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Novel Actions of Thyroid Hormone: The Role of Triiodothyronine in Cardiac Transplantation

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ABSTRACT

In clinical heart transplantation, the heart is procured from brain dead (BD) organ donors who acutely experienced a variety of critical illnesses. In all of these conditions, a profound derangement of the thyroid profile has been observed. Although the plasma levels of thyroid stimulating hormone (TSH) remain unchanged, there is a rapid decline in free triiodothyronine (FT_3) levels ($p < 0.0001$) as well as an elevation of reverse triiodothyronine (rT_3) ($p < 0.001$). Following induction of experimental brain death, the heart exhibits a progressive significant hemodynamic-biochemical deterioration (reduction of cardiac contractility, depletion of high energy phosphates, glycogen, and accumulation of tissue lactate). The administration of T_3 to BD animals resulted in rapid reversal of the hemodynamic and metabolic derangements. The impact of T_3 therapy to unstable human brain dead organ donors has resulted in rapid hemodynamic stability allowing significant reduction of inotropic support ($p < 0.001$). These hearts, following cardiac transplantation, exhibited excellent hemodynamic function in the recipients. The low FT_3 state has also been observed during and following open heart surgery on cardiopulmonary bypass (CPB). Therefore, at the completion of the heart transplant procedure, T_3 was also administered to the recipient to prevent relapse of the hemodynamic-metabolic abnormality observed in the donor. The impact of T_3 therapy to initially unstable donors allowed for rapid inotropic reduction and recovery of the heart, thus enlarging the donor organ pool and improving the outcome of the recipients following cardiac transplantation.

INTRODUCTION

FOLLOWING ACUTE ILLNESSES and shock states, a low free plasma triiodothyronine (FT_3) has been observed. Associated with the low FT_3 state, there are significant elevation of reverse triiodothyronine (rT_3) and normal thyroid-stimulating hormone (TSH) levels that have been considered as an adaptive beneficial response the so called "euthyroid sick syndrome" (ESS) (1,2). During this state, the current conventional wisdom is not to administer thyroid hormone replacement as this would be deleterious to the patient.

Experimental and clinical studies have confirmed the beneficial effects of thyroid hormone replacement in multiple conditions exhibiting the ESS such as in brain dead organ donors (3), open heart surgery on cardiopulmonary bypass (4), stunned myocardium (5), hemorrhagic shock (6), and sepsis (7). The role of T_3 replacement in cardiac transplantation has been well studied.

As a result of extensive experimental studies on brain death, two major sets of tissue injuries have been described in the heart. The first is directly related to an acute catecholamine release (Fig. 1) triggered by the sudden increase of intracranial pressure, which is Ca^{2+} mediated, and manifested by electrocardiographic and histological injury patterns (8) (Fig. 2). The second is a metabolic injury affecting the body as a whole resulting from a significant reduction of hormonal plasma levels affecting mainly the thyroid profile. This progressive metabolic disintegration is related to inhibition of the aerobic metabolism at the mitochondrial level (9). Both types of tissue injury occur simultaneously. The first occurrence is usually at the time of the initial insult and the second becomes evident within hours or days. The autonomic "storm" occurs at the time of the initial event leading towards brain death. During this phase of excessive sympathetic activity, the tissue monodeodinase is activated converting thyrosine (T_4) into rT_3. As a result of the adrenergic "storm," there is a marked imbalance of oxygen supply and demand as evidenced by ECG abnormalities. During the same phase, significant systemic arterial hypertension and increased vascular resistance are associated with various types of ventricular dysrrhythmias occasionally resembling acute myocardial infarction (8). It is also noteworthy

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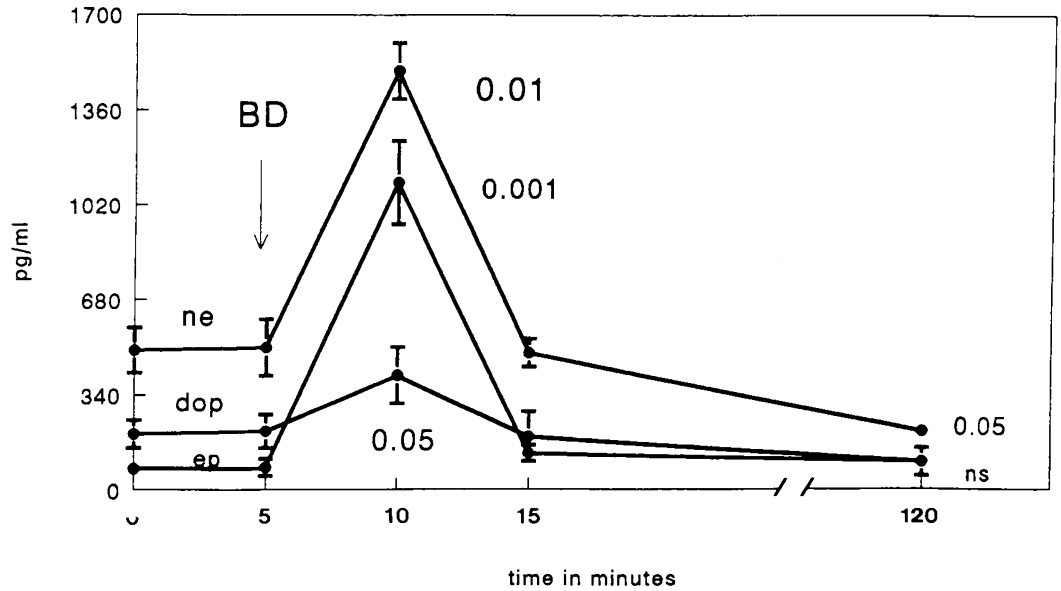

FIG. 1. Plasma catecholamines levels observed in experimental brain death in the baboon. The arrow indicates the time at which intracranial hypertension occurs (values expressed in mean ± SEM).

to mention that in the experimental BD model in the baboon, there are significant systemic and pulmonary hemodynamic alterations that occur at the peak of the systemic vascular resistance (8).

Autonomic storm

Experimental brain death studies in the baboon have shown during the acute phase of intracranial hypertension excessive parasympathetic and sympathetic activities. The parasympathetic activity is short-lived and rapidly replaced by a profound response to circulating and endogenous catecholamines (Fig. 2). Within 5 min following the rise of the intracranial pressure, circulating epinephrine, norepinephrine, and dopamine have risen significantly (Fig. 1); by 15 min, plasma levels were similar to control values; by 3 h, the plasma norepinephrine levels fell below controls (8,10).

Endocrine changes

Following induction of BD in the baboon, rapid endocrine disintegration was documented. There was a significant

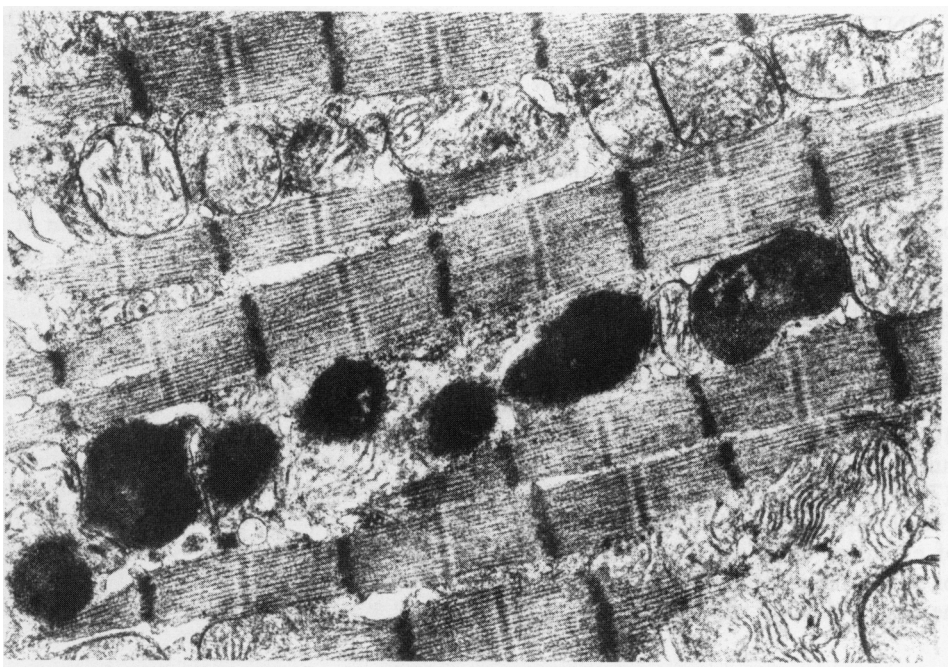

FIG. 2. Ultrastructure of a donor human heart immediately after cardioplegic arrest and explantation. Various degrees of mitrochondrial injury are observed; loss of membrane integrity, disruption of the matrix, and accumulation of electron dense material resembling calcium deposits. (Original magnification ×10,000.)

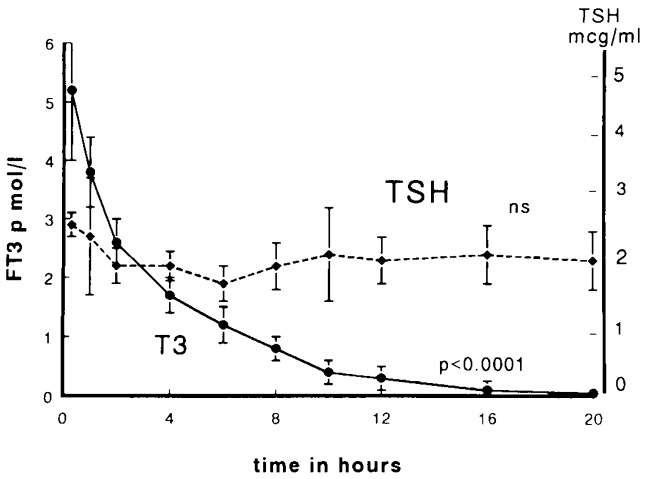

FIG. 3. Plasma free T_3 (FT_3) and TSH following induction of experimental brain death in the baboon (values expressed in mean ± SEM).

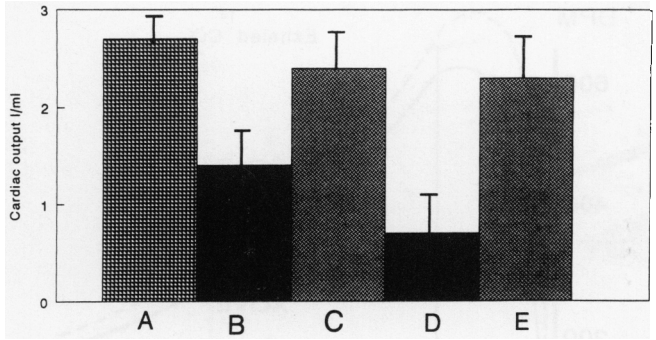

FIG. 4. Hemodynamic testing of hearts in a modified Langendorf model. The hearts were procured from the following: (A) live, (B) brain dead, (C) brain dead, T_3 treated, (D) brain dead and stored, and (E) brain dead, T_3 treated, and stored animal hearts. The hearts from brain dead animals had a significant reduction of the cardiac output: B vs. A $p < 0.01$ and D vs. A $p < 0.001$; the treated groups (C and E) were no different from group A.

rapid plasma reduction of FT_3 (Fig. 3) and FT_4 (not shown) and a marked plasma elevation of rT_3 (not shown). No changes of plasma thyroid-stimulating hormone (TSH) levels were noted (Fig. 3). Similarly, rapid plasma cortisol and insulin reduction were observed; however, glucagon remained unchanged. Antidiuretic hormone disappeared within a few hours after onset of brain death (8).

The low plasma FT_3, unchanged T_4, and TSH are characteristic of the ESS (1,2). This abnormal profile has been observed in other stress-related conditions, including cardiopulmonary bypass (CPB) (11), acute myocardial infarction (12), hemorrhagic shock (6), sepsis (7), congestive heart failure (13), and in patients awaiting cardiac transplantation (13). In all conditions, depressed myocardial function has been observed. The lower FT_3/rT_3 ratios correlated with poor patient outcome and were accurate predictors of death (14).

Hemodynamic and endocrine changes

Hearts procured from living and brain dead animals were tested *ex vivo* in a modified Langendorf model (15) and significant myocardial depression was observed. There was a reduction of the cardiac output (Fig. 4), stroke volume, and *dp/dt*. The LVEDP for fixed preload was elevated. There was significant myocardial tissue and plasma lactic acidosis, reduction of myocardial high energy phosphates [adenosine triphosphate (ATP), creatine phosphate (CP)], and tissue glycogen (Fig. 5).

Further studies were performed by injecting an intravenous bolus of ^{14}C-R labeled metabolites (glucose, pyruvate, and palmitate) to live and brain dead baboons (9). Measurements of the plasma half-life of ^{14}C-R and exhaled $^{14}CO_2$ confirmed the inability of brain dead animals to metabolize aerobically. The half-life of the injected metabolites was significantly prolonged, and the amount of exhaled $^{14}CO_2$ was markedly reduced. Practically no $^{14}CO_2$ was detectable following palmitate administration (Fig. 6). These findings further supported the evidence that mitochondrial function is inhibited after BD, and that a change from aerobic (live animals) to anaerobic (brain dead animals) metabolism has occurred.

Hormonal therapy in the experimental animal

Hormonal replacement consisting of T_3 (2 μg/h), cortisol (100 mg/h), and insulin (10 U/h) was administered to BD animals for 2 h (Table 1). There was significant myocardial recovery restoring the biochemical (Figs. 4 and 5) and hemodynamic abnormalities. These treated hearts were no different than hearts procured from live animals (15).

The administration of T_3 alone to BD baboons restored the ^{14}C-R half-life; and the exhaled $^{14}CO_2$ counts were no different from live animals, thus indicating the restoration of aerobic pathways via the mitochondria (9).

Similar neuroendocrine responses to BD were observed in patients who potentially could become organ donors (3). The presence of a low FT_3 state was observed in all potential organ donors. The longer the time elapsed from the

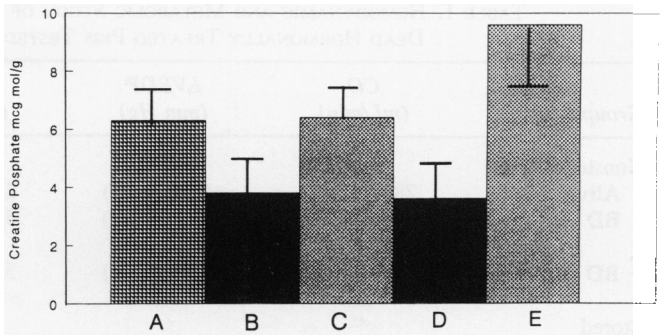

FIG. 5. Creatine phosphate (CP) measured in hearts procured from the following: (A) live, (B) brain dead, (C) brain dead, T_3 treated, (D) brain dead and stored, and (E) brain dead, T_3 treated, and stored animal hearts. The CP levels were reduced in brain dead untreated animals: B vs. A $p < 0.02$ and D vs. A $p < 0.05$. The CP in T_3-treated hearts remained unchanged or improved: C vs. A ns and E vs. A $p < 0.05$.

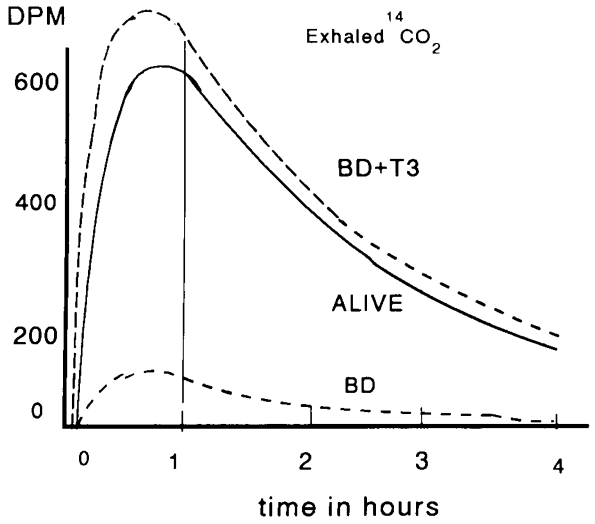

FIG. 6. Best fit curves of exhaled $^{14}CO_2$ following administration of a single intravenous bolus of [^{14}C]palmitate. Note the inability of the brain dead animal to produce $^{14}CO_2$. Following T_3 therapy to the brain dead animal, $^{14}CO_2$ production is no different from the live animal.

actual brain death, the lower the FT_3 levels (3). Furthermore, once the donor required significant progressive increments of inotropic support for hemodynamic stability, the worse the performance of the donor heart in the recipient post-transplant. Development of tachyphylaxis to catecholamines precludes the use of the heart for transplantation purposes. In human brain dead organ donors, plasma lactate and free fatty acid accumulation resulted in a metabolic acidosis. Sodium bicarbonate replacement was only helpful temporarily. Eventually, the cellular metabolism becomes anaerobic with the loss of the high energy phosphates and the inability to supply ATP to cellular ATPases. This leads to elevated cytosolic Ca^{2+} resulting in further calcium-induced injury (16).

Following BD, metabolic acidosis develops, and frequent aliquots of sodium bicarbonate are necessary to maintain pH. Despite these measures, within 72 hs from the actual death of the brain, 82% of the potential donors will develop ventricular fibrillation as a terminal event (17).

MANAGEMENT OF THE POTENTIAL ORGAN DONOR

In brain dead organ donors, dopamine is the standard inotrope of choice because of its enhancement of renal and splanchnic perfusion. Many institutions consider the donor heart unsuitable if the dopamine requirements exceed 10–15 μg/kg/min for hemodynamic stability providing the intravascular volume has been optimized. All correctable factors are normalized (18).

Hormonal therapy in the organ donor

The early observations of the effects of hormonal replacement were very encouraging. Patients were treated with intravenous T_3 (2–3 μg), cortisol (100 mg), and insulin (10–20 U) on an hourly basis (3,19). As T_3 has potent peripheral vasodilatory effects (20), a decline in the arterial blood pressure was occasionally observed. Vasopressin infusion of 0.1 U/min resulted in the recovery of blood pressure.

The hormonally treated patients showed a marked hemodynamic improvement allowing for a rapid reduction of excessive inotropic support and correction of the metabolic acidosis. The conventionally treated donors did not exhibit hemodynamic improvement, required higher levels of inotropic support, and metabolic improvement was not observed. Of this group, 19% of the hearts were no longer suitable for transplantation purposes while hormonally treated hearts were all transplanted ($p < 0.02$). Good cardiac function was observed in the recipients (3).

It became evident that more frequent and larger T_3 doses were required in donors receiving high inotropic support. Hearts requiring up to 40 μg/kg/min of dopamine were successfully weaned, and dopamine requirements were reduced to levels less than 10 μg/kg/min (21) (Table 2).

TABLE 1. HEMODYNAMIC AND METABOLIC STUDY OF HEARTS PROCURED FROM LIVE, BRAIN DEAD, AND BRAIN DEAD HORMONALLY TREATED PIGS TESTED IN A MODIFIED *EX VIVO* LANGENDORF MODEL[a]

Groups	*CO (mL/min)*	*LVEDP (mm Hg)*	*ATP (μmol/g)*	*CP (μmol/g)*	*Lactate (μmol/g)*	*Glycogen (μmol/g)*
Nonstored						
Alive	2820 (220)	5.30 (1.03)	3.73 (0.25)	6.61 (0.72)	5.0 (0.7)	29.6 (3.14)
BD	1850 (329)	4.30 (0.59)	3.29 (0.22)	3.69 (0.85)	12.9 (3.39)	12.7 (2.95)
	$p < 0.02$	ns	ns	$p < 0.02$	$p < 0.01$	$p < 0.005$
BD and HT	2357 (406)	3.80 (1.68)	3.75 (0.38)	6.80 (1.14)	7.07 (1.56)	30.5 (4.21)
	ns	ns	ns	ns	ns	ns
Stored						
Alive	2500 (90)	4.8 (1.05)	3.5 (0.20)	5.30 (0.52)	5.1 (0.8)	26.1 (2.42)
BD	742 (65)	16.0 (1.98)	2.49 (0.37)	4.07 (0.17)	2.80 (1.19)	25.4 (4.57)
	$p < 0.0001$	$p < 0.0001$	$p < 0.02$	ns	ns	ns
BD and HT	2074 (276)	4.6 (1.80)	3.10 (0.18)	9.66 (0.38)	9.64 (1.66)	21.2 (3.92)
	ns	ns	ns	$p < 0.0001$	$p < 0.05$	ns

[a]NS, not significant; values in parentheses, SEM; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; ATP, adenosine triphosphate; CP, creatine phosphate; BD, brain dead; BD and HT, brain dead and hormonal therapy (T_3 + insulin and cortisol).

TABLE 2. IMPACT OF T_3 THERAPY ON DOPAMINE REQUIREMENTS[a]

Group stratification: Dopamine (μg/kg/min)	*Patients*	*Dopamine (μg/kg/min)*			*Total*	*Cardiac ischemic time*
	(n)	*Pre-T_3*	*Post-T_3*	p<	*T_3 dose*	*(min)*
(1) 0–5	46	1.52 (.31)	1.24 (.29)	ns	9.55 (.78)	163.76 (8.32)
(2) 6–10	53	8.92 (.31)	5.71 (.4)	0.05	12.7 (.73)	157.34 (1029)
(3) 11–15	12	13.5 (.48)	6.75 (1.52)	0.003	17.16 (1.49)	194.63 (7.63)
(4) 16–20	28	18.67 (.34)	7.5 (.69)	0.0001	19.76 (1.32)	199.5 (8.07)
(5) 21–40	15	34.00 (1.48)	7.81 (.95)	0.0001	22.14 (1.80)	184.85 (18.32)

[a]The impact of T_3 administration to brain dead human organ donors. The patients were stratified in five groups according to the dopamine requirements. The dopamine requirements and the statistical difference before and after T_3 therapy are indicated, as well as the total T_3 dosage required to obtain hemodynamic stability. The total cardiac ischemic time was not different between the groups. Total 154 patients. NS, not significant. Values in parentheses, SEM.

Following open heart surgery on CPB, ESS has also been observed (4,11). FT_3 levels remain significantly reduced for 4–5 days. As the T_3 rescued heart will therefore be subjected again to a low T_3 state, T_3 supplementation was administered during CPB, at the time of the aortic cross clamp release, with the objective of preventing the myocardial metabolic-hemodynamic relapse observed initially in the donor. Using this new T_3 therapeutic modality, T_3 was administered to both donor and recipient with resultant excellent hemodynamic function (21) (Fig. 7).

Although the benefits of hormonal therapy were first published in 1984 (8), it was not until recently that this therapeutic modality for the management of brain dead organ donors has gained acceptance in major transplant centers (22–24). Currently, multiple OPOS initiate early low dose T_3 therapy in stable organ donors to prevent the occurrence of the metabolic abnormalities. However, in the unstable donor, larger T_3 doses are required to allow reduction of the inotropic support and reversal of the metabolic injury, thus providing an organ acceptable for transplantation purposes (Table 2).

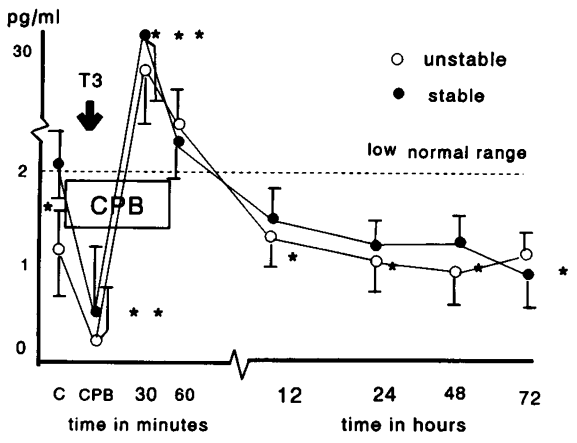

FIG. 7. Plasma FT_3 levels in elective and unstable hospital patients awaiting heart transplantation. Plasma levels were measured prior to the surgical procedure (C $p < 0.05$), during cardiopulmonary bypass (CPB), prior to T_3 therapy, and for the following 72 h ($^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.0005$; values expressed in mean ± SEM).

CONCLUSIONS

The two mechanisms of tissue injury have been outlined. The first is directly related to the toxic effects of endogenous catecholamine release occurring during the intracranial hypertension and the various processes leading to the death of the brain (8). This catecholamine injury is calcium-mediated (26). Scattered areas of myocyte necrosis are observed as early as 30 min following induction of BD. Outside of the hospital environment, this type of injury is unavoidable as the catecholamine "storm" lasts only for a few minutes. In animals, cardiac sympathetic denervation prevents the diffuse myocyte injury (25).

The second set of cellular events leading to further injury is directly related to the endocrine disintegration that follows brain death. The rapid reduction of circulating FT_3, FT_4, cortisol, insulin, and ADH (8) results in diabetes insipidus, which requires a great deal of attention toward prevention of hypovolemia. As vascular tone is lost, the organ donor will require the use of vasoconstrictive agents, such as Neo-Synephrine or vasopressin, the latter having the advantage of controlling the excessive diuresis (27). As T_3 cellular receptors become unsaturated (28), cellular metabolism becomes progressively anaerobic leading to excessive lactate production and an inability to metabolize the fatty acids aerobically. Concomitantly, there is significant loss of high energy phosphates (29) essential for adequate function of cellular ATPases which maintain ionic gradients and fluxes (30). As a result, cytosolic ionized calcium levels increase (31) and the impaired calcium uptake and calcium released by the sarcoplasmic reticulum induces further cellular injury (32) potentiating the initial catecholamine-induced injury. At this stage, the downward spiral resulting in the cellular death is inevitable. Ventricular fibrillation is a terminal event.

The metabolic derangement may be initiated at the same time as the catecholamine storm but does not become evident until later, as progressive increments of inotropic support are required to maintain adequate hemodynamics. The early initiation of the hormonal therapy will prevent the donor from lapsing into anaerobic metabolism (3,9,19). The cumulative experience with T_3 replacement has shown that hemodynamically unstable donors on high inotropic support can rapidly be rescued allowing reduction of supporting catecholamines. The loss of potential organ donors

may be prevented, increasing the pool of organs required for transplantation.

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