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Joseph DuBose, MD, and Ali Salim, MD, FACS

As of August 2007, 96 900 people are awaiting organ transplantation in the United States, while only 28 930 transplants were performed in 2006. With such a large gap between organ need and organ availability, it is inevitable that many will die while awaiting transplantation. This organ shortage has become a national public health crisis, and as a response, the United States Department of Health and Human Services launched the Organ Donation Breakthrough Collaborative, an ambitious campaign to dramatically increase the number of transplantable organs. One of the suggested strategies involves maximizing the number of organs obtained from the available cadaveric "brain dead" donor pool by using donor management protocols that optimize and treat the profound physiological disturbances that are associated with brain death. The use of these standardized and aggressive donor management protocols has been shown to increase the number of transplanted organs and prevent the number of donors lost due to medical failures. A protocol-driven approach by a dedicated organ donor management team should be considered a key component of any program designed to bridge the gap between organ supply and demand.

Keywords: transplantation; organ donor; aggressive donor management; in-house coordinator; solid organ transplant; brain death; organ donation

Introduction

The technological advancements in transplantation today have made organ donation a common and culturally accepted practice. Yet despite improvements in recipient selection and important advances in transplant prioritization, a persistent shortage of organs and inexhaustible waiting lists continue to result in many people dying while awaiting transplantation. According to Organ Procurement and Transplantation Network figures, there are currently over 96 000 candidates awaiting organ donation, with the number of new additions to the waiting list for transplantation growing each year since 1995.[1] In 2006 alone 7193 patients died awaiting organ transplantation, a significant increase from the figure of 4269 documented in 1996.[1] This increasing shortage in the availability of transplantable organs has become a public health crisis in the United States with numerous public, private, and governmental agencies attempting to find ways to increase the recovery of organ donors.

The U.S. Department of Health and Human Services launched the Organ Donation Breakthrough Collaborative in 2003 in response to this growing national crisis. This ambitious campaign was designed to dramatically increase the number of transplantable organs through an enhanced commitment towards spreading best known practices to the Nation's largest hospitals with the greatest potential for organ donation. The Collaborative initiative set a goal to achieve organ donation rates of 75% or higher in these hospitals.[2]

A variety of methods have been used to increase the donor pool. Both younger and older donors are

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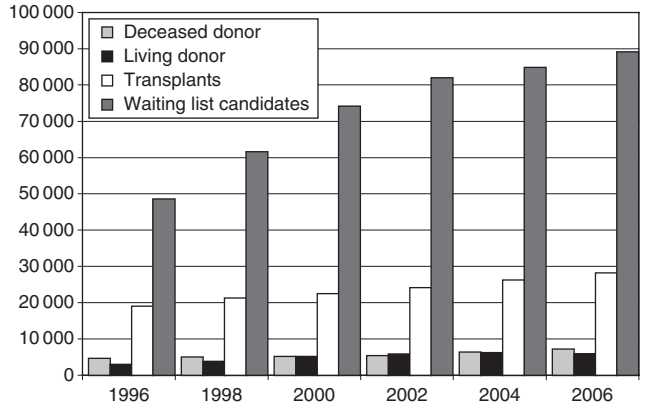

Figure 1. Organ Donation and Candidate Waiting List Discrepancies 1996-2006.[1]

routinely used. In fact, the use of cadaveric donors older than 50 has increased by 135% in the past decade as aggressive pharmacologic donor management has resulted in more transplanted organs.[3] The use of organs from living-related, living-unrelated, and asystolic donors has also increased.[4] The use of marginal, high risk donors, and bacteremic donors, once thought to be contraindications, have been used with some success.[5-7] The use of extended donor criteria, while controversial, has been increasingly advocated in the recent medical literature.[8-11] Among strategies with proven success in providing measurable increases in organ donation; aggressive donor management (ADM) protocols and in-house transplant coordinator (IHC) programs have gained increased attention. These interventions, though time and resource consuming, have significant potential in improving the identification of potential donors, increasing consent and conversion rates, and helping to close the widening gap between organ supply and demand.

Types of Organ Donors

Organs for transplantation generally come from 3 sources: donation after cardiac death; DCD), cadaveric "brain-dead" donors, and living (related and unrelated) donors. Donation after cardiac death accounts for only 7% of the organs for transplantation. However, the number of DCD donors has significantly increased over the past few years due to the growing disparity between recipient demand and the donor pool.[12,13] In the United States, these types of DCD donors are broadly classified as "controlled" (donors with terminal prognosis awaiting cardiac arrest) and "uncontrolled" (patients with unexpected cardiac arrest). The European Maastricht classification[14,15] further specifies 5 classes of donors: class 1—patients who are dead on arrival to medical care; class 2—patients who arrive in extremis and have unsuccessful resuscitative attempts; class 3—patients with terminal prognosis awaiting cardiac arrest; class 4—patients declared brain dead who experience unexpected cardiac arrest; and class 5—inpatient donors who have documented cardiac arrest. Under this classification system, class 3 would be considered "controlled" while the remainder of the classes would be termed "uncontrolled". As of January 2007, the Joint Commission has implemented a standard requiring that hospitals with necessary resources develop donation policies and protocols that address opportunities for asystolic recovery of organs. Despite this support, DCD practices remain limited due to the practical and ethical concerns of caregivers and families.[13,16] Recent reports in the mainstream media accusing transplant surgeons of hastening death to harvest organs do not help the cause of DCD.[13]

Despite the promise that DCD may hold for further expanding the donor pool, to date the majority of donated organs originate from either living or brain-dead cadaveric sources. Living related and unrelated donors provide nearly 40% of organs for transplantation. It remains the preferred source of organs for kidney transplantation. Novel approaches such as the Living-Donor Exchange have helped increase the number of living related donors over the past few years.[17-19] Cadaveric, brain-dead donors constitute the largest pool of available organs for transplantation, accounting for 54% of all donors in the past year (Figure 1). Among cadaveric donors, the most common causes of death included cerebrovascular accident/stroke (CVA), head trauma, and anoxia.[2] Traumatic brain injury, once the most common cause of brain death, has been surpassed by CVA. This has important implications, as organs from younger and healthier trauma patients have been replaced by older, sicker stroke patients. Regardless, cadaveric donors will continue to contribute a significant number of organs as nearly 50 000 U.S. residents die from traumatic brain injury and nearly 54 per 100 000 citizens die from CVA per year.[20] Improving the ability of the medical community to identify and preserve potentially

transplantable organs from this large pool of patients is paramount to the success of present and future transplantation efforts in the United States and abroad.

Pathophysiology of Brain Death

Brain death is associated with profound physiologic alterations that result in diffuse vascular regulatory disturbances and widespread cellular injury.[21,22] Severe alterations in metabolism,[23-25] endocrine function,[26-29] immunology,[30] and coagulopathy[31-37] also commonly manifest. These disturbances frequently lead to multiorgan system failure, cardiovascular collapse (CVC), and asystole in up to 60% of patients if not appropriately managed.[23]

It is known from animal studies that this cardiovascular deterioration is associated with impaired oxygen use, a shift from aerobic to anaerobic metabolism, a depletion of glycogen and myocardial high-energy stores, and the accumulation of lactate.[23,25,29] This irregular metabolism has been associated with low levels of triiodothyronine (T_3), thyroxin (T_4), and to a lesser extent cortisol and insulin.[26-29] Therapeutic replacement with T_3 has been associated with complete reversal of anaerobic metabolism and subsequent stabilization of cardiac function when applied to human brain-dead subjects.[26,27] In addition, the use of T_3 has been associated with significant improvements in cardiovascular status, reductions in inotropic support, and decreases in donors lost from cardiac instability.[25,38-40] In a study of 19 brain-dead hemodynamically unstable organ donors at our center, we found a statistically significant decrease in vasopressor support after T_4 administration (11.1 ± 0.9 μg/kg/min before vs. 6.4 ± 1.4 μg/kg/min after T_4 administration, $P = .02$).[41] In addition, 10 of the 19 patients (53%) were completely weaned off vasopressors. In another study of 123 brain-dead–organ donors who underwent successful organ donation, T_4 administration was associated with significantly more organs procured per donor group (3.9 ± 1.7 vs. 3.2 ± 1.7, $P = .048$), when compared to donors managed without T_4.[41] The etiology of this functional "hypothyroid state" is poorly understood, but may be a result of lower than normal thyroid stimulating hormone levels caused by the irreversible damage to the hypothalamus and pituitary from ischemia. Another explanation is a decrease in the peripheral conversion of T_4 to its more potent analogue T_3, similar to the euthyroid sick syndrome.[42]

The complex hemodynamic, endocrine, and metabolic dysfunction associated with brain death is frequently associated with major complications in the potential donor. If inappropriately treated, these complications can progress to CVC with loss of valuable organs for transplantation. In a recent examination of 69 brain-dead–organ donors from our center, high rates of vasopressor requirement (97.1%), coagulopathy (55.1%), thrombocytopenia (53.6%), diabetes insipidus (46.4%), cardiac ischemia (30.4%), lactic acidosis (24.6%), renal failure (20.3%), and acute respiratory distress syndrome (13.0%) were identified.[43] Interestingly, with the implementation of an aggressive organ donation management protocol, including hormonal supplementation, these complications did not adversely affect the average number of organs retrieved from this donor pool.

Organ Donor Protocols and Studies

Optimization of the potential for organ salvage is a complex effort. From the time of injury to operative harvest of salvageable organs, significant organizational, clinical, ethical, and social challenges must be overcome. An institutional and individual appreciation for the importance of identifying potential organ donors must be disseminated throughout the acute-care environment. In the setting of brain death, a potentially complex physiologic response must be appropriately managed to prevent CVC and loss of salvageable organs. The education and support of a grieving family must also be effectively conducted to secure appropriate consent. Each of these critical components requires specialized education and enhanced clinical and social awareness. The use of protocolized approaches to identification and care of the potential organ donor has proven an effective strategy for overcoming these obstacles and improving organ donation rates.[44-50] A successful ADM protocol must provide both clinical management guidance and the social supports necessary to accomplish this task.

The clinical component of ADM consists of 3 aspects: (1) early identification of potential donors, (2) intensive care unit admission and management by a dedicated team, and (3) early and aggressive resuscitation with fluids, vasopressors, and hormone

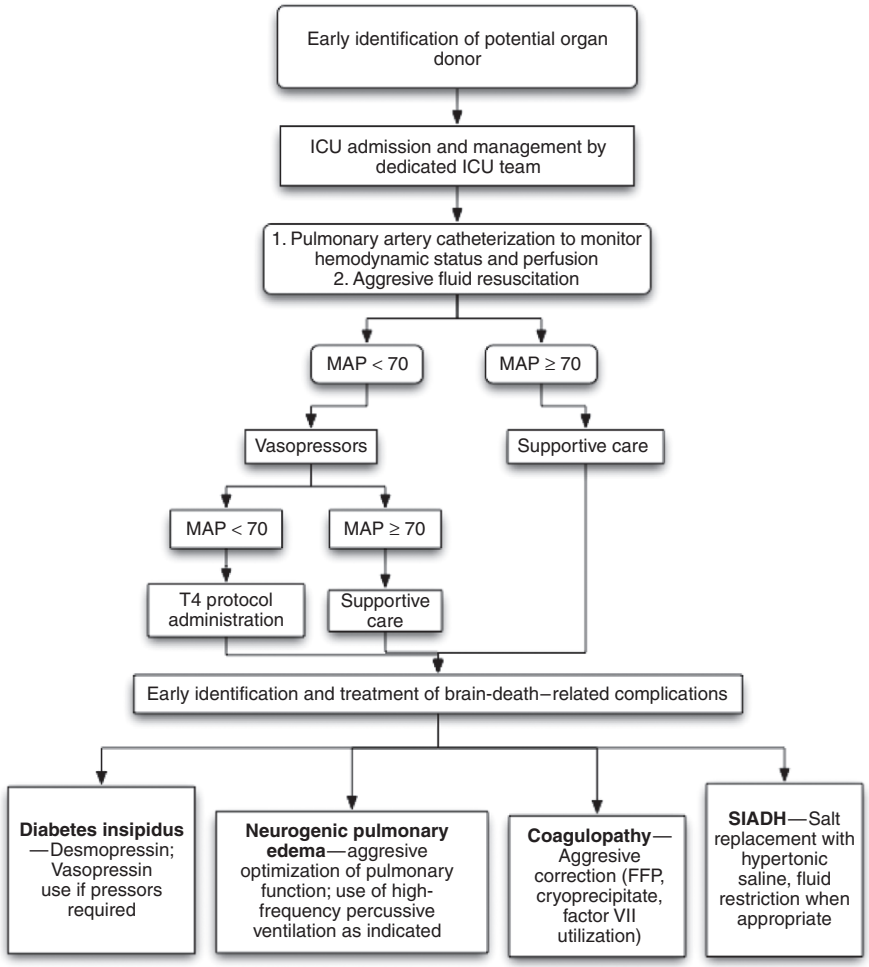

Figure 2. Protocol for aggressive donor management utilized at the Los Angeles County and University of Southern California Medical Center. FFP = fresh frozen plasma; MAP = mean arterial pressure; ICU = intensive care unit.

therapy before consent for donation (Figure 2). Hormone therapy is routinely used at our own facility to augment these efforts, and has been adopted by our regional organ procurement agency as a routine component of their organ recovery protocol following declaration of brain death in hemodynamically unstable donors. Vasopressors such as epinephrine and dopamine are used if the mean arterial pressure (MAP) remains less than 70 mm Hg despite adequate fluid resuscitation. Donors who required a combined vasopressor need of greater than 10 μg/kg/min (either epinephrine or dopamine alone, or in combination) are given a "T4 protocol" consisting of 1 ampule 50% dextrose, 2 g solumedrol, 20 units regular insulin, and 20 μg of thyroid hormone (T_4), followed by a continuous infusion of 10 μg/h. Our ADM protocol also stresses early identification and management of brain death related complications such as disseminated intravascular coagulation (DIC), diabetes insipidus (DI), neurogenic pulmonary edema (NPE), hypothermia, and cardiac arrythmias.[51]

A number of studies have demonstrated that implementation of clinical ADM protocols result in a reduced incidence of CVC in the donor and improved organ recovery and function in the recipient. Wheeldon et al[52] demonstrated that a policy of ADM including optimization of cardiovascular performance resulted in a 30% increase in donor hearts. Of note, 92% of organs that were initially thought unacceptable for transplantation were successfully transplanted with good results. Similarly, Straznicka et al[53] showed that ADM with invasive monitoring, steroids, vasopressors, fluid restriction, and diuretics resulted in successful transplantation of "unacceptable" lungs without compromise of 30-day or 1-year

graft survival. In a prospective pilot study involving 10 organ procurement organizations (OPOs) and 88 critical care units that evaluated the efficacy of a donor management "critical pathway," a 10.3% greater number of organs recovered per 100 donors was observed, when compared with standardly managed donors.[3,54] Jenkins et al[44] demonstrated a significant increase in the number of organs per donor and a decrease in medical failures with a rapid brain death determination protocol and aggressive resuscitation guided by invasive monitoring. Other facilities have demonstrated similar experiences.[55-57] With the emergence of more effective noninvasive monitoring modalities to guide fluid resuscitation and vasopressor use, newer technologies may also prove beneficial the resuscitative management of this unique population.

In a recent study from our center, adoption of a protocol of ADM was associated with an 82% increase in the number of actual donors, a 71% increase in the number of organs recovered, and an 87% decrease in the number of donors lost from hemodynamic instability.[48] The net result was a significant increase in the number of organs available for transplantation. In a study comparing the incidence of CVC in potential organ donors at centers with and without a policy of ADM, not surprisingly, the number of donors lost due to CVC was significantly less at centers with a policy of ADM.[48] Preventing, or even decreasing the number of donors lost from CVC increases the number of organs available for transplantation. Other proposals for interventions to optimize organ function prior to potential donation have included the use of high-frequency chest wall oscillation for pulmonary optimization[58,59] and inhaled nitric oxide to support cardiopulmonary function and improve solid organ optimization.[60]

In addition to the clinical management component, social aspects of organ donation must be carefully considered. Traditionally, the consent process has been the single largest impediment to donation. Siminoff et al[16] have demonstrated that the best and strongest predictor of donation decisions may be the family's initial response to the request for donation by the health care provider. This initial interaction is likely paramount to the process of consent, and requires special emphasis in the development of any protocol approach to donation.[61] Franz et al[62] demonstrated that only 53% of nondonor families felt they had not received an adequate explanation of brain death, and that next of kin who decided against donation had far less understanding of brain death than those who decided in favor of it. Senior physician or experienced health care provider involvement in family interactions may be particularly important. In one 3-year retrospective study, Vane et al.[63] noted that attending physician involvement with families of brain-dead pediatric trauma victims resulted in a donation success rate of 86%. This was compared to a success rate of 23% when an attending physician was not actively involved. An important component of these critical interactions is the need to avoid confusion regarding the role of the physician. Every effort should be made by the physician and other members of the health care team to establish themselves as allies of the grieving family and purveyors of information regarding organ donation, as opposed to a de facto agent of the health care system or OPO.

Education of all health care providers is important, as is the involvement of uniquely trained and experienced individuals. Transplant coordinators, in the form of a dedicated physician or other specially trained health care provider, have demonstrated their effectiveness in coordinating efforts to facilitate both consent and transition of care to aggressive organ preservation and harvest. An excellent example of the importance of the transplant coordinator has been demonstrated in Spain. Since the introduction of the Organizacion Nacional de Transplantes, Spain has led developed nations with respect to organ donation rates.[64] The success of the "Spanish Model" has largely been attributed to the use of transplant coordinators (usually physicians) located directly within hospitals. These coordinators are an established part of the hospital and are responsible for identifying donors, managing their hospital course, and consenting family members. Throughout the process, the coordinators spend a significant amount of time with family members, providing education and attending to the unique social and ethical concerns of each individualized situation. Attempts to duplicate this success have started on smaller scales, with placement of fully trained OPO staff within hospitals with large donor potential. Implementation of in-house coordinator (IHC) programs have led to significant improvements in conversion and consent rates in public trauma,[49,65,66] teaching,[67] and even community hospitals.[68] Increasing the IHC program to more trauma centers covered by the same OPO has demonstrated

similar results, even maintaining consent and conversion rates as high as 67%.[69] This early success was also replicated in several Level I trauma centers throughout the United States.[70] Most impressively, the use of IHCs has proven particularly effective in trauma centers with a primarily minority donor population.[65,69,70]

The increased donation resulting from an IHC program has been attributed to several factors: (1) a consistent donation process based on early and intensive family support; (2) more extended interaction and support with donor families; and (3) sustained relationships with key medical, nursing, and hospital leadership.[70] By spending significantly more time with families and ensuring that donation becomes a hospital priority, the IHC program differentiates itself from the conventional OPO referral method. Not surprisingly, total time spent with families was found to be significantly associated with favorable consent.[70] At our own center, we have observed a significant increase in the consent and conversion rate after implementation of an IHC program.[49] Following introduction of this intervention, which includes IHC interaction with donor families at very early intervals, we have demonstrated a sustained increase in both consent (52% vs. 35%, $P < .01$) and conversion (50% vs. 34%, $P < .01$) rates for donation among our population of brain-dead trauma donors, while also significantly decreasing the number of missed referrals.

The Future

There is evidence that the government-led initiatives launched to raise awareness regarding the importance of organ and tissue donation are starting to show some positive results. To date, the Organ Donation Breakthrough Collaborative has been extremely successful. The number of deceased donors have increased to 7593 in 2005, the second consecutive year that more than 7000 deceased donors were realized in a calendar year.[2,71] The Collaborative helped facilitate a partnership between OPOs, transplant centers, and donor hospitals, disseminating their most effective strategies for converting potential donors to actual donors resulting in a 10.8% increase in donors between 2004 and 2003, and a subsequent 9.5% increase in 2005 over 2004.[2,71] More than 33% of participating hospitals achieved the goal of a 75% conversion rate.[71] Despite these impressive results, there is still much work that needs to be done.

There is growing renewed interest in the use of DCD/non–heart beating donors as an avenue for expansion of the donor pool. Despite the considerable controversy regarding DCD donors, they remain the only source of donors that continue to demonstrate impressive growth. Organ procurement procedures of this type vary, depending on whether the DCD was "uncontrolled" or "controlled." Details of protocols vary, with a typical waiting period after asystole of several minutes to insure that cessation of cardiac activity is final. After pronouncement of death, the organs are then rapidly harvested to reduce the deleterious effects of a prolonged warm ischemia time.

As with brain-dead donors, non–heart beating donors require early identification, coordination by specialized providers such as an IHC, and aggressive protocols that facilitate the early mobilization of resources to minimize the detrimental effects of prolonged warm ischemia. Unlike the other forms of donation, the period following cessation of cardiac activity theoretically results in the potential for the adverse sequelae of anoxia, acidosis, loss of intracellular hemostasis, and activation of inflammatory pathways during the brief period from declaration to subsequent harvest in "controlled" DCD. Unresolved issues with regard to DCD include the appropriate identification of potential donors, the role of the intensivist or surrogate in this identification process, ambiguities which attend withdrawal of support to allow cardiac death and subsequent organ procurement, the impact of warm ischemia duration, preservation options, donor comorbidities, and the appropriate modification of recipient management. Nevertheless, a growing body of evidence suggests that despite warm ischemia times, outcomes for a variety of transplanted organs are promising.[72,12,13]

Standardized protocols for DCD have been proposed,[73] and are seeing increased use both in Europe and the United States.[74-76] It has been estimated that the expanded use of DCD donors might result in a 5.5% to 25% increase in the number of organs available for transplantation.[77-79] The Hospital Clinico San Carlos, Madrid, is only one of a growing number of institutions that have clearly demonstrated that the use of DCD is a viable and effective method of improving organ availability.[80]

Conclusion

Future efforts to increase the organ donor pool must be multifaceted. Improved education of health care providers on the early recognition and special needs of this population and implementation of clinical ADM protocols should continue to improve the yield of transplantable organs. The propagation of IHC programs will also aid in this effort. With early family interaction and support, the IHCs can further facilitate the identification and recruitment of suitable donors. Through coordinated efforts with the health care team, organ donation can become a priority in their respective facilities. Education of the community regarding the growing need for donation is also likely to be of great importance.

Aggressive donor protocols, including early aggressive clinical management of donors and the use of dedicated health care specialists to aid in the identification and management of potential organ donors, have demonstrated considerable promise. Implementation of these programs have decreased rates of medical failure by preventing CVC and the subsequent loss of organs, increasing consent and conversion rates, and increasing the overall number of potential organ donors. The net result is an increase in the number of organs available for transplantation. Expanded use of coordinated ADM protocols may help alleviate the public health crisis of the growing shortage of transplantable organs.

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