. Is it ethically feasible and practical to obtain consent for organ donation form this group of patients?

INTRODUCTION

Since the first observational descriptions of brain dead patients by French and German neurologists in the late 1950s[1,2], many thousands of artificially ventilated patients in intensive care units worldwide have been declared dead after the determination of irreversible failure of brain function, in favor of organ donation for transplantation. Brain death is always been a rare outcome of intensive care treatment of severe brain damage due to traumatic brain injury, or severe forms of stroke (subarachnoid hemorrhage and intracerebral hemorrhage). Because of changes in demographics, improved treatment options and of legislation prohibiting smoking in public places we anticipate a further decline of patients that eventually will become brain dead.[3] Considering the fact that the brain dead organ donor is the ideal organ donor because of the possibility to procure a heart and the overall better quality of organs this means a further setback to the transplantation medicine. Many initiatives are developed and deployed in order to decrease the gap between patients awaiting an organ and the number of actual organ donors. These initiatives include a better organization of donor care on a national, regional and hospital level inspired by the Spanish model[4] or a change of the system of consent. Many Central and South European countries adapted a form of presumed consent or opt-out. North European countries like the UK and the Netherlands have considered a system of opt-out but eventually choose to maintain their current system of opt-in.[5,6] Considering the diminishing supply one have to pursue and analyze every potential area of improvement.

The ICU is considered a last resort for many patients with severe and multiple organ dysfunction. Therefore it is the hospital department with the highest mortality rate. Approximately 15% of all admitted patients die on the intensive care unit. End of life care is considered a vital part of the ICU. The majority of the patients that die on the ICU are the result of withholding or withdrawing life sustaining treatment.[7] According to a paper by Sprung and colleagues the primary reasons for the end of life decisions are unresponsive of therapy (no diagnosis reported in the paper), neurological reasons, chronic disease and multi organ failure.[8] In a recent paper Verkade and colleagues studied the incidence of withdrawal of life-sustaining treatment in various group of patients in a single center mixed ICU in the Netherlands.[9] In the period between 1 November 2006 and 31 October 2007, 1353 patients were admitted to the ICU of which 218 eventually died. In 174 patients life sustaining treatment was withdrawn. Patients with primary brain failure constituted the largest group of patients (86/174, 49.4%) in which life sustaining treatment was withdrawn.[9] The group of patients with primary brain failure consisted of patients admitted with intracerebral-, subdural- or subarachnoid hemorrhage (ICH/SDH/SAH) and traumatic brain injury (TBI). This group of patients are most likely to be eligible to eventually donate their organs after death, but only few reach the state of brain death. For this reason donation of organs after circulatory arrest is increasingly

considered. In the Netherlands the number of donations after circulatory arrest increased from 118 patients in the period between 1995-1999 to 453 patients in the period 2005-2009 according the annual reports of the Dutch Transplant Foundation.[3,10] In literature this procedure is named 'controlled non-heart-beating organ donation' of controlled donation after circulatory death'. Nowadays, in many countries, controlled organ donation after circulatory death, forms an important source for kidneys, livers and lungs for transplantation. Before withdrawal of mechanical ventilation, relatives are asked consent for organ retrieval after the death of their loved one. If they consented, mechanical ventilation is withdrawn, pending circulatory arrest. After a 'hand-off' period of five minutes, the patient is declared dead and rushed to the operation theatre for organ retrieval. All these patients are deeply unconscious on the moment life-sustaining measures is withdrawn. But sometimes competent ICU patients, who are dependent from intensive care measures like mechanical ventilation, state that they do not want to live anymore because of the severity of their illness and the poor prognosis and ask for withdrawal of life-sustaining measures in order to die.[11] In the Netherlands, respecting the autonomy of these patients, in most cases, life-sustaining treatment is then withdrawn. Recently we described two conscious patients who died on the ICU after they asked for withdrawal of life sustaining treatment. In which way do they differ, beside the level of consciousness, from patients in which we withdraw treatment and in which we consider organ donation? Why don't we consider these conscious patients as potential organ donors before withdrawal of mechanical ventilation? There is some experience with organ donation after planned deliberate termination of life (euthanasia) in Belgium[12,13], but we are not aware of documented cases in which ICU physicians ask patients if they are willing to donate their organs after death which will occur after withdrawal of mechanical ventilation on the ICU. Maybe, in light of the scarcity of organ donors, we have to reconsider this point of view. The aim of this paper is to discuss the pros and cons of such a change in end of life care with regard to current ethics and practicality.

Scenarios

To improve the discussion we present you two cases that we use for further ethical analysis.

Patient A, a 45-year-old electrician, is admitted to the general ICU after he had fallen from a ladder. During this fall, he struck the wall of a building. This resulted in fractures of three cervical and one lumbar vertebra, and mild traumatic head injury.

An MRI scan shows a rupture of the anterior longitudinal ligament of the spinal column and a hemorrhagic contusion of the spinal cord at the C5-C6 level, but no further damage to the vital organs. In the weeks thereafter it is impossible to wean the patient from the mechanical ventilator. During his stay on the ICU he showed no improvements of his tetraplegic status. He eventually regains full consciousness and can communicate with eye blinking and later

by lip reading. He is informed about his clinical situation. The patient is well aware of his situation and the unavoidable restrictions for his future daily activities. Several weeks after admission, he repeatedly expresses a clear wish to have life sustaining treatment withdrawn and asked the ICU team to take him off the mechanical ventilator. After several deliberations between family members, various physicians, nurses and a clinical ethicist we agreed to offer him, according to his will, deep palliative sedation, followed by withdrawal of life sustaining treatment. After initiation of intravenous administration of midazolam the patient enters a deep sleep. Inotropic support and mechanical ventilation were withdrawn. After 15 minutes the patient died peacefully in the presence of his family.

Patient B, a 45-year-old business administrator, is admitted to the ICU with severe neurological injury after a high-speed road traffic accident. A CT-scan shows several subdural hematomas, a skull fracture and compression of the brainstem. Because of the low GCS score the patient is intubated and connected to a mechanical ventilator. When the patient is neurologically assessed by a neurosurgeon he has a Glasgow Coma Score of $E_1M_1V_1$, an absent pupil and corneal reflex. However because of some intact brainstem reflexes the patient is not considered to be brain dead. After several weeks of ICU treatment, the patient shows no neurological improvement. In a multidisciplinary meeting it is decided to withdraw life-sustaining treatment seen the poor prognosis of the patient. When discussing this decision with the family the treating physician also mentions the option of organ donation. Because the patient is not registered in the national donor register, the relatives of the patient are mandated by law to make a decision regarding organ donation. After much discussion they agree with organ donation according to the protocol of donation after circulatory death (DCD). In the presence of the family the mechanical ventilator and other life sustaining therapy are withdrawn. The patient dies after 30 minutes of cardiopulmonary arrest. After a mandatory 5-minute 'no-touch' period the patient is transferred to the operation theatre for organ retrieval.

DISCUSSION

When comparing both scenarios there are many similarities but also some striking differences. Both patients die as result of an action, namely the withdrawal of life-sustaining measures, which is done by the physician after multidisciplinary deliberation.[9] While in first scenario the patient explicitly asks for the withdrawal of life sustaining measures in order to die, in the latter case the decision is made by a multidisciplinary group of physicians and other health care workers. Both patients were suitable for organ transplantation after death but only one patient donated after physicians asked consent of the family. The other, conscious, patient could have decided if he wants to donate one or more organs, but was never approached with the question concerning organ donation.

Essential in the decision process surrounding the withdrawal of life sustaining treatment in patients that are awake, as we discussed in detail in our previous paper, is respect for the autonomy of a patient. Dutch caregivers have to respect, by law, the wishes of the patient if they are understandable and within the accepted possibilities of medical care. There has to be no doubt concerning the cognitive functioning and competency of the patient.[11] According to Beauchamp and Childress an autonomous action should be made by someone (1) who acts intentionally, (2) with understanding of the consequences at hand, and (3) without controlling influences that determine their action.(14) In the first case the decision to withdraw life sustaining therapy is made by the treating physician after the explicit request of the patient. The patient made this request with the knowledge that the withdrawal of the mechanical ventilator and inotropic medication mean a certain death. He acted intentionally with the limited means of communication he had as his disposal and family or friends did not influence his actions. Nevertheless he was not asked if he wanted to use the option to donate after his demise.

The ethical base of deciding to donate organs after death is that it is ideally an autonomous choice, made by the individual when he or she was healthy of mind. The central donor register (see www.donorregister.nl), which is an essential tool concerning organ donation in The Netherlands, is based on respect for the autonomy. If an individual has registered refusal of donation of organs and tissues after death, no donation will follow. When an individual decided that he or she wants donate organs or tissues after death, this is followed, if possible, in almost all cases. In case of no registration in the donor register, the relatives of the patient are approached to consider permission for organ removal after death of the patient, as is described in the second scenario.

In the Netherlands, individuals can ask a physician for withdrawal of treatment, but also for intentional termination of life. This presupposes voluntariness (seen from the patient) and a deliberate act (seen from the physician). It excludes every form of intentional, active, direct, non-voluntary termination of life. In the Dutch 'Termination of Life on Request and Assisted Suicide Act', the requirements of due care are described.[15]

The Act[15] requires that the physician:

- Holds the conviction that the request by the patient is voluntary and well considered
- Holds the conviction that the patient's suffering is lasting and unbearable
- Has informed the patient about the situation and about the prospects
- Holds the conviction that there is no other reasonable alternative in the light of the patients situation
- Has consulted at least one other independent physician who must have seen the patient and given a written opinion on the due care criteria

– Has terminated a patient's life or provided assisted suicide with due medical care and attention.

The same requirements, with exception of the last one, are applicable for the scenario in which a competent patient on the ICU ask for termination of mechanical ventilation and other life sustaining measures, *without* deliberate termination of life due to the injection of euthanatica. In such a situation, taking the above-mentioned requirements in consideration, the request has to be seriously considered. If approved, the patient is brought to sleep with sedatives after which mechanical ventilation is withdrawn and the patient die. Some say that in this scenario the patient die from the underlying disease or condition, but we think this is a moral fiction. As in euthanasia, where the patient die after injection of euthanatica, in withdrawal of life-sustaining measures as mechanical ventilation, the patient die as a consequence of the action of the physician.[9] Euthanasia is however not the same as palliative administration of sedatives and/or opioids. No evidence exists that adequate therapeutic use of opioids and benzodiazepines to treat discomfort hasten death[16-20], although both actions will lead eventually to death of the patient. Euthanasia (deliberate termination of life after injection of euthanatica) is very rare in the ICU setting in the Netherlands.[21] Withdrawal of life sustaining measures is however common.[7,8,22]

Organ donation after circulatory death is legally and ethically accepted in many Western countries, taking the dead donor rule in consideration. The dead donor rule is the ethical and legal rule that requires that donors are not to be killed to obtain their organs.[23] Organ retrieval itself may not cause death so the removal of organs necessary for life, like the heart or the lungs, prior for death of donor would violate the dead donor rule. However the removal of one kidney or a partial liver will not violate the dead donor rule because this will not lead to the death of the patient. The dead donor rule is vital for the donation and transplantation system and helps to maintain the public trust in organ donation after death.

After five minutes of circulatory arrest with no ventilation the patient is considered dead and organ removal can take place. The situation is equal in cases where an unconscious patient with devastating neurological damage die after withdrawal of mechanical ventilation, as in cases where a sedated patient, who was conscious before sedation, die after withdrawal of mechanical ventilation. Both patients are then equal and suitable for organ donation. For this reason we see few obstacles for the organ donation in itself. Why then don't we ask patients before withdrawal of mechanical ventilation if they are willing to donate their organs? Some scholars will reason that there is a conflict of interest in such a situation, but we see this also as a moral fiction. The autonomous patient asks for termination of life (as in the Belgium cases of organ donation described by Ysebaert et al[12]) or termination of life sustaining measures. It is not the physician who initiated this, it is the patient. The physician follows the voluntary

and well-considered request. What if the patient asks beside the request for termination of life or withdrawal of mechanical ventilation for organ donation after death? Do we have reasons to reject this? We cannot reason them. So we think that there are no moral objections for asking the patient for organ donation if the request for life termination of withdrawal of ventilation is granted.

Another point of concern some will mention is the distrust of society in this scenario. Medical mistrust, especially the fear that doctors will prematurely declare death to procure organs[24], is one the non-rational factors that could be seen as a real danger for this scenario. However, everything that has been proposed in this paper is within the law. Therefore we anticipate that this proposal will not meet much discussion in the lay press, as it is in fact the intention of the Organ Donation Act[25] to give everyone the chance to donate his or her organs after they die.

CONCLUSIONS

In a medical community in which withdrawal of life-sustaining measures in unconscious and in conscious ICU patients is accepted, where organ donation after death is common practice, and in which is a shortage on organs for transplantation, there can be no moral objection to ask conscious patients to donate their organs after death. Although withdrawal of mechanical ventilation on request of the patient on the ICU is rare and therefore the number of organs that come available is limited, it is worth considering. Anyway, there are no valid moral objections against it. It is ethically feasible to ask the patients for it.

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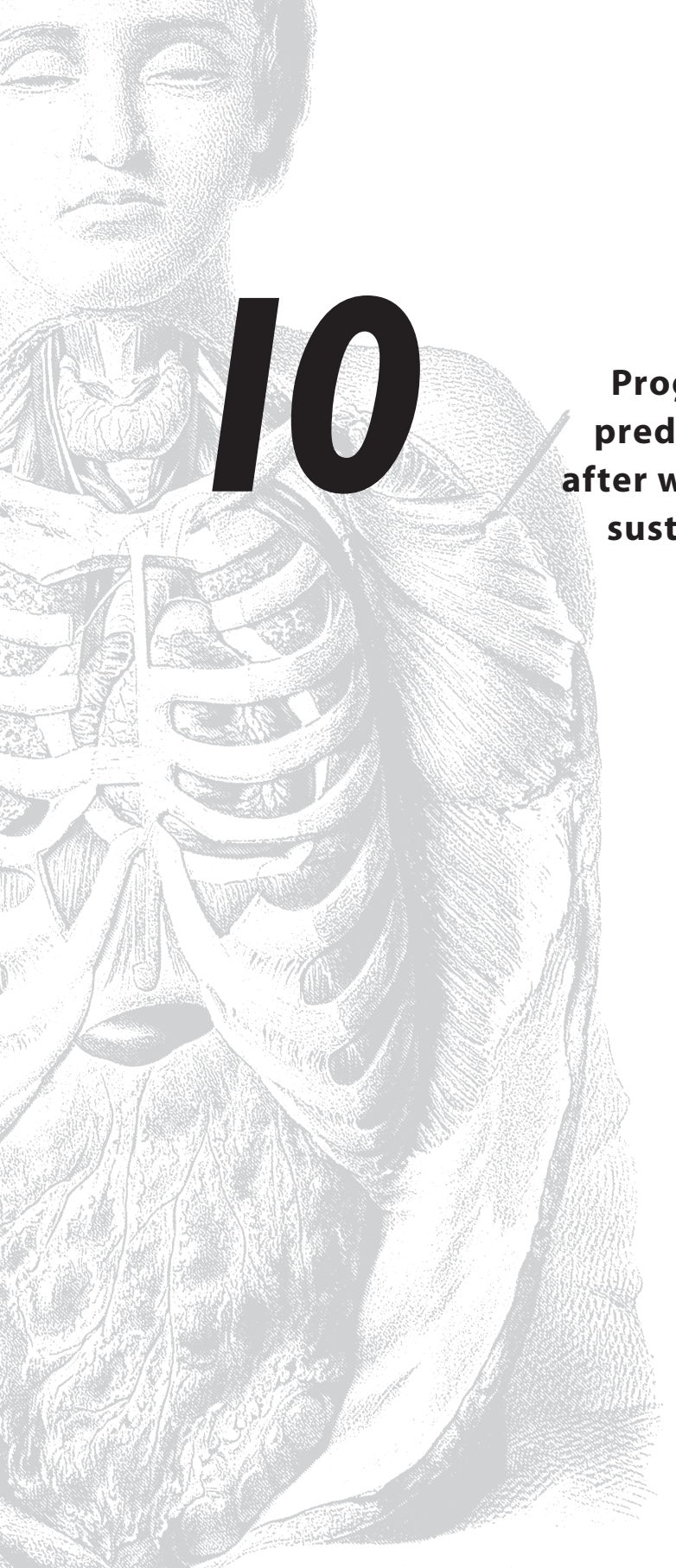
Prognostic modelling in the donation process



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Prognostic model to predict time of death after withdrawal of life sustaining measures

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ABSTRACT

Objective: The ability to predict the time of death after withdrawal of life support is of specific interest for organ donation after cardiac death. We aimed to externally validate a previously developed model to predict the probability of death within the time constraint of 60 minutes after withdrawal of life sustaining measures.

Design: The probability to die within 60 minutes for each patient in this validation sample was calculated based on the model developed by Yee et al, which include four variables (absent corneal reflex, absent cough reflex, extensor or absent motor response and an oxygenation index > 4.2). Analyses included logistic regression modeling with bootstrapping to adjust for over optimism. Performance was assessed by calibration (agreement between observed and predicted outcomes) and discrimination (distinction of those patients who die within 60 minutes from those who do not, expressed by the Area under the Receiver Operating Characteristic curve (AUC)).

Setting: Mixed Intensive Care Unit in the Netherlands

Patients: We analyzed data from 152 patients who died as a result of a neurological condition in the period 2007-2009.

Main Results: A total of 82 patients had sufficient data. Fifty (61%) died within 60 minutes. Univariable and multivariable odds ratios of the predictors were very similar between the development and validation sample. The prediction model showed good discrimination with an AUC of 0.75 (95% CI: 0.63-0.87) but calibration was modest. The mean predicted probability was 80%, overestimating the 61% overall observed risk of death within 60 minutes. Modeling oxygenation index as a linear term led to an improved version of the Yee model (AUC (95%CI)= 0.774 (0.69-0.90), bootstrap validated AUC (95% CI)=0.74 (0.66-0.87).

Conclusions: The model discriminated well between patients who died within 60 minutes after withdrawal of life support and those who did not. Further prospective validation is needed.

INTRODUCTION

Donation after circulatory death (DCD) is an important source of kidneys, livers and lungs for transplantation. A report of the Institute of Medicine suggests that the use of DCD is the most effective way to improve the donor supply.[1] DCD is most often performed in patients with devastating neurologic conditions who died after life-sustaining treatment was withdrawn in the intensive care unit (ICU).

The quality of organs of DCD donors is highly dependent of the time between withdrawal of life sustaining measures (WLSM) and death. Death beyond 1 hour can result in donor ineligibility because of inferior quality of organs due to suboptimal oxygen levels.[2] Therefore, for practical and ethical reasons, the ability to predict if a patient will die within one hour after WLSM is of interest for the transplantation and critical care community. Prediction models can be used to combine different characteristics of an individual patient in order to make such a prediction.

Since such prediction models are mathematical models based on available patient data from a certain setting, external validation is an absolutely necessary step to determine the ability of a model to reliably predict outcome in other populations and settings, before its use in clinical practice can be recommended. However, in the clinical literature, many prognostic models are developed and very few are externally validated.

Yee and colleagues recently published a prediction model using four, easy to obtain, clinical variables (absent corneal reflex, absent cough reflex, extensor or absent motor response and an oxygenation index>4.2) in order to calculate the probability of death within 60 minutes after WLSM in ICU patients that were not pharmacologically paralyzed or anesthetized before WLSM.[3] WLSM was performed according to the national protocol concerning end of life care in ICU patients. All patients were intubated and mechanically ventilated before WLSM. WLSM involves the withdrawal of all supportive measures including mechanical ventilation (including extubation), antibiotics and administration of inotropic agents. Oxygen levels were always reduced to 21% before withdrawal of mechanical ventilation.[4] Until now the model of Yee and colleagues (further phrased as 'Yee model') has not been validated in an external population. The aim of this study is to investigate whether the model performs adequately and could be generalized to another cohort of neurocritical care patients in whom withdrawal of life support was performed after the decision was made that further treatment was futile.

METHODS

Data

For our validation sample, medical charts were retrospectively obtained of all patients who died on the intensive care unit of the Erasmus MC University Medical Center Rotterdam, the Netherlands as consequence of a subarachnoid hemorrhage (SAH), traumatic brain injury (TBI) or an intracereberal hemorrhage (ICH) between 2007 and 2009. The Institutional Review Board waived the need for review and approval of this study due to the retrospective observational nature.

The outcome of interest was death within 60 minutes after WLSM. The predictors assessed by Yee and colleagues were age, sex, cause of death, last known Glasgow Coma Score (GCS), brain stem reflexes (pupil-, corneal- and cough reflex and respiratory drive), Full Outline of UnResponsive score (FOUR) score[5], blood gas (pH, PaO_2, $PaCO_2$ (both in mmHg)) and ventilator settings (type of ventilation, positive end-expiratory pressure (PEEP), peak airway pressure, fraction of inspired oxygen (FiO_2). Neurological parameters were at most two hours before WLSM assessed by a neurologist or neurosurgeon. We calculated with the above parameters the oxygenation index (OI). OI is calculated as mean airway pressure x FiO_2 x 100/ PaO_2, whereas the mean airway pressure is calculated as (peak inspiratory pressure + PEEP)/2, the A-a gradient (A-aDO_2 = (760-47mmHg) x FiO_2 - $PaCO_2$/0.8-PaO_2) and the P/F ratio (P/F = PaO_2/FiO_2). Patients were included if all these predictors and variables and the time between of WLSM and death could be retrieved from the medical chart. Coding of all variables was based on the paper of Yee et al. The FOUR score is a neurological assessment tool that combines four neurological parameters (eye, brainstem reflexes, movement and respiration) to calculate a score from 0 (worst neurological score) to 16. (4) Arterial blood gas pH was considered abnormal if a pH was below 7.30 or above 7.50. An arterial blood gas was considered abnormal if $PaCO_2$ was above 45 mmHg or PaO_2 was below 80 mmHg.

Statistical analyses

First, univariable logistic regression analyses were performed to establish the effect of the different predictors on death within 60 minutes after WLSM in the validation sample. The resulting univariable odds ratios were compared with odds ratios in the development sample, as reported by Yee and colleagues. Second, the final multivariable model of Yee and colleagues, containing absent corneal reflex, absent cough reflex, extensor or absent motor response and an oxygenation index>4.2 was refitted in the validation sample and the multivariable odds ratios were compared with those reported by Yee et al. Finally the predicted probabilities to die within 60 minutes reported by Yee et al. were calculated for each patient in the validation sample. The Yee model contained three categorical binary variables (corneal reflex, cough reflex, motor response), but one continuous variable that was dichotomized (oxygenation

index, OI). Dichotomization of continuous variables implies a loss of information compared to analyzing the full continues version. Specifically for prediction, dichotomization hampers external validity since the optimal cut-off might be different in another setting.[6] For these two reasons, we also explored the relationship between the OI as a continuous predictor and outcome.

Model performance

We assessed the performance of the model in terms of discrimination and calibration when applied to our validation data. Discrimination describes how well a model distinguishes between those who die within 60 minutes from those who survive longer. Calibration indicates how closely predicted outcomes match observed outcomes.

To assess discrimination, we calculated the Area Under the receiver operating characteristic curve (AUC). An AUC of 1 implies perfect discrimination, whereas an AUC of 0.5 implies that a model's prediction is no better than chance. The 95% confidence intervals of the AUCs were obtained through drawing 500 samples with replacement from the original data, and consequently applying the model to each sample. The distribution of the AUCs over all these samples gives an indication of the uncertainty and can be used to calculate the 95% confidence interval. Such a procedure is called 'bootstrapping' or 'bootstrap resampling'.

To assess calibration, we plotted the proportion of patients who actually died within 60 minutes against the proportion of patients to have this outcome. We also compared overall mean predicted and observed probabilities.

Model updating

Finally we updated the Yee model to incorporate all available information from both the development and validation data.[7] First the coefficients of cornea reflex, cough reflex and motor score were updated. We hereto calculated a linear predictor based on the Yee coefficients. This linear predictor was used as an offset in a model containing the three predictors, to estimate the differences between the Yee coefficients and the coefficients in our data. The estimated differences were shrunken by a factor $chi^2/(chi^2\text{-}df)$ and finally these shrunken differences were added to the original Yee coefficients to obtain the final coefficients of cornea reflex, cough reflex and motor score, which could be considered best estimates of the predictive effects given both datasets.[8] With these final coefficients, the model including OI was refitted to obtain the coefficients for OI and the intercept, resulting in the final updated model.

All analyses were performed using SPSS Statistics (Version 17.0.2, IBM Corporation, Somers, NY, USA) and the R software environment (Version 2.7.1, The R Foundation for Statistical Computing, Vienna, Austria) with the Design and Hmisc packages.

RESULTS

Descriptives

By scanning medical records from the period 2007-2009 a total of 152 patients were identified who died as a result of TBI, SAH or ICH after WLSM. Among those 152 cases 82 patient files contained relevant data for further statistical analysis. There were no statistically significant differences in age, gender and diagnosis between the 70 patients with incomplete data and those included in the analysis. The mean age at death was 52 years (range 15-80). Fifty patients (61%) were male and 32 patients female (39%). Thirty-one patients died as a result of a SAH, 27 patients of an ICH and 24 patients as a result of TBI. Fifty patients (61%) died within 60 minutes after WLSM (Table 1).

Univariable effects

In our validation sample, the strongest univariable predictors of death within 60 minutes after WLSM were an absent corneal reflex (OR= 6.8, 95% CI= 2.4-18.9, p=<0.001), breaths at ventilatory set rate/apneic (OR= 11.1, 95% CI= 3.8-32.9, p=<0.001) and a FOUR score<4 (OR= 16.4, 95% CI= 3.4-79.8, p=<0.001) (Table 1). All univariable effects were of comparable magnitude in the development and validation samples, with the exception of abnormal blood gas pH (OR development sample=1.6, OR validation sample=0.7).

Multivariable effects

The predictors included in the final multivariable model were absent corneal reflex, absent cough reflex, extensor/absent motor response and oxygenation index (OI)>4.2. The prevalence of these predictors was very similar between the development and validation sample (Table 2). Absent motor score was an exception, being more prevalent in our validation sample (96% in patients who died within 60 minutes and 69% in patients who did not). Also the multivariable odds ratios were reasonably similar between the development and the validation sample. The predictive effect of extensor/absent motor response was larger in the validation sample, while the predictive effects of absent corneal reflex, absent cough reflex and oxygenation index>4.2 were somewhat weaker in the validation sample (Table 3). Since the effect of continuous OI was very similar in both samples (OR=1.10 vs. 1.17, table 1) we conclude that the difference in the effect of OI>4.2 is most likely due the cut-off of 4.2 chosen by Yee and colleagues. We explored the shape of the relationship between OI and the probability of death. We found an approximately linear relationship, implying the OI could better be analyzed continuously (Figure 1).

Table 1. Patient characteristics and comparison of univariable odds ratios

Variable	Yee et al.			Present study		
	n (%)	OR	p-value	n (%)	OR	p-value
Number of patients	149	NA	NA	82	NA	NA
Patients died within 60 min	75 (50)	NA	NA	50 (61)	NA	NA
Female sex	not. av.	1.34 (0.70-2.56)	0.37	32 (39)	1.33 (0.55-3.47)	0.491
Age	not. av.	0.99 (0.68-1.45)	0.97	median: 56 IQR: 40-67	0.98 (0.96-1.01)	0.164
Neurologic examination						
Absent pupil reflex	97 (65)	5.32 (2.51-11.2)	<0.001	58 (71)	2.43 (0.92-6.41)	0.074
Absent corneal reflex	97 (65)	9.01 (4.02-20.4)	<0.001	56 (68)	6.75 (2.41-18.9)	<0.001
Absent cough reflex	60 (40)	7.00 (3.34-14.7)	<0.001	31 (38)	5.85(1.94-17.6)	0.002
Breaths at ventilatory set rate/apneic	81 (54)	4.08 (2.04-8.20)	<0.001	42 (51)	11.1 (3.78-32.9)	<0.001
motor response (extensor or absent	98 (66)	6.67 (3.04-14.7)	<0.001	70 (85)	10.9 (2.20-54.0)	0.003
FOUR score <4	97 (65)	7.23 (3.29-15.9)	<0.001	67 (82)	16.4 (3.38-79.8)	0.001
Pulmonary						
PF ratio <200	40 (27)	1.82 (1.19-2.78)	0.006	20 (24)	2.31 (0.748-7.16)	0.145
PF ratio 201-300	NA	1.72 (0.88-3.38)	0.11	22 (27)	1.17 (0.425-3.21)	0.765
PF value	median: 269 (range: not. av.)	1.00 (1.00-1.01)	0.043	median: 299 (range: 75-772)	0.99 (0.99-1.00)	0.229
Oxygenation index	median: 3.3 (range: 1-41)	1.10 (1.00-1.22)	0.041	median: 3.5 (range: 1-36)	1.17 (0.977-1.39)	0.089
Abnormal arterial BG pH	36 (24)	1.63 (0.80-3.29)	0.17	11 (13)	0.74 (0.21-2.65)	0.639
Abnormal arterial BG	30 (20)	2.09 (1.06-4.13)	0.033	15 (18)	1.35 (0.46-4.39)	0.618
A-a gradient > 100 mm Hg	121 (81)	2.09 (0.82-4.90)	0.09	53 (65)	1.82 (0.07-4.57)	0.206

NA: Not applicable, BG: Blood gas, Not av: Not available

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We therefore also evaluated an adapted version of the model of Yee et al. with OI as a continuous variable. The relatively strongest predictors of death within 60 minutes after WLSM were absent cornea reflex (univariable AUC (95% CI)=0.70 (0.61-0.80)) and absent cough reflex (AUC=0.68 (0.58-0.76)), followed by absent motor score (AUC=0.64 (0.55-0.72)) and OI (AUC OI>4.2=0.57 (0.50-0.67) and AUC OI continuous =0.62 (0.50-0.73))

Table 2. Factors predicting dead within 60 minutes from withdrawal of life-sustaining measures included in the final model of Yee et al.

	Yee et al.		Present study	
Variable	Patients dying < 60 minutes	Patients dying > 60 minutes	Patients dying < 60 minutes	Patients dying < 60 minutes
	(total n=75), n(%)	(total n=74), n(%)	(total n=50), n(%)	(total n=32), n(%)
Absent corneal reflex	65 (87)	32 (43)	42 (84)	14 (44)
Absent cough reflex	45 (64)	15 (20)	26 (52)	5 (16)
Extensor/absent motor response	64 (85)	34 (46)	48 (96)	22 (69)
Oxygenation index >4.2	34 (45)	17 (23)	23 (46)	10 (31)

Table 3. Comparison of multivariable associations between predictions and time to death within 60 minutes from withdrawal of life-sustaining measures

	Yee et al.		Present study	
Variable	**Odds ratio (95% CI)**	**p value**	**Odds ratio (95% CI)**	**p value**
Absent corneal reflex	4.24 (1.57-11.5)	<0.01	2.94 (0.85-10.1)	0.09
Absent cough reflex	4.47 (1.93-10.3)	<0.01	2.69 (0.77- 9.48)	0.12
Extensor/absent motor response	2.83 (1.01-7.91)	0.05	5.51 (0.91-33.3)	0.06
Oxygenation index >4.2	3.36 (1.33-8.50)	0.01	1.88 (0.62-5.70)	0.26

CI= Confidence interval

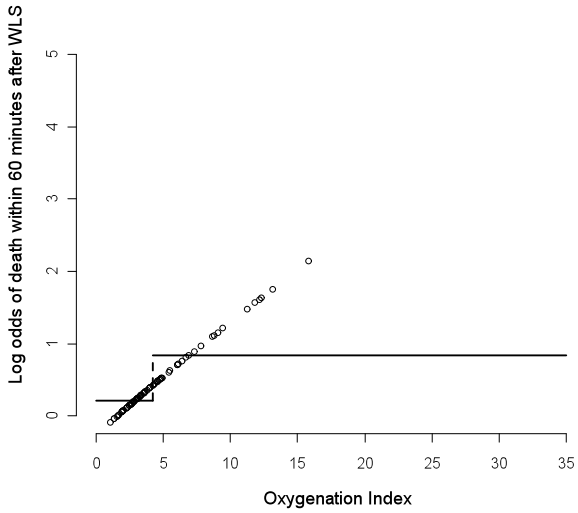

Figure 1. Relationship between oxygenation index (OI, x-axis) and probability of death within 60 minutes after withdrawal of life support (y-axis). Points represent continuous relationship based on model fit, line represent assumed relationship when using a cut-off value of OI=4.2

Model performance

Six patients in our validation sample were classified into the lowest risk group, since they had none of the risk factors (absent corneal reflex, absent cough reflex, absent motor response and an OI<4.2) for death within 60 minutes. However, Yee and colleagues did not report an actual probability of death within 60 minutes for this lowest risk group in their paper. We were therefore unable to compare their prediction (unknown) to the actual outcome. Therefore these patients were excluded for the model validation, and also for the refitting and the development of the adapted model to ensure comparability.

The prediction Yee model showed good discrimination with an AUC of 0.75 (95% CI: 0.63-0.87) (Table 4). The refitted model discriminated slightly better with an AUC of 0.76(95% CI: 0.64-0.88). Calibration was only modest. The mean predicted probability of death within 60 minutes after WLSM was 80%, while the observed mean probability was 61%. The calibration plot (Figure 2) shows that in the higher quartiles of predicted probabilities there is a small but systematic miscalibration. The points are above the reference line, i.e. the predicted risks are systematically (slightly) higher than the observed risks. The lowest quartile of predicted probabilities suffers from severe miscalibration, the mean predicted probability of death within 60 minutes in this group was 66%, while the observed probability was 20%. Calibration of the refitted model was not assessed since in refitting the model, the new coefficients (weights of the predictors) and the intercept (the average probability of death within 60 minutes) are based on the new data, resulting by definition in perfect calibration.

Table 4 Area under the curve

	Apperant	Internally validated AUC
Yee model refitted	0.759	0.727
Yee model external validation	0.753	NA
Present model	0.774	0.743

NA = not applicable

We developed an updated version of the model with OI as a continuous predictor, which discriminated better (AUC (95%CI)=0.77 (0.69-0.90)) then the refitted model with OI>4.2. This finding confirms our hypothesis that with dichotomization some predictive information is lost and that the cut-off of 4.2 may have limited generalizability beyond the development sample. The updated version of the Yee model was:

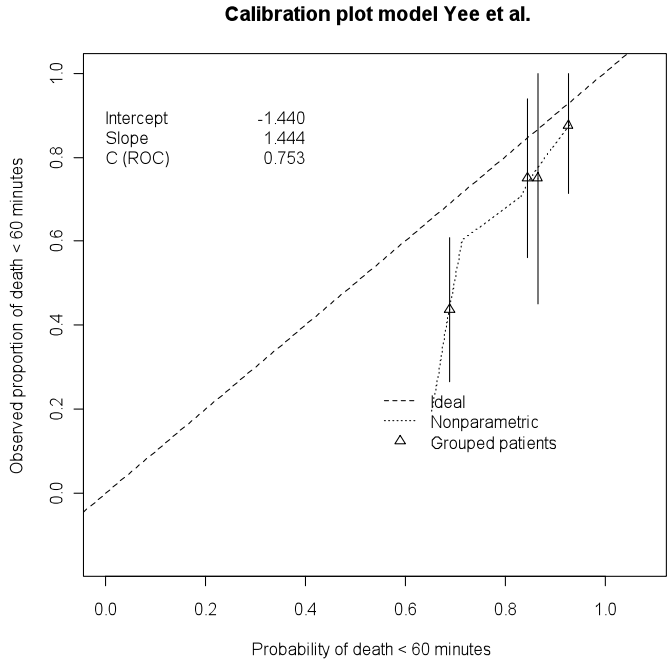

Figure 2. Calibration plots for external validation of the model of Yee et al. for prediction of death within 60 minutes after withdrawal of life support. Predicted probabilities are on the *x*-axis and observed outcomes on the *y*-axis. The triangles indicate the observed frequencies by quartiles of predicted probability with 95% confidence intervals (vertical lines).

*Linear predictor = −2.52 + absent corneal reflex (yes=1, no=0) *1.54 + absent cough reflex (yes=1, no=0) *1.08 + extensor or absent motor response (yes=1, no=0) *1.18 + oxygenation index*0.13*

Probability of death within 60 minutes after WLSM= exp(Linear predictor) / 1 + exp (Linear predictor)

This model equation can be used to calculate the probability of death within 60 minutes for individual patients. E.g. for a patient with a present corneal reflex, absent cough reflex, absent motor response and an OI of 4, the linear predictor is −2.52 + 0*1.54 + 1*1.08 + 1*1.18 + 4 *0.13=0.26. The predicted probability of death within 60 minutes for this patient is exp(0.26)/1+exp(0.26)=0.56 (56%).

DISCUSSION

In this study we externally validated the model of Yee et al. and propose an updated version of this model to improve the discrimination between patients who die before 60 minutes

and after the timeframe of 60 minutes after withdrawal of life support in the ICU. The performance of prognostic models was judged in terms of discrimination and calibration. Discrimination describes how well a model distinguishes patients who die within 60 minutes from those who die after the timeframe of 60 minutes. Calibration indicates how closely predicted outcomes match observed outcomes. For identification of potential donors, discrimination is particularly important. To provide relatives with a realistic estimate of the probability of death within 60 minutes after WLSM, calibration is more important. The Yee model discriminated very well, while calibration was modest. For a subgroup of patients with a low probability of death within 60 minutes, the model severely overestimated their probability. In the higher-risk patients there was a small systematic overestimation. This finding implies that it is important to assess calibration of a model for the setting it will be used in and to consider recalibration, to be able to give realistic estimates to relatives. Recalibration would involve refitting the intercept (representing the average probability of death within 60 minutes) while keeping the coefficients (weights of the predictors) fixed.[7] Such a recalibration will improve calibration and not affect discrimination.

The distributions of the predictors in the model were remarkably similar between the development and validation population. The only predictor with a different prognostic effect between the development and validation sample was an abnormal pH, being associated with earlier death in the development population and with later death in the validation population. Not all blood samples, used to determine the arterial pH, were taken at the time of WLSM. A possible explanation is the actual low number of patients with an abnormal pH. Eleven patients in our cohort had an abnormal pH. The majority of the patients that died within 60 minutes had a normal pH. In other words the pH is, at least in our cohort of patients, not a good discriminator for death within 60 minutes after WLSM. Suntharalingam and colleagues reported comparable results in relation to time of death and an abnormal pH.[9]

Previous studies that have identified predictors of time to death after WLSM used Cox proportional hazard analysis to study predictors of time to death instead of death within a defined time period.[9,10] We performed Cox regression with time to death as an outcome and the four variables in the model as predictors, and found that they were also highly predictive for time to death. Although we consider Cox regression a sensible and statistically more powerful approach, clinical applicability requires the additional step of translating multivariable effects (e.g. odds ratios from logistic models or hazard ratios from Cox models) into predictions for individual patients. This step was lacking in the studies mentioned. The study of Suntharalingam and colleagues[9] identified FiO_2 as an independent predictor. Since FiO_2 might be less influenced by ventilation policy incorporated in the OI, we compared their predictive strength. We found that OI was a stronger predictor in our dataset (AUC FiO_2=0.60, AUC OI=0.62) and we therefore kept it in the final model. The strength of the OI is that it gives an index of the

airway pressure needed against its goal oxygenation. An elevated OI has been demonstrated to be an independent risk factor for mortality in patients with ARDS.[11]

Yee et al. included oxygenation index (OI) as a binary variable in their model, with a cut-off of 4.2. Although dichotomization increases simplicity, it results in a loss of information.[6] In addition, dichotomization is clinically implausible. In this example, a higher OI is related to a higher of risk of death within 60 minutes. But this risk does not suddenly increases when the OI is 4.3 compared to 4.1, since the underlying relationship is more likely to be continuous. This is also shown in figure 1. Specifically for prediction, dichotomization causes overfitting since the best (often data driven) cut-off in the development data is not necessarily the best cut-off in new patients. The risk of overfitting is particularly high when the development dataset is relatively small. A preferred approach in general is to analyze the prognostic factors as continuous variables.[12] We therefore propose an adapted version of the Yee model with OI as a continuous variable. Although this adaption improved the discrimination only modestly (AUC from 0.75 (95% CI: 0.63-0.87) to 0.77 (95% CI: 0.69-0.90)), theoretically the adapted version would perform better in external validation than the original model.

Newly collected patient data are often used to develop a new prediction model instead of validating an existing model.[13] As a result, many prognostic models are published in the medical literature, but external validation is rare. External validation is a crucial step to determine generalizability and is a necessary step to determine the ability of a model to predict outcome in other settings, before its use in clinical practice can be recommended.[14] In addition, when developing a completely new model, predictive information in previously published models is neglected.[13] Validation and updating, as we did in this study, will lead eventually to more stable and generalizable prediction models. Therefore, we prefer validation and updating over developing new models.

Since both the development and validation samples in this study were relatively small, further prospective validation and updating is required. A next step then is to develop a simple score chart based on all available data, for optimal precision, which could be used by every intensivist or neurologist involved in patients with catastrophic neurological conditions who are regarded as a potential DCD organ donor.

The strength of this model is the four easy to obtain clinical variables before WLSM to predict time of death. This is in contrast with the Wisconsin criteria for predicting asystole after withdrawal of life-sustaining therapy.[15] This prediction tool requires temporary disconnection of the ventilatory system in order to assess the probability of asystole after WLSM. Other criteria that are used are vasopressors, BMI, patient age, the use of an endotracheal tube or tracheostomy. This limits its use in a neurological intensive care because of the increased

risk of death during the assessment. The Yee model provides the treating ICU physician and the consulting neurologist or neurosurgeon an important insight in the probability of death within 60 minutes after WLSM of a patient with a catastrophic neurological condition with these four easy and clinically sensible variables. This knowledge can provide clarity to decide where to allocate the right resources to the patient with highest chance to become an organ donor after circulatory death.

There are some limitations of our study. This is a single center; single country study with a relatively small sample size, although the latter is of less importance in validation studies. Besides these limitations we used only three fairly common fatal neurological conditions (SAH, ICH and TBI). As with all studies using medical charts there is the possibility of bias. We tried minimizing this by using a second reviewer in the extraction of data from the medical charts. In case of a dispute concerning the data, the patient was excluded for further analysis. We further had to exclude a group of six patients with all risk factors absent since we could not obtain their predicted probability based on the Yee model. The excluded patients had a very low predicted probability of death within 60 minutes after WLSM in the refitted model (9%). Inclusion of these patients therefore would have led to even more miscalibration in the low-risk patients.

CONCLUSION

To conclude, the Yee model discriminated well between patients who died within 60 minutes after withdrawal of life support and those who did not, but in our validation set, calibration was modest. The model could be improved by including OI as a continuous predictor. The updated model we propose can be used to calculate predicted probabilities to die within 60 minutes after WLSM for individual patients. A next step should be to further validate and update the model based on a large prospective cohort, since reliable prediction of the probability of death within 60 minutes after withdrawal of life support is of important practical and ethical value.

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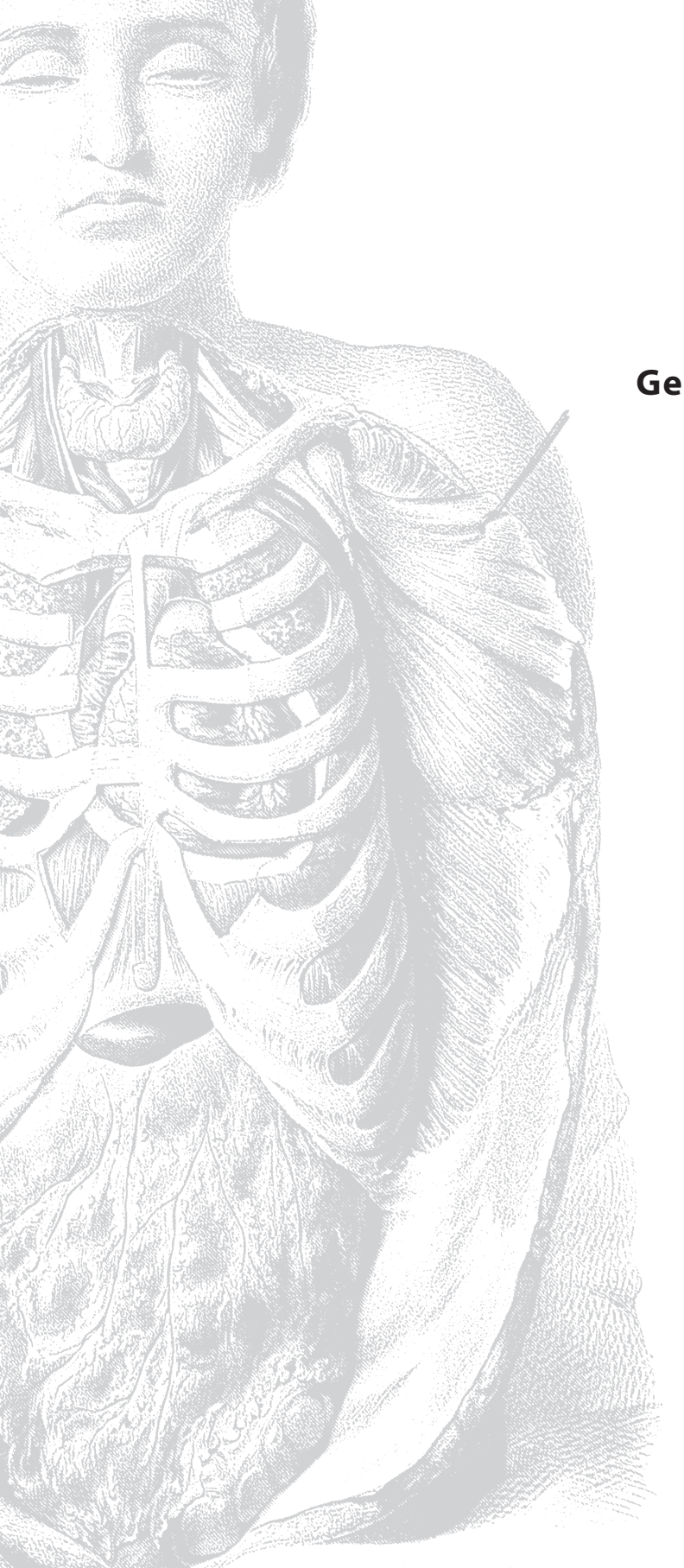

General discussion

INTRODUCTION

The research questions we posed in the general introduction of this thesis were:

1. Can the shortage of organs, especially hearts, obtained from deceased organ donors be solved?
2. How can a potential organ donor be recognized in daily intensive care practice and how can we identify bottlenecks in the process of organ donation?
3. What is the best moment to contact the relatives of a potential organ donor to request organ donation?
4. Is presumed consent a realistic option to solve the shortage of organs?

1. ORGAN SHORTAGE

In the first chapter of this thesis we outlined the near future of organ donation. The three main conditions leading to brain death are subarachnoid hemorrhage, intracerebral hemorrhage and traumatic brain injury. We anticipate a further decrease in the number of brain dead organ donors because of improved prevention and better treatment options of the above-mentioned conditions. Improvements like car and traffic safety, better hypertension care (a precursor for subarachnoid hemorrhage and intracerebral hemorrhages), more treatment options in case of a subarachnoid or intracerebral hemorrhage are all societal and medical desirable advances. Beside this, we face a high refusal rate by relatives of possible organ donors. These developments have consequences for the number of brain dead organ donors and hence the increasing number of patients on a waiting list for a donor organ. Do we have to accept the diminishing supply of organs, seen that there are no definitive solutions in the near future to resolve the gap between donors and recipients?

Alternatives for brain dead organ donors

Living organ donation of genetically related or unrelated donors has become an alternative for post-mortem organ donors in order to expand the pool of kidney and liver donors and to cope with the on-going demand of organs for patients with end-stage organ failure. Living organ donation is considered the cornerstone of kidney transplantation worldwide.[1] Living organ donation is, seen from an ethical perspective, the most 'pure' form of donation. Every donor is well informed about the potential risks of surgery, is psychologically screened for eligibility and donates because he or she explicitly wishes to do so. In other words the autonomy of a patient is safeguarded in this form of organ donation. According to the annual reports of the Dutch Transplant Foundation the number of living related and living unrelated organ donations substantially increased over the past 14 years. The total number of living organ donation increased from 91 patients in 1997 to 473 in 2010.[2] However living organ

donation is only a marginal source for other organs than kidneys. The only other solid organ that can be donated during life is a part of the liver.

Donation after cardiac death (DCD), the other source of organs of post mortem organ donors, is increasing in the Netherlands since the 1990's.[3] This form of donation is a source for kidneys, liver and lungs. DCD is increasing because of the implementation of life saving measures like craniostomy, craniotomy, cooling after resuscitation and other intensive care measures, which prevent herniation. These measures have the potential to intercede with the progression of the brain injury to brain death. Whether this results in a shift of patients that normally would progress to brain death and now follow a pathway to donation after circulatory death remains uncertain but not unlikely.[4] From an ICU perspective it could be regarded as good clinical care not to wait before a patient progresses into brain death with unrecoverable neurological injuries. This would result in saving valuable and scarce ICU resources and would avoid unnecessary patient and family suffering.[4] However because of this development the overall quality of the organs is not of the same level as organs recovered from brain dead organ donors. According to a study performed by Halpern et al. there is still room for improvement. Optimal identification and improved management of controlled donation after cardiac death on the ICU could lead to an estimated increase of the number of donors with 10%.[5] Also new strategies of donor care can improve the quality of organs from donors who donate after cardiac death. In a recent report from the University of Wisconsin concerning the long-term outcomes for all lung transplant recipients who received lungs from DCD donors showed that graft survival rates were equivalent of those who received lungs from donors who donated after brain death.[6] With the current decreasing number of organs one can say that every organ donor must count.

Future perspectives

A possible alternative is a breakthrough in stem cell research recently published in *Nature* in which the authors report the discovery of a crucial growth factor; R-Spondin.[7] This new piece of the puzzle makes the scenario of 'growing' new organs more probable in the near future. A definitive solution would be the possibility to 'grow' the organ needed for transplantation and to be completely independent of organs from post mortem donors. However this form of research is still in a laboratory phase and it will take years before it can be utilized as a clinical therapy. Until that time we have to search for ways to optimize the full potential of the current pool of organ donors.

An alternative for the low availability of hearts is a continuous flow left ventricular device (LVAD).[8] Or the placement of two centrifugal pumps, which can serve as a total artificial heart after cardiectomy.[9] Developments in this field look promising and it is not unimaginable that total artificial hearts will fill the gap between the supply and demand of donor hearts.

2. IDENTIFICATION OF A POTENTIAL ORGAN DONOR

In order to make the most optimal use of the donor pool, it is essential to identify every potential organ donor regardless if he or she eventually donates one or more organs. Recognition of potential organ donors is essential to get a clear insight in the actual pool of potential organ donors. Derived from that, one can identify reasons, and thus the potential barriers, of non-procurement. With this knowledge, organ procurement organizations and hospitals can initiate actions to improve logistics and patient care around donation and transplantation. To compare donor conversion rates between hospitals and countries it is essential to use a uniform point of departure for the analysis. Several organizations, like the Organ Procurement and Transplantation Network (see www.optn.transplant.hrsa.gov) and the DOPKI project (a European Consortium of organ procurement organizations),[10] developed recognition tools used for data analysis, but do not specify what the inclusion criteria are for a potential organ donor eligible for further analysis.[10-13] Because it is difficult to compare the results of different organizations without a uniform definition of a potential organ donor, we introduced a new definition of a potential organ donor, based on a universally used neurological assessment tool, the Glasgow Coma Scale. An adapted version of the newly introduced definition is based on the FOUR score, which stands for the Full Outline of UnResponsiveness. Our criteria, which are based on the Glasgow Coma Scale and the FOUR score to recognize a potential organ donor, proved to be useful to assess the reasons of non-procurement in a group of patients who died of a devastating neurological injury. It also proved to be an easy identification tool for clinical practice. Important to notice is that imminent brain death is not equivalent with brain death as suggested by two authors who responded to our article.[3] As explicitly stated, a patient that fulfills the criteria of 'imminent brain death' represents no more than a certain risk estimate. Also these authors incorrectly remarked that patients, regarded to be in a state of 'imminent brain death', are not suitable for organ donation. Most patients with devastating neurological injuries will die within an hour after withdrawal of life sustaining measures. Especially those patients who satisfy the conditions of 'imminent brain death' with at least three out of six absent brain stem reflexes and no motor response to pain stimuli. As shown by Yee et al. in 2010, the absence of corneal reflexes, cough reflex and motor response represents a probability of 84.9% to die within 60 minutes after withdrawal of life sustaining measures.[14]

Another essential part in the identification of a potential organ donor is the probability of death within 60 minutes, if a patient is going to donate according to the donation after circulatory death protocol. The quality of the organs is highly dependent of the warm ischemic time after the cessation of circulation. However, the time between the withdrawal of life sustaining measures and actual death cannot be too long due to suboptimal oxygen levels which results in progressive deterioration of the organs.[15] An essential identification tool, which we externally validated, is the 'Mayo NICU model'.[14] A physician can assess the prob-

ability of death within 60 minutes using this model with four easy to obtain clinical variables. This information can help the team of physicians to assess the probability and therefore the eligibility of a patient to become an organ donor. This is relevant information because families can be informed and ICU resources are not misused.

Donor conversion rate

The donor conversion rate, defined as the actual number of organ donors divided by the number of patients who are regarded as potential organ donor, is a tool to measure quantitative success of an organ procurement organization and to compare hospitals and countries. Essential for this tool is a uniform definition of potential organ donor. Our proposal of a potential organ donor cast in the definition of 'imminent brain death' proved to be an unambiguous starting point for the analysis of the pool of potential organ donors. The 'imminent brain death' definition based on the FOUR score was the most restrictive of three used definitions ('imminent brain death' (GCS and FOUR-score version) and 'imminent neurological death' defined by the Organ Procurement Transplantation Network). If defining a group of potential organ donors one would like to have a realistic estimation of the outcome of a patient. A too loose definition results in inclusion of patients that are ineligible for heart-beating organ donation. A too strict definition results in small group of patients that are mostly eligible for heart-beating organ donation but also in an underestimation of the reasons of non-procurement. Therefore using 'imminent brain death' based on the FOUR score gives the most accurate estimation of the actual pool of potential organ donors. An excellent example is shown by the comparison between the old definition used by the Dutch Transplant Foundation which is called 'severe brain damage' and the new definition of 'imminent brain death' based on the GCS-score. In a cohort of patients the donor conversion rates differs with 10.5% in favor of the 'imminent brain death' definition. A limitation of our definition of a potential organ donor is that it identifies solely patients that are expected to become brain death. Patients that eventually become donors after cardiac death are not always detected. It is therefore not useable as assessment tool for an analysis of the areas of improvement in the pool of potential cardiac death organ donors.

When analyzing the major reasons of non-procurement two reasons stand out; medical reasons of non-procurement and family refusal. Medical reasons of non-procurement are often malignancy, sepsis, viral infections or poor condition of the organs. Age and medical reasons of non-procurement are restrictive exclusion criteria that cannot be modified. Family refusal is on the other hand the major area where improvement is still feasible.

3. APPROACHING THE RELATIVES OF A POTENTIAL ORGAN DONOR TO REQUEST ORGAN DONATION

The only area of improvement in the Netherlands with significant potential is the rate of family refusal. We have to accept that the death of a relative who dies as the result of catastrophic neurological injury is not only a personal event but also a family matter. The wishes and emotions of families, who have to decide about organ donation under these harsh circumstances, should be respected and accepted. This is important because otherwise the trust in the organ donation process will be seriously undermined by society, the lay press and potentially the medical professional. We should therefore study the reasons why families refuse organ donation and how we can decrease this rate in an acceptable way. Especially, if the refusal is based on a lack of knowledge and insufficient information concerning organ donation. In the case of determination of death based on brain death criteria we ask a high level of trust from the family. They are confronted with a relative who is not declared dead based on the conventional criteria (cardiopulmonary death, cold corpse, a blue or gray facial appearance, and eventually stiffening of the muscles), but who is declared dead based on neurological criteria, which are not easily verified and understood by a non-clinician. Detailed explanation of every aspect of the process to determinate brain death and the voluntary involvement of family members during the process could lead to a greater acceptance of brain death as death.

Known barriers for consent

The process of consent by a family of a potential organ donor is complex and not easy to analyze. However, several studies and reviews have been conducted to shed some light on possible barriers to consent for organ donation.[16-21] Barriers that have been identified are the amount and quality of information provided during the request, the perceived quality of care by the family of the donor, the understanding of brain death, the timing of the request, the setting in which the request is made and the approach, expertise and experience of the person making the request.[21]

Amount and quality of the information discussed during the request

Discussing organ donation with the relatives is an emotional process in which the physician has the task to inform the family in such a way that they can make an informed and weighted decision. Essential in this discussion is to eradicate several misconceptions or misunderstandings about organ donation.[22] Families are more willing to consent when they are told that they have the potential to help others, if they are aware that organ donation is cost neutral, that a regular funeral is still possible after organ donation and that they have the feeling that they received enough information.[16,20] To tell the family that it is required to ask about donation has a negative impact on the consent rate for organ donation.

Perceived quality of care

A negative perception by the family of the quality of care has a negative impact on the consent rate. This is related to the information provided to the family by nurses and physicians during their presence with the patient. Families need to know that all therapeutic efforts applicable for their loved one were utilized.

Understanding of brain death

Brain death is a difficult medical concept (in the sense of an abstract idea) that is not easily explained to families. A concept is usually associated with corresponding language and symbols. In the case of brain death, physicians name the brain dead patient 'dead' or 'a ventilated corpse' to convince the uncomprehending not medically educated citizens. But even for members of the medical and nursing community, brain death is hard to understand. Some speak of brain death as a moral or legal fiction.[23,24] To accept brain death as death there has to be features of emotionally and culturally accepted criteria and features of death. For example, permanent absence of breathing and complete absence of consciousness (no reactions to pain) can be very convincing to accept brain death as death. The study we described in chapter 7 is based on the hypothesis that the presence of relatives during brain death determination should lead to a greater acceptance of brain death as death. Besides this new idea, the information provided to the family was also better because of the stringent study protocol. To make the abstract idea of brain death (the concept) comprehensible it can be helpful to see the features. In a review of 285 families conducted by Rodrigue et al., 71% of the families that had complete knowledge of brain death agreed to donation while only 29% of the families agreed to donation who had only a incomplete or inaccurate knowledge of brain death.[18] Offering families to be present during brain death determination results in a higher quality of information, a better-perceived quality of care by the families and a better understanding of the concept, as an abstract idea, of brain death.

The timing of the request

"Decoupling" or separation of the notification and acceptance of brain death and the request for organ donation has a positive impact on the rate of family consent. Niles and Mattice showed that there were no differences in consent rate if the families were approached about organ donation before or after the death of the patient. However, when organ donation was discussed in the same session where the death of patient was mentioned it declined with more than 25%.[25] There is no clear consensus what the optimal moment is to discuss organ donation with the relatives of a patient. Nevertheless families should be given enough time to consider organ donation and should not be pressed to consent.[18] With this and above-mentioned knowledge it is strange, to say the least, that in The Netherlands we try to obtain consent for organ donation before the formal determination of brain death. The request is often made in the same session in which the family is informed about the poor prognosis of

the patient. At that moment no information is provided about brain death, because this will be determined after consent for organ donation by the family. There is no decoupling of the notification of the poor prognosis and the request for organ donation.

The setting in which the request is made

Two studies show that a private setting in which the request is made has a positive influence on the rate of consent for organ donation.[16,17] Obtaining consent by telephone or in a public place should be avoided. Studies showed that the number of families that gave permission for organ donation in this type of setting decreased with 26%.

The approach and expertise and experience of the person making the request

Training of staff how to request organ donation, how to approach a grieving family and explaining brain death has shown to be of influence on the consent rate.[26] The duration of a session discussing organ donation and brain death (the longer, the better) is also strongly associated with donation.[20]

Recommendations

When reviewing all of these factors that can influence the decision of a family of a potential organ donor one can say there are several possibilities to improve the Dutch situation. As already stated in chapter 6 we should only seek consent after we have determined brain death as stated by law.[27] When we involve families in the process of brain death determination several factors are combined that can positively influence the consent rate by making brain death a less abstract idea. First, we inform the family thoroughly about what we are going to do in order to ascertain the absence of brain stem reflexes (information). Second, we show the care of the patient surrounding the process of brain death determination (better perceive quality of care) and third, we are separating the notification of death and the moment to obtain consent for organ donation because the family is present when the patient is declared death (decoupling of notification).

4. PRESUMED CONSENT

Other improvements that are proposed to increase the rates of organ donors are changes in the legal system that regulates organ donation and the required form of consent of the patient or family to commence with organ donation. The Dutch Organ Donation Act was forced into service in 1998.[27] The Act makes explicit consent the fundamental principle underpinning the lawful removal of organs for transplantation. This system of consent is also referred to as 'opt-in'. Consent is considered valid if the deceased registered his or her will concerning organ donation in the national Donor Register. If no prior consent has been given by the de-

ceased, consent may be given or withheld by the direct relatives of the patient. The relative has to be in a qualifying relationship to the deceased. In practice this means that the spouse or partner, followed by a child (18 years or older) has the right to decide if organ donation will take place after the confirmed death of the patient.

A resident in the Netherlands is offered four options if he or she wants to register their preferences regarding post-mortem organ donation. Registering in the national Donor Register is not mandatory.

The four options are:[27]

1. to consent to be a donor;
2. to decline to be a donor;
3. to leave the decision to their surviving relatives or to some other, specified person;
4. to consent to the donation of all but certain organs and/or tissues.

The Act does not provide how to act as a clinician if a family veto's the wish of a deceased patient to donate. The four options that are given to the register is to opt-in for organ donation (option 1,4), to leave the decision to the surviving relatives or a specified person (option 3) or to opt-out for organ donation (option 2). The Dutch system is in fact a combined opt-in/opt-out register.

Under a system of presumed consent or 'opt-out' everyone is presumed to be willing to donate after death and are deemed to have given consent unless they explicitly 'opted-out' by registering their will in a registry. There are two versions of presumed consent used in the world. Under a 'soft' version of presumed consent the default position is that everyone is regarded a donor, unless he or she registered an explicit refusal to donate. If a patient has not registered his refusal, the will to donate is presumed, although the views of the relatives are taken into account. Organ retrieval will not take place in case of strong objection of the family to donate. This form of 'soft' presumed consent is used in Belgium, Spain and many other South- and Central European countries that have laws based on Catholic views.[28] Under a 'hard' opt-out system the family does not have a right to veto and their views are not taken into account. This form of opt-out is used in Austria and Singapore, this means doctors can remove the organs of every deceased adult unless there is a registration that he or she did not want to donate.

When considering the implementation of presumed consent there are several viewpoints. When looked from a utilitarian standpoint the introduction of presumed consent may result in an increase of organ donors in a country as suggested by many authors.[29,30] Spain and Belgium are often used as an example of a successful introduction of presumed consent

with staggering numbers of organ donors as a result.[29] Spain and Belgium, who have both a 'soft' presumed consent policy, have numbers of 34 respectively 27 deceased organ donor rate per million population. The Netherlands with a combined system has a deceased donor rate per million population of 13.[31] As stated before in this discussion, the form of presentation of these statistics doesn't take in account the differences between countries, which are sometimes subtle. For instance in Belgium relatives need to take affirmative action in order to prevent organ donation if wished so, while in Spain doctors regard it as good clinical practice to inform the relatives of the grave situation of the patient and ask for consent. Coppen et al. described in 2005 whether different consent systems could explain the differences in donation rates when taking the difference in relevant mortality rates into account.[32] When looked at actual donors per million population, in countries with a system of presumed consent, one would say that, at first glance, a system based on presumed consent is successful. However when corrected for the relevant mortality rates per country (cardiovascular accidents and road traffic accidents) the differences between countries with different decision system are marginal.[32] Another important observation is that the rate of organ donation and the refusal rate in Spain from 1979 (year of the introduction of presumed consent system) and 1989 did not remarkably change in comparison to other large European countries. Only after the introduction of a comprehensive, nationally organized organ donation system, that included many innovations, resulted in a gradual rise of the organ donation rate to the current level. This illustrates that the system of consent is only one factor, among many, that can influence the rate of organ donors. Other factors are for instance the predominant cause of death (such as the number of road traffic accidents or the number of patients that died as a result of subarachnoid hemorrhage), the availability of intensive care beds and staff, the number, efficiency and enthusiasm of transplant coordinators, the number of transplant surgeons, the number of specialized hospitals in the region and the number and characteristics of the patients on the waiting list.[33,34] This and other more subtle differences between countries, as mentioned above, are not always taken into account in studies concerning the rates of donation between countries with explicit or presumed consent.[35] Therefore one should be very cautious to conclude, based on this type of studies that presumed consent is the solution to increase the rate of organ donors.[36]

Not much improvement of the consent rate can be expected of changing the currently used combined register system, in which residents already can opt-in or opt-out for organ donation. In practice, patients with devastating neurological injuries of which further treatment is deemed futile may be regarded as potential organ donors unless the family chooses otherwise. If a system of presumed consent should be introduced in the Netherlands only option 2 (to decline to be a donor) remains for registration, which is in fact a downgrade of the Donor Register. Presuming that we introduce a 'soft' system of presumed consent, in which families retain their right to veto, the end result may well be that we do not see any improvements in

the donation rate. It could even result in a higher rate of registration of people that do not want to donate. A 'hard' system of presumed consent may seriously backfire in the Netherlands as happened in Brazil. In February 1997 a 'hard' presumed consent system was introduced in Brazil that did not require the consent of the family. In response to the widespread public and medical unrest the law was amended to make family consent mandatory. But by then the damage to system had already been done.[37] Besides this, the cost of implementing and maintaining presumed consent in a country would cost a large sum of money. The UK organ donation Taskforce estimated the costs in the UK approximately £45 million (€ 51.6 million) in establishment costs and several million pounds per annum thereafter.[38] This might divert resources that could be spent on real improvements.

RECOMMENDATIONS

The goal of this thesis was to investigate possible areas of improvement in the whole process of post mortem organ donation. We reviewed the practical process in the intensive care unit, especially organ donor recognition and the procedure of the process of obtaining consent for organ donation from the relatives of a patient. Furthermore we studied the possibilities of prognostic modeling in order to assess the eligibility of a potential organ donor to become a real organ donor and examined the implications of legal positions as the consent model of presumed consent.

After reviewing the results of the different studies in this thesis a few recommendations can be made. One of those improvements is to recognize a potential donor in daily intensive care practice. We introduced 'imminent brain death' which proved to be a more sensitive tool for recognition and analysis of the pool of potential heart-beating organ donors. We propose the Dutch Transplant Foundation to replace the old definition of 'Severe Brain Damage' for this new definition, which could lead to a standardization that makes comparison between countries and hospitals possible and scientifically more sound.

Several recommendations can be made in order to fine-tune the process of obtaining consent for organ donation. First and foremost we should respect the wishes of the family even if this means that organ donation cannot be performed. There is no secret recipe that leads to a 100% consent score but several factors can be improved. The quality of information provided to the relatives could be further improved by giving the relatives the opportunity to witness parts of the process of brain death determination. This might improve the rate of understanding of the medical and philosophical concept of brain death. Witnessing the process of brain death determination can also improve the perceived quality of care of the patient. Besides this interventional approach there is also room for improvement concerning the timing of

the request for organ donation. In the Netherlands consent for organ donation is most often asked before the formal determination of brain death and thus before death. At this moment this is in violation with the Donation Act and more important, may constitute an important reason in the high refusal rate we have nowadays. Because the consequences of early asking are unclear, we recommend reviewing the whole consent process of organ donation in the intensive care unit by a committee formed by intensivists, neurologists, neurophysiologists, ethicists and legal scholars. They should study the practical, ethical and legal implications of asking consent for organ donation before formal determination of brain death. Only after this evaluation legislation may be changed in favor of or against early asking for organ donation. Besides, we think that the process of brain death determination should be further formalized. We esthablished that in the period before 1998 several independent experts reviewed the whole process of brain death determination to assess whether practice was according to protocol. To this date in Belgium three independent experts review the process of brain death determination. We believe that returning to such a careful procedure could have two great benefits in the Netherlands. Relatives of a patient are convinced that the whole process of the determination of neurological death is extensive and thorough. It may be assumed that this will result in more trust in the process of organ donation and subsequently to a higher consent rate. Secondly, physicians are encouraged to be more aware of the whole process of brain death determination as a highly sensitive procedure.

Prognostic modeling in order to calculate the possibility of death within 60 minutes after the withdrawal of life sustaining measures has much benefit. It is non-invasive for the patient and relatives, it provides the physician with reliable information which he can communicate to the relatives of a patient and it might result in a better use of the sparse resources of an organ procurement agency but also of the intensive care unit. We validated such a prognostic model that can be used for recognition of possible organ donors after circulatory death. We would recommend to fine-tune this model in a prospective fashion.

In my opinion, considering presumed consent to be the solution of the diminishing supply of organ donors is not realistic. The Netherlands has already an expensive and thorough registration system, which could be regarded as a combined system. In fact implementing presumed consent would mean downgrading of the system as we now know it. Practical problems on the intensive care are not accounted for because there still is a need to ask relatives for consent or at least assent for organ donation. Relatives still possess the moral right to veto in order to block organ donation. A system of 'hard' presumed consent (families do not have a veto) will probably have serious repercussions and would eventually damage the trust in organ donation. In the near future we should invest our effort and money for improvements as mentioned above to realize a successful increase in the organ donation rate.

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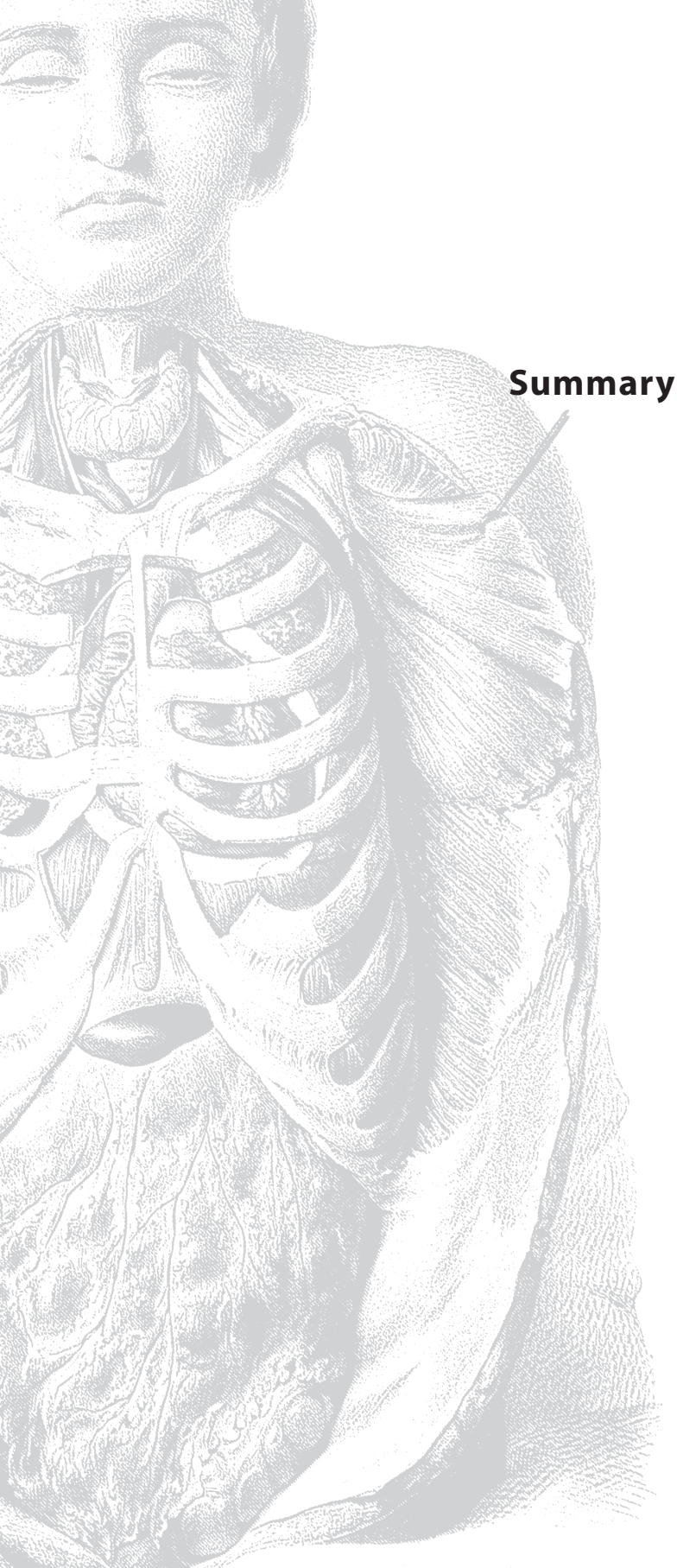


Summary and conclusions

SUMMARY AND CONCLUSIONS

In **chapter 2** we established that the main conditions leading to brain death are subarachnoid hemorrhage, traumatic brain injury and intracerebral hemorrhage. A subarachnoid hemorrhage is the most common condition associated with brain death. According to annual reports of the Dutch Transplant Foundation the number of donations after brain death declined with 30% over a period of 15 years. This decrease is completely compensated by donations after cardiac death, which increased with 282% in that same period. The overall number of deceased donors, regardless of the type of donation, remained the same. The reason of the (on-going) decline of donations after brain death are prevention and improved treatment, especially early endovascular coiling and early neurosurgical clipping are associated with a reduction in case fatality. In chapter 2 we also described the most common risk factors of two out of the three main conditions leading to the state of brain death. Cigarette smoking and untreated hypertension are two independent risk factors of subarachnoid and intracerebral hemorrhage. Because of legislation in Europe and many other countries that ban smoking from public places, we anticipate a further decrease in the incidence of these diseases. Furthermore it has been shown that effective hypertension care (identification, follow-up and treatment) lead to a notable reduction in the incidence of subarachnoid and intracerebral haemorrhage. The other main condition leading to the state of brain death, traumatic brain injury, is often the result of a road traffic accident or fall from height. The number of people dying in traffic is declining every year in the Netherlands and because of on-going improvements in car and traffic safety we anticipate a further decline of deaths and injuries as a consequence of road traffic accidents. In summary, we foresee an inescapable and political and societal desirable decline in the number of patients that are declared brain death over the coming two decades.

Because of the diminishing supply of brain dead organ donors there have been proposals put forth that simply abandon the dead donor rule. In **chapter 3** we examined how we can increase the donor conversion rates without violating the dead donor rule. First we have to face the fact that not all patients with devastating neurological injuries are identified as a potential organ donor, while other patients deteriorate too much between identification and the actual brain death determination. Furthermore we reasoned that it was timely and appropriate to propose a new definition of a potential organ donor that could be used for clinical identification of a potential organ donor. International comparison was used as a benchmark but also to identify weaknesses in the donation process. For constructing our new definition we used two important neurological assessment tools. The Glasgow Coma Scale, widely known and universally used, and the FOUR score, developed by prof. Wijdicks and colleagues in the United States. The latter assessment tool uses four testable components and is validated for emergency and intensive care use. The maximal grade for the total of all testable com-

ponents is sixteen (4 times 4) and consists of the eye response, motor response, brainstem reflexes and respiration. Because brain stem reflexes and respiration were included in this score we anticipated that it could be useful for the determination of what we call 'imminent brain death'. We determined a patient to be in a state of imminent brain death if he or she is:

'*A mechanically ventilated, deeply comatose patient, admitted to an intensive care unit, with irreversible, catastrophic brain damage of known origin (e.g. traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, etc.). A condition of imminent brain death requires either a Glasgow Coma Scale of* $E_1M_1V_1$ *(total of 3) and the progressive absence of at least 3 out of 6 brain stem reflexes or a FOUR score of* $E_0M_0B_0R_0$ *(total of 0)*'

We furthermore added that analysis of a pool of patients, who meet the criteria of imminent brain death, should be done in a hierarchical order. This required to first asses the restrictive exclusion criteria like age, medical condition. The result is the actual pool of organ donors that are medically suitable to donate. However a substantial part of this pool will not donate because of societal reasons like family refusal or prior patient refusal. Using this structural method more widely will give important insight in potential areas of improvements in the donation process. We conclude that the definition of imminent brain death can be used as a point of departure in donor recognition but also as analysis tool in a retro- or prospective fashion.

In **chapter 4** we looked at the implications for the donor conversion rate if we use different definitions of a potential organ donor. Organ donation rates are often expressed as donor rate per million population. We think that this tool is too biased because several factors like intensive care beds, the number of road traffic accidents or neurosurgical facilities differ per country and are not considered in this measurement tool. Another measurement tool is the donor conversion rate, which is defined by the actual number of organ donors divided by the number of patients who were regarded as potential organ donors. We used three different definitions in this retrospective observational study.

1. Imminent brain death based on the Glasgow Coma Scale defined by a GCS score of 3 and at least 3 out 6 absent brain stem reflexes.
2. Imminent brain death based on the Full Outline of UnResponsiveness (FOUR) score of $E_0M_0B_0R_0$ which represents eyelids remaining closed with pain (E_0), no response to pain or generalised myoclonus status (M_0), absent pupillary, corneal and cough reflex (B_0), and absence of spontaneous ventilation or apnea (R_0)
3. Imminent neurological death as defined by the Organ Procurement Transplantation Network (OPTN) in the United States. The OPTN defined imminent neurological death as "a patient…with severe neurological injury and requiring ventilator support, who upon clinical evaluation…has an absence of at least three brain stem reflexes".

Age, a part of the OPTN definition, was excluded from our statistical analysis because it could influence the comparison between the three definitions.

We applied these three definitions on a cohort of patients that died in a university hospital intensive care unit as a result of a subarachnoid hemorrhage, intracerebral hemorrhage or traumatic brain injury. Twenty-three patients of the total cohort of 179 patients donated one or more organs and this was used at the actual number of organ donors in the equation to calculate the donor conversion rate. Regardless of the used definition we identified a considerable number of patients with a high risk to become organ donor. The definition of imminent brain death based on the FOUR score showed the highest donor conversion rate of 36.5%. The main reasons of non-procurement were family refusal (around 50%) in all the definitions and prior patient refusal. In rare cases a patient was not identified as potential organ donor or the relatives of a patient were not present or reachable to give consent for organ donation. We concluded that, the definition of a potential organ donor based on the FOUR score gives the most reliable donor conversion rate.

In the last chapter of this section (**chapter 5**) we analyzed another database that was constructed by the Dutch Transplant Foundation. The database consisted of patients who died on the ICU in the Netherlands in the period 2007-2009. In this study we used two different definitions of a potential organ donor.

1. The definition of 'severe brain damage' as used by the Dutch Transplant Foundation. The Dutch Transplant Foundation defined severe brain damage as 'patients that were mechanically ventilated, with a severe and irreversible brain damage, defined by a GCS of E1, M1, V-tube and absence of at least one brain-stem reflex. These patients had no medical contraindication to organ donation, and were under the age of 76 years'
2. Imminent brain death based on the Glasgow Coma Scale defined by a GCS score of 3 and at least 3 out 6 absent brain stem reflexes.

A total 4814 patients died in the ICUs of 7 Dutch university hospitals between 2007 and 2009. We identified that 559 patients were medically suitable for organ donation, who suffered from irreversible severe brain damage with a GCS-score of 3, and a minimum of one absent brain stem reflex. In total 165 patients donated one or more organs after they were determined brain dead. Fifty-six patients donated one or more organs according to the donation after cardiac death protocol. The heart beating organ donor conversion rate of the imminent brain death definition based on the Glasgow Coma Scale was 40% while the donor conversion rate based on the 'severe brain damage' definition of the Dutch Transplant Foundation was 29.5%. The latter is a result of a too loose definition of a potential organ. The main reasons of non-procurement was family refusal, prior patient refusal or no relatives reachable or

present to give consent for organ donation of their loved one. We concluded that the donor conversion rate is highly dependent on the used definition of a potential organ donor.

In the next section of this thesis we looked at the possible consequences of the changes in the practice of discussing organ donation with the relatives of a patient. In **chapter 6** we researched three components of the process of acquiring consent for organ donation. First, we studied the choice of timing to initiate a discussion about organ donation with the relatives of patient with catastrophic brain injury. Secondly we looked at how thorough the process of brain death determination was over time and thirdly, we studied the possible influence of the donor register on the consent rate. We did this by reviewing the medical charts of effectuated brain dead organ donors who donated one or more organs in the period 1987-2009 in a large university hospital. For studying the choice of timing to discuss organ donation we determined three scenarios:

1. First formal determination of brain death by full neurological examination, followed by an EEG and apnea test as described in the Dutch brain death protocol. After determination of brain death the patient is declared death and the relatives are approached for the first time to discuss organ donation
2. First full neurological examination thereafter followed by discussing organ donation for the first time with the relatives of a patient. If consent is given the mandatory ancillary tests are performed (EEG and apnea test) after which the patient is declared death.
3. First the relatives of a patient are approached to discuss organ donation for the first time. If consent is given the patient will have a full neurological examination to determine brain death. After this examination the mandatory ancillary tests are performed (EEG and apnea test) after which the patient is declared death.

In our analysis we included 228 patients. Before 1998, scenario 1 was the most common practice with 87% of the cases. After 1998 we observed a shift in which this scenario only occurred in 18% of the cases. Scenario 2 was after 1998 most common with 58%. The donor register made obviously an impact on consent rate by patients. Before 1998 94.3% of the consent for organ donation was obtained from the next of kin. After the introduction of the donor register in 1998 that number decreased to 59% while the number prior patient consent increased from 5.7% to 41%. The timing for approaching the relatives for consent is relevant because an important reason of non-procurement of organs of potential organ donors is family refusal. Several studies have established that decoupling of the notification and acceptance of brain death and the request for organ donation have a positive effect on the consent rate. Relatives decline more often if they are emotionally overwhelmed, if there is an inappropriate notification of brain death or if the question for consent to donate organs of their loved one came unexpectedly. We concluded that, ideally, organ donation should only be requested and obtained after the full formal brain death determination.

Trying to improve the rates of consent for organ donation of families of potential organ donors is one of the keys to success. In **chapter 7** we described the results of a multi-center study in which we studied the hypothesis that the presence of family members during the brain death determination of their loved one would improve the consent rate for organ donation. The hypothesis was derived from the same concept of family presence during resuscitation, which proved to have clear benefits. We did not reach our predefined goal of 50 patients due to several factors. Although our hypothesis was promising, in practice it was very difficult to conduct. Eventually, we evaluated 15 patients for inclusion of which in 8 cases the relatives witnessed the process of brain death determination. The most important reasons why the study did not reach its goal was the rarity of brain death as outcome of neurocritical care and the common practice in the Netherlands to obtain consent for organ donation before formal brain death testing. Uneasiness of the medical and technical staff with the presence of relatives of patient also played an important role, as they were the key figures to obtain consent from the relatives for the study. While we cannot draw any significant conclusions based on firm statistical evidence we would recommend to offer the relatives to be present during formal brain death testing, especially during the apnea test.

Chapter 8 describes how we can avoid pain and suffering of patients that are awake and competent but receive life sustaining therapy and request to stop therapy because they cannot recover from their disease, or because independence from organ function supportive or replacement therapy cannot be achieved anymore outside the intensive care unit. We describe two patients, one with permanent mechanical ventilator dependency who was offered palliative sedation, after extensive consultations with family, physicians and an independent physician. Patient B suffered from traumatic spinal cord injury at the C6-C7 level and was unable to wean from the ventilator. Resulting from his spinal cord injury, he remained tetraplegic. After several consultations of two independent physicians and a clinical ethicist he was granted his wish to withdraw therapy and to die. Paramount in this chapter is the autonomous choice of the patient. Dutch caregivers have to respect the wishes of the patient if these are understandable and within accepted possibilities of medical care. In the cases as described above and in chapter 8 there were no reasons to doubt the cognitive functioning and competency of the patients. Concerning palliative sedation and the doctrine of double effect we conclude that this is a myth and using it to label palliative sedation and the administration of opiates at the end of life questionable and only defendable from the perspective of the doctrine of double effect, unsound. We conclude that respecting the autonomous wishes of a competent patient, if reasonable and understandable, should be followed, which makes withdrawal of life-sustaining measures leading to the death of the patient, ethically sound.

Considering the diminishing supply of organ donors we investigated in **chapter 9** if consent for organ donation should be obtained from awake and competent patients but who are de-

pendent of life sustaining treatment and do not want to live anymore, as we have described in chapter 8. We rarely consider post mortem organ donation in conscious patients in which life-sustaining measures are withdrawn. We discussed the pros and cons of such a change in end of life care with regard to the current ethics and practice. Essential in the decision process surrounding the withdrawal of life sustaining measures (such as mechanical ventilation) in patients that are awake is the respect of autonomy of a patient. There has to be no doubt concerning the cognitive functioning and the competency of a patient. An autonomous choice should be made by someone:

1. Who acts intentionally.
2. With understanding of the consequences at hand.
3. Without controlling influences that determine their action.

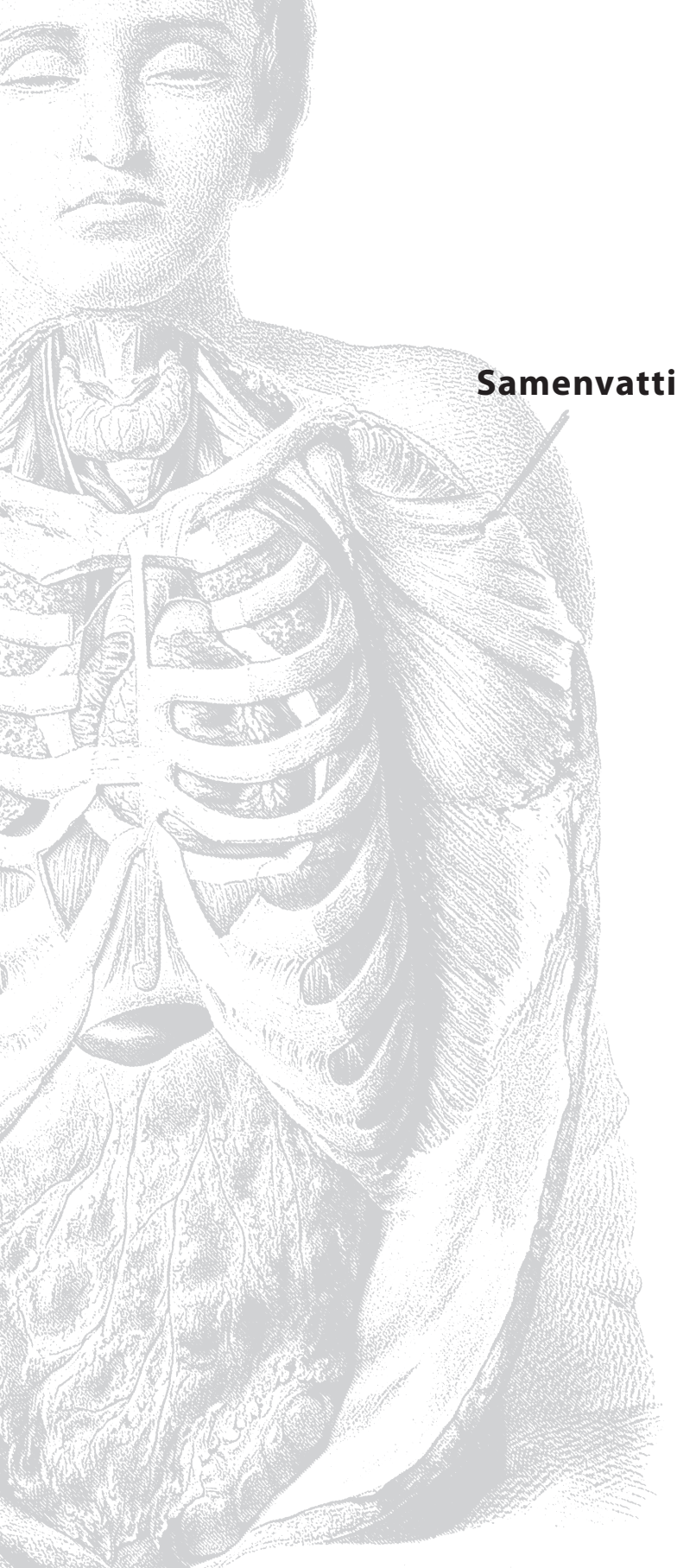
With regard to consenting to organ donation this is ideally be done by the patient itself. So why don't we ask patients before withdrawal of mechanical ventilation if they are willing to donate their organs? We conclude that there are no valid ethical objections to do so.

The last chapter (**chapter 10**) of this thesis is dedicated to the external validation of the model described by Yee and colleagues in 2010. External validation is an essential step between the initial model and a prospective multicenter study to further validate the model for the intended group of patients. The model is developed to predict the probability of death within the time constraint of 60 minutes after withdrawal of life sustaining measures in patients with catastrophic brain injury but not (yet) brain death. The model uses four easy to obtain neurological parameters: corneal reflex, cough reflex, motor response and the oxygenation index. The oxygenation index is calculated as mean airway pressure x FiO_2 x 100 / PaO_2. The performance of the model was assessed by calibration (agreement between observed and predicted outcomes) and discrimination (distinction of those patients who die within 60 minutes for those who do not). For the analysis we used a database of 152 patients who died as a result of a traumatic brain injury or a subarachnoid or intracerebral haemorrhage. Eventually 82 patients satisfied the inclusion criteria. The model of Yee showed good discrimination with an area under curve of 0.75 (95%CI: 0.63-0.87). Calibration was only modest. The mean predicted probability of death after the withdrawal of life sustaining measures within 60 minutes was 80%, while the observed mean probability was 61%. We further improved the model by using the oxygenation index as a continuous variable in contrast by using it as a binary variable as proposed Yee et al. The updated version of this model discriminated better (AUC (95%CI) = 0.77 (0.69-0.90)). The updated version of the Yee model is:

*Linear predictor = −2.52 + absent corneal reflex (yes=1, no=0) *1.54 + absent cough reflex (yes=1, no=0) *1.08 + extensor or absent motor response (yes=1, no=0) *1.18 + oxygenation index*0.13*

Probability of death within 60 minutes after WLSM= exp(Linear predictor) / 1 + exp(Linear predictor)

We conclude that the model developed by Yee and coworkers is valid and is a valuable tool in intensive care practice in neurocritical care. A next step should be to further validate this model in a large prospective cohort of patients.



Samenvatting en conclusies

SAMENVATTING EN CONCLUSIES

In **hoofdstuk 2** hebben we vastgesteld dat vandaag de dag de meest voorkomende oorzaken van hersendood een subarachnoïdale bloeding, traumatisch hersenletsel of een intracerebrale bloeding zijn. Een subarachnoïdale bloeding is van die groep de meest voorkomende oorzaak die geassocieerd is met hersendood. Volgens de jaarverslagen van de Nederlandse Transplantatie Stichting zijn over een periode van 15 jaar het aantal donaties na hersendood afgenomen met 30%. Deze afname wordt volledig gecompenseerd door donaties na cardiopulmonale dood, die in dezelfde periode toenamen met 282%. Het totale aantal postmortale orgaandonaties, ongeacht het type, is gelijk gebleven. De redenen van deze (voortdurende) afname van orgaandonatie na hersendood zijn verbeterde behandelingsopties, met name endovasculair coilen is geassocieerd met een afname in 'case fatality' na een subarachnoïdale bloeding. In hoofdstuk 2 beschreven we ook de meest voorkomende risicofactoren die geassocieerd zijn met twee van de drie meest voorkomende oorzaken van hersendood. Roken en onbehandelde hypertensie zijn twee onafhankelijke risicofactoren voor een subarchnoïdale en een intracerebrale bloeding. Wetgeving inzake een rookverbod in openbare plaatsen in Europa en landen buiten Europa zal er toe leiden dat de incidentie van deze ziekten verder zal afnemen. Wat betreft hypertensie is aangetoond dat het succesvol aanbieden van zorg rondom hypertensie (identificatie, follow-up en behandeling) leidt tot een aanzienlijke reductie van cardiovasculaire aandoeningen, waaronder subarachnoïdale en intracerebrale bloedingen. De andere belangrijkste oorzaak van hersendood, traumatisch schedelhersenletsel, is vaak het gevolg van een verkeersongeval of een val van hoogte. In Nederland nemen het aantal verkeersdoden elk jaar weer af. Door voortdurende verbeteringen in auto- en verkeersveiligheid verwachte wij een verdere afname van verkeersdoden. Samenvattend, we voorzien een niet te vermijden, en politiek en sociaal gewenste, afname van het aantal hersendode patiënten in de komende twee decaden.

Als gevolg van het afgenomen aanbod van hersendode orgaandonoren zijn er voorstellen gedaan om het aantal orgaandonoren toe te laten nemen. Deze voorstellen overtreden alleen simpelweg de zogenaamde 'overleden-donor-regel'. Deze regel schrijft voor dat het verkrijgen van organen niet mag leiden tot de dood van de patiënt. Daarnaast mogen patiënten niet gedood voor het verkrijgen van organen. In **hoofdstuk 3** hebben we gekeken naar de mogelijkheden om de donor conversie ratio te vergroten zonder dat we de 'overleden-donor-regel' overtreden. Ten eerste moeten we accepteren dat niet alle patiënten met catastrofale neurologische schade worden geïdentificeerd als potentiële orgaandonor. Andere patiënten verslechteren te snel in de periode tussen identificatie en de daadwerkelijke hersendood vaststelling. Bovendien wilden wij een nieuwe definitie van een potentiële orgaandonor voorstellen die gebruikt kan worden als klinisch identificatie van een potentiële orgaandonor, als een criterium om internationale vergelijking mogelijk te maken, maar ook

om zwaktes in het donatieproces bloot te leggen. Voor het realiseren van onze nieuwe definitie hebben we gebruik gemaakt van twee belangrijke neurologische beoordeling scores. De welbekende Glasgow Coma Score die in vrijwel elk ziekenhuis ter wereld wordt gebruikt. Daarnaast hebben we gebruik gemaakt van de FOUR score, ontwikkelt door prof. dr. Wijdicks in Verenigde Staten. De FOUR score maakt gebruik van vier componenten en is gevalideerd voor gebruik op een spoedeisende hulp en de intensive care. De maximale score voor alle componenten is zestien (4 keer 4) en bestaat uit de oog respons, motor respons, hersenstam reflexen en respiratie. Doordat deze score gebruik maakt van de componenten hersenstamreflexen en respiratie verwachten wij dat deze score bruikbaar kan zijn voor het vaststellen van een staat van, wat wij noemen, 'dreigend hersendood'. Een patiënt is in een staat van dreigend hersendood als hij of zij:

'mechanisch wordt geventileerd, in diepe comateuze staat is, opgenomen is op een intensive care met onherstelbare catastrofale hersenschade veroorzaakt door bekende oorzaak (bijvoorbeeld traumatisch schedelhersenletsel, subarachnoïdale bloeding, intracerebrale bloeding, etc.). Een staat van dreigend hersendood vereist of een Glasgow Coma Score van $E_1M_1V_1$ (totaal 3) en de progressieve afwezigheid van op zijn minst 3 van de 6 hersenstamreflexen of een FOUR score van $E_0M_0B_0R_0$ (totaal 0)'

Daarnaast voegen wij er aan toe dat de analyse van de groep van patiënten, die voldoen aan de criteria van dreigend hersendood, gedaan moet worden in een hiërarchische volgorde. Dit vereist dat er eerst gekeken werd naar restrictieve exclusiecriteria zoals leeftijd en medische aandoeningen. Het resultaat van die analyse is een groep van potentiële orgaandonoren die medisch geschikt zijn om te doneren. Echter, een aanzienlijk deel van deze groep patiënten zal niet doneren vanwege sociale redenen zoals familieweigering of een eerder gedocumenteerde patiëntweigering. Het op gestructureerde wijze gebruik maken van deze methode geeft inzicht in potentiële gebieden ter verbetering van het donatieproces. De definitie van dreigend hersendood kan worden gebruikt als een vertrekpunt voor donor herkenning maar kan daarnaast ook gebruik worden als een gereedschap voor retro- en prospectieve analyse.

In **hoofdstuk 4** keken we naar de gevolgen voor de donor conversie ratio als we gebruik maken van verschillende definities voor een potentiële orgaan donor. Cijfers over orgaan donatie worden vaak uitgedrukt in als aantal per miljoen populatie. We vinden deze manier van orgaandonatie cijfers uitdrukken te gevoelig voor bias omdat er niet gecorrigeerd wordt voor factoren zoals het aantal intensive care bedden in een land, het aantal verkeersslachtoffers of de neurochirurgische faciliteiten in een land. Een ander meetinstrument is de donor conversie ratio, die gedefinieerd is als het aantal gerealiseerde orgaan donoren gedeeld door het aantal potentiële orgaandonoren. Voor deze studie hebben we drie definities van een potentiële orgaandonor gebruikt:

1. Dreigend hersendood, gebaseerd op de Glasgow Coma Score, gedefinieerd als een GCS score van 3 en op zijn minst drie (van de zes) afwezige hersenstamreflexen.
2. Dreigend hersendood, gebaseerd op de FOUR score van $E_0M_0B_0R_0$. Dit representeert ooglеden gesloten bij pijnprikkel (E_0), geen motorische reactie op pijnprikkel of een gegeneraliseerd myclonus (M_0), afwezige pupil-, cornea- en hoestreflex (B_0) en afwezigheid van spontane ademhaling of het aanwezig zijn van apnoe (R_0).
3. Dreigend neurologische dood zoals deze is gedefinieerd door de Organ Procurement Transplantation Network (OPTN) in de Verenigde Staten. De OPTN definieerde dreigend neurologische dood als "een patiënt…met ernstige neurologische schade en de noodzaak tot mechanische beademing, die bij klinische evaluatie…op zijn minst drie afwezige hersenstamreflexen heeft.

Hoewel de leeftijd van een patiënt onderdeel was van de definitie van de OPTN hebben wij deze geëxcludeerd bij onze statistische analyse omdat deze van invloed kon zijn voor de vergelijking van de drie definities.

We hebben de drie bovenstaande definities toegepast op een cohort van patiënten die overleden zijn op de intensive care als het gevolg van een subarachnoïdale bloeding, intracerebrale bloeding of traumatisch schedelhersenletsel. Drieëntwintig patiënten van het totale cohort van 179 patiënten doneerde een of meerdere organen en zijn gebruikt als het aantal gerealiseerde orgaandonoren in de vergelijking die de donor conversie ratio berekent. Ongeacht welke definitie we gebruikt hebben vonden we een aanzienlijke groep patiënten met een verhoogd risico om orgaan donor te kunnen worden. De definitie van dreigend hersendood gebaseerd op de FOUR score liet de hoogste donor conversie ratio zien met 36.5%. De meest voorkomende redenen niet te doneren was familieweigering (rond de 50%) en eerdere patiëntweigering. In zeldzame gevallen ging orgaandonatie niet door vanwege het niet identificeren van een patiënt als potentiële orgaan donor of doordat familieleden niet aanwezig of bereikbaar waren om toestemming te verlenen voor orgaandonatie.

In het laatste hoofdstuk van deze sectie (**hoofdstuk 5**) hebben we een andere database gebruikt die was ontwikkelt door de Nederlandse Transplantatie Stichting. De database bestond uit patiënten die waren overleden op een intensive care afdeling tussen een periode van 2007-2009. Voor deze studie hebben we gebruik gemaakt van twee verschillende definities.

1. 'Ernstig hersenletsel' zoals deze wordt gebruikt door de Nederlandse Transplantatie Stichting. De Nederlandse Transplantatie Stichting definieerde ernstige hersenschade als volgt: 'patiënten die mechanisch worden beademt, met ernstig en onherstelbaar hersenletsel, gedefinieerd door een GCS score van $E_{1,}M_1$, V-tube en de afwezigheid van op zijn minst één hersenstamreflex. Deze patiënten hadden geen medisch contra-indicatie voor orgaandonatie en hadden leeftijd bij overlijden van onder de 76 jaar.

2. Dreigend hersendood, gebaseerd op de Glasgow Coma Score, gedefinieerd door een GCS score van 3 en op zijn minst drie (van de zes) afwezige hersenstamreflexen.

In totaal overleden er 4814 patiënten op de intensive care afdelingen van zeven onderzochte universitaire medische centra tussen 2007 en 2009. Wij identificeerden 559 patiënten die medisch geschikt waren voor orgaandonatie, die ernstig onherstelbaar hersenletsel hadden opgelopen, een GCS score van 3 hadden en minimaal één afwezige hersenstamreflex. In totaal doneerde 165 patiënten een of meerdere organen nadat bij deze groep de hersendood was vastgesteld. Vijfenvijftig patiënten hebben gedoneerd volgens het donatieprotocol na cardiopulmonale dood. De 'heart-beating' orgaan donatie conversie ratio van de dreigend hersendood definitie, gebaseerd op de Glasgow Coma Score, was 40% terwijl dezelfde ratio gebaseerd op de definitie van 'ernstig hersenletsel' zoals gebruikt door de Nederlandse Transplantatie Stichting 29,5% was. Deze laatste ratio is het gevolg van een brede definitie van een potentiële orgaan donor. De meest voorkomende redenen om niet te doneren waren familieweigering, eerdere patiënt weigering of geen familie aanwezig of bereikbaar of toestemming te verlenen voor orgaandonatie.

In de volgende sectie van dit proefschrift hebben we gekeken naar de mogelijke gevolgen van de verandering in de praktijk rondom het bespreken van orgaandonatie met de familieleden van een patiënt. In **hoofdstuk 6** keken we naar drie onderdelen in het proces van het verkrijgen van toestemming voor orgaandonatie van familieleden van patiënten met catastrofale hersenletsel. Allereerst keken we naar het moment waarop een discussie tot het verkrijgen van orgaandonatie werd geïnitieerd. Ten tweede keken we naar hoe zorgvuldig het proces van het vaststellen van de hersendood in een bepaalde periode verliep. En ten derde bestudeerde we de mogelijke invloed die het Donorregister heeft op de mate van toestemming voor orgaandonatie. Hiervoor hebben we de medische dossiers doorgenomen van alle geëffectueerde hersendode orgaan donoren over een periode van 1987 tot 2009. Om te onderzoek op welk moment voor het eerst een discussie over orgaandonatie werd geïnitieerd hebben we drie scenario's vastgesteld:

1. Eerst formele vaststelling van de hersendood door een volledig neurologisch onderzoek gevolgd door een EEG en een apnoetest zoals is beschreven en vastgelegd in het Nederlandse hersendoodprotocol. Na vaststellen van de hersendood waarmee de patiënt dood is verklaart wordt de familie voor het eerst benaderd om orgaan donatie te bespreken.
2. Eerst een volledig neurologisch onderzoek gevolgd door een discussie over orgaandonatie met de familieleden van de patiënt. Als er toestemming voor orgaandonatie wordt verleend worden de aanvullende onderzoeken zoals het EEG en de apnoetest uitgevoerd. Waarna de hersendood formeel is vastgesteld.

3. Eerst wordt de familieleden van de patiënt benadert om orgaandonatie te bespreken. Als er toestemming voor orgaandonatie wordt verleend volgt er een volledig neurologisch onderzoek gevolgd door de aanvullende onderzoeken EEG en apnoetest. Waarna de hersendood formeel is vastgesteld.

Voor onze analyse includeerde we 228 patiënten die voldeden aan alle criteria. Voor 1998 was scenario 1 het meest voorkomend in 87% van alle gevallen. Na 1998 heeft er een verschuiving plaatsgevonden waarin de praktijk van hersendood volgens scenario 1 nog maar in 18% van de gevallen plaats vond. Het meest voorkomende scenario na 1998 was scenario 2 in 58% van de gevallen. Ook het Donorregister heeft een impact gehad op het toestemmingspercentage voor orgaandonatie van patiënten. Voor 1998 werd voor 94.3% van alle toestemming voor orgaandonatie verkregen van familieleden van de patiënt. Na de invoering van het Donorregister in 1998 daalde dat percentage naar 59%. Het percentage patiënten die bij leven toestemming had gegeven voor orgaandonatie steeg van 5.7% voor 1998 naar 41% na 1998. Het moment om een discussie met familieleden te initiëren over orgaandonatie is relevant aangezien de belangrijkste reden waarom orgaandonatie geen doorgang heeft familieweigering is. Meerdere studies hebben aangetoond dat het splitsen van het gesprek over de hersendood van een patiënt en het gesprek waarin toestemming gevraagd word voor orgaandonatie een positief effect hebben op het toestemmingspercentage. Familieleden weigeren eerder als ze emotioneel overweldigd zijn, als er op een inadequate wijze de hersendood wordt gemeld of als ze verrast zijn om toestemming te verlenen voor orgaandonatie. We concluderen dat toestemming voor orgaandonatie alleen verkregen kan worden na de volledige formele vaststelling van de hersendood.

Het vergroten van de toestemmingspercentages voor orgaandonatie van families van potentiële orgaandonoren is mogelijk een van de sleutels tot succes. In **hoofdstuk 7** presenteren we de resultaten van een multicenter studie waar de hypothese toetsen dat de aanwezigheid van familieleden gedurende de hersendooddiagnostiek het toestemmingspercentage verhoogt. De hypothese is afgeleid van hetzelfde concept waar familieleden aanwezig zijn gedurende de reanimatie van een familielid. Dit concept liet duidelijke voordelen zien. We hebben ons vooraf gestelde doel van 50 patiënten niet gehaald door meerdere factoren. Hoewel onze hypothese veelbelovend was, was het helaas moeilijk uitvoerbaar in de praktijk. Uiteindelijk hebben we 15 patiënten geëvalueerd voor de inclusie, waarvan in 8 gevallen de familieleden getuige waren van het determineren van de hersendood. De belangrijkste redenen waarom de studie zijn doel niet heeft bereikt is de zeldzaamheid van hersendood als eindpunt van neuro intensive care en de gebruikelijke praktijk in Nederland om reeds om toestemming te vragen voor orgaandonatie voor het vaststellen van de hersendood. Ook het feit dat de technische en medische staf zich ongemakkelijk voelde bij de aanwezigheid van familieleden bij de patiënt speelde een belangrijke rol omdat zij de sleutelfiguren waren

die toestemming moesten verkrijgen voor de studie. Hoewel we geen definitieve conclusies kunnen trekken gebaseerd op degelijk statistisch bewijs zouden we het aanbieden van het bijwonen van de hersendooddiagnostiek (in het bijzonder bij de apnoetest) door familieleden willen aanbevelen.

Hoofdstuk 8 beschrijft hoe we pijn en lijden zo veel mogelijk kunnen vermijden bij patiënten die wakker en competent zijn, levensverlengende therapie krijgen maar de behandeling willen staken omdat zij niet meer kunnen herstellen van hun onderliggend lijden. Soms wordt de behandeling ook gestaakt vanwege feit dat deze patiënten afhankelijk blijven van orgaanfunctie vervangende therapie en zodoende niet zonder deze technieken kunnen overleven buiten de intensive care. We beschrijven twee patiënten, een met permanente beademingsafhankelijkheid, die na uitvoerige consultaties met familie, artsen en een onafhankelijk arts, palliatieve sedatie werd aangeboden. Patiënt B leed aan een traumatische dwarslaesie op het niveau van de laagste halswervels (C6-C7) en was niet te ontwennen van de beademing. Als gevolg van zijn dwarslaesie bleef hij tetraplegisch. Na meerdere consultaties van twee onafhankelijke artsen en een klinisch ethicus werd zijn wens ingewilligd om de behandeling te staken zodat dat hij kon overlijden. Belangrijk in dit hoofdstuk is de autonome keus van de patiënt. Nederlandse zorgverleners zijn verplicht om de wens van de patiënt te respecteren als deze begrijpelijk en binnen de grenzen van het medisch acceptabele liggen. In de casus zoals hierboven beschreven was er geen reden om te twijfelen aan de het cognitief functioneren en competentie van beide patiënten. Met betrekking tot de palliatieve sedatie en de doctrine van het dubbel effect concluderen wij dat de doctrine een mythe is die enkel in stand wordt gehouden om het toedienen van palliatieve sedatie en opiaten bij het einde van het leven te kunnen verdedigen. We concluderen dat de autonome wens van een competente patiënt, als deze redelijk is en begrijpelijk, gerespecteerd en gevolgd moeten worden. Dit maakt het staken van levensverlengende therapie dat leidt tot de dood van de patiënt ethisch juist.

Overwegende het afgenomen aanbod van organen hebben we onderzocht over toestemming gevraagd moet worden van patiënten die wakker en competent zijn maar die afhankelijk zijn van levensverlengende therapie en niet verder willen leven, zoals we beschreven hebben in hoofdstuk 8 (**hoofdstuk 9**). Zelden overwegen post mortale orgaandonatie bij patiënten die bij bewustzijn zijn waarbij de levensverlengende therapie staken. In dit hoofdstuk hebben we de voor- en nadelen tegenover elkaar gelegd wat de gevolgen zijn voor de zorg rondom het levenseinde. Essentieel in de discussie rondom het staken van de levensverlengende therapie (zoals de beademing) bij wakkere patiënten, is het respecteren van de autonome keus van de patiënt. Er mag geen twijfel bestaan over de cognitieve functioneren en competentie van een patiënt. Een autonome keus moet worden gemaakt door iemand die:

1. Die handelt met opzet

2. Met begrip voor de gevolgen van zijn handeling
3. Zonder druk van buitenaf die zijn actie kunnen beïnvloeden

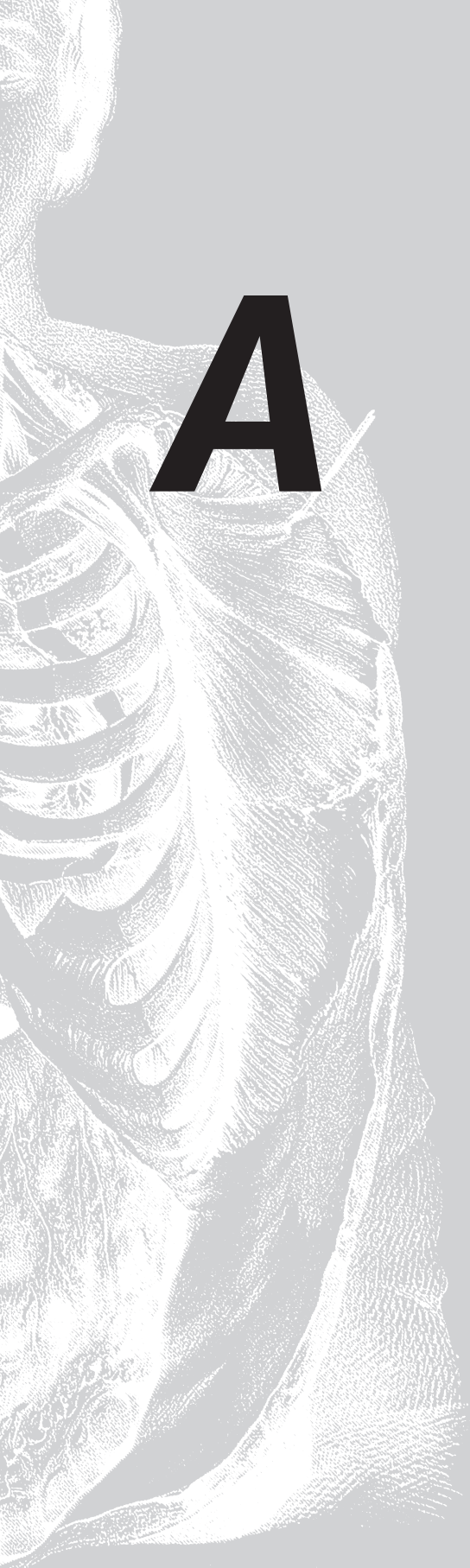
Het toestemmen in orgaandonatie wordt idealiter gedaan door de patiënt zelf. Dus waarom vragen patiënten niet om toestemming voor orgaandonatie voordat we de beademing staken? We concluderen hiervoor geen ethische bezwaren zijn

Het extern valideren van een prognostisch model is een essentiële stap tussen het initiële model en een prospectieve multicenter studie die het model verder valideert voor groep patiënten waar het model betrekking op heeft. In **hoofdstuk 10** hebben we een model gevalideerd van Yee en collega's. Het model is ontwikkeld om de waarschijnlijkheid te voorspellen van overlijden binnen 60 minuten na het stoppen van levensverlengende therapie bij een patiënt met catastrofaal hersenletsel maar (nog) niet hersendood. Het model gebruikt vier makkelijk te verkrijgen neurologische parameters: de cornea reflex, de hoest reflex, de motor reactie op pijn en de oxygenatie index. De oxygenatie index wordt als volgt berekent: gemiddelde luchtweg druk x FiO_2 x 100/PaO_2. De kwaliteit van het model wordt beoordeeld door te kijken naar de calibratie (overeenstemming tussen de waargenomen en de voorspelde uitkomsten) en de discriminatie (onderscheid tussen patiënten die overlijden binnen 60 minuten en patiënten die overlijden na 60 minuten). Voor de analyse gebruikte we een database van 152 patiënten die waren overleden als een gevolg van traumatisch schedelhersenletsel, of een subarachnoïdale of intracerebrale bloeding. Uiteindelijk voldeden er 82 patiënten aan onze inclusiecriteria. Het model van Yee liet een goede discriminatie zien met een area under curve van 0.75 (95%BI: 0.63-0.87). Calibratie van het model was bescheiden. De voorspelde gemiddelde waarschijnlijkheid van overlijden binnen 60 minuten na het stoppen van levensverlengende therapie was 80%, terwijl de geobserveerde gemiddelde waarschijnlijkheid 61% was. We hebben het model verder verbeterd door de oxygenatie index als continue variabele te gebruiken in contrast met wat Yee et al. voorstelde om de oxygenatie index als binaire variabele te gebruiken. De geüpdate versie van dit model discrimineerde beter (AUC (95%BI) = 0.77 (0.69-0.90)). De geüpdate versie van het Yee model is:

*Lineaire predictor = –2.52 + afwezige cornea reflex (ja=1, nee=0) * 1.54 + afwezige hoestreflex (ja=1, nee=0) * 1.08 + extensie of afwezige motor reactie (ja=1, nee=0) * 1.18 + oxygenatie index * 0.13*

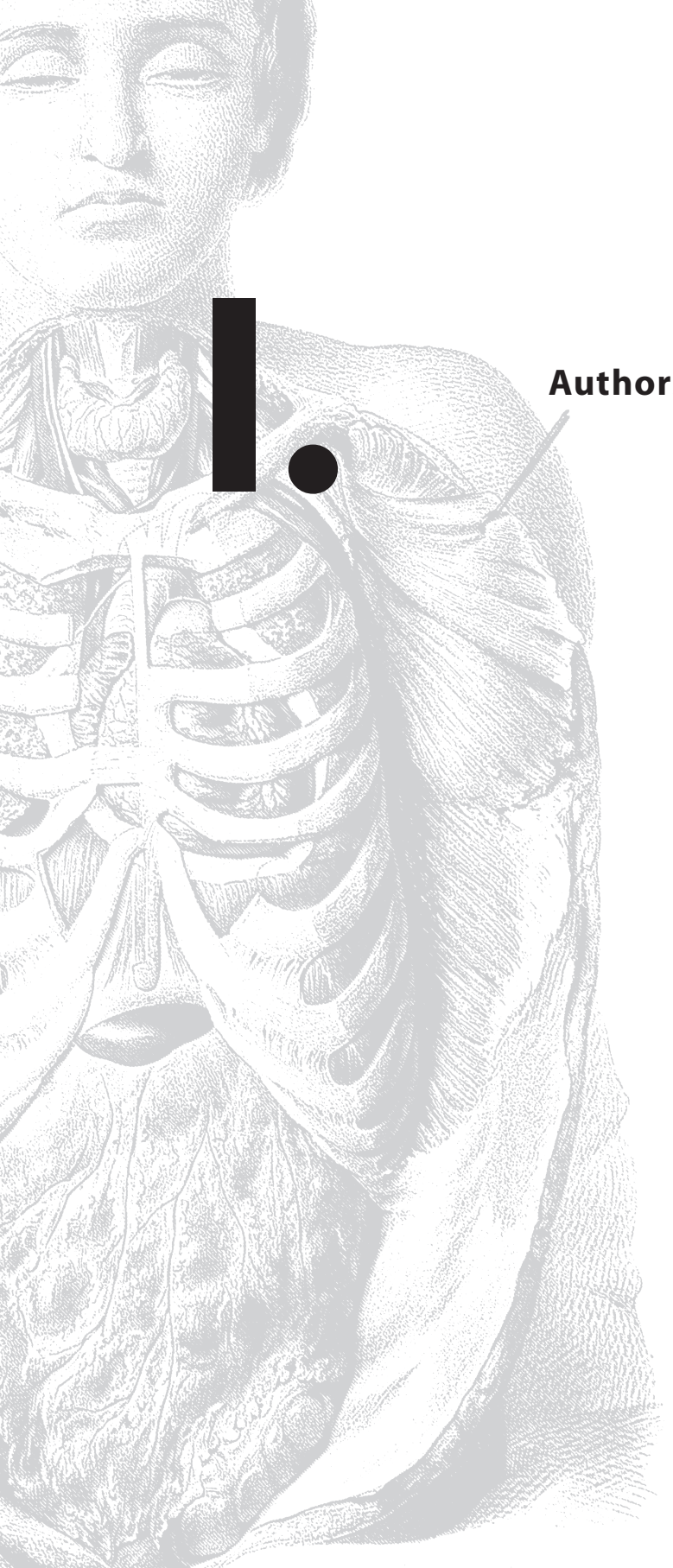
De waarschijnlijkheid van overlijden binnen 60 minuten na het stoppen van levensverlengende therapie = exp (Lineaire predictor) / 1 + exp (Lineaire predictor)

Een volgende stap zou het verder valideren van dit model moeten zijn in een groot prospectief cohort.



A

Appendices



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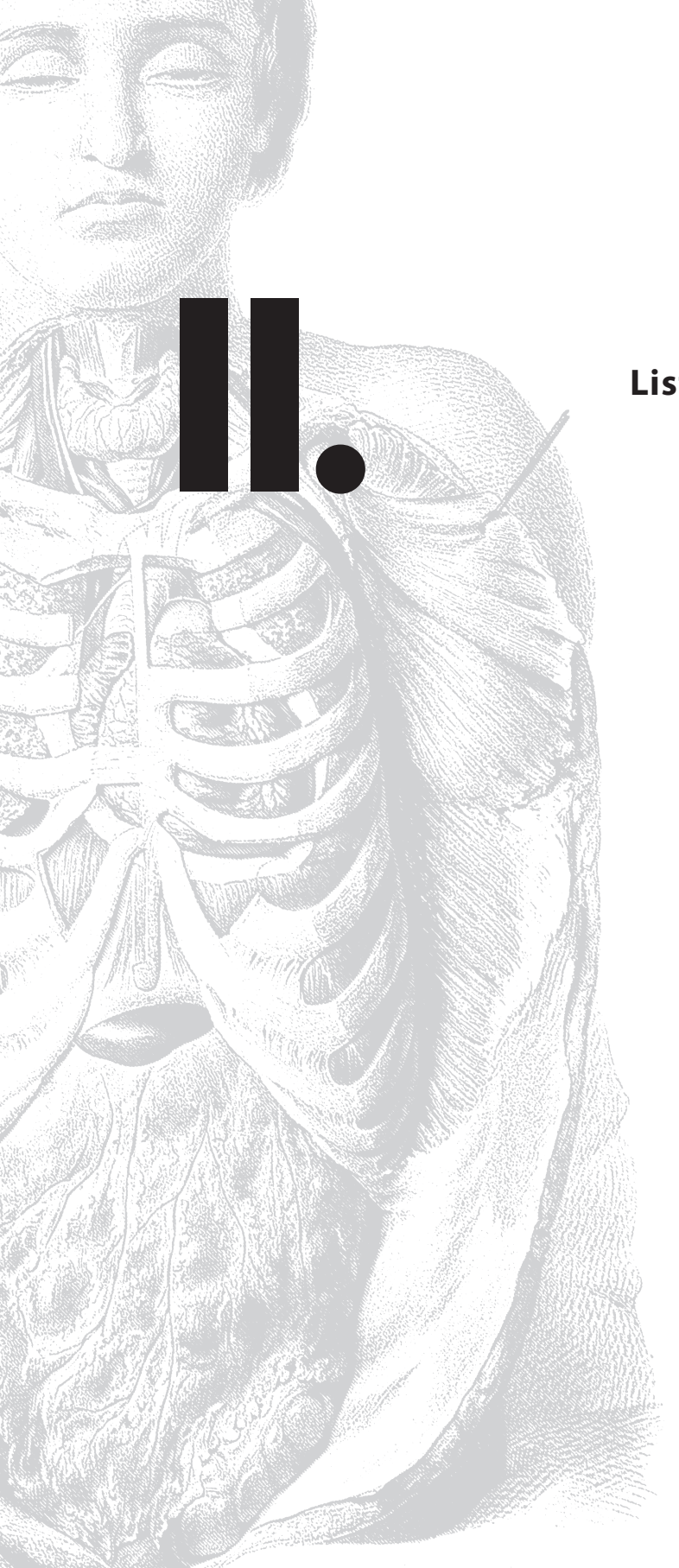

II.

List of publications

INTERNATIONAL PUBLICATIONS

Kompanje EJO, de Groot YJ, Bakker J, IJzermans JNM. A national multi center trial on family presence during brain death determination: the FABRA study. Neurocritical Care, Published ahead of print

de Groot YJ, Lingsma HF, van der Jagt M, Bakker J, IJzermans JNM, Kompanje EJO. Remarkable changes in the choice of timing to discuss organ donation with the relatives of a patient. A retrospective observational study in 228 effectuated brain dead organ donors between 1987 and 2009 Critical Care 2011 Oct 7; 15(5):R235

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Kompanje EJO, de Groot YJ, Bakker J. Is organ donation from brain dead donors reaching an inescapable and desirable nadir? Transplantation 2011 Jun 15;91(11):1177-1180

Kompanje EJO, Walgaard C, de Groot YJ, Stevens M. Historical sources of basilar artery occlusion. Neurology 2011 Apr 26;76(17):1520-1523

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A discription and illustration of a necrotizing fasciitis by John Bell in 1801, hypothetically caused by Vibrio vulnificus. International Journal of Infectious Diseases 2010 Sep;14 Suppl 3:e341-3

NATIONAL PUBLICATIONS

Kompanje EJO, de Groot YJ, IJzermans JNM, Bakker J, G.H. Visser, Van der Jagt M. Communicatie met familieleden van een vermoedelijk hersendode patiënt. Nederlands Tijdschrift voor Geneeskunde 2011;155(11):A3404

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Kompanje EJO, de Groot YJ. Autoresuscitation is not a determinant to lower the observation time in declaring death for organ donation. Critical Care Medicine 2011, Accepted for publication

de Groot YJ, Lingsma HF, Kompanje EJO. Rates of kidney donation in nation with presumed consent. Annals of Internal Medicine 2011 Jun 7;154(11):778

Epker JL, de Groot YJ, Kompanje EJO
Respiratory support withdrawal in intensive care units: international differences stressed and straightened! Critical Care 2011 Mar 2;15(2):405

de Groot YJ, Bakker J, Wijdicks EFM, Kompanje EJO Imminent brain death and brain death are not the same: Reply to Verheijde and Rady. Intensive Care Medicine 2011 Jan; 37(1):174

de Groot YJ, Kompanje EJO. Dead donor rule and organ procurement
Pediatric Critical Care Medicine 2010 11(2): 314

de Groot YJ, Kompanje EJO. Policies on children's hospitals on donation after cardiac death. Journal of the American Medical Association (JAMA) 2009 Aug 26;302 (8): 844

ABSTRACTS

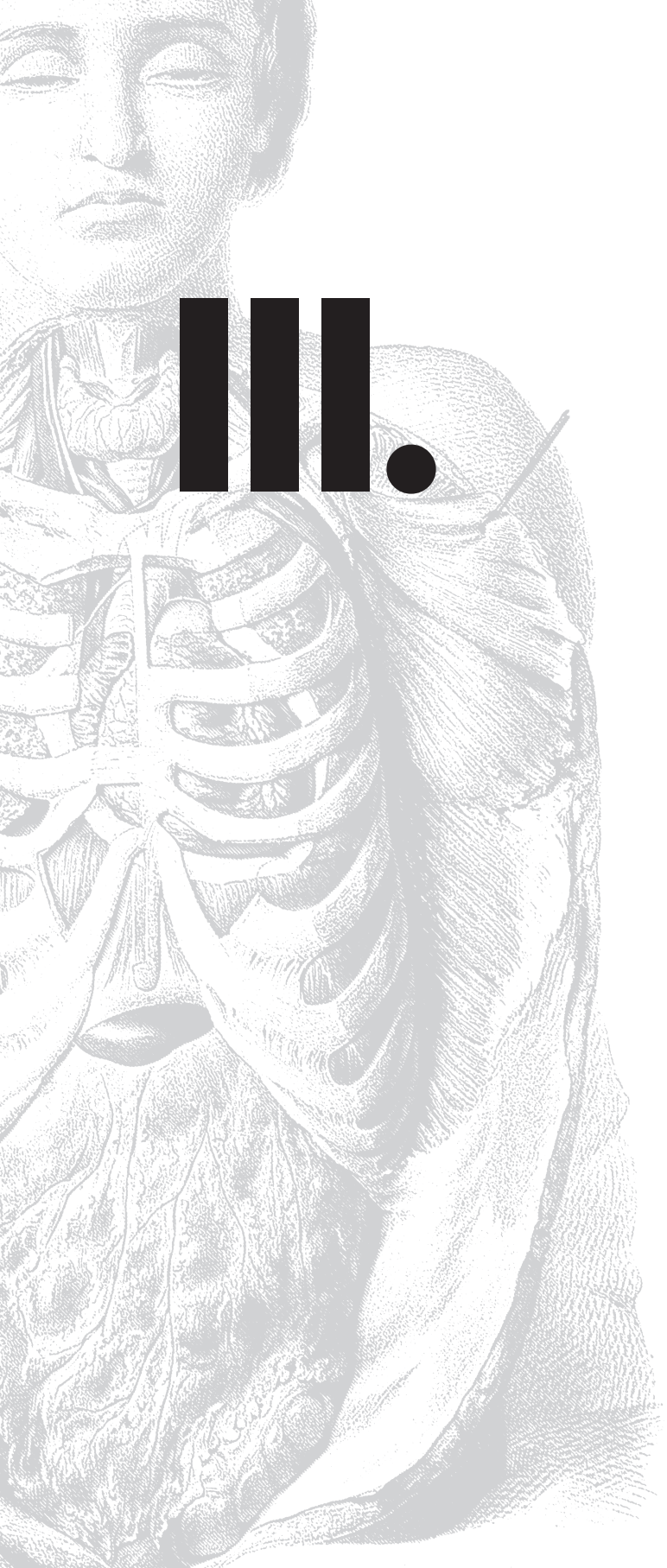
de Groot YJ, Bakker J, Epker JL, van der Hoven B, Kompanje EJO. Brain death determination in patients with basilar artery occlusion; some pitfalls: a case serie. Intensive Care Medicine 2011 Sep;37 Suppl 1: S72 (poster presentation) ESICM 2011 Berlin

Kompanje EJO, De Groot YJ, Bakker J. Trends and demographics of 154 brain dead patients between 1995 and 2009. Intensive Care Medicine 2010 Sep;36 Suppl 2: S211 (oral presentation) ESICM 2010 Barcelona

de Groot YJ, Jansen NE, Bakker J, Hoitsma AJ, Kompanje EJO. Consequences of a strict definition of the potential heart-beating organ donor. A three year retrospective analysis in a Dutch university hospital. Intensive Care Medicine. 2009 Sep;35 Suppl 1: S264 (poster presentation) ESICM 2009 Vienna

BOOK CONTRIBUTIONS

de Groot YJ, Kompanje EJO. Intensive Care Capita Selecta 2010. Heeft orgaandonatie van hersendode patiënten nog toekomst? Redactie: Bakker J, M.H.W.A van den Boogaard, B. de Lange, P.H.J. van der Voort Pag. 201-206, *ISBN 978-90-72651-26-6*

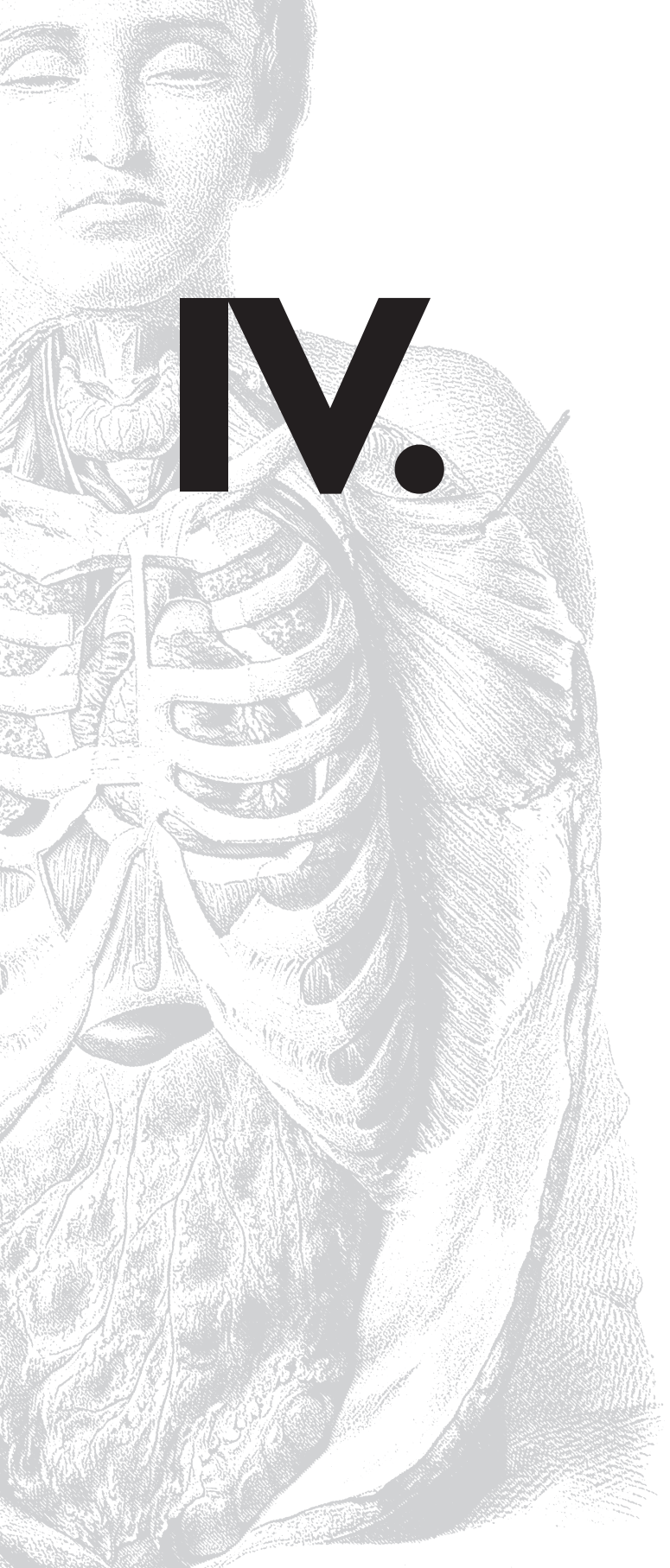


III.

Curriculum Vitae

CURRICULUM VITAE

Yorick Jasper de Groot was born on December 14th 1979 in Dordrecht, the Netherlands. After finishing secondary school (VWO, Griftland College, Soest) he started studying Technical Business Administration at the University of Twente in Enschede. In 1999 he attended medical school at the Erasmus MC University Medical Center Rotterdam. He obtained his medical degree in 2006 after which he worked as a resident (ANIOS) Intensive Care at Erasmus MC University Medical Center Rotterdam from 2007 to 2008. In April 2008 he started this PhD project at the same department under supervision of prof. dr. J. Bakker. He will start his speciality training in Anesthesiology under supervision of prof. dr. J.T.A. Knape (University Medical Center Utrecht) in April 2012. He is living together with Nathalie van der Ploeg with whom he has one lovely daughter, Hélène.



IV.

Portfolio

PhD Portfolio

Name PhD student:	Y.J. de Groot
Erasmus MC Department:	Department of Intensive Care
Research School:	COEUR
PhD period:	April 2008 – February 2012
Promotors:	Prof.dr. J. Bakker and Prof.dr. J.N.M. IJzermans

1. PhD Training	**Year**	**Workload (ECTS)**
General courses		
NWO Talent Class	2009	1
Course in Statistics in Intensive Care (prof. dr. E. Lesaffre)	2009	1
Specific courses		
Principles of research in Medicine and Epdidemiology (NIHES)	2008	2
Biostatistics for Clinicians (NIHES)	2009	1
SPSS course for Clinicians (NIHES)	2009	1
Basiscursus Regelgeving en Organisatie voor Klinisisch		
Onderzoekers (Good Clinical Practice)	2009	2
Intensive Care Research (COEUR)	2009	1.5
Research seminars		
Novel aspects in Intensive Care Medicine, Amsterdam	2008	0.5
Coagulation management in massive bleeding, Rotterdam	2009	0.5
Medical Ethical Committee (NTV), Utrecht	2009	0.5
Intensive Care Adults, Erasmus MC, Rotterdam (monthly)	2008-2011	1.5
Conferences (national and international)		
Startconferentie Masterplan Orgaandonatie, Amersfoort	2009	0.4
Venticare, Utrecht	2010	0.4
Committees		
Donatiecommissie Erasmus MC, Rotterdam	2009-2011	0.8
National presentations		
Research seminar Intensive Care (COEUR)	2009	0.5
Symposium Masterplan Orgaandonatie, Driebergen	2010	0.5
Venticare, Utrecht	2011	0.5

1st Erasmus Critical Care Days, Rotterdam	2011	0.8
Presentations within Erasmus MC, Rotterdam	2008-2011	2
Begeleidingscommissie Masterplan Orgaandonatie, Utrecht	2009-2011	1.5

International presentations

European Society of Intensive Care Medicine, Vienna	2009	1.5
Poster presentation		
European Society of Intensive Care Medicine, Barcelona	2010	1.5
Oral presentation		
European Society of Intensive Care Medicine, Berlin	2011	1.5
Poster presentation		

Dankwoord

DANKWOORD

Het proefschrift wat u zojuist van voor tot achter met veel interesse heeft gelezen (als het goed is), is aanbeland bij het meest gelezen onderdeel. In dit dankwoord tracht ik een ieder te bedanken, die bewust dan wel onbewust heeft bijgedragen aan dit proefschrift. Mocht ik mensen zijn vergeten dan hoop ik dat dit niet persoonlijk word opgevat en roep ik meteen een welgemeend 'Mea culpa'. Tot zover de disclaimer van dit dankwoord, over tot het echte doel van dit hoofdstuk.

Mijn promotoren

Prof.dr. J. Bakker, beste Jan, vier jaar geleden stond ik bij jou op de stoep om de mogelijkheden te bespreken voor een promotieonderzoek. Zoals ik inmiddels van je ben gewend, was het gesprek kort en to the point en liep ik naar buiten met een onderzoeksopdracht. In het eerste jaar is, ondanks de inzet van velen, niet het doel bereikt wat we voor ogen hadden. Mijn ongebruikelijke voorstel om mijn promotie door te starten bij Erwin werd door jou zonder problemen geaccepteerd, maar er diende wel gepresteerd te worden. Het vertrouwen wat je toen in mij stelde betaal ik je vandaag middels dit proefschrift terug. Mijn hartelijke dank voor je vertrouwen, hulp en tijd die je gegeven hebt om dit mogelijk te maken.

Prof.dr. J.N.M. IJzermans, beste Jan, in de loop van de ontwikkeling van de FABRA studie raakte je steeds meer betrokken bij onze andere projecten. Snel daarna werd je mijn tweede promotor. Onze besprekingen over de voortgang van mijn promotie en de FABRA studie heb ik altijd als constructief en prettig ervaren. Je humor zorgde voor de nodige relativering. In veel zaken zaten we op dezelfde golflengte en waren de punten die geregeld moesten worden snel afgestemd. Ik wil je hartelijk danken voor je betrokkenheid bij de afronding van dit manuscript en je kritische doch constructieve benadering gedurende mijn periode als promovendus.

De leden van de leescommissie

Prof.dr. D.W. Dippel, beste Diederik, hartelijk dank dat je wilde plaats nemen in de kleine leescommissie als lid en secretaris. De kritische noten die je had te kraken ten aanzien van het manuscript heb ik ter harte genomen en hebben geleid tot een verbetering van het proefschrift. Ik wil je hartelijk danken voor je adviezen in deze.

Prof.dr. A.I.R. Maas, beste Andrew, bij het aanbieden van het manuscript hebben we mogen genieten van je gastvrijheid. Hartelijk dank voor het feit dat je wilde plaatsnemen in de kleine leescommissie en dat je het manuscript zorgvuldig hebt willen doornemen. De opmerkingen en punten ter verbetering zijn uiteraard ter harte genomen.

Prof.dr. P.J. van der Maas, beste Paul, mijn eerste kennismaking met jou was in je hoedanigheid van decaan van de Faculteit Geneeskunde. Als vertegenwoordiger van de Medische Faculteits Vereniging heb ik toentertijd prettige en constructieve gesprekken gevoerd, waarvan we de resultaten tegenwoordig terug kunnen zien binnen de faculteit. Ik ben je dankbaar dat je wilde plaatsnemen in de kleine leescommissie en je snelle beoordeling van het manuscript.

De overige leden van de commissie

Prof.dr. J.G. van der Hoeven en prof.dr. A.J. Hoitsma hartelijk dank voor jullie bereidheid om mijn proefschrift door te nemen en zitting te nemen in de commissie ingesteld voor mijn promotie.

Prof.dr. E.F.M. Wijdicks, beste Eelco, hartelijk dank voor je hulp en constructieve opmerkingen bij een aantal manuscripten waarin je hebt geparticipeerd. Bij problemen of vragen konden wij dezelfde dag nog een deskundig antwoord terug verwachten. Ik beschouw het als een grote eer dat jij bereid bent om plaats te nemen in de commissie ingesteld voor mijn promotie.

Mijn copromotor

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De co-auteurs

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Mijn paranimfen Christa Walgaard en Taco de Groot

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En verder…

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