[Frontiers in Bioscience 14, 3750-3770, January 1, 2009]

A review of studies relating to thyroid hormone therapy in brain-dead organ donors

David K.C. Cooper[1], Dimitri Novitzky[2], Winston N. Wicomb[3], Murali Basker[4], John D. Rosendale[5], H. Myron Kauffman[5]

[1]Thomas E. Starzl Transplantation Institute, Department of Surgery, University of Pittsburgh, Pittsburgh, PA, [2]Tampa General Hospital Heart Transplantation Program, University of South Florida, Tampa, FL, [3]Infectious Disease Research Institute, Seattle, WA, [4]Department of Surgery, Geisinger Medical Center, Danville, PA, [5]Research Department , United Network for Organ Sharing, Richmond, VA

TABLE OF CONTENTS

1. ABSTRACT

An acute decrease in cardiac performance can result from a reduced free triiodothyronine (FT_3) level following (i) brain death (euthyroid sick syndrome), (ii) a period of cardiopulmonary bypass, and possibly (iii) regional or global myocardial ischemia. The two major pathophysiologic effects of brain death are (i) vascular injury associated with the hemodynamic consequences of the autonomic 'storm', and (ii) a generalized inhibition of mitochondrial function, which results in diminished organ function from the loss of energy stores from a rapid loss of circulating FT_3. Deterioration of donor organ function can be reversed by hormonal replacement therapy, in which T_3 plays a critical role. This results in (i) an increased number of organs being functionally acceptable, and (ii) increased early and intermediate graft survival. Cardiopulmonary bypass is associated with a reduction in the circulating level of FT_3, and this can be associated with deterioration in cardiac function. The administration of T_3 at the time of discontinuation of cardiopulmonary bypass reverses this state. In patients undergoing heart transplantation, T_3 therapy to both donor and recipient is beneficial.

2. INTRODUCTION

In this review, we present evidence that decreased cardiac performance can result from an acute reduction of circulating free triiodothyronine (FT_3) level following (i) brain death associated with reduced anterior pituitary function, (ii) a period of cardiopulmonary bypass during open heart surgery, and possibly (iii) regional or global myocardial ischemia.

3. OBSERVATIONS LEADING TO THE RECOGNITION OF THE DELETERIOUS EFFECTS OF BRAIN DEATH ON DONOR ORGANS

In 1980, a hypothermic perfusion system for storing isolated hearts was developed at the University of Cape Town (1-10) (Figure 1). After it had been tested successfully on pig and baboon hearts, including storage of hearts for 24 and 48 hours followed by orthotopic transplantation (1, 3, 4, 8, 9), it proceeded to clinical trial (4, 6, 10).

In the experimental laboratory, baboons' hearts had been excised and stored for 24 to 48 hours, after which

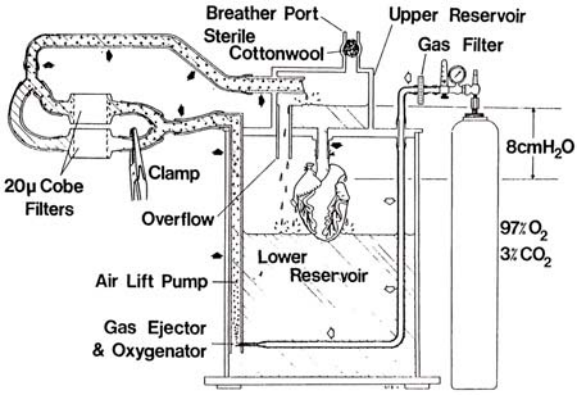

Figure 1. Diagram of the portable hypothermic perfusion system developed at the University of Cape Town and used clinically at Groote Schuur Hospital in 1981.

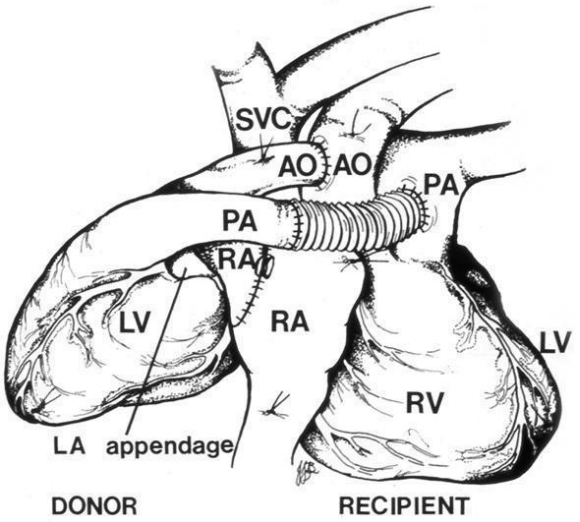

Figure 2. The completed operation of heterotopic heart transplantation. AO = aorta; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

they were replaced in the original baboons as autologous grafts, the baboons having been maintained alive in the interim by orthotopic allografts (5, 8, 9).These studies demonstrated conclusively that the heart supported the circulation immediately after transplantation and continued to function well for periods of >2 years (5, 9). Normal physiologic data were obtained by cardiac catheterization, and histologic examination of the myocardium showed no evidence of significant injury as a result of the storage procedure.

At that time, all heart grafts in Cape Town were being placed heterotopically (11-15), i.e., as an auxiliary heart within the chest, leaving the native heart *in situ* (Figure 2). The reasons for this have been detailed previously (12, 14, 16-19), the main considerations being that the presence of the native heart could provide some support when there was either (i) primary graft failure, or (ii) graft failure from acute rejection; in the days when the immunosuppressive drugs available were frequently inadequate to prevent rejection, support of the graft could be provided while rejection was being treated.

The hypothermic perfusion storage system was first used clinically in 1981 in a patient with cardiomyopathy (4, 6, 10). After a donor heart storage period of just under 13 hours, although the heart began to beat with a regular rhythm, it generated virtually no cardiac output, the patient being maintained by his native heart supported by considerable inotropic therapy. This situation continued for several hours, at which point, over a period of just 2 or 3 hours, the donor heart began to generate a significant cardiac output, and eventually took over support of the circulation. If the heart had been transplanted in the orthotopic position, it is very doubtful that the patient would have survived.

These observations caused us to consider why the donor heart in the clinical case had taken some hours to recover from the storage period, whereas, in the experimental animals, recovery had been rapid. The major difference between the two circumstances was that, experimentally, the heart was taken from a healthy baboon under anesthesia, whereas, in the clinical case, the heart had been taken from a subject who had recently undergone brain death. (Recipients in both groups – baboons and humans – underwent cardiopulmonary bypass which reduces FT_3 levels – see below.) The hypothesis was generated that brain death was injurious to the heart (and probably to all organs used in transplantation), although the exact nature of this injury remained unknown. It was clear, however, that the insult to the heart was at least partially reversible, and it appeared that this delayed function must presumably result from ischemia followed by a loss of myocardial energy stores and/or other reversible damage sustained during and following the onset of brain death.

It was determined that a series of experiments should be carried out to ascertain the changes that take place during the development of brain death and their sequelae, particularly as they relate to the heart. The adverse effects of brain death were studied first in the experimental animal and, subsequently, in the human brain-dead potential organ donor.

A review of the literature revealed very little information on the sequelae of brain death, although as early as 1901, Cushing had documented the hemodynamic changes that take place during the onset of brain death in dogs (20). A rise in the intracranial pressure exceeding the blood pressure ('coning') produced massive autonomic stimulation resulting in an increased vasomotor response.

Subsequent studies from our own group and from others (21) demonstrated that, following a *sudden* rise in intracranial pressure, a pronounced vagal stimulation produces a complete cessation of the heartbeat, which resumes after a few seconds. The blood pressure rapidly ascends to or above the normal level, and then gradually falls to a subnormal level. In contrast, a *gradual* increase

in intracranial pressure produces a gradual increase in blood pressure while the heart rate and respiration continue normally. A *sudden* increase in intracranial pressure is associated with an almost 1000-fold increase in epinephrine level as compared to a *gradual* increase, which produces a less marked hemodynamic response and only a 200-fold increase in epinephrine level (21). The extent of ischemic myocardial damage varies from 93% in the former case to only 23% in the latter (21).

Before our own studies were commenced in 1980, there were very few reports in the literature about the effects of brain death on the hormonal status of the body. In 1980, Schrader *et al* (22) reported on six patients with clinical and electroencephalographic signs of brain death in whom some pituitary hormones (prolactin, human growth hormone, luteinizing hormone, and thyrotropin) were measured in the blood. No patient had a general decrease in hormone levels, according to their biological half-lives, suggesting that there was still some function in the hypothalamus and pituitary. This conclusion was supported by the results of stimulation tests. The data suggested that, in brain death, some basal parts of the brain may still be perfused despite the fact that angiography indicates circulatory arrest in these areas.

Hall *et al* (23) also took blood samples from five patients after brain death had been established by neurological tests. No significant changes in pituitary hormone levels (thyroid stimulating hormone, prolactin, cortisol) were observed during the first 24 hours after brain death had first been diagnosed. They concluded that hypothalamic-pituitary function is maintained for at least 24 hours after the diagnosis of brain stem death, and that hormonal evaluation of such patients would be of no value in confirming the diagnosis.

4. MANAGEMENT OF THE POTENTIAL ORGAN DONOR IN 1981

A review of the heart transplant data in Cape Town indicated that approximately 20% of donor hearts from brain-dead potential organ donors were deemed unsuitable for transplantation due to myocardial deterioration (24, 25). There was also a small, but significant number of hearts that, although appearing functionally satisfactory before excision from the donor, did not function adequately after transplantation, sometimes leading to the demise of the recipient. It was presumed that the intervening ischemic period after excision of the heart from the donor contributed to the deterioration of function seen after transplantation. Indeed, it had been just such an experience that initially motivated Barnard and Losman to develop a technique of heterotopic heart transplantation (14, 15).

At that time, supportive therapy of the donor took the form of (i) intravenous (i.v.) fluids to replace the large urine output that brain-dead patients produce and to maintain a central venous pressure of between 5-10cm H_20 to enhance the Starling effect on the heart, (ii) inotropic support to maintain a mean arterial pressure of >60mmHg, and (iii) vasopressin, given either by i.v. infusion or by intermittent intramuscular injection, both to reduce urine output and help maintain an adequate arterial pressure through peripheral vasoconstriction (26).

5. STUDIES OF BRAIN DEATH IN THE EXPERIMENTAL ANIMAL AND HUMAN POTENTIAL ORGAN DONOR

In the baboon, an experimental model was designed to study changes occurring during and after brain death (27). Brain death was produced by creating intracranial hypertension. Under full inhalation anesthesia, a Foley catheter was introduced into the subdural space through a frontal burr hole in the skull, and filled with 20-30ml of saline. Brain death occurred within 20 minutes. Following induction of brain death, the animals were maintained on a ventilator. During a 24-hour period, observations were made before inducing brain death and at 5, 15, 60 minutes and at three-hour intervals after brain death. Electrocardiographic (ECG) and hemodynamic parameters, blood chemistry, and hormone levels were recorded (27).

5.1. Electrocardiographic

The following sequence of ECG changes, related to both excessive parasympathetic and sympathetic nervous activity, were seen in all animals over a matter of hours. Initially parasympathetic activity was characterized by sinus bradycardia, and sometimes by sinus standstill and/or nodal rhythm. The sympathetic impact was more impressive, and lasted for a longer period of time. This was characterized by sinus tachycardia, ventricular ectopic activity, ventricular tachycardia that was multifocal in origin, and a final episode of sinus tachycardia that gradually slowed as time progressed (27-29) (Figure 3). Ischemic changes were present at the onset of ventricular tachycardia, although these changes reverted to normal within hours. However, even after 24 hours, the ECG remained significantly different from the control trace; the QRS complex showed reduced amplitude, there was right bundle-branch block, a J wave was evident, there were ST changes, and inversion of biphasic T waves were noted.

5.2. Hormonal

The blood levels of the catecholamines measured increased 5 minutes after the induction of endocranial hypertension and the onset of brain death (Figure 4). Epinephrine (adrenaline) levels increased by 1100%, norepinehrine (noradrenaline) by 300%, and dopamine by 200%. These levels then slowly returned to control levels and eventually to subcontrol levels during the course of the experiment (27, 29). Thyroid hormone (FT_3 and thyroxine [T_4]) levels fell significantly by 6 hours and became undetectable 9 hours after brain death (Figure 5). Cortisol levels increased at 5 minutes, then declined progressively to subcontrol levels. Insulin levels also fell progressively to half of control values by 3 hours, and continued to fall subsequently to 10% of control values. Antidiuretic hormone fell after brain death. Glucagon and ionized calcium showed no significant changes from the control levels.

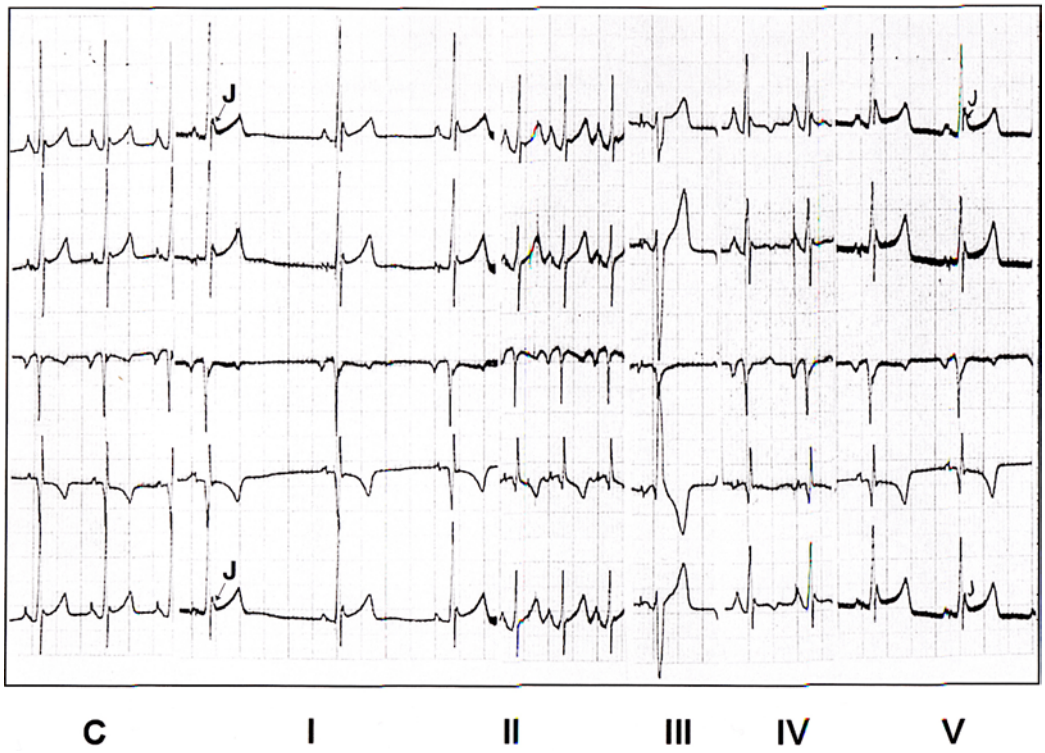

Figure 3. Electrocardiogram taken at regular time-points (stages) after the induction of brain death.

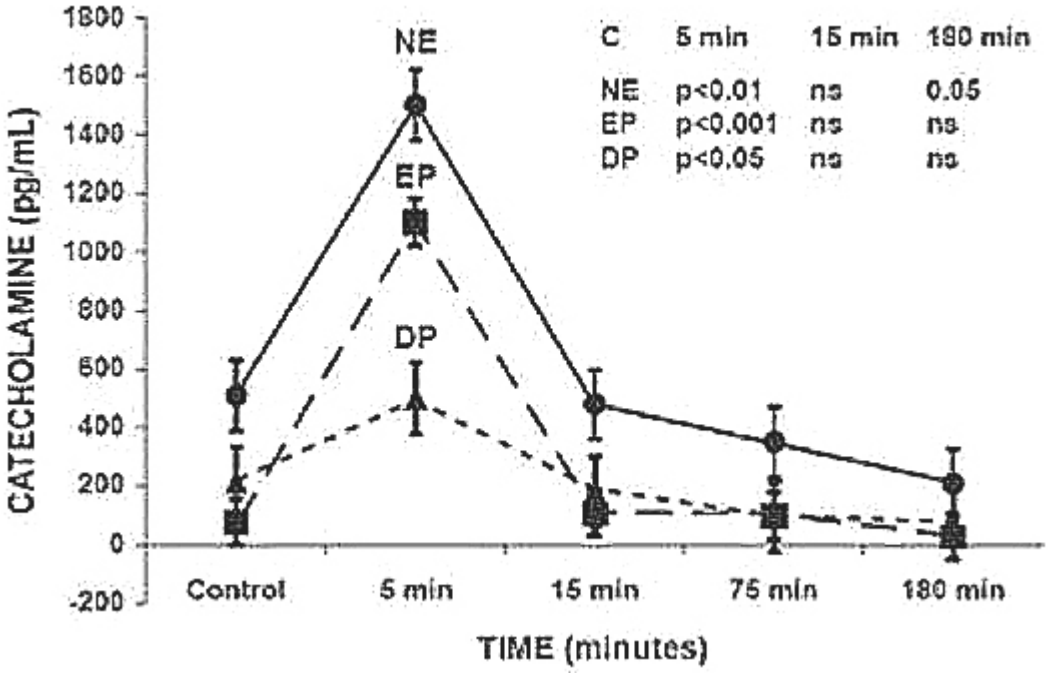

Figure 4. Changes in norepinephrine (NE), epinephrine (EP), and dopamine (DP) levels (all in pg/mL) after experimental brain death in the baboon. Statistical significance of differences in levels at various time intervals compared to pre-brain death (control) is indicated.

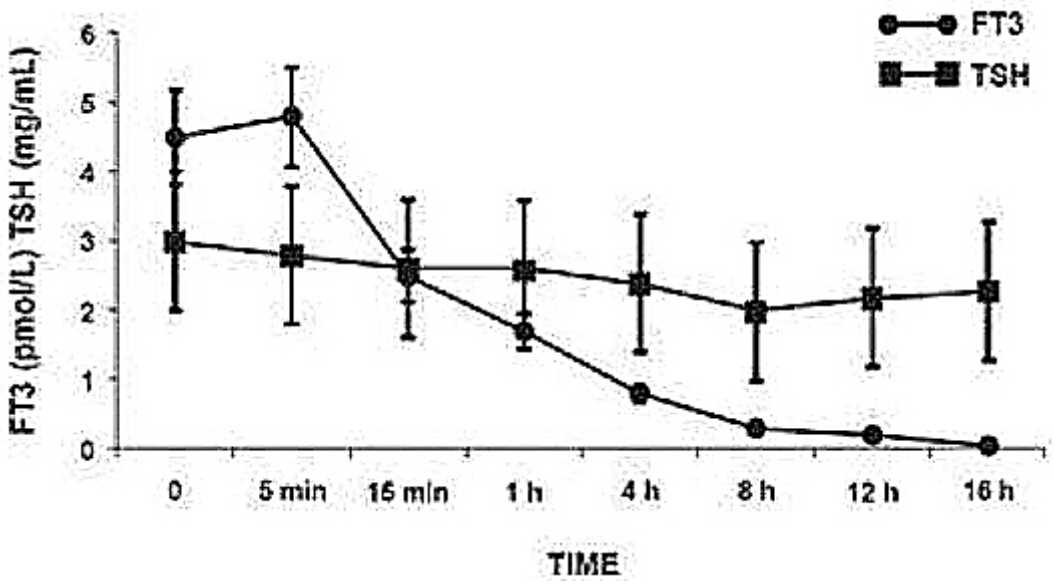

Figure 5. Changes in the levels of free triiodothyronine (FT3) (in pmol/L) and thyroid stimulating hormone (TSH, in µg/mL) in baboons after the induction of brain death. The FT3 **(**and T4**)** levels at 16h are highly significantly reduced from those before the induction of brain death (C) ($p<0.0001$), but the level of TSH is not significantly different.

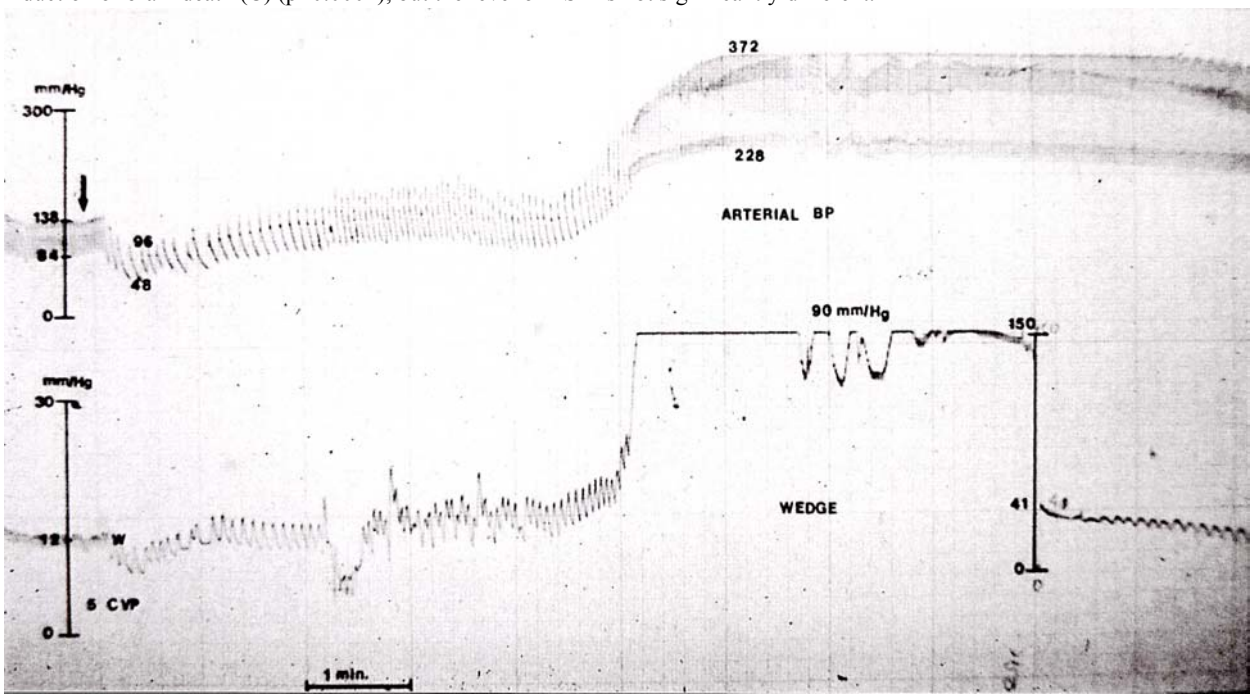

Figure 6. Extreme example of changes in systemic arterial pressure (above) and pulmonary artery (and pulmonary capillary wedge) pressure (below) occurring immediately after the induction of intracranial hypertension following inflation of the balloon of a Foley catheter in the subdural space in a baboon (marked by an arrow).

5.3. Hemodynamic

Mean arterial pressure rose significantly during the induction of brain death, remaining high for a variable period (from minutes to up to 3 hours), when it stabilized at a mean pressure of 40-50mmHg (27, 29) (Figures 6-8). Cardiac output dropped markedly during the induction of brain death, rising when the heart rate stabilized. During the hypertensive period, although the right atrial pressure showed little change, the pulmonary artery wedge pressure increased up to 10-fold. Systemic vascular resistance showed a marked elevation during induction of brain death, but was subsequently followed by a statistically significant fall. Once stabilization of the hemodynamic parameters occurred, challenging the animal with i.v. fluids caused a

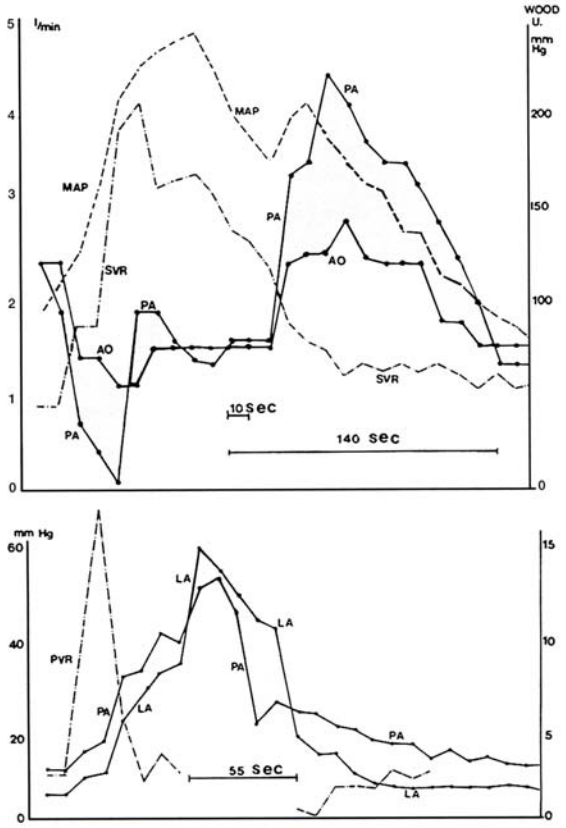

Figure 7. Systemic and pulmonary hemodynamic data during induction of brain death in a single baboon.

disproportionate rise in the pulmonary artery wedge pressure compared with the right atrial pressure.

Systemic and pulmonary hemodynamics were studied during the induction of brain death in the baboon (30). Continuous recording of blood flow through both the pulmonary artery and the aorta was obtained by electromagnetic flow meters placed around these vessels. Mean arterial, central venous, pulmonary arterial, and left atrial pressures were recorded continuously. Systemic and pulmonary vascular resistances were calculated.

During the agonal period, the surge in endogenous and circulating catecholamines resulted in a significant increase in systemic vascular resistance, culminating in acute transient left ventricular systolic and diastolic dysfunction. Mean left atrial or pulmonary capillary wedge pressure rose above the mean pulmonary arterial pressure in most animals (Figures 6-8). As the systemic vascular resistance rose, a significant difference between pulmonary artery and aortic blood flows occurred, leading to blood pooling within the lungs. For a short period of time, a mean of 72% of the total blood volume of the animal accumulated within these organs. The increase of left atrial pressure to levels higher than pulmonary artery pressure indicated a state of pulmonary capillary blood flow arrest. This, associated with the blood pooling within the lungs, almost certainly resulted in disruption of the anatomic integrity of the pulmonary capillaries (blast injury); four of 11 animals developed pulmonary edema, with alveolar septal interstitial hemorrhage.

Subsequent studies by others have demonstrated that, although initiated by the catecholamine storm, this pulmonary injury is multifactorial, some of it relating to an inflammatory response.

5.4. Myocardial energy stores

Myocardial biopsies were taken in pigs before the induction of brain death and at the end of the experiment to determine adenosine triphosphate, creatine phosphate, glycogen, and lactate tissue content. Brain-dead pigs that had received large amounts of i.v. fluid showed depletion of myocardial adenosine triphosphate and creatine phosphate stores and an increase in the tissue lactate levels when compared with animals that received little or no fluids (27). These observations suggested modalities of donor management to prevent loss of myocardial energy stores and limit myocardial deterioration (and possibly deterioration of other organs) before donor heart excision and transplantation.

5.5. Myocardial histology

The induction of brain death was followed by myocardial structural damage in 60% of baboons (Figure 9). This damage, which was believed to be related to intense sympathetic nervous system activity resulting in the prolonged release of myocardial endogenous catecholamines, predominantly consisted of various forms of myocardial necrosis (contraction bands, coagulative myocytolysis, coagulative necrosis) and focal interstitial mononuclear cell infiltration and edema (27). The injury resulting from brain death could be confused with that seen in acute rejection (31).

We subsequently reviewed those patients who died following heart transplantation at the Universities of Cape Town and Munich from hitherto unexplained causes either at operation or in the early post-transplant period (24). Five out of 106 patients (4.7%) showed donor heart histopathological features almost identical to those seen in our experimental study. These observations suggested that myocardial damage sustained during the agonal period was a major factor in those patients in whom donor heart failure occurred early in the post-transplant period.

Electron microscopic examination of left and right ventricular biopsies showed moderate-to-severe ultrastructural injury in approximately 25% (25). There was a higher incidence of injury in those hearts excised from donors initially dependent on high inotropic support.

6. STUDIES TO ELUCIDATE THE MECHANISM OF MYOCARDIAL INJURY DURING BRAIN DEATH

Although unrelated to the loss of circulating FT_3, we carried out investigations to clarify the causative mechanism involved in the development of this myocardial structural damage. Our findings suggested that the myocardial damage was likely related to endogenous

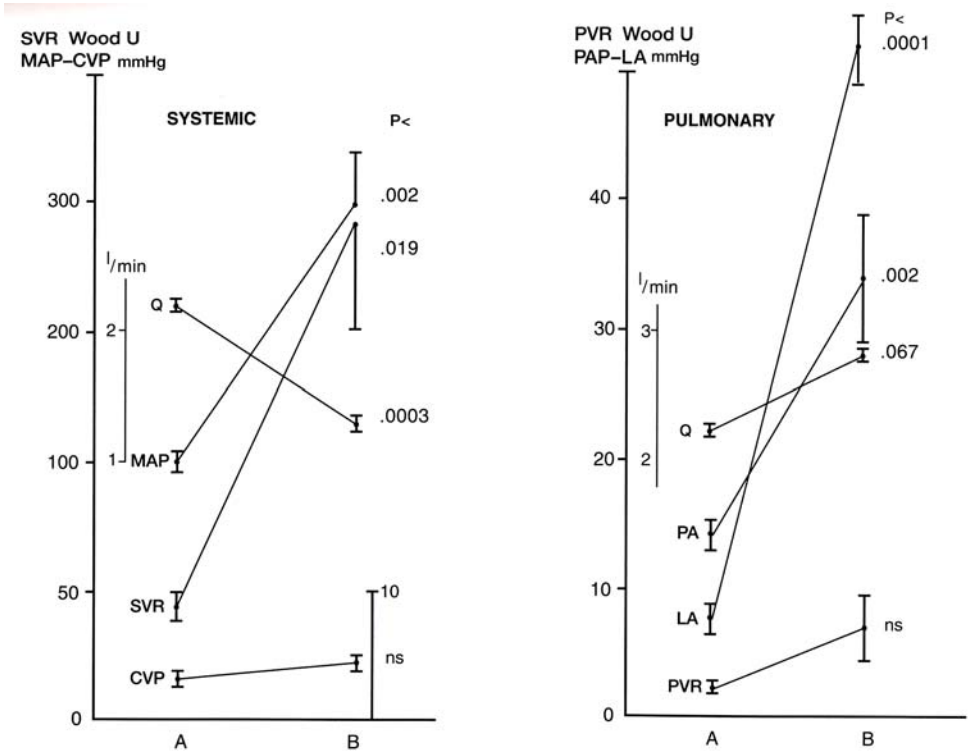

Figure 8. Mean changes (+SEM) in systemic and pulmonary hemodynamic data during the induction of brain death in eight baboons. Left: changes in systemic hemodynamics between control levels (A) and those recorded at the peak of systemic vascular resistance (B), which occurred at a mean time of 90 seconds (SEM+ 10). Changes in mean arterial pressure (MAP, mmHg), systemic vascular resistance (SVR, Wood units), and aortic blood flow (Q, l/min) reached statistical significance; CVP, central venous pressure (mmHg). Right: changes in pulmonary hemodynamics; control levels (A) and levels obtained at peak systemic vascular resistance (B) are shown. Changes in pulmonary artery pressure (PA, mmHg) and left atrial pressure (LA, mmHg) reached statistical significance. PVR, pulmonary vascular resistance (Wood units); Q, pulmonary artery blood flow (l/min). (Reproduced with permission from ref 171).

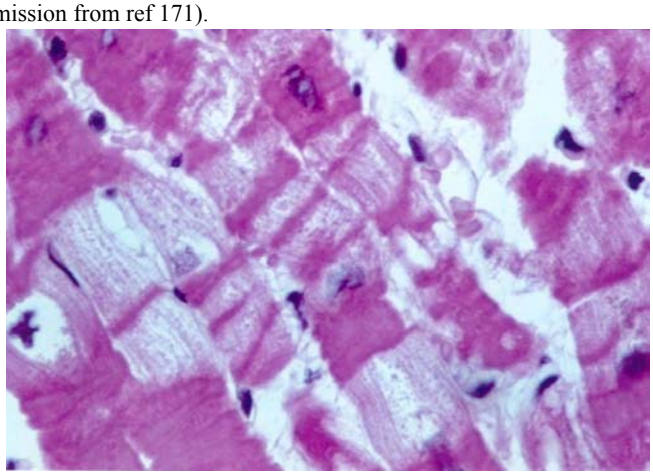

Figure 9. Microscopic section of myocardium in a baboon after induction of brain death, showing widespread contraction bands and edema (H&E x 450). (Above) Changes in systemic vascular resistance (SVR, Wood units), mean arterial pressure (MAP, mmHg), pulmonary artery blood flow (PA, l/min) and aortic blood flow (AO, l/min). The discrepancy between pulmonary artery and aortic blood flows (shaded area) represents the period and extent of blood pooling within the lungs; in this case, blood pooling extended for a period of 140 seconds. (Below) Changes in mean left atrial pressure (LA, mmHg), mean pulmonary artery pressure (PA, mmHg), and pulmonary vascular resistance (PVR, Wood units). The shaded area represents the period of 55 seconds during which the left atrial pressure exceeded the pulmonary artery pressure. (Reproduced with permission from ref 171).

catecholamine release, since prior cardiac sympathectomy or total denervation (autotransplantation) prevented this injury (32). Furthermore, pretreatment with verapamil hydrochloride prevented both the peripheral and central hemodynamic changes that result from increased sympathetic activity, and thus prevented myocardial structural damage, which may have been associated with increased calcium uptake by the myocytes (33). The released endogenous catecholamines, inducing calcium overload injury, also affected the conduction tissue and the smooth muscle of the coronary arteries (34). This was prevented by calcium channel blockade or cardiac denervation (autotransplantation) or sympathectomy (34).

Many other events may participate in the organ injury seen after brain death, e.g., endothelial injury, production of adhesion molecules, P-selectins, and pro-inflammatory cytokines, and the adverse effects of blood transfusions, surgical procedures, and infections (reviewed in 35).

7. IMPAIRMENT OF RENAL FUNCTION FOLLOWING BRAIN DEATH

Although not investigated so intensively, indications were obtained that brain death had significant detrimental effects on the function of other organs, such as the kidney, as well as the heart (36). The effects of the agonal period and subsequent donor management on renal slice function, using the K^+:Na^+ ratio, were studied in the pig. Brain ischemia or death resulted in a reduction in renal slice function, whether the pig was maintained normovolemic or hypovolemic by i.v. fluid and dobutamine therapy. (This deterioration in function was, however, reversed or prevented by a period of therapy with T_3, insulin, and cortisol.) A period of 24 hours storage of the kidney slice in a low ionic strength solution in ice resulted in a further deterioration in slice function in all animals studied.

8. THE EFFECTS OF BRAIN DEATH AND 24 HOURS STORAGE BY HYPOTHERMIC PERFUSION ON DONOR HEART FUNCTION

The effects on the myocardium of the agonal period and subsequent management were also studied in the pig (37). Under anesthesia, brain death was induced by ligation of both brachiocephalic arteries, from which arise the carotid and vertebral arteries. Acute ischemia of the brain led to major temporary hemodynamic changes. This was an important observation as it indicated that the sudden onset of endocranial hypertension was not essential for the subsequent effects of brain death. Brain death, with or without hemodynamic support of the circulation, led to a significant reduction in subsequent myocardial function, associated with some depletion of the myocardial high-energy phosphate and glycogen reserves, although the rate of this depletion was reduced by anaerobic glycolysis.

Although 24 hours' storage by continuous hypothermic perfusion of hearts taken from control (non-brain-dead) animals led to only a minimal reduction in myocardial function, storage increased the reduction in function associated with brain death when i.v. fluid and dobutamine support had been given to maintain the brain-dead pig in a normotensive state. Storage, however, reduced the anaerobic metabolism seen in hearts functioning in hypotensive brain-dead pigs, and led to replenishment of the glycogen stores.

9. REVERSAL OF FUNCTIONAL DETERIORATION OF THE HEART AFTER BRAIN DEATH

9.1. Change from aerobic to anaerobic metabolism after brain death, and reversal following T_3 therapy

The principle of (i.v.) single-bolus kinetics with labeled carbon compounds (^{14}C-R), with subsequent measurement of both plasma activity (half-life and plasma clearance) and of exhaled $^{14}CO_2$ was used to study glucose, pyruvate, and palmitate utilization under conditions of (i) sedation, (ii) brain death, and (iii) brain death with T_3 therapy in the baboon (38). Serum lactate and plasma-free fatty acid concentrations were also measured.

There was a major change in metabolic oxidative processes following brain death. The rate of glucose, pyruvate, and palmitate utilization was markedly reduced, and there was an accumulation of lactate and free fatty acids in the plasma, indicating a general change from aerobic to anaerobic metabolism (Figure 10). The administration of T_3 to the brain-dead baboon resulted in a dramatic increase in the rate of metabolite utilization, and a reduction in the plasma concentrations of plasma lactate and free fatty acids, indicating an apparent reversal from anaerobic to aerobic tissue metabolism. This suggested that T_3 should be administered to all brain-dead potential organ donors to correct and maintain a more physiologic metabolic status, and thus improve organ function.

9.2. Effect of hormonal therapy after brain death and storage of the heart

We investigated the effect of the administration of the hormones (T_3, cortisol, and insulin) to the brain-dead pig (39). Their value was assessed on both the freshly-excised heart and the stored heart by continuous hypothermic perfusion for 20-24 hours (1, 3, 7). Hearts were biopsied for estimation of tissue levels of adenosine triphosphate, creatine phosphate, lactate, and glycogen, and were subsequently functionally tested using an *ex vivo* (modified Langendorff) blood perfusion system (37).

The induction of brain death was followed by a decrease in myocardial energy stores (Figure 11), and this was associated with reduced myocardial function (Figure 12). The administration of hormones to the brain-dead pig led to some replenishment of myocardial energy and glycogen reserves, and reduction in lactate, with associated improvement in hemodynamic function. A period of hypothermic perfusion storage appeared to reverse the anaerobic metabolism occurring in the heart in the non-hormonally-treated brain-dead animal, and led to replenishment of glycogen reserves in untreated animals.

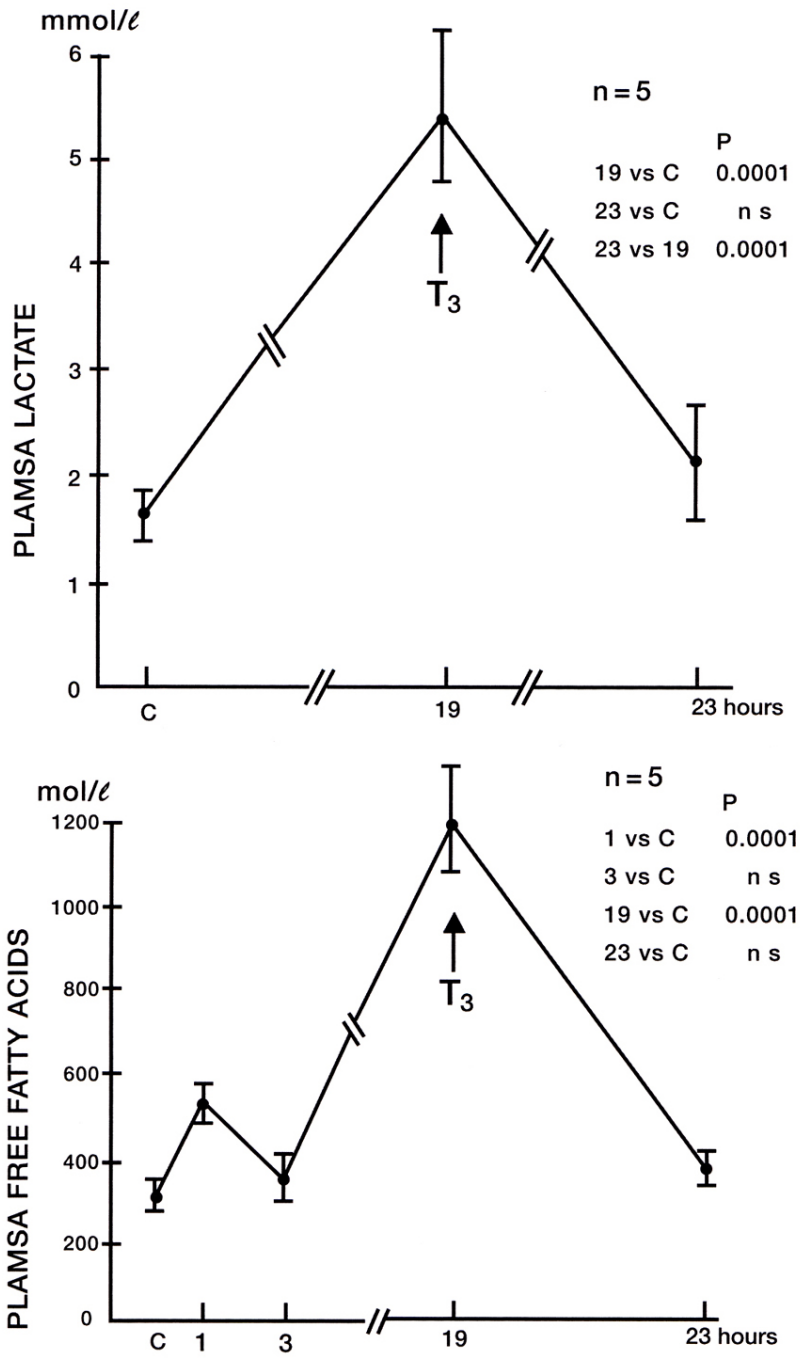

Figure 10. Changes in plasma lactate (above) and plasma free fatty acids (below) after induction of brain death (C) and the administration of T3 in baboons (n=5).

This reversal was not evident in the hormonally-treated animals.

The observation that both better function and an increase in myocardial energy stores occurred in hormonally-treated, stored hearts, even though tissue lactate levels remained high, suggested that hormonal therapy, particularly T_3, promoted aerobic metabolism in the brain-dead animals in an environment that was initially dominated by anaerobic metabolism.

9.3. Reversal of functional deterioration of the heart in the brain-dead human potential donor by hormonal therapy

After initial studies that indicated that a dose of 20μg of T_3 was excessive and induced a hyperthyroid state,

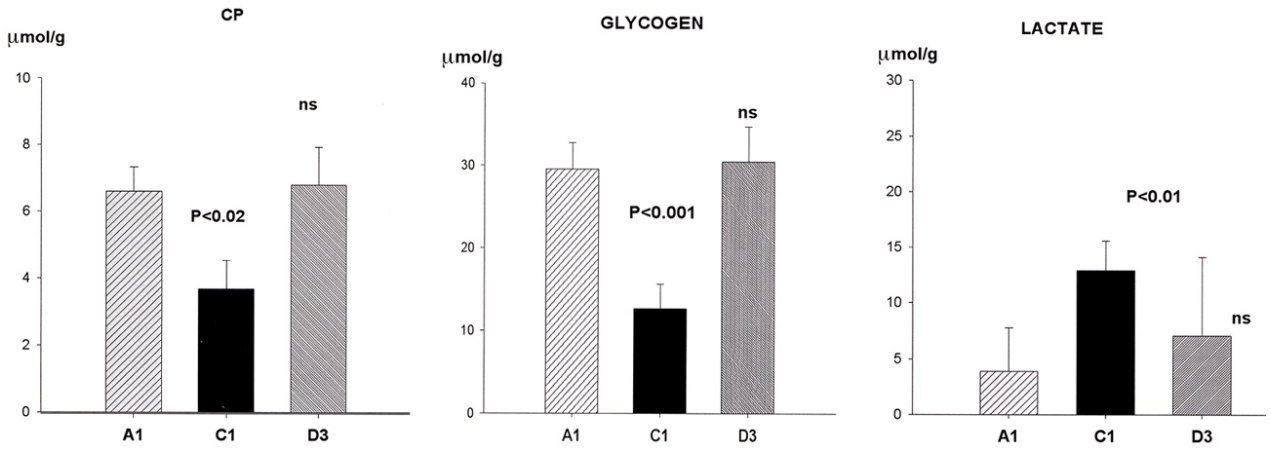

Figure 11. Myocardial creatine phosphate (CP), glycogen, and lactate in (A1) freshly excised hearts, (C1) hearts taken from brain-dead pigs, and (D3) hearts taken from brain-dead pigs that had received hormonal therapy (T_3, insulin, and cortisol). The statistical differences between the control group (A1) and the two experimental groups (C1 and D3) are shown.

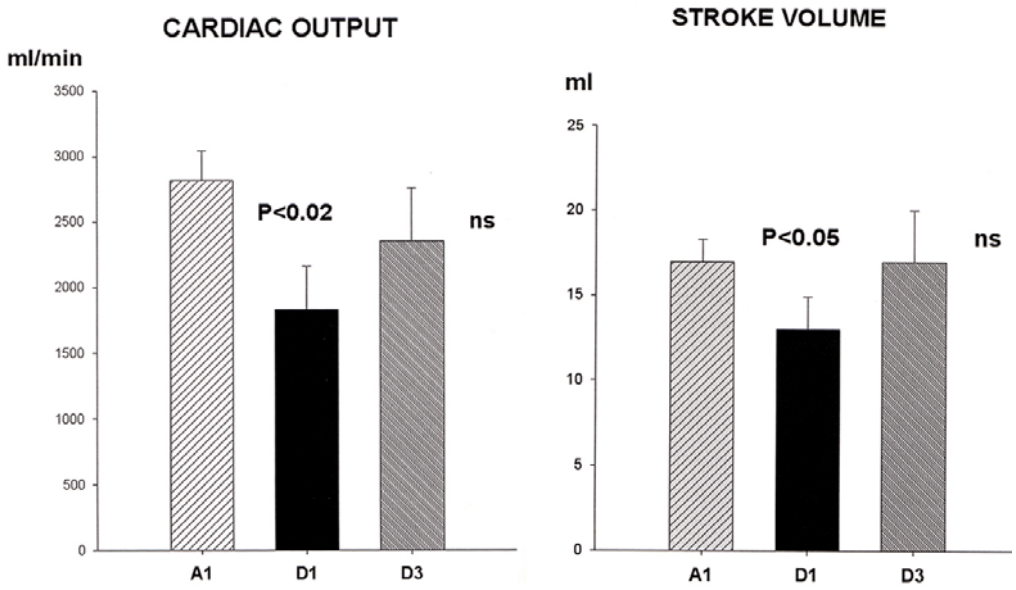

Figure 12. Cardiac output and stroke volume in (A1) freshly excised hearts, (D1) hearts taken from brain-dead pigs, and (D3) hearts taken from brain-dead pigs that had received hormonal therapy (T_3, insulin, and cortisol). The statistical differences between the control group (A1) and the two experimental groups (D1 and D3) are shown.

an evaluation of the beneficial effects of hormonal therapy, consisting of T_3 (2µg), cortisol (100mg), and insulin (20units), administered i.v. at hourly intervals, was assessed in brain-dead patients referred for organ donation (40).

Twenty-six conventionally-treated donors showed a progressive hemodynamic deterioration, requiring significant increments of inotropic support in order to maintain cardiovascular stability, and necessitating a significant increase in bicarbonate requirements in order to maintain a normal acid-base balance. Of this group, 5 (20%) of the donors were considered unsuitable as cardiac donors due to progressive cardiovascular deterioration or sudden ventricular fibrillation.

Hormonal therapy was administered to 21 donors, resulting in a significant improvement of cardiovascular status, and requiring less inotropic support and significantly less bicarbonate. A significant reduction of serum lactate-pyruvate followed the initiation of hormonal therapy. In these donors, all organs (heart, heart and lungs, and kidneys) were suitable for transplantation, with excellent organ function following implantation of the graft.

Two types of changes have therefore been documented in the brain-dead potential organ donor (29, 41). The first is due to diffuse injury to vascular regulatory mechanisms, and the second results from diffuse metabolic cellular disturbances. The former is secondary to the autonomic storm that takes place during the development of brain death from sympathetic activity. The latter is due to endocrine abnormalities with lack of hypothalamic control, leading to a state of generalized metabolic hypoxia.

10. SUBSEQUENT STUDIES ON BRAIN DEATH AND THE EFFECT OF HORMONAL THERAPY

The studies by the Cape Town group were followed by a large number of experimental and clinical studies on the effect of brain death and hormonal therapy (42-143). Although at least four groups demonstrated a beneficial clinical effect of hormonal therapy on the unstable donor (42-46) not all studies showed a benefit from hormonal therapy, and hormonal therapy did not achieve rapid, universal acceptance.

At Papworth Hospital in the UK, after conventional donor management consisting of ventilation, fluid replacement, and optimizing serum electrolytes, 52 donors failed to meet minimal acceptance criteria for heart donation due to low mean arterial pressure (MAP) (<55mmHg), elevated central venous pressure (CVP) (>15mmHg), elevated pulmonary capillary wedge pressure (PCWP) (>15mmHg), low left ventricular stroke work index (<15gm), or high inotrope requirements (>20μg/kg/min) (42). After hormonal replacement therapy, consisting of methylprednisolone, T_3, arginine vasopressin, and insulin, 44 of the 52 donors had improved enough to be used as heart donors. Thirty-day recipient survival was 89%, and none of the five early deaths was due to cardiac failure.

At Temple University, 22 potential donors with impaired left ventricular function, elevated left atrial pressures, and high inotrope requirement received T_3, and all demonstrated an improvement in cardiac and circulatory function concomitant with a significant reduction in inotrope requirement (43, 44). In 17 of the donors, the heart recovered and was transplanted successfully (44). In Los Angeles, hormonal resuscitation with methylprednisolone, T_4, and insulin enabled similar improvement in function of 19 inadequate donor hearts (45). At the University of Pennsylvania, 91 pediatric brain-dead donors receiving T_4 had a significant reduction in their vasopressor requirements. No data were given on organ yield or quality (46).

Some published studies failed to document low levels of FT_3, T_4, cortisol, and insulin after brain death (47, 48), and/or failed to demonstrate any beneficial cardiac and circulatory effect of T_3/T_4 administration (49, 50). This may possibly have been associated with one or more of the following points. (i) Some groups failed to measure plasma FT_3, but may have measured total T_3 which includes that bound to pre-albumin. (ii) Not all brain-dead donors have total absence of anterior pituitary function (and therefore some have measurable FT_3 levels); these donors may not be hemodynamically unstable, and the benefit from T_3/T_4 therapy might therefore not be seen. (iii) An inadequate dosage of T_3/T_4 may have been administered. (iv) At that time, some assays were less sensitive than others, and may have provided inadequate data.

11. WIDER ADOPTION OF HORMONAL THERAPY IN THE MANAGEMENT OF HUMAN BRAIN-DEAD POTENTIAL ORGAN DONORS

For several years, few transplant groups incorporated hormonal therapy into their protocols for the management of the brain-dead potential organ donor. However, in 2001, a conference was held to discuss this form of therapy (144-147). Guidelines were developed for maximizing the number of organs recovered and transplanted from deceased donors (144-147). Multivariate studies on hormonal treatment of brain-dead donors revealed significant increases in the number of organs from each donor that could be transplanted, and an improvement in the one-year survival of kidneys and hearts after transplantation (148-150). In recipients of heart grafts, a 46% reduced risk of death within 30 days and a 48% reduced risk of early graft dysfunction was documented if the donor had received 3-drug hormonal replacement therapy (148-150). Similar guidelines have been developed by the Canadian Council for Donation and Transplantation Forum, '*Medical Management to Optimize Donor Organ Potential*' in 2004 (151).

A heart donor management algorithm was suggested that included 4-drug hormonal resuscitation for donors with a left ventricular ejection fraction <45% and/or with unstable hemodynamics (148). Recommended hemodynamic management included a pulmonary artery catheter to assess the effect of hormonal resuscitation in meeting six *target criteria:* (i) mean arterial pressure >60mmHg, (ii) central venous pressure 4-12mmHg, (iii) pulmonary capillary wedge pressure 8-12mmHg, (iv) systemic vascular resistance 800-1200dynes/sec-cm^5, (v) cardiac index >2.4L/min-m^2, (vi) dopamine or dobutamine <10μg/kg-min.

The United Network for Organ Sharing (UNOS) implemented these recommendations (147), and carried out a retrospective analysis of all brain-dead potential donors from January, 2000, to September, 2001, inclusive (149, 150). Hormonal resuscitation is now becoming more widely accepted with an increase in 3-drug therapy from 8.8% of brain-dead organ donors reported in the US in the year 2000 to 19.9% of donors in 2004 (148).

12. STUDIES ON THE EFFECTS OF T_3 FOLLOWING MYOCARDIAL ISCHEMIA AND CARDIOPULMONARY BYPASS IN EXPERIMENTAL ANIMALS

A significant reduction in plasma FT_3, which was known to have an inotropic effect, had been documented in patients undergoing open-heart procedures (152, 153). Our observations of the effect of T_3 administration to brain-dead

organ donors suggested that the reduction in circulating FT_3 levels was responsible for a deterioration of cardiac function in patients following cardiopulmonary bypass (CPB). To investigate the effect of this observation, 22 pigs underwent 2 or 3 hours of myocardial ischemia during CPB at 26°C (154). The myocardium was protected by a standard cardioplegic solution and cold saline solution at 30-minute intervals. After the pig was rewarmed to 37°C, CPB was discontinued, and measurements of hemodynamic function were made 10 and 70 minutes later. Half of the pigs received 6μg of T_3 i.v. immediately after removal of the aortic cross-clamp; the remainder received no T_3.

After 2 hours of ischemia (cross-clamping of the ascending aorta), untreated pigs showed significantly reduced myocardial function 10 minutes after discontinuation of CPB. By 70 minutes, 2 of 5 untreated pigs had died of low cardiac output, but all 5 T_3-treated pigs survived. After 3 hours of ischemia, both groups showed some reduced function at 10 minutes, though the reduction was more marked in untreated animals. By 70 minutes, 4 of 6 untreated pigs had died of myocardial failure and all T_3-treated pigs remained alive. Surviving pigs in both groups still demonstrated some reduced function compared with values obtained before CPB.

When all pigs were considered together, overall survival of those that did not receive T_3 was significantly less than those that did. T_3 clearly had a significant beneficial cardioprotective effect when administered after a period of myocardial ischemia and CPB. These data suggested that its administration might be indicated in patients undergoing open-heart operations.

To clarify the effect of T_3 on myocardial high energy phosphate stores and lactate, a series of experiments was carried out in baboons undergoing 3 hours of myocardial ischemia while supported by CPB (155). Seven baboons received no T_3 and six received 6μg of T_3 at the end of the ischemic period. Seventy minutes after CPB, the myocardial adenosine triphosphate level was significantly higher in the treated animals. In untreated animals, a steady increase in myocardial lactate levels occurred after CPB; by 120 minutes after ischemia (70 minutes after CPB) there was a significant difference in lactate levels between the two groups.

From these data, it was postulated that a combination of global ischemia and depletion of T_3 resulted in reduced mitochondrial function, inhibition of the tricarboxylic acid cycle, inability to utilize oxygen aerobically with resulting increased anaerobic metabolism, and depletion of myocardial phosphates. T_3 replacement therapy was presumed to improve mitochondrial function and increase aerobic metabolism that led to a measured increase in myocardial phosphates. These observations strengthened the indication for the administration of T_3 to patients undergoing cardiac operations under CPB with a prolonged myocardial ischemic period, or in whom there was any evidence of low cardiac output after discontinuation of CPB.

13. STUDIES ON THE EFFECTS OF T_3 FOLLOWING MYOCARDIAL ISCHEMIA AND CARDIOPULMONARY BYPASS IN PATIENTS UNDERGOING OPEN HEART SURGERY

Initially, we administered T_3 (4-10μg i.v.) to 10 patients, either when difficulty was being experienced in weaning from CPB support (n = 5), or when myocardial function remained extremely poor (n = 5), despite inotropic and intra-aortic balloon pump support (156, 157). Mean preoperative NYHA functional class of the 10 patients was 3.2, left ventricular end- diastolic pressure 20mmHg, and ejection fraction 40%. The mean myocardial ischemia time was 72 (range 40-120) minutes.

Within 1 hour of T_3 administration, the mean plasma free T_3 level had risen from 1.03 to 3.56 μg/ml, and CPB was able to be discontinued in all cases. Balloon pump support (n = 2) was no longer essential within 3 hours. At 1 hour, the mean arterial pressure had risen from 42 to 78mmHg, and heart rate from 90 to 104 beats/min. The left atrial pressure had fallen from 30 to 14mmHg, and the central venous pressure from 20 to 11cm H_2O. All changes were statistically significant. Inotropic support had been significantly reduced or discontinued.

To our knowledge, T_3 had not been administered previously as an inotropic agent to patients who had undergone cardiac surgery. Although this small trial was not randomized, the observations suggested that T_3 could play an important role in the rescue of failing hearts following a period of myocardial ischemia in patients who had undergone open heart surgery.

In two small randomized trials in patients undergoing myocardial revascularization on CPB, postoperative T_3 therapy was associated with a reduced need for inotropic support and diuretic therapy in the first study and improved cardiac output in the second study (158) (Figure 13). A later study added support to this conclusion (159).

Others continued to study the effects of CPB on thyroid hormones and the effect of thyroid hormone on myocardial function (160-165); the mechanisms of action have also been investigated (166).

14. THE POTENTIAL ROLE OF T_3 IN THE TREATMENT OF BOTH DONOR AND RECIPIENT IN CARDIAC TRANSPLANTATION

In view of our findings following brain death and following CPB, it became our policy to hormonally treat both the brain-dead potential organ donor and the recipient who had undergone heart transplantation (167, 168) (Figure 14). Donors were treated with a combination of T_3, cortisol, insulin (and sometimes vasopressin), whereas recipients received T_3 before being weaned from CPB. One hundred and sixteen consecutive potential donors were treated, as well as 70 of the recipients. Immediate posttransplant cardiac function was good in all but 3, and

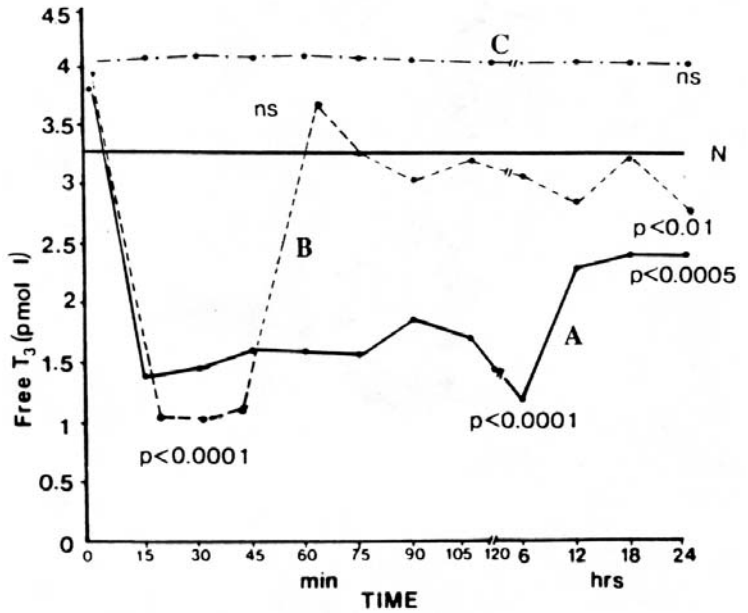

Figure 13. Mean level of plasma free triiodothyronine (T_3, in pmol/L) in 30 patients who underwent open heart surgery using cardiopulmonary bypass (CPB) at Groote Schuur Hospital, Cape Town (A). Levels are shown during CPB (0 to 120 minutes) and for 24 hours after CPB. The lower limit of normal plasma free T_3 is shown (N); normal range, 3.3 to 5.0 pmol/L. There was a significant reduction of free T_3 after 15 minutes CPB ($p<0.0001$), initially from hemodilution, which was maintained for 6 hours; free T_3 levels remained low 24 hours after operation ($p<0.0005$). The mean level in an additional group of 20 patients in whom T_3 was administered before the end of CPB is also shown (B). It can be seen that 4-10 µg of T_3 administered intravenously raised circulating levels of the hormone to the lower limit of the normal range. Twenty-four hours after operation, plasma free T_3 levels had fallen significantly ($p<0.01$) suggesting an inability of patients to produce sufficient T_3 for their needs. For comparison, the mean level in 12 patients who underwent major abdominal or thoracic operations not involving CPB is shown (C). (Reproduced with permission from ref 172).

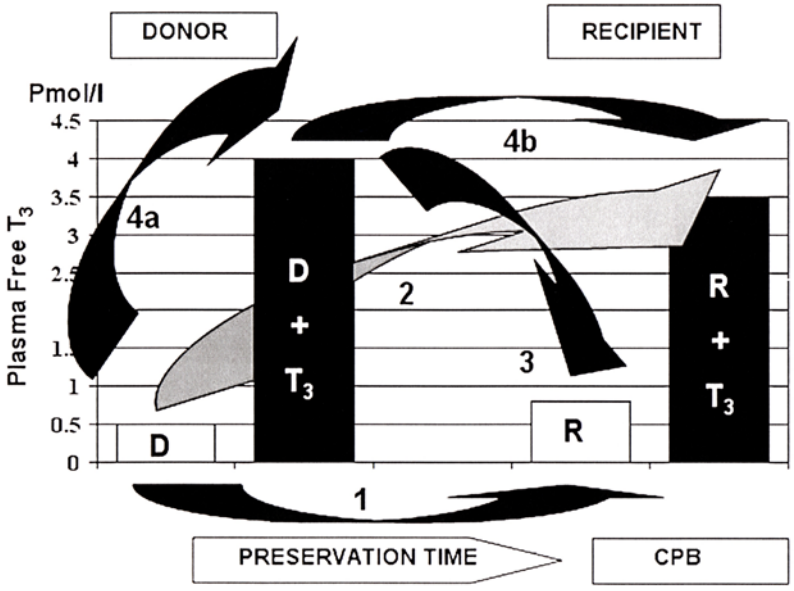

Figure 14. Mean plasma free T_3 levels (in pmol/L) in 22 human donors (D) at the time of referral, and 22 human heart transplant recipients (R) at the time of release of the aortic cross-clamp during cardiopulmonary bypass (CPB). After hormonal therapy to donors (D + T_3) and recipients (R + T_3), values have become normalized. Four different therapeutic options are possible. Implantation of the donor heart may be from: (1) an untreated donor to an untreated recipient, (2) an untreated donor to a treated recipient, (3) a treated donor to an untreated recipient, or (4) a treated donor to a treated recipient. Option 4 is clearly the most physiologically sound and is to be preferred.

these hearts recovered to normal within a maximum of 24 hours of mechanical support.

We therefore advocate the use of hormonal therapy to the donor and T_3 therapy to the recipient (166-169). By correcting the metabolic derangements that take place in the donor, the heart will be excised with close to normal levels of energy stores that can be utilized during the period of myocardial ischemia while the heart is transported to the recipient center and transplanted into the recipient. T_3 replacement therapy to the recipient, administered before removal of the aortic cross-clamp (if this has been applied), will lead to rapid restoration of energy stores that may have decreased during CPB, with associated improvement in myocardial function.

Our studies therefore clearly indicate that T_3 and additional hormonal therapy significantly (i) increased the number of donor hearts considered acceptable for transplantation, (ii) reduced the incidence of inadequate heart function early after transplantation, and (iii) increased graft survival. Hormonal therapy of the brain-dead donor is therefore associated with encouraging outcomes. In patients undergoing heart transplantation, we would advocate additional T_3 therapy of the recipient at the end of the period of CPB.

15. EXPERIMENTAL STUDIES ON T_3 IN REGIONAL MYOCARDIAL ISCHEMIA

In further studies, two groups of dogs were subjected to a 15-minute period of regional myocardial ischemia by snaring the left anterior descending coronary artery proximal to its first diagonal branch (170). After release of the snare, the dogs were given either placebo or T_3 (0.2μg/kg) at 30-minute intervals.

Plasma FT_3 levels fell significantly during the ischemic period in both groups and continued to fall after reperfusion in the untreated group. In both groups, cardiac function deteriorated significantly during the period of ischemia, but rapidly returned to control level after reperfusion. After 90 minutes of reperfusion, however, deterioration of left ventricular function was observed in untreated dogs, and was significantly worse than in the T_3-treated dogs, in which hemodynamic function was maintained and, in fact, improved to levels superior to control.

The studies indicated that regional myocardial ischemia alone reduces FT_3 levels, and that T_3 therapy might be worthy of a trial in patients in whom reperfusion of the myocardium takes place after a relatively short ischemic period (the 'stunned myocardium').

Thyroid hormone therapy therefore may be beneficial in several conditions, and, indeed, may have a place in the treatment of other pathologic entities; it is worthy of further exploration.

16. ACKNOWLEDGEMENTS

David K.C. Cooper and Dimitri Novitzky contributed equally to this work. DKCC, DN and WNW thank their many former colleagues in Cape Town and Oklahoma City who contributed to the studies reviewed here. Dr H. Myron Kauffman died during the preparation of this manuscript.

17. REFERENCES

1. W. N. Wicomb, S.T. Boyd, D.K.C. Cooper, A.G. Rose and C.N. Barnard. *Ex vivo* functional evaluation of pig hearts subjected to 24 hours preservation by hypothermic perfusion. *S Afr Med J* 60:245-248 (1981)

2. W.N. Wicomb, D.K.C Cooper and C.N. Barnard. Twenty-four hour preservation of the pig heart by a portable hypothermic perfusion system. *Transplantation* 34:246-250 (1982)

3. W.N. Wicomb, D.K.C. Cooper, J. Hassoulas, A.G. Rose and C.N. Barnard. Orthotopic transplantation of the baboon heart after 20 to 24 hours' preservation by continuous hypothermic perfusion with an oxygenated hyperosmolar solution. *J Thorac Cardiovasc Surg* 83:133-140 (1982)

4. D.K.C. Cooper, W.N. Wicomb, and C.N. Barnard. Storage of the donor heart by a portable hypothermic perfusion system: experimental development and clinical experience. *J Heart Transplant* 2:104-110 (1983)

5. D.K.C. Cooper, W.N. Wicomb, A.G. Rose and C.N. Barnard. Orthotopic allotransplantation and autotransplantation of the baboon heart following twenty-four hours storage by a portable hypothermic perfusion system. *Cryobiology* 20:385-394 (1983)

6. W.N. Wicomb, D.K.C. Cooper, D. Novitzky and C.N. Barnard. Cardiac transplantation following storage of the donor heart by a portable hypothermic perfusion system. *Ann Thorac Surg* 37:243-248 (1984)

7. W.N. Wicomb, D.K.C. Cooper and D. Novitzky. An airlift pump device for low pressure perfusion storage of the isolated heart. *Cryobiology* 22:401-408 (1985)

8. W.N. Wicomb, D. Novitzky, D.K.C. Cooper and A.G. Rose. Forty-eight hours hypothermic perfusion storage of pig and baboon hearts. *J Surg Res* 40:276-284 (1986)

9. W.N. Wicomb, A.G. Rose, D.K.C. Cooper and D. Novitzky. Haemodynamic and myocardial histological and ultrastructural studies in baboons three to twenty seven months following autotransplantation of hearts stored by hypothermic perfusion for 24 or 48 hours. *J Heart Transplant* 5:122-129 (1986)

10. D.K.C. Cooper, W.N. Wicomb and D. Novitzky. Cardiac transplantation following storage of the donor heart by a portable hypothermic perfusion system: the initial clinical experience. In: Terasaki, P.I. (Ed). Clinical

Transplants, *Terasaki Foundation Laboratory,* Los Angeles (2006)

11. C.N. Barnard and J.G. Losman. Left ventricular bypass. *S Afr Med* J 49:303-312 (1975)

12. J. G. Losman, H. Levine, C.D. Campbell, R.L. Replogle, J. Hassoulas, D. Novitzky, D.K.C. Cooper and C.N. Barnard. Changes in indications for heart transplantation: an additional argument for the preservation of the recipient's own heart. *J Thorac Cardiovasc Surg* 84:716-726 (1982)

13. D. Novitzky, D.K.C. Cooper and C.N. Barnard. The surgical technique of heterotopic heart transplantation. *Ann Thorac Surg* 36:476-482 (1983)

14. D.K.C. Cooper, D. Novitzky, E. Becerra, and B. Reichart . Are there indications for heterotopic heart transplantation in 1986? A 2 to 11 year follow up of 49 consecutive patients undergoing heterotopic heart transplantation. *The Thor Cardiovasc Surgeon* 34:300-304 (1986)

15. E. Becerra, D.K.C. Cooper, D. Novitzky and B. Reichart. Are there indications for heterotopic heart transplantation today? *Transplant Proc* 19:2512-2513 (1987)

16. D. Novitzky, D.K.C. Cooper and C.N. Barnard. Reversal of acute rejection by cyclosporine in a heterotopic heart transplant. *J Heart Transplant* 3:117-120 (1984)

17. D. Novitzky, D.K.C. Cooper, A.G. Rose and C.N. Barnard. The value of recipient heart assistance during severe acute rejection following heterotopic cardiac transplantation. *J Cardiovasc Surg* 25:287-295 (1984)

18. D. Novitzky, D.K.C. Cooper and C.N. Barnard. Circulatory assistance with allograft. *Ann Thorac Surg* 37: 2 (1984)

19. D.K.C. Cooper, D. Novitzky, C.A. Romero, R.M.Clark, J.S. Chaffin, A.E. Greer, D. Novitzky, C.N. Barnard and N. Zuhdi. Indications for heterotopic heart transplantation, and report on two patients. *J Okla State Med Assoc* 81:513-517 (1988)

20. H. Cushing. Some experimental and clinical observations concerning states of increased intracranial tension. *Am J Med Sci* 124:373-.400 (1902)

21. B. Shivalkar, J. Van Loon, W. Wieland, T.B. Tjandra-Maga, M. Borgers and C. Plets. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. *Circulation* 87:230-239 (1993)

22. H. Schrader, K. Krogness, A. Aakvaag, O.Sortland and K. Purvis. Changes of pituitary hormones in brain death. *Acta Neurochir* 52:239-248 (1980).

23. G.M.Hall, K. Mashiter, J. Lumley and J.G. Robson. Hypothalamic-pituitary function in the 'brain-dead' patient. *Lancet* ii:1259 (1980)

24. D. Novitzky, D.K.C. Cooper, A.G. Rose, W.N. Wicomb, E. Becerra and B. Reichart. Early donor heart failure following transplantation - the possible role of myocardial injury sustained during brain death. *Clin Transplantation* 1:108-113 (1987)

25. D. Novitzky, J. Rhodin, D.K.C. Cooper, Y.Ye, K-W. Min and L.Debault . Ultrastructure changes associated with brain death in the human donor heart. *Transplant Int* 10:24-32 (1997)

26. D.K.C. Cooper, J.C.De Villiers, L.S. Smith, Y.Crombie, S.T.Boyd, J.E.Jacobson and C.N. Barnard. Medical, legal and administrative aspects of cadaveric organ donation in the Republic of South Africa. *S Afr Med J* 62:933-938 (1982)

27. D. Novitzky, W.N. Wicomb, D.K.C. Cooper, A.G. Rose, R.C. Fraser and C.N. Barnard. Electrocardiographic, haemodynamic and endocrine changes occurring during experimental brain death in the Chacma baboon. *J Heart Transplant* 4:63-69 (1984)

28. D. Novitzky, A. Horak, D.K.C Cooper and A.G. Rose. Electrocardiographic and histopathologic changes developing during experimental brain death in the baboon. *Transplant Proc* 21:2567-2569 (1989)

29. D.K.C. Cooper, D. Novitzky and W.N. Wicomb. The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. *Ann R Coll Surg Engl* 71:261-266 (1989).

30. D. Novitzky, W.N. Wicomb, A.G. Rose, D.K.C. Cooper, and B. Reichart. Pathophysiology of pulmonary edema following experimental brain death in the Chacma baboon. *Ann Thorac Surg* 43:288-294 (1987)

31. D. Novitzky, A.G. Rose, D.K.C. Cooper and B. Reichart. Interpretation of endomycordial biopsy after heart transplantation – potentially confusing factors. *S Afr Med* J 70;789-792 (1986)

32. D. Novitzky, W.N. Wicomb, D.K.C. Cooper, A.G. Rose, R.C. Fraser and B.Reichart. Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. *Ann Thorac Surg* 41:520-524 (1986)

33. D. Novitzky, D.K.C. Cooper, A.G. Rose and B. Reichart. Prevention of myocardial injury by pretreatment with verapamil hydrochloride following experimental brain death: efficacy in a baboon model. *Am J Emerg Med* 15:11-18 (1987)

34. D. Novitzky, A.G. Rose and D.K.C. Cooper. Injury of myocardial conduction tissue and coronary artery smooth muscle following brain death in the baboon. *Transplantation* 45: 964-966 (1988)

35. J. Pratschke, M.J. Wilhelm, M. Kusaka, M. Basker, D.K.C. Cooper, W.W.Hancock and N.L. Tilney. Brain death and its influence on donor organ quality and outcome after transplantation. *Transplantation* 67:343-348 (1999)

36. W.N. Wicomb, D.K.C. Cooper and D.Novitzky. Impairment of renal slice function following brain death, with reversibility of injury by hormonal therapy. *Transplantation* 41:29-33 (1986)

37. W.N. Wicomb, D.K.C. Cooper, R.P. Lanza, D. Novitzky and S. Isaacs. The effects of brain death and 24 hours storage by hypothermic perfusion on donor heart function in the pig. *J Thorac Cardiovasc Surg* 91:896-909 (1986)

38. D. Novitzky, D.K.C. Cooper, D. Morrell and S. Isaacs. Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine (T3) therapy. *Transplantation* 45:32-36 (1988)

39. D. Novitzky, W.N. Wicomb, D.K.C. Cooper and M.A. Tjaalgard. Improved cardiac function following hormonal therapy in brain dead pigs: relevance to organ donation. *Cryobiology* 24:1-10 (1987)

40. D. Novitzky, D.K.C. Cooper and B. Reichart. Haemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. *Transplantation* 43:852-854 (1987)

41. D. Novitzky. Heart transplantation, euthyroid sick syndrome, and triiodothyronine replacement. *J Heart Lung Transplant* 11:196-198 (1992)

42. D.R. Wheeldon, C.D.O. Potter, A. Oduro, J. Wallwork and S.R. Large. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. *J Heart Lung Transplant* 14:734-742 (1995)

43. V. Jeevanandam, B. Todd, T. Regillo, S. Hellman, C. Eldridge, and J. McClurken. Reversal of donor myocardial dysfunction by triiodothyronine replacement therapy. *J Heart Lung Transplant* 12:681-687 (1994)

44. V. Jeevanandam. Triiodothyronine: spectrum of use in heart transplantation. *Thyroid* 7:139-145 (1997)

45. A. Salim, P.Vassiliu, G.C. Velmahos, J. Sava, J.A. Murray, H. Belzberg, J.A. Asensio and D. Demetriades. The role of thyroid hormone administration in potential organ donors. *Arch Surg* 136:1377-1380 (2001)

46. A.F. Zuppa, V. Nadkarni, L. Davis, P.C. Adamson, M.A. Helfaer, M.R. Elliott, J. Abrams and D. Durbin. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med* 32:2318-2322 (2004)

47. D.J. Powner, A. Hendrich, R.G. Lagler, R.H. Ng and R.L. Madden. Hormonal changes in brain dead patients. *Crit Care Med* 18:702-708 (1990)

48. H-J. Gramm, H. Meinhold, U. Bickel, J. Zimmermann, B. Hammerstein, F. Keller, R. Dennhardt and K. Voigt. Acute endocrine failure after brain death? *Transplantation* 54:851-857 (1992)

49. T. Randell and K.A. Hockerstedt. Triiodothyronine treatment in brain-dead multiorgan donors – a controlled study. *Transplantation* 54:736-738 (1992)

50. J.P. Goarin, S. Cohen, B. Riou, Y. Jacquens, R. Guesde, F. LeBret, A. Aurengo and P. Coriat. The effect of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. *Anesth Analg* 83:41-47 (1996)

51. B. M.Power and P.V. Van Heerden. The physiological changes associated with brain death – current concepts and implications for treatment of the brain dead organ donor. *Anesth Intensive Care* 23:26-36 (1995)

52. P.M.Mertes, K.E. Abassi, Y. Jaboin, P. Burtin, G. Pinelli, J.P. Carteaux, C. Burlet, M. Boulange and J.P. Villemot. Changes in hemodynamic and metabolic parameters following induced brain death in the pig. *Transplantation* 58:414-418 (1994)

53. B. Lagiewska, M. Pacholczyk, M. Szostek, J. Walaszewski and W. Rowinski. Hemodynamic and metabolic disturbances observed in brain-dead organ donors. *Transplant Proc* 28:165-166 (1996)

54. M. Szostek, Z. Gaciong, R. Danielelelewicz, B. Lagiewska, M. Pacholczky, A. Chmura, I. Laskowski, J. Walaszewski and W. Rowinski. Influence of thyroid function in brain stem death donors on kidney allograft function. *Transplant Proc* 29:3354-3356 (1997)

55. H. Pienaar, I. Schwartz, A. Roncone, Z. Lotz and R. Hickman. Function of kidney grafts from brain-dead donor pigs. *Transplantation* 50:580-582 (1990)

56. F. Masson, M. Thicoipe, H. Gin, A. Mascarel, R.M.Angibeau, J-F. Favarel-Garrigues and P. Erny. The endocrine pancreas in brain-dead donors. *Transplantation* 56:363-367 (1993)

57. J. Harms, F-E. Isemer and H. Kolenda. Hormonal alteration and pituitary function during course of brain-stem death in potential organ donors. *Transplant Proc* 23:2614-2616 (1991)

58. I.E. Sazontseva, I.A. Kozlov, Y.G. Moisuc, A.E. Ermolenko, V.V. Afonin and V.V. Ilnitskiy. Hormonal response to brain death. *Transplant Proc* 23:2467 (1991)

59. J. Mariot, L-O. Sadoune, F. Jacob, B. Dousset, J.F. Perrier, C. Jacob, P. Strub and C. Voltz. Hormone levels, hemodynamics and metabolism in brain-dead organ donors. *Transplant Proc* 27:793-794 (1995)

60. J.J. Colpart, S. Ramella, M. Bret, B. Coronel, D. Dorez, A. Mercatello, A. H.Aissa and J.F. Moskovtchenko. Hypophysis-thyroid axis disturbances in human brain-dead donors. *Transplant Proc* 28:171-172 (1996)

61. J. A. Macoviak, I.R. McDougall, M.F. Bayer, M. Brown, H. Tazelaar and E.B. Stinson. Significance of

thyroid dysfunction in human cardiac allograft procurement. *Transplantation* 43:824-826 (1987)

62. H. Yoshida, A. Hiraide, A. Iwai, N. Kawaguchi, T. Yoshioka and T.Sugimoto. Preservation of pancreatic endocrine function by hemodynamic stabilization following brain death. *Clin Transplant* 11:420-425 (1997)

63. G. Szabo, C. Sebening, T. Hackert. C. Hagl, U. Tochermann, C.F. Vahl and S. Hagl. Effects of brain death on myocardial function and ischemic tolerance of potential donor hearts. *J Heart Lung Transplant* 17:921-930 (1998)

64. G. Baroldi, G. Di Pasquale, M.D. Silver, G. Pinelli, A.M. Lusa, and V. Fineschi. Type and extent of myocardial injury related to brain damage and its significance in heart transplantation: a morphometric study. *J Heart Lung Transplant* 16:994-1000 (1997)

65. J. A. Amado, F. Lopez-Espadas, A. Vazquez-Barquero, E. Salas, J.A. Riancho, J. J. Lopez-Cordovilla and M.T. Garcia-Unzueta. Blood levels of cytokines in brain-dead patients: relationship with circulating hormones and acute-phase reactants. *Metabolism* 44:812-816 (1995)

66. H.J. Gramm, J. Zimmermann, H. Meinhold, R. Dennhardt and K. Voigt. Hemodynamic responses to noxious stimuli in brain-dead organ donors. *Intensive Care Med* 18:493-495 (1992)

67. M. Washida, R. Okamoto, D. Manaka, T. Yokoyama, Y. Yamamotom, K. Ino, N. Yamamoto, N. Osaki, Y. Shimahara, Y. Yamaoka, K. Kumada and K. Ozawa. Beneficial effect of combined 3,5,3'-triiodothyronine and vasopressin administration on hepatic energy status and systemic hemodynamics after brain death. *Transplantation* 54:44-49 (1992)

68. J. Link, R. Rohling, and H.J. Gramm. Preservation of homeostasis following the onset of brain death. *Anaesthesiol Reanim* 4:249-260 (1990)

69. J. Mariot, F. Jacob, C. Voltz, J.F. Perrier, and P. Strub . Value of hormonal treatment with triiodothyronine and cortisone in brain dead patients. *Ann Fr Anesth Reanin* 4:321-328 (1991)

70. G.J.B.B. Bruinsma, M.G.J. Nederhoff, B.C.M. te Boekhorst, J.J. Bredee, T.J.C. Ruigrok and C.J.A. van Echteld. Brain death-induced alterations in myocardial workload and high-energy phosphates: a phosporus 31 magnetic resonance spectroscopy study in the cat. *J Heart Lung Transplant* 17:984-990 (1998)

71. M. Galinanes and D.J. Hearse. Brain death-induced contractile dysfunction and long-term cardiac preservation. *Circulation* 88:270-280 (1993)

72. H. B.Bittner, S.W.H Kendall, E.P. Chen and P. VanTrigt. The combined effects of brain death and cardiac graft preservation and cardiopulmonary hemodynamics and function before and subsequent heart transplantation. *J Heart Lung Transplant* 15:764-777 (1996)

73. D. Tixier, G. Matheis, G.D. Buckberg, and H.H. Young. Donor hearts with impaired hemodynamics. Benefit of warm substrate-enriched blood cardioplegic solution for induction of cardioplegia during cardiac harvesting. *J Thoracic Cardiovasc Surg* 102:207-213 (1991)

74. S. Darracott-Cankovic, J. Hutter, J. Wallwork, D. Wheeldon and T. A. English. Biopsy assessment of myocardial preservation in 160 human donor hearts. *Transplant Proc* 20 (5, Suppl 7):44-48 (1988).

75. H. B. Bittner, E.P. Chen, C.A. Milano, S.W. Kendall, R.B. Jennings, D.C. Sabiston and P. Van Trigt. Myocardial β-adrenergic receptor function and high-energy phosphates in brain death-related cardiac dysfunction. *Circulation* 92 (9 suppl): II472-II478 (1995)

76. S. Darracott-Cankovic, P.G. Stovin, D. Wheeldon, J. Wallwork, F. Wells and T.A. English. Effect of donor heart damage on survival after transplantation. *Eur J Cardiothorac Surg* 3:525-532 (1989)

77. M. Galinanes and D.J. Hearse. Brain-death induced cardiac contractile dysfunction: studies of possible neurohormonal and blood-borne mediators. *J Mol Cell Cardiol* 26:481-498 (1994)

78. B. Riou, S. Dreux, S. Roche, M. Arthaud, J.P. Goarin, P. Leger, M. Saada and P. Viars. Circulating cardiac troponin T in potential heart transplant donors. *Circulation* 92:409-414 (1995)

79. T. Kiitai, A. Tanaka, M. Terasaki, R. Okamoto, K. Ozawa, S. Morikawa and T. Inubushi. Energy metabolism of the heart and the liver in brain-dead dogs as assessed by ^{31}P NMR spectroscopy. *J Surg Res* 55:599-606 (1993)

80. G. Pinelli, P.M. Mertes, J.P. Carteaux, Y. Jaboin and J.P. Villemot. Consequences of brain death of myocardial metabolism: experimental study using ^{31}P-nuclear magnetic resonance spectroscopy. *Transplant Proc* 27:1650-1651 (1995)

81. G. Pinelli, P.M. Mertes, J.P. Carteaux Y. Jaboin, J.M. Escanye, F. Brunotte and J.P. Villemot. Myocardial effects of experimental acute brain death: evaluation by hemodynamic and biological studies. *Ann Thorac Surg* 60:1729-1734 (1995)

82. S. Taniguchi, S. Kitamura, K. Kawachi, Y. Doi and N. Aoyama. Effects of hormonal supplements on the maintenance of cardiac function in potential donor patients after cerebral death. *Eur J CardioThorac Surg* 6:96-102 (1992)

83. V. Jeevanandam, B. Todd, S. Hellman, C. Eldridge, J. McClurken and V.P. Addonizio. Use of triiodothyronine replacement therapy to reverse donor myocardial dysfunction: creating a larger donor pool. *Transplant Proc*

25:3305-3306 (1993)

84. C. Sebening, C. Hagl, G. Szabo, U. Tochtermann, G. Strobel, P. Schnabel, K. Amann, C.F. Vahl and S. Hagl. Cardiocirculatory effects of acutely increased intracranial pressure and subsequent brain death. *Eur J Cardiothorac Surg* 9:360-372 (1995)

85. C.H. Meyers, T.A. D'Amico. D.S. Peterseim, A.M. Jayawant, C. Steenbergen, D.C. Sabiston, and P. Van Trigt. Effects of triiodothyronine and vasopressin on cardiac function and myocardial blood flow after brain death. *J Heart Lung Transplant* 2:68-80 (1993)

86. T.S. Huber, M.A. Groh, K.P. Gallagher and L.G. D'Alecy. Myocardial contractility in a canine model of the brain-dead organ donor. *Crit Care Med* 21:1731-1739 (1993)

87. H.B. Bittner, S.W.H. Kendall, E.P. Chen, R.D. Davis and P. Van Tright. Myocardial performance after graft preservation and subsequent cardiac transplantation from brain dead donors. *Ann Thorac Surg* 60:47-54 (1995)

88. M. Galinanes and D.J. Hearse. Brain death-induced impairment of cardiac contractile performance can be reversed by explantation and may not preclude the use of hearts for transplantation. *Circ Res* 71:1213-1219 (1992)

89. G. J. Bruinsma, M.G. Nederhoff, H.J. Geertman, A.C. van Huffelen, P.J. Slootweg, R. Ferrari, M. Galinanes, D.J. Hearse, J.J. Bredee and T.J. Ruigrok. Acute increase of myocardial workload, hemodynamic instability and myocardial histologic changes induced by brain death in the cat. *J Surg Res* 68:7-15 (1997)

90. T.A. D'Amico, D.A. Schwinn , C. H. Meyers, D.C. Sabiston and P. Van Trigt. Desentization of myocardial β-adrenergic receptors after brain death. *Surg Forum* 43:249-251 (1992)

91. H. B. Bittner, S.W.H. Kendall, K.A. Campbell, T.J. Montine and P. Van Tright. A valid experimental brain death organ donor model. *J Heart Lung Transplant* 14:308-317, (1995)

92. T. T.Randell and K.A.V. Hockerstedt . Triiodothyronine treatment is not indicated in brain dead multiorgan donors: a controlled study. *Transplant Proc* 25:1552-1553 (1993)

93. S.H. Pennefather and R. E. Bullock. Triiodothyronine treatment in brain dead multiorgan donors – a controlled study. *Transplantation* 55:1443 (1993)

94. Y. Kinoshita, K.Okamoto, K. Yahata, T. Yosioka, T. Sugimoto, N. Kawaguch and S. Onishi. Clinical and pathophysiological changes of the heart in brain death maintained with vasopressin and epinephrine. *Path Res Pract* 186:173-179 (1990)

95. H. Van Houten, H.G. Gooszen, P.J. van den Akker , H.H. Lemkes, M. Frolich, M. Van Gurp, F.J. van der Woude, J. Rischen-Vos and J.L. Terpstra. Plasma insulin, C-peptide, HbAlc, plasma glucose levels in organ donors. *Transplant Proc* 22:435-436 (1990)

96. A. Iwai, T. Sakano, M. Uenishi, H. Sugimoto, T. Yoshioka and T. Sugimoto. Effect of vasopressin and catecholamines on the maintenance of circulatory stability in brain-dead patients. *Transplantation* 48:613-617 (1989)

97. P.F. Gores, A.Viste, U.J. Hesse, K.C. Moudry-Munns, D.L. Dunn and D.E. Sutherland. The influence of donor hyperglycemia and other factors on long-term pancreatic allograft survival. *Transplant Proc* 22:437-438 (1990)

98. U.J. Hess, P.F. Gores and D.E.R.Sutherland. Serum amylase and plasma glucose levels in pancreas cadaver donor: correlation with functional status of the pancreatic graft. *Transplant Proc* 21:2765 (1989)

99. H. Yoshida, A. Hiraide, T. Yoshioka and T. Sugimoto. Transient suppression of pancreatic endocrine function in patients following brain death. *Clin Transplant* 10:28-33 (1996)

100. K. Okamoto, Y. Kinoshita, T. Yushioka, N. Kawaguchi, S. Onishi and T. Sugimoto. Myocardial preservation in brain-dead patients maintained with vasopressin and catecholamine. *Clin Transplant* 6:294-300 (1992)

101. T. Nagareda, Y. Kinoshita, A. Tanaka, M. Takeda, T. Sakano, K. Yawata, T. Sugimoto, Y. Nishizawa and N. Terada. Clinicopathology of kidneys from brain-dead patients treated with vasopressin and epinephrine. *Kidney Int* 43:1363-1370 (1993)

102. T. Yoshioka, H. Sugimoto, M. Uenishi, T. Sakamoto, D. Sadamitsu, T. Sakano and T. Sugimoto. Prolonged hemodynamic maintanence by the combined administration of vasopressin and epinephrine in brain death: clinical study. *Neurosurgery* 18:565-567 (1986)

103. T. Nagareda, Y. Kinoshita, A. Tanaka, Y. Hasuike, N. Terada, Y. Nishizawa, M. Fujita, H. Kuroda, K. Yawata, K. Aozasa, T. Sakano, T. Sugimoto and K. Kotoh. Clinicopathological study of livers from brain-dead patients treated with a combination of vasopressin and epinephrine. *Transplantation* 47:792-797 (1989)

104. T.A. Howlett, A.M. Keogh, A. Perry, R. Touzel and L.H. Rees. Anterior and posterior pituitary function in brain-stem-dead donors. A possible role for hormonal replacement therapy. *Transplantation* 47:828-834 (1989)

105. Y. Kinoshita, K. Yahata, T. Yoshioka, S. Onishi and T. Sugimoto. Long-term renal preservation after brain death maintained with vasopressin and epinephrine. *Transplant Int* 3:15-18 (1990)

106. E. Arbustini, R. Pozzi, M. Grasso, C. Campana, A. Martinelli, C. Montemartini, A. Gavazzi, A. Pucci,

M.Diegoli, G.Graziano, C. Goggi and M.Vigano. Endomyocardial biopsy of normal donor hearts before cardiac transplantation. A morphological and morphometrical study in 97 cases. *Am J Cardiovasc Pathol* 4:1-8 (1992)

107. K. Arita, T. Uozumi, S. Oki, M. Ohtani, H. Taguchi and M. Morio. Hypothalamic pituitary function in brain death patients -- from blood pituitary hormones and hypothalamic hormones. *Neurol Surg* (Tokyo) 16:1163-1171 (1988)

108. T. Aruga, K. Ono, N. Kawahara, M. Sasaki, H. Tsutsumi, H.Toyooka, K. Mii, M. Tsuzuki and K. Takakura. Some practical problems of clinical diagnosis of brain death. *Brain and Nerve* (Tokyo) 35:777-785 (1983)

109. P. Herinjgers, V. Leunens, T. B. Tjandra-Maga, K. Mubagwa and W. Flameng. Changes in organ perfusion after brain death in the rat and its relation to circulating catecholamines. *Transplantation* 62:330-335 (1996)

110. D. Powner, A. Hendrich, A. Nyhuis and R. Strate. Changes in serum catecholamine levels in patients who are brain dead. *J Heart Lung Transplant* 11:1046-105 (1992)

111. I. Finkelstein, L.H. Toledo-Pereyra and J. Castellanos. Physiologic and hormonal changes in experimentally induced brain dead dogs. *Transplant Proc* 19:4156 (1987)

112. F. Masson, M. Thicoipe, M.J. Latapie MJ and P. Maurette. Thyroid function in brain- dead donors. *Transplant Int* 3:226-233 (1990)

113. J. Harms, F-E. Isemer and H. Kolenda. Hormonal alteration and pituitary function during course of brain-stem death in potential organ donors. *Transplantation* 56:363, (1993)

114. K. Arita, T. Uozumi, S. Oki, M. Ohtani and T.Mikami. The function of the hypothalamo-pituitary axis in the brain dead patients. *Acta Neurochir* 123:64-75 (1993)

115. D. H. Fiser, J. Jimenez, V. Wrape and r. Woody. Diabetes insipidus in children with brain death. *Crit Care Med* 15:551-553 (1987)

116. T. Sugimoto, T. Sakano, Y. Konoshita, M. Masui and T. Yoshioka. Morphological and functional alterations of the hypothalamic-pituitary system in brain death with long term bodily living. *Acta Neurochir* 115:31-36 (1992)

117. P. M. Mertes, P. Burtin, J.P. Carteaux, Y. Jaboin, C. Dopff, G. Pinelli, J.P. Villemot, C. Burlet and M. Boulange. Brain death and myocardial injury: role of cardiac sympathetic innervation evaluated by *in vivo* interstitial microdialysis. *Transplant Proc* 26:231-232 (1994)

118. K.M. Outwater and M.A. Rockoff. Diabetes insipidus accompanying brain death in children. *Neurology* 34:1243-1246 (1984)

119. K.M. Robertson, I.M. Hramiak and A.W. Gelb. Endocrine changes and hemodynamic stability after brain death. *Transplant Proc* 21:1197-1198 (1989)

120. E. M.Blaine, R.D. Tallman, D. Frolicher, M.A Jordan, L.L. Bluth and M.B. Howie. Vasopressin supplementation in a porcine model of brain-dead potential organ donors. *Transplantation* 38:459-464 (1984)

121. J.P. Orlowski and E.K. Spees. Improved cardiac transplant survival with thyroxine treatment of hemodynamically unstable donors: 95.2% graft survival at 6 and 20 months. *Transplant Proc* 25:1535 (1993)

122. T. Timek, A. Bonz, R. Dillmann, C.F. Vahl and S. Hagl. The effect of triiodothyronine on myocardial contractile performance after epinephrine exposure: implications for donor heart management. *J Heart Lung Transplant* 17:931-940 (1998)

123. A. Salim, M. Martin, C. Brown, K. Inaba, B. Roth, P Hadjizacharia, A. Mascharenhas,P.Rhee and D. Demetriades. Using the thyroid hormone in brain-dead donors to maximize the number of organs available for transplantation. *Clin Transplant* 21:405-409 (2007)

124. A. Salim, G.C. Velmahos, C. Brown, H. Belzberg and D. Demetriades. Aggressive organ donor management significantly increases the number of organs available for transplantation. *J Trauma* 58:991-994 (2005)

125. L.C. Garcia-Fages, M. Antolin, C. Cabrer, R. Talbot, A. Alcaraz, F. Lozano and M. Manyalich. Effects of substitute triiodothyronine therapy on intracellular nucleotide levels in donor organs. *Transplant Proc* 23:2495-2496 (1991)

126. K. Karayalcin, J.P. Umana, J.D. Harrison, J.A. Buckels, P. McMaster, and A.D. Mayer. Donor thyroid function does not affect outcome in orthotopic liver transplantation. *Transplantation* 57:669-672 (1994)

127. T. Walhers, H.G. Fieguth, M. Jurmann, *et al.* Does hormone depletion of organ donors impair myocardial function after cardiac transplantation? *Transplant Proc* 20:792 (1988)

128. J.P. Orlowski. Use of T_4 for managing hemodynamically recovery systems. *Transplant Management* 2:13. (1990)

129. J. P. Orlowski. Evidence that thyroxine (T4) is effective as a hemodynamic rescue agent in management of organ donors. *Transplantation 55*:959-960 (1993)

130. A. Perez-Blanco, J. Caturla-Such, J. Canovas-Robles and J. Sanchez-Paya. Efficiency of triiodothyronine treatment on organ donor hemodynamic management and adenine nucleotide concentration. *Intensive Care Med* 31:943-948 (2005)

131. H. Schrader, K. Krogness, A. Aakvaag, O. Sortland and K. Purvis. Changes of pituitary hormones in brain death.

Acta Neurochir (Wien) 52:239-248 (1980)

132. A.J. Hing, M. Hicks, S.R. Garlick, L. Gao, S.H. Kesteven, S.C. Faddy, M.K. Wilson, M.P. Feneley and P.S. Macdonald. The effects of hormone resuscitation on cardiac function and hemodynamics in a porcine brain-dead organ donor model. *Am J Transplant* 7:809-817 (2007)

133. C. Seguin, Y. Devaux, S. Grosjean, E.M. Sighy, P. Mairose, F. Zannad, N. deTalance, D. Ungureanu-Longrois and P.M. Mertes . Evidence of cuntional myocardial ischemia associated with myocardial dysfunction in brain-dead pigs. *Circulation* 104[12 Suppl 1]:I197-I201 (2001)

134. M.J. Wilhelm, J. Pratschke, I.A. Laskowski, D.M. Paz and N.L. Tilney. Brain death and its impact on the donor heart-lessons from animal models. *J Heart Lung Transplant* 19:414-418 (2000)

135. R.R. Gifford, A.S. Weaver, J.E. Burg, P. J. Romano, L.M. Demers and J.L. Pennock. Thyroid hormone levels in heart and kidney cadaver donors. *J Heart Transplant* 5:249-253 (1986)

136. J. Pratsche, G. Kofla, M.J. Wilhelm, A. Vergopoulos, I. Laskowski, G.D. Shaw, S.G. Tullius, H.D. Volk, P. Neuhaus and N.L. Tilney. Improvements in early behavior of rat kidney allografts after treatment of the brain-dead donor. *Ann Surg* 234:732-740 (2001)

137. M. Takada, K.C. Nadeau, W.W. Hancock, H.S. Mackenzie, G.D. Shaw, A.M. Waaga, A. Chandraker, M.H. Sayegh and N.L. Tilney. Effects of explosive brain death on cytokine activation of peripheral organs in the rat. *Transplantation* 65:1533-1542 (1998)

138. H.B. Bittner, E.P. Chen, D. Craid and P.Van Trigt. Preload-recruitable stroke work relationships and diastolic dysfunction in the brain-dead organ donor. *Circulation* 94 [9 Suppl]:II320-II325 (1996)

139. J.M. Lyons, J.M. Pearl, K.M. McLean, S.A. Akhter, C.J. Wagner, P.K. Pandalai and J.Y. Duffy. Glucocorticoid administration reduces cardiac dysfunction after brain death in pigs. *J Heart Lung Transplant* 24:2249-2254 (2005)

140. J.B. Ryan, M. Hicks, J.R. Cropper, S.R. Garlick, S.H. Kesteven, M.K. Wilson, M.P. Feneley and P.S. Macdonald. Functional evidence of reversible ischaemic injury immediately after sympathetic storm associated with experimental brain death. *J Heart Lung Transplant* 22:922-928 (2003)

141. T.A. D'Amico, C.H. Meyers, T.C. Koutlas, D.S. Peterseim, D.C. Sabiston, P. Van Trigt and D.A. Schwinn. Desensitization of myocardial beta-adrenergic receptors and deterioration of left ventricular function after brain death. *J Thoracic Cardiovasc Surgery* 110:746-751 (1995)

142. P. Chiari, G. Hadour, P. Michel, V. Piriou, C. Rodrigues, C. Budat, M. Ovize, O. Jegaden, J.J. Lehot and R. Ferrara. Biphasic response after brain death induction: prominent part of catecholamines release in this phenomenon. *J Heart Lung Transplant* 19:675-682 (2000)

143. E. P. Chen, H. B. Bittner, S.W. Kendall and P. Van Trigt. Hormonal and hemodynamic changes in a validated animal model of brain death. *Crit Care Med* 24:1352-1359 (1996)

144. B. R. Rosengard, S. Feng, E.J. Alfrey, J. G. Zaroff, J. C. Emond, M.L. Henry, E. R. Garrity, J.P. Roberts, J.J. Wynn, R.A. Metzger, R.B. Freeman, F.K. Port, R.M. Merion, R. B. Love, R.W. Busuttil and F.L. Delmonico. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. *Am J Transplant* 2: 701-711 (2002).

145. J.G. Zaroff, B.R. Rosengard, W.F. Armstrong, W.D. Babcock, A. D'Alessandro, G.W. Dec, N.M. Edwards, R.S. Higgins, V. Jeevanandum, M. Kauffman, J.K. Kirklin, S.R. Large, D. Marelli, T.S. Peterson, W.S. Ring, R.C. Robbins, S.D. Russell, D.O. Taylor, A. Van Bakel, J. Wallwork, and J.B. Young. Consensus Conference report: Maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, VA. *Circulation* 106: 836-841 (2002)

146. J.G. Zaroff, B.R. Rosengard, W.F. Armstrong, WD. Babcock, A. D'Alessandro, G.W. Dec, N.M. Edwards, R.S. Higgins, V. Jeevanandum, M. Kauffman, J. K. Kirklin, S.R. Large, D. Marelli, t.s. Peterson, W.S. Ring, R.C. robbins, S. D. Russell, D.O. Taylor, A. Van Bakel, J. Wallwork and J.B. Young. Maximizing use of organs recovered from the cadaver donor: cardiac recommendations. *J Heart Lung Transplant* 21: 1153-1160, 2002.

147. J.D. Rosendale, F.L. Chabalewski. M.A. McBride, E.R. Garrity, B.R. Rosengard, F.L. Delmonico and H.M. Kaufmann. Increased transplanted organs from the use of a standardized donor management protocol. *Am J Transplant* 2: 761-768 (2002)

148. D. Novitzky, D.K.C. Cooper, J.D. Rosendale and H.M. Kauffman. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation* 82:1396-1401 (2006)

149. J.D. Rosendale, H.M. Kauffman, M.A. McBride, F.L. Chabalewski, J.G. Zaroff, E.R. Garrity, F.L. Delmonico and B.R. Rosengard. Aggressive pharmacological donor management results in more transplanted organs. *Transplantation* 75: 482-487 (2003)

150. J. D.Rosendale, H.M. Kauffman, M.A. McBride, F. L. Chabalewski, J.G. Zaroff, E.R. Garrity, F.L. Delmonico and B.R. Rosengard. Hormonal resuscitation yields more transplanted hearts with improved early function. *Transplantation* 75: 1336-1341 (2003)

151. http://www.ccdt.ca/external/english/publications/organ-donor-guidelines.pdf. Accessed 2/15/06.

152. W. F. Bremner. K.M. Taylor, S. Baird, J. E. Thomson,

J.A. Thomson, J.G. Ratcliffe, T.D. Lawrie and W.H. Bain. Hypothalamo-pituitary thyroid axis function during cardiopulmomary bypass. *J Thorac Cardiovasc Surg*;75;392-399 (1978)

153. G. Robuschi, D. Medici, F. Fesani, G. Barboso, M. Montermini, L. D'Amato, E. Gardini, E. Borciani, E. Dall'Aglio, Salvi M.. Cardiopulmonary bypass: a lot T4 and T3 syndrome with blunted thyrotropinin (TSH) response to thyrotropin-releasing hormone (TRH). *Horm Res* 23:151-158 (1986)

154. D. Novitzky, P.A. Human and D.K.C. Cooper. Inotropic effect of triiodothyronine following myocardial ischaemia and cardiopulmonary bypass: an experimental study in pigs. *Ann Thorac Surg* 45:50-55 (1988)

155. D. Novitzky, P.A. Human, and D.K.C. Cooper. Effect of triiodothyronine (T3) on myocardial high energy phosphates and lactate following ischemia and cardiopulmonary bypass - an experimental study in baboons. *J Thorac Cardiovasc Surg* 96:600-607 (1988)

156. D. Novitzky, D.K.C. Cooper, and A. Swanepoel. Inotropic effect of triiodothyronine (T3) following myocardial ischemia and cardiopulmonary bypass: Initial experience in patients undergoing open heart surgery. *Eur J Cardiothorac Surg* 3:140-145 (1989)

157. D. Novitzky and D.K.C. Cooper. Changes in triiodothyronine during cardiopulmonary bypass: a clinical problem? *J Thorac. Cardiovasc Surg* 100:465 (1990)

158. D. Novitzky, D.K.C. Cooper, C.I., Barton, A. Greer, J. Chaffin, J. Grim and N. Zuhdi. Triiodothyroinine as an inotropic agent after open heart surgery. *J Thorac Cardiovasc Surg* 98;972-978 (1989)

159. D. Novitzky, H. Fontanet, M. Snyder, N. Coblio, D. Smith and V. Parsonnet. Impact of triiodothyronine on the survival of high risk patients undergoing open heart surgery. *Cardiology* 87:509-515 (1996)

160. C. M. Dyke, T. Yeh, J.D. Lehman, A. Abd-Elfattah, M.Ding, A. S. Wechsler and D.R. Salter. Triiodothyronine-enhanced left ventricular function after ischemic injury. *Ann Thorac Surg* 52:14-19 (1991)

161. R. Clark. Cardiopulmonary bypass and thyroid hormone metabolism. *Ann Thorac Surg* 56:35-42 (1993)

162. E. Lowenstein. Implications of triiodothyronine administration before cardiac and noncardiac operations. *Ann Thorac Surg* 56:43-47 (1993)

163. T.R. Snow, M.T. Deal, T.S. Connelly, Y. Yokoyama and D. Novitzky. Acute inotropic response of rabbit papillary muscle to triiodothyronine. *Cardiology* 80:112-117 (1992)

164. P. J. Davis and F.B. Davis. Acute cellular action of thyroid hormone and myocardial function. *Ann Thorac Surg* 56:16-23 (1993)

165. L. B.Gotzsche. Acute increase in cardiac performance after triiodothyronine: blunted response in amiodarone-treated pigs. *J Cardiovasc Pharmacol* 23:141-148 (1994)

166. K. Sterling, P.O. Milvch, M.A. Brenner and J.H.Lazarus. Thyroid hormone action: the mitochondrial pathway. *Science* 197:996-999 (1977)

167. D. Novitzky, D.K.C. Cooper, P. A. Human, B. Reichart and N. Zuhdi. Triiodothyronine therapy for heart donor and recipient. *J Heart Transplant* 7:370-376 (1988)

168. D. Novitzky, D.K.C. Cooper, J.S. Chaffin, A.E. Greer, L.E. Debault and N. Zuhdi. Improved cardiac allograft function following triiodothyronine therapy to both donor and recipient. *Transplantation* 49:311-316 (1990)

169. S. Taniguchi and D.K.C. D.K.C. Cooper. The potential role of thyroid hormone substitutes in cardiac surgery and transplantation. *Asia Pacific J Thorac Cardiovasc Surg* 5:40-46 (1996)

170. D. Novitzky, N. Matthews, D. Shawley, D.K.C. Cooper and N. Zuhdi. Triiodothyronine in the recovery of stunned myocardium in dogs. *Ann Thorac Surg* 51:10-17 (1991)

171. D.K.C. Cooper, D. Novitzky, and W.N. Wicomb. Hemodynamic and electrocardiographic responses. *Transplant Proc*, 20 [5 Suppl 7]:25-28 (1988)

172. D. Novitzky, D.K.C. Cooper, and N. Zuhdi. Triiodothyronine therapy in the cardiac transplant recipient. *Transplant Proc*, 20 [5 Suppl 7]:65-68 (1988)

Abbreviations: CPB = cardiopulmonary bypass, ECG = electrocardiographic, FT_3 = free triiodothyronine, T_3 = triiodothyronine

Key Words: Brain Death, Cardiopulmonary Bypass, Corticosteroids, Insulin, Organ Donation, Thyroid Hormones, Triiodothyronine, Review

Send correspondence to: David K.C. Cooper, FRCS, Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Starzl Biomedical Science Tower, W1540 , 200 Lothrop Street, Pittsburgh, PA 15261, Tel: 412-383-6961, Fax: 412-624-1172, E-mail: cooperdk@upmc.edu

http://www.bioscience.org/current/vol14.htm