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

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1. ABSTRACT

An acute decrease in cardiac performance can result from a reduced free triiodothyronine (FT₃) 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 FT₃. Deterioration of donor organ function can be reversed by hormonal replacement therapy, in which T₃ 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 FT₃, and this can be associated with deterioration in cardiac function. The administration of T₃ at the time of discontinuation of cardiopulmonary bypass reverses this state. In patients undergoing heart transplantation, T₃ 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 (FT₃) 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
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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 F[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
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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 H2O 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%, norepinephrine (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 (FT3 and thyroxine [T4]) 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...
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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 FT₃, 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
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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 support. 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).

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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 T₃ therapy

The principle of (i.v.) single-bolus kinetics with labeled carbon compounds (¹⁴C-R), with subsequent measurement of both plasma activity (half-life and plasma clearance) and of exhaled ¹⁴CO₂ was used to study glucose, pyruvate, and palmitate utilization under conditions of (i) sedation, (ii) brain death, and (iii) brain death with T₃ 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 T₃ 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 T₃ 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 (T₃, 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 T3, 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 T3 was excessive and induced a hyperthyroid state,
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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 (T3, 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 (T3, 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 T3 (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.
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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, T₃, 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 T₃ 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, T₃, and insulin enabled similar improvement in function of 19 inadequate donor hearts (45). At the University of Pennsylvania, 91 pediatric brain-dead donors receiving T₃ 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 FT₃, T₄, cortisol, and insulin after brain death (47, 48), and/or failed to demonstrate any beneficial cardiac and circulatory effect of T₃/T₄ administration (49, 50). This may possibly have been associated with one or more of the following points. (i) Some groups failed to measure plasma FT₃, but may have measured total T₃ 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 FT₃ levels); these donors may not be hemodynamically unstable, and the benefit from T₃/T₄ therapy might therefore not be seen. (iii) An inadequate dosage of T₃/T₄ 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-cm⁵, (v) cardiac index >2.4L/min-m², (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 T₃ FOLLOWING MYOCARDIAL ISCHEMIA AND CARDIOPULMONARY BYPASS IN EXPERIMENTAL ANIMALS

A significant reduction in plasma FT₃, 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 T₃ administration to brain-dead
organ donors suggested that the reduction in circulating FT₃ 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 cardiopлегic 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 T₃ i.v. immediately after removal of the aortic cross-clamp; the remainder received no T₃.

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 T₃-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 T₃-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 T₃ was significantly less than those that did. T₃ 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 T₃ 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 T₃ and six received 6µg of T₃ 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 T₃ 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. T₃ 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 T₃ 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 T₃ FOLLOWING MYOCARDIAL ISCHEMIA AND CARDIOPULMONARY BYPASS IN PATIENTS UNDERGOING OPEN HEART SURGERY

Initially, we administered T₃ (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 T₃ administration, the mean plasma free T₃ 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 H₂O. All changes were statistically significant. Inotropic support had been significantly reduced or discontinued.

To our knowledge, T₃ 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 T₃ 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 T₃ 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 T₃ 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 T₃, cortisol, insulin (and sometimes vasopressin), whereas recipients received T₃ 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
Thyroid hormone therapy in brain-dead organ donors

Figure 13. Mean level of plasma free triiodothyronine (T3, 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 T3 is shown (N); normal range, 3.3 to 5.0 pmol/L. There was a significant reduction of free T3 after 15 minutes CPB (p<0.0001), initially from hemodilution, which was maintained for 6 hours; free T3 levels remained low 24 hours after operation (p <0.0005). The mean level in an additional group of 20 patients in whom T3 was administered before the end of CPB is also shown (B). It can be seen that 4-10 µg of T3 administered intravenously raised circulating levels of the hormone to the lower limit of the normal range. Twenty-four hours after operation, plasma free T3 levels had fallen significantly (p<0.01) suggesting an inability of patients to produce sufficient T3 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 T3 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 + T3) and recipients (R + T3), 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 T₃ 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. T₃ 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 T₃ 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 T₃ therapy of the recipient at the end of the period of CPB.

15. EXPERIMENTAL STUDIES ON T₃ 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 T₃ (0.2µg/kg) at 30-minute intervals.

Plasma FT₃ 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 T₃-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 FT₃ levels, and that T₃ 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.

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17. REFERENCES


Thyroid hormone therapy in brain-dead organ donors

Transplants, Terasaki Foundation Laboratory, Los Angeles (2006)


Thyroid hormone therapy in brain-dead organ donors


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


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...
Thyroid hormone therapy in brain-dead organ donors


106. E. Arbusini, R. Pozzi, M. Grasso, C. Campana, A. Martinelli, C. Montemartini, A. Gavazzi, A. Pucci,
Thyroid hormone therapy in brain-dead organ donors


Thyroid hormone therapy in brain-dead organ donors


152. W. F. Brenner, K.M. Taylor, S. Baird, J. E. Thomson,
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Abbreviations: CPB = cardiopulmonary bypass, ECG = electrocardiographic, FT₃ = free triiodothyronine, T₃ = triiodothyronine

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