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Liver Transplantation

Procedures and Management

PREFACE

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Logistics of the Multiple Organ Donor Procurement

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INTRODUCTION

During the past 30 years solid organ transplantation (heart, lung, liver, kidney, pancreas and intestine) has become a successful and widely accepted form of treatment for a variety of conditions. However, the shortage of cadaveric organs is hindering the larger use of this therapeutic option. In spite of the progressive evolution of public and professional understanding and acceptance of organ donation during the past 30 years, only a little over 25% of all potential brain-dead organ donors will actually come to donation [1-3]. As of September 30, 1993, there were 32,532 transplant candidates on the United Network for Organ Sharing (UNOS) waiting list [4], representing an increase of 338% from December, 1986 (9,632). At the same time, the supply of organ donors underwent a marginal increase between 1986 and 1991 (from approximately 4,000 to 4,500), and has been stable in the past 2 years, with 4,534 in 1992 [5-7] (Fig. 4.1). It is also estimated that every day 7 potential organ recipients in the United States will die before a suitable organ is found [8]. Consequently, while the need has increased dramatically, we observe with mounting concern the persistent wastage of available organs, and the death of potential recipients. These are both mainly related to unwillingness to donate, or a lack of awareness regarding donation, as well as delays or failure by the medical staff to consider organ donation [3]. In addition, there are other forces at work that have significantly decreased organ availability for the sicker patients, such as a policy implemented by UNOS in 1991 that substantially changed previous allocation criteria [9].

As a result of this, there is now an even more limited number of organs available for the most severely ill patients, and some advocate their outright exclusion from transplant candidacy, in favor of the elective cases [10].

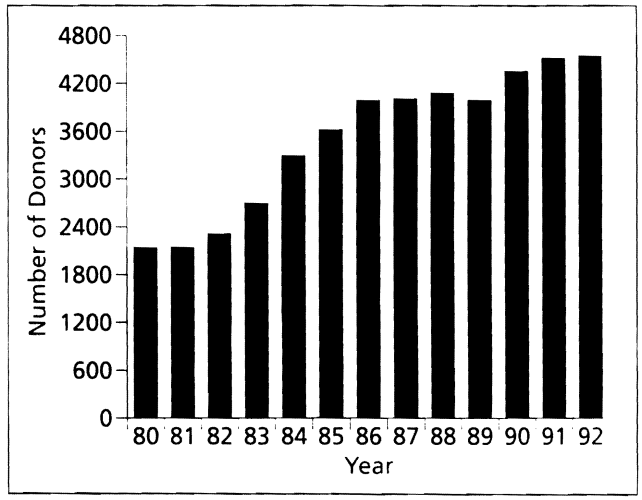

Fig. 4.1. *Organ donor supply in the United States, 1980 through 1992* (from [19]).

Many routes have been explored in an attempt to remedy this situation, including the development of artificial organs [11], utilization of living donors even for extra-renal organs [12, 13], xenotransplantation [14-17] (see also Chapter 22), and non-heartbeating donors [18].

However, a more immediate impact on organ shortage could be effected by improving our current mechanisms for organ recovery, and the management of potential donors.

In this chapter we will address the logistics of multiple organ procurement, as well as the clinical management of the multiple organ donor, as currently practiced in the United States and, particularly, at the Pittsburgh Transplantation Institute [19].

ORGAN RECOVERY

Standardized criteria for the determination of brain death were defined by the Ad Hoc Committee of the Harvard Medical School [20], and have been the subject of a more recent report [21]. Today the concept of brain death is widely accepted by the scientific community, and once a potential brain dead organ donor is identified, the multiple organ procurement process should be triggered. This starts by contacting the local Organ Procurement Organization (OPO) as soon as the irreversibility of brain injury has been established. In 1992, there were 68 OPOs and 266 transplant centers in the United States. These represent the largest organ procurement and transplant network in the world. Most intensive care units (ICU) have the telephone number of the local agency available. However, the phone number and location of the area's OPO can be obtained from the UNOS, who has a 24-hour phone line (800-243-6667). These OPOs, originally set up to organize the recovery of kidneys, coordinate the complex logistics of multiple organ recovery, and their distribution within a predetermined geographical area. They are also responsible for the payment of all charges incurred during the process of organ donation, ensuring that donor families are not billed for any of them. Once contacted, the local OPO will send a procurement coordinator to the referring hospital. These coordinators perform a number of administrative and technical functions, covering every aspect of the donation process. Upon receiving a referral they will perform an evaluation and discuss organ donation with the potential donor's family, making sure the relatives have a complete and satisfactory explanation of the diagnosis of brain death and a clear understanding of the organ procurement process.

Families should be informed separately, but as soon as possible, after the irreversibility of the lethal brain damage has been established, and given a clear explanation of the prognosis. This will give them time to accept the patient's death, and allow them to deal with their grief. It is extremely important to respect this phase, as it has been demonstrated that consent for donation increases from 18% to 60% if the family is allowed to deal with the concept of brain death first, and the issue of organ donation is brought up at a later time [3]. Religious beliefs about human life, the dead body, and life after death are extremely important considerations for those involved in organ donation and transplantation. No major religion specifically prohibits organ donation, although in some situations there may be restrictions. Table 4.1 summarizes some of the major religious and cultural beliefs associated with organ donation and transplantation [22]. Families may feel the need to discuss the matter with a church representative before making a decision.

Table 4.1. *Major religious and cultural beliefs associated with organ donation and transplantation* (from [19]).

Group	Donation	Transplantation
Amish	Reluctant if transplant outcome uncertain	Acceptable for the well-being of the candidate
Baha'i	Acceptable	Acceptable
Baptist	Individual decision	Acceptable
Buddhist Church of America	Individual decision	Buddha's teachings on the middle path (i.e. the avoidance of extremes) could be applicable to this
Christian Sciences	Individual decision	Individual decision
Church of Jesus Christ of Latter Day Saints	Individual decision	Individual decision
Episcopal Church	Encouraged	Encouraged
Evangelical Covenant Church	Encouraged	Encouraged
Greek Orthodox Church	Acceptable (although not for research)	Acceptable for the well-being of the candidate
Gypsies	Against	Against
Hinduism	Individual decision	Individual decision
Islam	Acceptable (organs of Moslem donors must be trasplanted immediately, and not stored in organ banks)	Acceptable
Jehovah's Witness	Individual decision (not encouraged)	May be considered acceptable (organs should be completely drained of blood before transplantation)
Judaism	Encouraged	Encouraged
Protestant Denominations	Individual decision	Acceptable
Religious Society of Friends (Quakers)	Individual decision	Individual decision
Roman Catholic Church	Encouraged	Acceptable
Unitarian Universalist	Acceptable	Acceptable
United Methodist Church	Encouraged	Acceptable

Donor Information **Donor ID#** **UNOS ID#**

Name _____ Admitting Date: _____ Referral Date: _____

Age: _____ Sex: _____ Race: _____ Recovery Date: _____ Clamp Time: _____ AM PM

Date of Birth: _____ Hospital: _____

Next of Kin: _____ City/State: _____

Relationship: _____ Referred By: _____

Address: _____ Phone #: _____

_____ Program: _____

_____ Program 24 hr #: _____

Next of Kin Phone: _____ Attending: _____

Consulting: _____

Medical Records No.: _____

Pronouncement Date: _____ Time: _____

Consent For: _____

_____

Cause of Death: _____

Past Medical History: (Complete history please)

Heart Disease: (Y/N) _____

Liver Disease: (Y/N) _____

Renal Disease: (Y/N) _____

Diabetes: (Y/N) _____

Neurological: (Y/N) _____

Cancer: (Y/N) _____

Lung Disease: (Y/N) _____

Arthritis or Joint Disease: (Y/N) _____

Recent Flu-like Symptoms: (Y/N) _____

Unexplained Weight Loss: (Y/N) _____

Toxic Exposure: (Y/N) _____

Drug Use: Prescribed or Other: (Y/N) _____

Alcohol Abuse: (Y/N) _____

Smoker: (Y/N) _____

Blood Transfusion History: (x 2 yrs.) (Y/N) _____

Previous Surgery: (Y/N) _____

Immunization or Vaccinated: (x 6 mo.) (Y/N) _____

Travel outside U.S.A. since 1977: (Y/N) _____

Homosexual or Bisexual: (Y/N) _____

Received pit-hGh: (Y/N) _____

Recent Infections: (Y/N) (if yes give treatment) _____

_____

G.I. Disorders: (Y/N) _____

Hematologic Disorders: (Y/N) _____

Under Physician's Care: (Y/N) _____

Physician, Phone #, Address: _____

Donor Information **Donor ID#**

ABO: _____ HLA: _____ DR: _____ LE Type: _____ WT: _____ HT: _____

Chest Cir: _____ Girth: _____ RC/BRR: _____ LC/BLR: _____

Hospital History (Include E.R., V/S, Arrests, O.R. Procedures, Injuries, Infection, ect.)

EKG, Echo & Cardiac Consult:

Chemistries					Urinalysis				ABG'S & Lytes			
Date					Date				Date			
BUN					Color				pH			
Creat.					Appear.				PO2			
T. Bil.					pH				PCO2			
D. Bil.					Sp. Grav.				O2 Sat.			
SGOT					Glucose				FIO2			
SGPT					Protein				PEEP			
LDH					Blood				VT			
GGT					RBC				Rate			
Amylase					WBC				Na +			
CPK					Epith.				K +			
Glucose					Casts				Cl -			
Hgb/Hct.					Bact.				Ca ++			
PT												
PTT												
Plat.												
WBC												

Blood Pressure (Note B/P< 90.Time)	Urine Output (Note Anuria/Oliguria)	Med. During ADM
		Blood & Blood Products

Serology

Date	Time	Test	Pre	Post Result	Local/Import	Reported By	Reported To
		RPR/VDRL					
		HBs Ag					
		HAA					
		HIV					
		HTLV-I					
		CMV					
		HCV					

Cultures (Blood, Urine, Sputum) Date, Results

Fig. 4.2. *Donor data sheet used by the Western Pennsylvania Organ Procurement Organization, CORE* (Center for Organ Recovery and Education). (Courtesy of Mr. Brian Broznick) (from [19]).

If the family decides to donate, a "consent for donation" form is supplied by the hospital or by the procurement coordinator, and is completed and signed by the next-of-kin. In addition, the coordinator sees to it that all medicolegal requirements are met, from adequate documentation of brain death in the chart to securing permission from the coroner when necessary. Medical staff privileges for the recovery teams are also arranged. Hospitals differ in their policies for granting such privileges. Some hospitals do not consider the organ procurement as a surgical procedure, because a determination of brain death has already been made. In this circumstance, temporary privileges are not required for outside surgeons.

At the same time the procurement coordinator assumes control of three main activities:

- donor evaluation;
- donor management and coordination of donor and recipient matching;
- donor operation, organ preservation, and shipment to the recipient's hospitals.

The role of the coordinator in each of these is critical, because the most important issue in organ procurement, once the decision to proceed has been made, is to have someone who "directs traffic", maintaining clear lines of communication between the members of the different teams involved. A lack of communication at this point can disrupt donor care and compromise organ stability. Therefore, the needs and protocols of the individual teams should be discussed in detail before any donor surgery is begun. In addition, if at all possible, the logistic arrangements between teams should be expedited so that no time constraints are placed on the host team. On the other hand, the host team must be tolerant, because different organs often have to be flown to distant parts of the country, and some recipient surgery may be quite complex and time consuming. To facilitate matters the host team should make available basic information on the donor, to expedite the evaluation by the visiting teams (Fig. 4.2).

MULTIPLE ORGAN DONOR EVALUATION

There are very few absolute contraindications to organ donation, and they can be grouped into three broad categories:

- severe trauma;
- malignancy outside of the Central Nervous System (CNS);
- active infections.

The first category, that of trauma, refers only to injury to the organ itself, and will not preclude donation of those organs that are not affected. Malignancy, other than primary CNS tumors, will also disqualify the prospective donor. An important group of exclusionary criteria is the presence of active infections. Systemic sepsis, active tuberculosis, viral encephalitis and Guillain-Barr syndrome are contraindications to organ donation, as well as active hepatitis, or the presence of the hepatitis B surface antigen. Past infection with hepatitis B virus, as evidenced by the presence of antibodies, does not preclude donation. Whether organs should be used if the donor has hepatitis C antibodies has been the subject of controversy in the last few years. There is evidence in the literature for HCV transmission after transplantation [23]. However, the donor shortage is so serious at this time that HCV positive donors need to be considered, at least for life-saving organs like liver, heart and lungs [24]. Policies concerning other organs, like kidney and pancreas, are currently being debated [23, 25].

The human immunodeficiency virus (HIV) has had a great impact on the field of transplantation, and donors who test positive for HIV antibody are rejected. Prospective donors should also have a Venereal Disease Research Laboratory test (VDRL), as well as cytomegalovirus (CMV) titers, determined as soon as possible. The significance of a positive VDRL is difficult to ascertain, but it is our practice to treat recipients of VDRL-positive donors with a course of benzathine penicillin. The CMV status of the donor has prognostic significance regarding the incidence, and severity, of subsequent CMV infections. Recipients of organs harvested from seronegative donors have a lesser chance of developing a CMV infection, regardless of their own serologic status [26-28]. Epstein-Barr (EBV) and Varicella Zoster virus (VZV) are not part of the usual viral screening. The only situation where these viruses become relevant is when the donor has active disease related to them (infectious mononucleosis or systemic VZV infection). If this is the case, organ donation should not be considered.

Donors with infections under control, or those affecting organs not specifically considered for donation (i.e. an abdominal organ donor suffering from pneumonia) may still be suitable. Children who die due to bacterial meningitis related to *Hemophilus influenzae* or *Neisseria meningitidis* can still be considered for donation, if the organism and its sensitivity are known beforehand.

Prolonged organ ischemia related to severe hypotension or cardiac arrest might represent a contraindication to donation. However, it is the policy of the Pittsburgh Transplantation Institute to critically evaluate all donors, including those with cardiac arrest and prolonged CPR. In fact, many of these donors have been found acceptable by post-CPR physiological and biochemical criteria, and their organs have been successfully transplanted [18, 29, 30].

Other patients that may not be acceptable as donors are those with a long-standing history of diabetes mellitus, hypertension, cardiac or peripheral vascular disease. But, again, the donor and organ viability assessments should be carried out on a case by case basis, and a patient not acceptable as a heart or lung donor might still be an excellent abdominal organ donor. Sometimes the suitability of individual

Table 4.2. *Age guidelines for organ and tissue donation used at the Pittsburgh Transplantation Institute* (from [19]).

Organ/Tissue	Age (year)
Heart	≤60(1)
Heart-lungs	≤60(1)
Lungs	≤60(1)
Kidney	1 month-75(1)
Liver	≤75(1)
Pancreas	≤65(1)
Intestine(2)	
Bone	15-65
Bone marrow	≤75
Cornea	1-65
Skin	15-65
Heart valves	≤55

(1) Donors beyond these age limits could be accepted on the bases of the individual organ function.

(2) No age limits have been set for intestinal donors. Intestines should be available from most organ donors and are always evaluated on an individual bases.

organs can be assessed only after direct examination by the donor surgeon, at the time of procurement.

The donor age deserves special mention. The chronological age is less important than the physiologic age, when assessing for specific organ donation. For some organs age may not be an important limiting factor [31]. The liver is, in a certain way, protected from aging, and we have successfully used livers from donors as old as 75 years. Popper, in 1985, dedicated an extensive review to the aging of the liver [32]. According to his study, the organ's great functional reserve, its regenerative capacity, and its large blood supply are the key factors in delaying aging in the liver, as compared to other organs. Table 4.2 shows the age guidelines for individual organs used in our institution. In general it is rare to find a suitable heart or lung allograft from donors over the age of 60 due to the increased incidence of coronary artery disease and chronic pulmonary disease.

In summary, given the enormous need for organs and the very few criteria that absolutely disqualify a potential donor, the local OPO should be contacted in virtually every case. Figure 4.2 shows the data collection form used by the Center for Organ Recovery and Education (CORE: the Western Pennsylvania, Southern New York and West Virginia organ procurement agency). These data should be promptly faxed to those involved in the evaluation process.

INDIVIDUAL ORGAN ASSESSMENT: ABDOMINAL ORGANS

The criteria used to determine the suitability of kidneys are very flexible. As shown in Table 4.2, a kidney donor can be between 1 month and 75 years of age. Serum creatinine and blood urea nitrogen (BUN) are used as markers of donor renal function, and should be normal. Obviously, donors with chronic renal disease are not considered for kidney donation. However, patients with transient creatinine and BUN elevations, related to dehydration and/or hypotension, are not excluded from kidney donation if the BUN and creatinine fall after appropriate volume correction.

Attempts at predicting liver allograft function following transplantation, based upon donor information, have met with little success. The diverse literature [24, 33-44] devoted to the topic is testimony to our lack of a clear understanding, one that can translate into well-informed decision making during donor evaluation. As a rule, the donor should have normal or near-normal serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), bilirubin, and prothrombin time, but we have successfully used livers from donors with AST and ALT that were 15 times over the upper limit of normal. The important parameter is not an isolated AST and/or ALT value, but the trend established since the ICU admission [45]. The bilirubin can be elevated due to massive blood transfusions used during the resuscitation of a shocked patient. A history of hepatitis or alcoholism is certainly a warning sign, but does not preclude the use of the liver. In general, in the case of a marginal liver donor, the intraoperative assessment by the donor surgeon is the best single piece of information.

There is only one absolute exclusion criterion in the evaluation of a pancreas donor, and that is a history of diabetes mellitus. Amylase elevations have been seen in as many as 39% of pancreas donors, without any evidence of pancreatitis, and thus isolated hyperamylasemia does not contraindicate the use of the pancreas [46]. The serum glucose may be falsely elevated in donors receiving steroid therapy, or as a result of decreased circulating insulin [47].

Intestinal transplantation is emerging as a valuable modality for the treatment of patients with intestinal failure. Early in 1993 UNOS formed a subcommittee responsible for systematizing the listing of recipients, help identify suitable donors, and establish guidelines for the equitable allocation of intestinal grafts, both at the local and national levels. Because of the time constraints, it is impossible to perform a functional assessment of the donor bowel. Relatively young age, hemodynamic stability, and donor-recipient size match are the critical parameters used in evaluating an intestinal donor [48]. At our institution, preference was initially given to infant and juvenile donors with stable hemodynamics. However, the age range has been gradually expanded, provided the donor is stable and receiving minimal vasopressor support (≤10 μg/kg/min of dopamine). Size matching is always given special consideration. The majority of intestinal transplant recipients have undergone extensive intestinal resections, leading to a significant reduction in the size of the abdominal cavity. Therefore, donors are chosen that are 15% to 40% smaller in body weight than the selected recipients [48]. The details of the management of the intestinal donor are discussed extensively in Chapter 24.

INDIVIDUAL ORGAN ASSESSMENT: THORACIC ORGANS

Besides a negative history of cardiac disease and a normal chest X-ray, the donor should have a normal heart physical exam and 12-lead electrocardiogram. However, a number of electrocardiographic changes might be detected in brain dead patients, which do not preclude thoracic organ donation [49, 50]. A brain dead patient able to maintain a systolic blood pressure greater than 90 mmHg with a dopamine requirement less than 10 μg/kg/min is considered a suitable candidate for heart donation [51, 52]. Cardiac isoenzymes are recommended in case of chest trauma, to rule out myocardial contusion, and when the potential donor has suffered a cardiac arrest or prolonged hypotension. The incidence of coronary artery disease clearly increases in male donors over the age of 35, especially in the face of risk factors such as hypercholesterolemia, family history and a history of smoking. Coronary angiography may be helpful in the evaluation of high risk and older donors, but it is not routinely required, and most hospitals will find the logistics of performing it prohibitive. Therefore, a decision will have to be made based on a cardiologic consultation, evaluating the history, electrocardiogram, and echocardiogram. As is the case for the liver, and due to the severe shortage, it is prudent even in high risk donors to have the heart examined on the table following sternotomy. Visualizing and palpating the coronary arteries will give a significant amount of information with respect to the incidence of coronary artery disease. If plaques are felt along the left main coronary artery or left anterior descending artery, the heart, in most cases, will not be suitable for transplantation. In extreme cases of a very sick recipient, however, the transplant team may make a decision to take this heart, and isolated cases of coronary artery bypass being performed at the time of transplantation have been reported. Indeed, reports exist stating that in cases of isolated mild coronary artery disease, the donor allograft functions well with no increase in early mortality.

Transesophageal echocardiography has recently been demonstrated to be an important adjuvant in the evaluation of a potential cardiac donor. Severe cardiac hypertrophy, valvular defects and global myocardial dysfunction or segmental wall abnormalities have been diagnosed in what appeared to be otherwise reasonable cardiac donors. At this time, limited information is available about the use of such hearts, and in most cases it will be prudent to avoid the use of a heart with demonstrated wall motion abnormalities [53]. In general, minor changes in the electrocardiogram or echocardiogram, localized infection [54], transitory hypotension, brief cardiac arrest and thoracic trauma, do not contraindicate heart donation. The importance of donor-recipient weight mismatch over 20% is critical only in the face of high pulmonary vascular resistance. In carefully selected donors, survival following transplantation with a donor between 40-55 years of age is no different than that observed in the case of younger donors [55]. As the limits for donor selection are extended, evidence becomes more clear that it is safe to extend donor age up to 55-60, and ischemic time farther than four to five hours [56-58].

All of the selection criteria mentioned in the case of a heart donor also apply to heart-lung or isolated single or double lung donors. In addition, a donor is not acceptable for lung or heart-lung donation when there is a history of heavy smoking, chronic lung disease, or pulmonary aspiration. The height, weight and chest circumference of the heart-lung donor should closely match those of the recipient. A number of physiological parameters can be used when assessing a lung donor, including the PaO_2/FIO_2 ratio ($\geq$250 torr) and peak airway pressure ($<$30 cm H_2O with 15 mL/kg of tidal volume and 5 cm H_2O of PEEP) [59-61].

Aspiration pneumonia is frequent in the brain dead patient, and thus the character of the sputum is a critical piece of information. The role of bronchoscopy is still being debated, considered mandatory by some authors [62], while others feel it is indicated only when there is a question of foreign-body aspiration, or to obtain sputum for Gram stain and culture [47].

Bronchoscopy will provide, however, important culture information to guide appropriate antibiotic therapy following transplantation. In cases where frank purulence is noted on bronchoscopy, the lungs will not be suitable. However, it is conceivable that one lung may be salvaged for transplantation from a set where one appears to be more infected than the other.

MULTIPLE ORGAN DONOR MANAGEMENT

Once the coordinator finishes the donor evaluation there are still many hours of intense work before completing the process. After obtaining the appropriate consent, therapeutic efforts should be geared to protect the donated organs, until the actual retrieval can be carried out.

While in the '70s and early '80s donor management mainly, if not exclusively, addressed kidney function, nowadays the patient must always be approached as a multiorgan donor, and this can present a real challenge to the physician managing the case. He or she should keep the patient hemodynamically stable, with optimal organ perfusion and oxygenation. This is not easy due to the loss of many body reflexes, and the dramatic changes in the hormonal milieu [63]. Several studies have shown a significant reduction of cortisol [64], insulin [64], and thyroid hormones [49, 64-68]. Also, 50-70% of brain-dead patients suffer from diabetes insipidus [69, 70]. A number of protocols that call for the use of hormones like triiodothyronine, cortisol, or insulin during donor management [47, 50, 65, 67, 68, 71] have given conflicting results.

HEMODYNAMIC MANAGEMENT

Arterial line, central venous line, and a bladder catheter are mandatory in the management of a brain dead donor, while a pulmonary artery catheter is optional. The rostral to caudal brain function loss following brainstem herniation, with the destruction of pontine and medullary vasomotor centers, causes the development of significant hemodynamic instability. Before herniation, Cushing's reflex can induce bradyarrhythmias and hypertension. If bradycardia needs to be treated, isoproterenol or epinephrine are the drugs of choice, since atropine is ineffective because it acts on the brain's vagal output. Hypertension, related to increased sympathetic activity, can result in cardiac microinfarcts and neurogenic pulmonary edema. Therefore, it must always be aggressively treated, to prevent damage to the thoracic organs. Beta-blockers have been shown to suppress the hypertension related to brain herniation in baboons, and esmolol is possibly the drug of choice in this clinical setting because of its short half-life. Later, when brainstem herniation results in the complete destruction of the pontine and medullary vasomotor centers, hypotension becomes the main hemodynamic problem, and 10-25% of brain dead donors sustain a cardiac arrest [47, 69, 72].

The main goal of this phase of their management is to maintain a satisfactory organ perfusion, and every attempt should be made to maintain a systolic blood pressure greater than 80 mmHg, which is considered critical to preserve good kidney and liver function [73-76]. It has been reported that a mean arterial pressure of 40 mmHg can still result in adequate cardiac preservation in the pig [77], and this information may be useful when trying to decide whether to use the heart of a hypotensive donor. However, the liver and the kidney do not tolerate such low perfusion pressures if they are sustained. The large majority of these patients are cared for using head trauma protocols and, consequently, they are dehydrated by the time they have progressed to brain death. Usually, many liters of crystalloid are needed to achieve adequate filling pressures and allow weaning of the vasopressors, if they are being used. Dopamine is the first choice among vasopressor drugs, because of its ability to maintain good renal and splanchnic blood flow when used at low doses. Dopamine doses greater than 10 μg/kg/min should not be necessary if good filling pressures have been achieved with fluid replacement, and the use of drugs such as phenylephrine hydrochloride or norepinephrine bitartrate should be avoided, in order to protect organ perfusion [78]. These drugs also increase myocardial oxygen consumption, and a correlation has been found between the use of catecholamines, including dopamine, and poorer renal allograft survival [79]. Dobutamine is a good choice in case an inotrope is needed. Other agents, such as isoproterenol, increase myocardial oxygen consumption more significantly than dobutamine.

We mentioned above that, in many cases, several liters of fluid are necessary to obtain good filling pressures and, consequently, assure adequate organ perfusion with minimal use of vasopressors. In general, we favor the use of crystalloids over that of colloids because of the cost, and the fact that there are no therapeutic advantages of one over the other. We use Ringer's lactate because the brain dead donor often presents with hypernatremia [47]. Blood products such as fresh frozen plasma, platelets, and cryoprecipitate may be used if a serious bleeding diathesis is present. Many brain dead donors have a coagulopathy related to release of plasminogen activator by the injured cerebral tissue into the systemic circulation. In these cases, ε-aminocaproic acid should be avoided because it can induce microvascular thromboses in the donor organs. As in other areas of medicine, there is no clear evidence regarding the ideal hematocrit in the multiorgan donor, although it has been suggested that it be kept between 25 and 35 [78, 80].

The fact that 50-70% of brain dead donors suffer from diabetes insipidus makes the maintenance of the intravascular volume a real challenge [78]. Diabetes insipidus, in this setting, is the result of damage to the hypothalamic-pituitary axis, with its accompanying decrease of antidiuretic hormone levels. The urine volume can easily reach 1.5-2 L/hr, and this should be completely replaced with a low-sodium solution. Desmopressin (a synthetic analogue of arginine vasopressin) is the drug of choice to treat diabetes insipidus in the brain dead donor, and it is usually administered in IV boluses of 0.5-2 μg every 8-12 hours. The dose is titrated in order to obtain a urinary volume of 100-250 mL/hr. An output below 100 mL/hr is not desirable because it has been shown to adversely affect kidney function after the transplant [73]. Desmopressin is preferred to other drugs due to its minor vasoconstrictive effects, when compared to other vasopressin preparations, which appears to be of some importance in the final outcome of the transplanted kidneys and livers [79, 81].

RESPIRATORY MANAGEMENT

Mechanical ventilatory support is obviously required for all brain dead donors. The management of the ventilator is the same as for other critically ill patients, and its principles will not be repeated here. Once again, treatment is aimed at ensuring that the prospective donor organs are maintained in the best possible state, and specific goals of ventilatory care are to maintain a PaO_2 between 70 and 100 mmHg, an oxygen saturation of arterial hemoglobin (SaO_2) greater than 95%, and a $PaCO_2$ within the range of 35 to 45 mmHg, to avoid pulmonary complications. High fractions of inspired oxygen should be avoided in lung and heart-lung donors to prevent oxygen toxicity and atelectasis. If an FIO_2 greater than 0.60 is necessary to obtain a PaO_2 of at least 100 mmHg the lungs should be re-evaluated, to exclude any pathology that might have been missed before. If any such pathology is now identified, and the lungs are no

longer acceptable for donation, higher levels of oxygen are preferable to a high PEEP, since this can have deleterious effects on the cardiac output and splanchnic perfusion. The decrease in brain metabolism, typical of the brain dead patient, results in a reduction of CO_2 production, and thus minute ventilation should be adjusted accordingly.

COORDINATION OF DONOR AND RECIPIENT MATCHING

During this phase the procurement coordinator asks local transplant programs about their needs for organs. Under the current U.S. system local programs have first priority, and only when organs are not used locally are inquiries made at the regional and national levels. An exception to this rule is when a prospective kidney recipient, who resides in another region, is found to have a so-called "six antigen match". These kidneys have to be sent away, with the receiving transplant center "paying back" at a later date. Organ allocation is a very complicated and controversial subject, and what system should be used is presently being debated [10]. As of this writing, amendments to the National Organ Transplant Act are being discussed in the Congress, and it is not clear what changes will be implemented. A point system for renal transplantation was developed in Pittsburgh in 1985, that gave credit points to renal transplant candidates. Credits were acquired for time waiting, quality of antigen match, degree of immunologic sensitization, medical urgency, and logistical considerations of getting the donor organ and the recipient together within the time limitations of safe organ preservation. The system went in effect in western Pennsylvania on January 1, 1986 [9]. Although initially adopted by UNOS on November 1, 1987, the point system never went into effect at the national level due to difficulties encountered in reconciling it to a myriad of local interests. A similar point system was developed for liver transplantation, having been in place at Pittsburgh since January, 1987. Our experience with organ allocation based upon point systems, where organs go to those who have been waiting longer or are sicker, has been most favorable. Graft and patient survivals have not suffered by giving organs to sicker or older patients.

At the same time, our observations provide some assurance that the concepts of equitable access and efficient use of a scarce societal resource are not mutually exclusive.

HLA matching is not a critical issue for extrarenal organs. However, we routinely perform HLA typing on all extra-renal organs, a practice that is at variance with what most other institutions do in this country. Although it is expensive, we consider it important because it allows us to determine the presence of microchimerism in the recipient, information that may be extremely useful in the future, when deciding how to manage the immunosuppression [82].

Whenever the recipients for all the abdominal and thoracic organs are identified, an operating room time in the donor hospital is arranged. The procurement coordinator contacts the recipient institutions to arrange for the simultaneous arrival of all the harvesting teams. Kidneys have been procured by local teams for many years, and shipped if not used locally. Today, a similar practice is being adopted in the United States for other organs, particularly livers [83].

The intestinal donor should receive intravenous ampicillin and cefotaxime, at the appropriate doses, when first evaluated, and every 6 hours after that. The last dose is given in the operating room at the time of harvesting. Also, poly-ethyleneglycol-electrolyte solution (*Golytely*®) is administered through the naso-gastric tube to flush the intestine. The total amount ranges from 250-2,000 mL, depending on the recipient's body size (250 mL in the infant - 2,000 mL in the adult) and the administration rate is 10-30 mL/min. After the intestinal flushing, an antibiotic mixture that includes polymixin E (100 mg), tobramycin (80 mg), and amphotericin B (500 mg) is given through the naso-gastric tube every 4 hours, until procurement. In pediatric donors the doses are halved, while infants receive only one fourth of the dose. Newborns receive no intestinal preparation. If pre-harvest flushing cannot be performed this is done after procurement, using cold Ringer's lactate. Also, polymixin B or kanamycin can be substituted for polymixin E, if the latter is not available at the donor hospital.

MULTIPLE ORGAN DONOR OPERATION

ANESTHESIA

The donor operation can be time consuming and the role of the anesthesiologist is very important, especially if we compare the multiple organ procurement that is now usually performed with those carried out in the past, when the kidneys were often the only organs removed. A complete review of the anesthetic aspects of organ donation was recently published [84], and we will restrict ourselves to its salient points.

The goal of medical management during organ procurement is to avoid ischemic organ damage by optimizing organ perfusion. Therefore, care of the donor is a continuation of the intensive care that was provided before brain death. The most important issue is the clear communication between the members of the procurement team because the surgical procedure and procurement protocol may differ depending on the procurement team and the specific organ. For the pre-operative evaluation of the donor the anesthesiologist should review the medical and surgical histories, including the cause of brain death, condition and supportive measures of vital organs,

drug allergies, and medications. Cardiopulmonary function is assessed by means of the hemodynamic profile, requirement of inotropic support, efficiency of gas exchange, degree of ventilatory support, chest X-ray, electrocardiogram, arterial blood gas tensions and acid-base state. Renal function is evaluated by urine output, blood urea nitrogen, and serum levels of creatinine and electrolytes. Hepatic function is evaluated by AST, ALT, and bilirubin, and pancreatic function by blood glucose level and serum amylase. Hemoglobin concentration and the blood type of the donor are identified to prepare blood products. In addition, the validity of brain death certification, consent from family members, and permission from the coroner are verified. The transition from the ICU to the operating room (OR) is a crucial period and the donor is continuously monitored, ventilated, and treated.

Intraoperative care of the donor is essentially similar to that of other critically ill patients undergoing major surgery, although management of pathophysiologic changes unique to the donor should be clearly understood. In general, equipment and medications routinely available for general anesthesia are satisfactory for the management of donors. However, a volume ventilator may be needed for donors requiring high levels of PEEP or airway pressure. The operating room should be kept warm, and a warming blanket and blood warmer are necessary to prevent hypothermia. A large volume of crystalloids, some colloid solutions (e.g., 5% albumin, plasma protein fraction, or hetastarch), and 5 units of packed red blood cells should be prepared. The electrocardiogram is monitored, preferably using lead V5, to detect arrhythmias or myocardial ischemia, particularly in heart donors. Blood pressure is monitored by an indwelling catheter in the radial artery or brachial artery. The femoral artery cannulation is avoided because the aorta will be cross-clamped. Central venous pressure monitoring is essential [85], and a pulmonary arterial catheter is useful in unstable donors. Two-dimensional transesophageal echocardiography may be used to assess preload and cardiac contractility in unstable heart donors. Urine output and body temperature are monitored, and all or some of the following laboratory tests may be needed: hemoglobin and hematocrit, arterial blood gas tensions and acid-base state, serum electrolytes, ionized calcium, lactate, and blood glucose level.

General anesthetics are required to blunt the sympathetic response that occurs during surgery [86]. This so-called "mass reflex" is caused by neurogenic vasoconstriction and stimulation of the adrenal medulla by the spinal reflex arc, and manifests as tachycardia hypertension, perspiration, and involuntary movements. These movements, also known as "Lazarus sign" (that includes arm and hand movements towards the body), can be very disturbing to those involved in the organ recovery, and muscle relaxants should be administered ahead of time.

Isoflurane is the agent of choice because the degree of myocardial depression is less than with other inhalation agents. Halothane is avoided in liver donors because hepatotoxicity may be a concern in the presence of potential hepatic ischemia. Enflurane is avoided in kidney donors because it increases the blood level of inorganic fluoride. Short-acting narcotics such as Pentanyl (5-10 μg/kg) may be used in hemodynamically unstable donors. In addition, muscle relaxants pancuronium bromide (0.05 to 0.1 mg/kg) or vecuronium bromide (0.05 to 0.1 mg/kg) are required to provide satisfactory abdominal muscle relaxation and to abolish involuntary movements. Other pharmacological interventions include systemic heparinization (300-500 U/kg) before cannulation of the aorta, mannitol (0.25 to 0.5 g/kg) and furosemide (40 mg) to induce diuresis before division of the renal pedicle, and prevent ischemia-induced acute tubular necrosis [87-89]. Alpha-adrenergic receptor blockers, such as phenoxybenzamine hydrochloride, may be used to promote renal vasodilation and prevent vasospasm [90]. However, these blockers are not recommended in multiple-organ procurement because their effects on other organs are unknown. Prophylactic administration of antibiotics such as broad-spectrum cephalosporins is recommended by some centers [91-92], although its efficacy is controversial [45, 93].

In hypothermic donors, a mild respiratory alkalosis (pH 7.4 to 7.5) may be preferred to improve tissue perfusion [94, 95]. This goal is frequently achieved by ventilating with a tidal volume of 10 to 15 mL/kg, a respiratory rate of fewer than 20 breaths per minute, FIO_2 of 30% to 40%, and a low level of PEEP (<5 cm H_2O). However, when pulmonary complications interfere with gas exchange the tidal volume is increased up to 20 mL/kg, the respiratory rate up to 20 breaths per minute, and the PEEP up to 10 cm H_2O.

The goal of circulatory care is to preserve perfusion of all organs that are to be procured by maintaining systolic blood pressure between 100 and 120 mmHg, with a CVP less than 10 cm H_2O and minimal vasopressor support [49, 74, 96]. Hypotension (systolic blood pressure <80 mmHg or mean arterial pressure <40 mmHg) is associated with an increased incidence of acute tubular necrosis and nonfunction of the donor kidneys [75, 77], as well as poor function of the liver [76]. However, maintaining a satisfactory blood pressure is difficult to achieve at times because of altered circulatory physiology in the brain dead donors. Preload frequently is decreased because of blood loss, vasomotor paralysis, diuretic therapy, or diabetes insipidus. Tachycardia, bradycardia, and arrhythmias caused by massive sympathetic discharge are not unusual, and myocardial contractility is frequently impaired by myocytolysis, coronary spasm, and reduction of myocardial energy storage [97]. Afterload may be increased by excessive sympathetic tone or decreased by vasomotor paralysis.

Intravascular volume is adjusted with the guidance of the CVP (<10 cm H_2O). Fluid deficit is corrected with the infusion of a balanced electrolyte solution (e.g. lactated Ringer's) or a colloid solution

Recovery Data **Donor ID#**

Surgeons Renal: _____ Assisting: _____
Hepatic: _____
Cardiac: _____
Heart/Lung: _____
Pancreas: _____
Coordinators/Technicians (Tissue): _____

In O.R. _____ AM PM Incision _____ AM PM Depart O.R. (0) _____ AM PM Depart O.R. (T) _____ AM PM

Condition During Surgery (include: Blood Pressure, Urine Output, Complications, Comments)

Operating Room Drugs (include dosage and time)

Methyprednisolone: _____ Mannitol: _____ Furosemide: _____
Heparin: _____ Vasodilator: _____ Blood Products _____
Antibiotics: _____ Others: _____

Nephrectomy Data

En Bloc: Y/N In Situ: Y/N
Flush Sol'n: _____ Vol: ____
Final Flush (Sol'n Vol): _____
Storage Sol'n: _____

	R	L
Art Clamp:		
Flush Start		
Flush End:		
Warm Ischemia Time		
Clamps Off:		
Cold Ischemia Time		

Hepatectomy Data

Precool Start _____
Sol'n/Vol: _____
Portal Flush Start: _____
Sol'n/Vol: _____
Aortic Flush Start: _____
Sol'n/Vol: _____
Final Flush (Sol'n/Vol) _____
Clamps Off: _____
Cold Ischemia Time _____
Anatomy: _____

Cardiectomy Data

Infusion Start: _____
Sol'n/Vol. _____
Clamps Off: _____
Cold Ischemia Time _____

Heart Lung Data

Infusion Start (R) _____
Sol'nVol: _____
Infusion Start (L) _____
Sol'n/Vol: _____
Clamps Off: _____
Cold Ischemia Time _____

Single or Double Lung Data

Infusion Start: _____
Sol'n/Vol. _____
Clamps Off: _____
Cold Ischemia Time _____

Pancreas Data

Infusion Start: _____
Sol'n/Vol. _____
Final Flush; (Sol'n/Vol) _____
Clamps Off: _____
Cold Ischemia Time _____
Anatomy _____

Renal Anatomy

R  L 

Biopsy Results: _____

Organs and Tissues Recovered (Check appropriate box and circle "T" for Transplant, "R" for Research)
☐ R-KI T/R ☐ L-KI T/R ☐ LI T/R ☐ LU T/R ☐ PA T/R ☐ HR T/R ☐ HV T/R ☐ MV T/R ☐ Bones T/R
☐ BM T/R ☐ Veins T/R ☐ Skin T/R ☐ Cornea T/R ☐ INT T/R ☐ Other T/R

Fig. 4.3. *Intraoperative data collection sheet used by the Western Pennsylvania Organ Procurement Organization, CORE* (Center for Organ Recovery and Education). (Courtesy of Mr. Brian Broznick) (from [19]).

(5% albumin or hetastarch) [98]. Urine output and insensible losses are replaced by a hypotonic solution with glucose (e.g. 5% dextrose in 0.45% NaCl, 1 mL/kg per hour). Adjustment of intravascular volume may decrease the need for vasopressors in many cases [99], but acute volume expansion may increase myocardial oxygen consumption, congestive heart failure, arrhythmias, and the need for inotropic support, because the compliance of the heart is decreased in most donors [77].

Severe cases of tachycardia and hypertension caused by the mass reflex may be controlled by the administration of general anesthetics, a beta-antagonist, such as labetalol hydrochloride or esmolol hy-

drochloride, or a calcium channel blocker, such as verapamil hydrochloride [64]. Occasionally, an alpha-blocker such as hydralazine or sodium nitroprusside may be given to reduce afterload. Supraventricular or ventricular arrhythmias are treated with conventional antiarrhythmic drugs. Circulatory arrest, which occurs in 10% of potential donors and in 66% of referred donors [72], is treated according to conventional circulatory resuscitative measures, but if bradycardia is a concern, a direct-acting agent such as isoproterenol or epinephrine is used because, as mentioned before, donors are unresponsive to centrally-acting chronotropic drugs, such as atropine.

Progressive hypothermia which is seen in up to 86% of donors because of the loss of hypothalamic function [49] which results in sinus bradycardia, atrioventricular dissociation, and ventricular arrhythmias. At a temperature lower than 28°C, prolonged PR and QT intervals and wide QRS complexes are replaced by T-wave inversion, ST-segment depression, and rise of ventricular fibrillation. Other effects of hypothermia are a leftward shift in the hemoglobin-oxygen dissociation curve, an increase in blood viscosity, decrease in splanchnic blood flow and glomerular filtration, hyperglycemia, and metabolic and respiratory acidosis. Body temperature is kept within the normal range (>35°C) by increasing the room temperature, infusing all fluids through a blood warmer, and using a warming blanket and a heated humidifier in the inspiratory limb of the ventilation circuit.

Adequate diuresis (>0.5 mL/kg per hour, preferably 1 to 1.5 mL/kg per hour) is important because urine output is an indirect indication of preload and is a prognostic indicator for renal and liver graft function [73]. The administration of fluid or dopamine may be effective in maintaining adequate renal perfusion and diuresis. However, a high dose of dopamine (>10 μg/kg/min) may lead to acute tubular necrosis and nonfunction of the renal graft [75]. For persistent oliguria, furosemide (1-2 mg/kg) and mannitol (0.5 g/kg) may be administered.

Metabolic acidosis caused by inadequate tissue perfusion may be compounded by respiratory acidosis. Because of potential myocardial depression, metabolic acidosis is corrected by administration of sodium bicarbonate.

When hypernatremia is a concern, tromethamine (tris-hydroxymethylaminomethane, THAM) may be used (0.3 molar THAM [mL] = body weight [kg] × base deficit [μmol/L]) instead of sodium bicarbonate. Electrolyte imbalances (hypernatremia, hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia) caused by fluid shifts and diabetes insipidus may result in arrhythmias and myocardial dysfunction. Hypernatremia and hypokalemia are treated by administration of a hyponatremic solution (0.45% NaCl) and KCl (20 μmol/L). Ionized hypocalcemia caused by large blood transfusions is corrected by the administration of calcium chloride or calcium gluconate to preserve cardiac contractility. Hypomagnesemia is treated with magnesium sulfate (50 mg/kg), also to preserve myocardial contractility [100]. Glucose metabolism is relatively well maintained, although hyperglycemia may occur as the result of a decreased level of insulin and as a complication of diabetes insipidus.

Once cardioplegia is induced, no further supportive care is necessary. After cross-clamping of the aorta (the time is recorded by the procurement coordinator - see Fig. 4.3) mechanical ventilation and monitoring are discontinued, and all cannulas are removed.

The organs are swiftly removed in the following sequence: heart, lungs, liver, pancreas, intestine, and kidneys. No supportive care is needed for procurement of corneas or bones because these tissues tolerate a prolonged ischemia without significant injury.

DONOR OPERATION

Before starting a multiorgan procurement it is mandatory that the different surgical teams discuss the techniques and sequence they want to adopt. A detailed discussion of the surgical procedure is critical because, after aortic cross-clamping, time is of the essence. Everything should proceed as smoothly and expeditiously as possible, to minimize organ damage. The basic principle of any donor operation is the core cooling of the organs to be removed. Cooling of a solid organ at the time of donor circulatory arrest was described for experimental liver transplantation 34 years ago [101]. It was then promptly applied to kidney preservation in clinical transplantation [102], and it still represents the single most important aspect of any organ preservation technique. The first solution used was chilled Ringer's lactate, replaced in the late 1960's by the so-called Collins solution, characterized by an electrolyte composition close to the intracellular one [103]. This solution was successfully used for about 20 years, until the introduction of the University of Wisconsin solution [104, 105], which extended the duration of organ viability. The easiest way to achieve almost immediate internal core cooling of the donor organs is by *in situ* infusion of the preservation solution, chilled to 4°C, at the time of the circulatory arrest. The remaining technical aspects of organ retrieval are secondary to this critical maneuver.

The technical details of the donor operation are provided in Chapter 5, and will not be repeated here. We will only stress a few points we believe to be important.

Mediastinal dissection is carried out removing the lungs and heart en bloc if the block is to be used for a heart-lung transplant. The more common situation is one where the heart is harvested by one group and lungs are to be used for separate transplants. In this situation, once the cardioplegia and lung perfusion has been completed, the heart is carefully dissected by the two teams ensuring that enough pulmonary

Fig. 4.4. *En-bloc harvesting of liver and small bowel from a pediatric donor* (from [19]).

artery and left atrial cuff remain on both the heart and the lungs making them both available for transplantation. Once the heart has been removed, the lung team can then proceed with extraction of the lungs.

During this phase the abdominal organs are untouched, while they are exsanguinated and the cold perfusion is continued. Following the removal of the thoracic organs, the abdominal team proceeds with the final dissection and removal of the liver, pancreas, intestine, and kidneys. The technical steps have been outlined elsewhere by us [48, 106-109] and others [110-112]. After the organ recovery long segments of the iliac arteries and veins, inferior vena cava and aorta [113] (and carotid arteries in children) should always be removed and stored under hypothermic conditions. This ensures the ability to deal with all possible vascular problems that might be encountered during the recipient operations [113-117].

With the development of the intestinal and multivisceral transplant program at the University of Pittsburgh (see Chapter 24), a technique was developed for the removal of essentially the entire abdominal visceral bloc (Fig. 4.4) [48]. Anatomical considerations are fundamental during intestinal and multivisceral procurement, because recipients require different types of intestinal transplantation (isolated small bowel, liver and small bowel, true multivisceral, etc.) based on different pathology and needs. These procurement techniques do not interfere with that of other organs. In our first 35 intestinal donor operations there were 62 kidneys, 35 livers, 18 hearts and 3 lungs procured simultaneously [48].

At the end of the operation the procurement coordinator completes the form shown in Figure 5.3. These data are of critical importance for the recipient operations, and subsequent follow-up of the transplanted patients, which are the endpoint of a successful multiple organ procurement.

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