Transplant Int (1990) 3: 226–233

TRANSPLANT
International

Thyroid function in brain-dead donors

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Received January 3, 1990/Received after revision May 11, 1990/Accepted August 7, 1990

Abstract. Twenty brain-dead potential organ donors were studied prospectively to establish thyroid function. Two or three consecutive blood samples were obtained during brain death. Seven times a sample was available before brain death occurred. Free triiodothyronine (FT3) fell in most patients (80%). Very low (< 1.6 pmol/l) and subnormal levels (between 2 and 3 pmol/l) were found in 65% and 15% of the patients, respectively. Serum reverse total triiodothyronine (rT3) was inversely correlated with FT3. Free thyroxine (FT4) was less often decreased (mean 14.68 ± 1.42 pmol/l) and 35% of the patients had normal levels. Mean thyroid stimulating hormone (TSH) remained normal (0.71 ± 0.15 μU/ml). The study of consecutive samples during brain death did not show a constant, progressive decrease in hormonal levels. There is no statistical difference between values observed before and after brain death. No correlation was found between FT3 levels and hemodynamic data or immediate allograft function. The pattern of thyroid function in these patients was typical of the sick euthyroid syndrome with a low T3 or low T3 and low T4 serum levels. This syndrome usually does not need to be treated. However, many experiment findings and some clinical data argue in favor of T3 therapy in donors and possibly in recipients. The dosage regimen must be adjusted to be effective without causing harm to multiorgan donors before it can be widely used. It remains to be proved that low FT3 serum indicates low intracellular FT3 and worse metabolic function in clinical conditions.

Key words: Brain death, thyroid function – Sick euthyroid syndrome – Thyroid function in brain death

Preservation of organs in brain-dead donors requires maintenance of homeostasis during preparation for organ procurement. However, hemodynamic deterioration occurring in the donor may damage the graft and cause its failure after transplantation. Novitsky et al. observed a rapid reduction in circulating hormones, mainly free triiodothyronine (FT3), in brain-dead animals [22]. They suggested hormonal replacement to improve donor cellular metabolism [26]. This therapy with total triiodothyronine (T3) seems to improve function of both donor and recipient [23].

Recent studies have pointed out that these disturbances are not constant [15, 30]. Moreover, this kind of hormonal thyroid depletion may be observed in patients with any kind of illness, in the absence of hypothyroidism [7, 30]. This sick euthyroid syndrome has already been demonstrated in head trauma patients [6, 40].

The objectives of this study were (1) to establish the thyroid function of the brain-dead donors, (2) to determine the evolution of changes in thyroid hormones before and during brain death, and (3) to correlate endocrine changes with hemodynamic function in potential organ donors and (4) immediate allograft function after transplantation.

Materials and methods

Potential donors managed by the Regional Transplant Center of the University Hospital of Bordeaux (Pellegrin Hospital, Bordeaux) were studied prospectively between February and July 1989. These patients were referred from the Trauma Center of the same hospital or from smaller hospitals in the southwest of France. Excluded were donors less than 10 years old or more than 50 years old. Thus, 20 patients in all were included. There were 5 women (25%) and 15 men (75%), ranging from 14 to 48 years. The diagnoses leading to brain death included traumatic injury ($n = 16$) [traffic accident ($n = 12$), fall on head ($n = 3$), gunshot wound, ($n = 1$)] and intracranial hemorrhage ($n = 4$).

All patients admitted for severe traumatic or vascular head injury were treated using conventional resuscitative measures, including cristalloid fluids with a negative fluid balance for 48 h, then normal fluid and electrolyte balance. No steroid therapy was administered. All patients received an analgesic, fentanyl R, and most patients received gamma hydroxybutyric acid (gamma-OH^R). In some cases, a benzodiazepine was used in its place. Control of increased intracranial pressure was performed with thiopental in place

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Table 1. Thyroid hormone levels during brain death. FT4, Free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; rT3, reverse total triiodothyronine; TA, traffic accident; BP, blood pressure; NS Dis, neurosedation (barbiturates) discontinued

Case	Age	Etiology of BD	FT4 pmol/l	FT3 pmol/l	TSH μU/ml	rT3 ng/100ml	BP	Time elapsed (h) since		
								Accient	BD	NS Dis
1	23	Head injury (TA)	16.9	1.4	0.95	114	100	46	1	NS +
			13	< 1	0.27	> 200	60	66	21	20
			9.7	< 1	0.45	> 200	70	71	26	22
2	29	Head injury (TA)	12	2	< 0.1	115.4	100	96	17	2
			12.1	3.7	1.9	60.3	100	126	47	30
3	25	Cerebral hemorrhage	21.4	4.8	0.2	38.5	110	17	15	–
			19.5	3.6	0.3	39	106	23	21	–
4	20	Cerebral hemorrhage	11.8	1.9	0.7	60.4	95	72	37	30
			11.8	1.3	1	58	110	80	45	34
5	44	Head injury	17.3	1.5	0.11	182	80	84	13	12
			14.1	1.4	0.12	176	80	88	17	16
			14.4	1.6	0.17	135.6	75	92	21	20
6	45	Head injury (fall)	28.3	2.7	0.4	48.4	60	12	11	–
			31	3	0.4	72	120	14	13	–
			32.6	2.5	0.4	50	87	21	20	–
7	48	Head injury (fall)	16.7	4.1	2.9	38.8	140	54	0	26
			18.4	4.4	2.6	30	110	59	5	30
			18.9	4.4	2.5	28.6	100	62	8	33
8	42	Cerebral hemorrhage	27.2	3.7	0.7	28.9	102	10	0	–
			25.9	3.7	0.7	35.6	93	14	4	–
9	18	Head injury (TA)	9.1	< 1	0.4	86.1	80	92	3	1
			10	< 1	0.8	106.3	94	100	11	9
			10.4	1.3	1.3	123.6	121	104	15	13
10	19	Head injury (TA)	13.4	< 1	0.7	122.4	104	4	0	NS +
			14.1	< 1	0.6	179.4	92	23	19	8
11	24	Head injury (TA)	5.1	< 1	0.27	89.6	90	130	5	2
			7.1	< 1	0.4	113	100	135	10	7
			7.2	1.3	1.5	86.7	118	149	24	23
12	42	Head injury (TA)	12.4	1.3	< 0.1	77.5	123	144	16	15
			12.1	1.6	< 0.1	74.7	110	149	21	19
13	35	Cerebral hemorrhage	11	4.2	0.8	16.8	90	3	1	–
			11.3	2.8	0.7	18	105	13	11	–
			10.2	2.9	0.3	19.3	117	17	15	–
14	20	Head injury (TA)	8	1.3	0.5	140.2	110	51	9	3
			8.2	1.1	< 0.1	130.4	83	55	13	7
15	30	Head injury (gunshot)	22.8	2.3	1.2	50.2	115	3	2	–
			19.8	1.1	0.7	43.8	141	14	13	–
			20.8	< 1	1	51.7	102	23	22	–
16	19	Head injury (TA)	10.1	1.2	0.12		140	112	2	0.5
			12.8	1.1	0.23		200	117	7	5
			12.2	1.1	0.7		180	123	13	11
17	14	Head injury (TA)	15.9	5	3.7	19.4	112	6	5	–
			21.2	< 1	0.5	87.1	98	10	9	–
			15.7	< 1	0.5	79.4	84	21	20	–
18	25	Head injury	17.4	1.3	0.18	106	97	43	7	2.5
			14.6	< 1	0.1	103	93	47	11	6.5
			11.8	< 1	< 0.1	87.6	91	55	19	14.5
19	45	Head injury (TA)	19.1	2	0.6	107.6	104	24	12	0.5
			18	2.6	0.7	98	115	28	16	4.5
			17.3	2.2	0.5	94.5	106	36	24	8.5
20	38	Head injury (fall)	10	0.5	< 0.1		92	163	24	26
			8.7	< 1	< 0.1		98	167	28	30

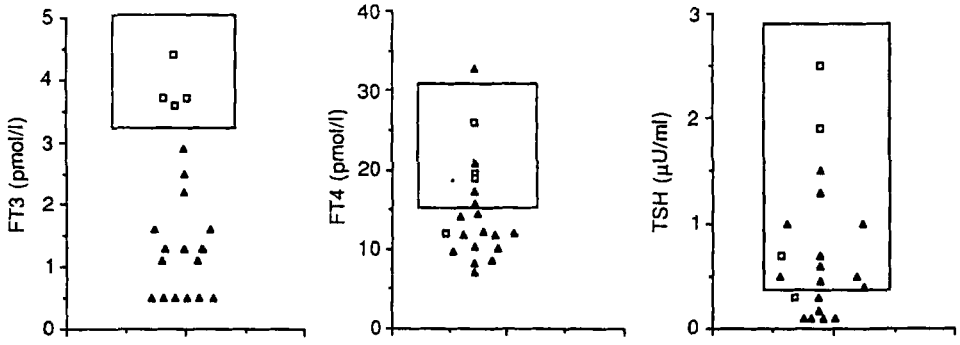

Fig. 1. Hormonal data at the time of organ procurement. *FT3* Free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid-stimulating hormone. ▲ Patients with subnormal or very low FT3, □ patients with normal FT3

of gamma-OH^R, in loading doses, followed by continuous infusion, in order to obtain burst suppression on the EEG.

At the time of brain death diagnosis, sedation was discontinued. A first EEG was performed when the barbiturate serum concentration was less than 10 µg/ml; a second was done 4–8 h later. Conventional resuscitative measures of brain-dead patients included IV fluids and electrolytes adjusted to hourly urine output. Systolic arterial pressure was maintained above 80 mm Hg, and central venous pressure between 3 and 8 cm H_2O by administration of albumin or blood and plasma, according to the circumstances. Inotropic support was sometimes necessary. Dopamine was added mainly to improve urine output in a concentration below 5 µg/kg per minute or at a higher dose if there was a hemodynamic deterioration. Dobutamine was preferred if central venous pressure was above 12–15 cm H_2O. Hypothermia was prevented in all patients.

At the time of referral to the transplant center, 10 ml of blood was obtained (sample T1). A second sample was taken 4 h later (sample T2). A third was obtained before operative organ procurement (sample Tprel) if more than 4 h had passed since the previous one. In 7 out of the 20 patients hospitalized in the trauma center of the same hospital for very severe head injury, an earlier sample was also obtained before brain death occurred.

The serum was separated and stored at −18°C until the study was concluded. All of the sera were assayed at the same time. Samples were analyzed for free thyroxine (FT4), free triiodothyronine (FT3), reverse T3 (rT3), and thyroid-stimulating hormone (TSH) contents by our routine laboratory tests: serum FT4 (normal range 16–28 pmol/l) and FT3 (normal range 3.2–6.1 pmol/l) using "Magic Lite" competitive immunoassays (Ciba Corning Diagnostics), serum rT3 (normal range 9–35 ng/100 ml) using Serono Diagnostics radioimmunoassay. FT3 levels lower than 1 pmol/l cannot be measured exactly. TSH (normal range 0.3–4.5 µU/ml) was determined by ultrasense immunoradiometric assay (IRMA Immunotech).

For each blood sample, the following parameters were noted:

1. Time elapsed since initial accident
2. Time elapsed since clinical onset of brain death (BD)
3. Blood pressure and heart rate
4. Inotropic support (dopamine, dobutamine)
5. Fluid intake (cristalloid or albumin solution, blood components)
6. Use of barbiturate therapy for the management of head trauma and time elapsed since this therapy was stopped

Clinical data concerning kidney and heart transplantation were collected retrospectively. In order to study comparable times of ischemia and anesthetic and surgical techniques, we considered only organ transplantation performed in the same hospital. After heart transplantation, the behavior of the transplanted organ at the end of the cardiopulmonary bypass and the use of catecholamine drugs in the immediate post-transplant period were also observed. As for kidney transplantation, the need for dialysis treatment within 5 days after transplantation was also noted. The function of liver transplants was studied in the 1st week post-transplantation.

Statistical comparative studies were performed using a linear regression test and Student's *t*-test with a P value less than 0.05 considered to indicate a significant difference. All results are expressed as mean ± standard error (SEM).

Results

Overall results for the group of 20 patients are summarized in Table 1. At the time of organ procurement (Fig. 1), serum FT3 was very low (< 1.6 pmol/l) in 13 cases (65%), subnormal (between 2 and 3 pmol/l) in 3 cases (15%), and normal (> 3.5 pmol/l) in 4 cases (20%). The mean FT4 was 14.68 ± 1.42 pmol/l. Seven patients (35%) had normal FT4 (> 16 pmol/l). The mean TSH was normal: 0.71 ± 0.15 µU/ml. Five patients had TSH below the normal range. The mean rT3 was 85.24 ± 12.02 ng/100 ml. There was a strong negative correlation between FT3 and rT3 ($r = -0.75$; $P < 0.005$). There was a weak positive correlation between FT3 and FT4 ($r = 0.44$; $P = 0.05$) and between FT3 and TSH ($r = 0.45$; $P < 0.05$). There was no correlation between TSH and FT4 ($r = 0.04$; $P > 0.5$). No correlation was observed between hormonal levels of FT3 and fluid hydration ($r = -0.13$; $P > 0.5$) or need for albumin solution. There was a positive correlation between FT3 and patient age ($r = 0.56$; $P < 0.02$).

Changes in hormonal levels between two consecutive samples during brain death are summarized in Table 2. Sixteen patients maintained the same level of FT3 from the first sample to the last. In 11 cases, values were very low (< 1.6 pmol/l); 2 cases were subnormal (between 2 and 3 pmol/l) and 3 cases were normal (≤ 3.5 pmol/l). In

Table 2. Hormonal changes during brain death

	No change		Drop	Rise
FT3	16	Normal levels: 3 Low levels: 13	3	1
FT4	17	Normal levels: 7 Low levels: 10	3	
TSH	12	Normal levels: 8 Low levels: 4	4[a]	4

[a] Three times out of four the levels drop but stay within the normal range

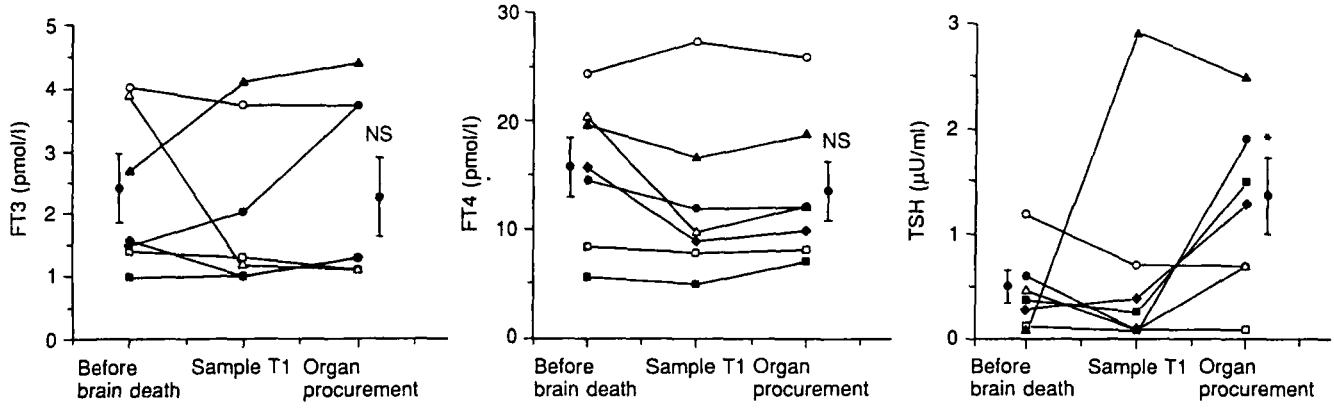

Fig. 2. Hormonal data before and after brain death in seven patients. *Vertical bars* represent mean hormonal values before and after brain death ($\bar{X} \pm$ SEM). $^*P < 0.05$

3 cases, the level of FT3 fell and in 1 case it rose. Seven patients maintained a normal level of FT4 (3 had a normal FT3, 2 a subnormal FT3, and 2 a very low FT3). A reduction in FT4 occurred in 3 cases. No rise in FT4 was observed. TSH levels remained within the normal range in most cases. It fell in 3 cases and rose in 4. Fifty-two samples were obtained during brain death. Thirty-two (61.54%) had a very low FT3 level, 10 (19.23%) were subnormal, and 10 (19.23%) were normal.

In seven cases the samples were available before brain death (in five cases, 1–24 h before; in two cases, 75 and 85 h before). The comparison of hormonal levels before and after brain death did not show any statistical difference. Differences in evolution of the seven patients are shown in Fig. 2.

There was a progressive reduction in FT4 with time elapsed since the accident leading to brain death ($r = 0.59$; $P < 0.01$; Fig. 3). FT3 is less dependent on time ($P > 0.1$)

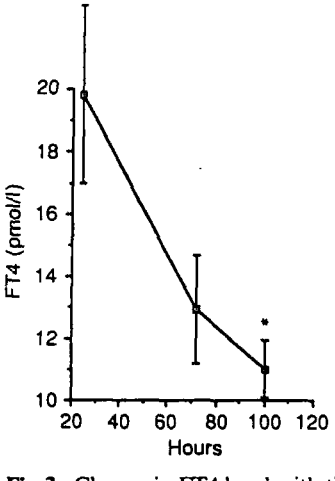

Fig. 3. Change in FT4 level with time elapsed since initial accident. *Points* represent mean level of samples taken between 1 and 23 h, 24 and 72 h, and more than 72 h after initial accident. Comparison is made with the first point. $^*P < 0.05$

and may fall abruptly within a few hours. There was no correlation between TSH and time elapsed since the accident ($P > 0.5$).

Thirteen patients received thiopental as therapy for increased intracranial pressure after a severe head injury. Seven patients did not receive any therapy because brain death occurred suddenly after the initial accident. There was a statistical difference between hormonal values of samples obtained less than 24 h after therapy was stopped ($n = 20$) and those from patients whose therapy was stopped earlier or who did not receive any barbiturate, with respective mean FT3 levels of 1.18 ± 0.16 pmol/l versus 2.48 ± 0.52 pmol/l, mean FT4 levels of 11.74 ± 0.87 pmol/l versus 18.27 ± 2.56 pmol/l, and mean TSH levels of 0.59 ± 0.15 µU/ml versus 0.9 ± 0.26 µU/ml (Fig. 4).

Eight patients did not require any inotropic support before organ procurement. Six had very low FT3 and two had normal FT3. Twelve patients required dopamine; four patients only received it in a dose of more than 3 µg/kg per minute at the time of retrieval (two with very low FT3 and two with subnormal FT3). Two patients were not harvested because of hemodynamic deterioration, including one patient who had severe hypoxemia due to bilateral pulmonary contusion. These two had very low FT3. There was no correlation between FT3 and blood pressure or heart rate considering FT3 and cardiovascular state at the time of organ procurement or overall blood samples (all $P > 0.5$).

Seven heart and three heart-lung transplants were performed in this center on these 20 donors. They were obtained from donors with very low FT3 in six cases, subnormal FT3 in two cases, and normal FT3 in two cases. All organs showed immediate good function at the end of cardiopulmonary bypass. The amount of Isuprel administered differed from case to case (with a ratio of 1:10) but did not depend on the hormonal status of the donor. Twelve kidneys were transplanted in this center from donors with very low FT3 ($n = 8$), subnormal FT3 ($n = 2$), and normal FT3 ($n = 2$). Acute tubular necrosis occurred in one case in the first group (very low FT3) and in one case in the last group (normal FT3). Six livers were transplanted on site; three donors had very low FT3 levels. No problem was noted in the immediate post-transplant period in any recipient.

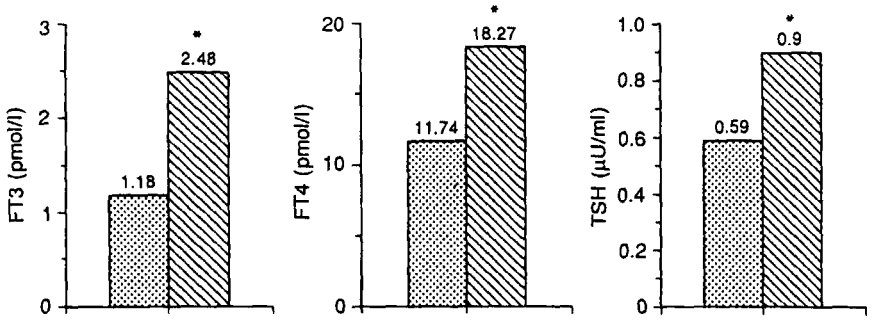

Fig. 4. Hormonal levels and barbiturate treatment. ▨ Mean level in samples taken less than 24 h after cessation of barbiturates, ▧ mean level in samples taken more than 24 h after cessation of barbiturates or without any treatment. $*P < 0.05$

Discussion

The results of this study confirm those in other recent reports [15, 30]. The drop in FT3 is frequent in about 80% of all patients but not universal. The level of FT3 may be normal: it was so in 4 cases in this series and in 6 out of 31 cases in the study by Howlett et al. [15] concerning total T3. FT4 is less often reduced and may remain normal in spite of a large drop in FT3. In fact, the hormonal profile of these potential donors is very different from one patient to another: 4 maintained normal hormonal levels (FT3, FT4, and TSH) while 11 had very low levels of FT3 and FT4, with a normal or low TSH. Hormonal values cannot be linked with etiology of brain death (BD).

This study fails to demonstrate interruption of TSH secretion. It is surprising to note such normal levels of TSH, even if its normal elimination half-life is short: 35–55 min. Normal pituitary function has already been reported [14, 15, 32]. These results suggest that in brain death, some basal parts of the brain may still be perfused.

The study of consecutive samples does not show a sharp drop in hormone levels of brain-dead human patients, as was the case in experimental brain-dead animals. In the seven cases where it was possible to obtain a sample T1, BD was followed by a large drop in FT3 in one case only. In this patient, the sample T1 was taken just after the initial accident, and brain death occurred 3 days later. The level of FT3 could fall during this period and cannot be attributed with certitude to BD. On the other hand, one patient had a very low level of FT3 before BD (1.3 pmol/l) and a normal level in the last sample (3.7 pmol/l).

The comparison of hormonal levels before and after BD shows that this syndrome is not necessarily due to BD. Brain injury leading to BD seems to be an important factor in the etiology of these disorders. Decreases in T3 and thyroxine (T4) have been observed in other severe, nonthyroidal illnesses [7, 36]. The thyroid gland of healthy adults secretes 100 nmol T4 per day. Of this amount, about 80 nmol undergoes deiodination in extrathyroidal sites and leads to T3 (active form) or rT3 (less potent product). The complex balance between stimulation of the thyroid gland, secretion of thyroxine, and peripheral deiodination can be disturbed in a wide variety of systemic illnesses [5]. The degree of thyroid dysfunction is related to the gravity of the disease [40]. A low T3 level is frequent and can be seen even after fasting alone. The decrease in T4 is associated with a more critical status. This sick euthyroid syndrome is attributed to several factors, the first of which is an impaired peripheral conversion of T4 to T3, mainly in the liver, owing to diminished tissue 5'-deiodinase activity [5]. This defect produces an elevation in serum rT3 concentration. Second, the presence of circulating inhibitors of hormone binding have been demonstrated [7], leading to abnormalities in the metabolic clearance rate. In some patients there is a reduction in hormone secretion. TSH remains normal in most cases. A decrease in the set point of TSH secretion is more than likely in these circumstances [12]. The two main mechanisms leading to this syndrome could be a decrease in carbohydrate ingestion [18] or an increase in the secretion of stress hormones (adrenocortical steroids [7] and catecholamines [18]). Plasma norepinephrine and epinephrine are inversely correlated with serum T3 concentration after trauma [19, 40]. The decreased serum T3 results in decreased metabolic activity of peripheral tissues. This is probably an adaptive mechanism, enabling the sick patient to conserve protein. A sick euthyroid syndrome was demonstrated in patients with multiple injuries [6]. Severe head injury was associated with lower levels of FT3 and TSH.

The different hormonal levels found in these patients with equally serious illnesses are difficult to explain. They are not due to hemodilution since amounts of perfused cristalloids or plasma are not related to T3 levels at the time of organ procurement. The decrease in FT4 levels seems to worsen with time elapsed since the accident, as has been demonstrated after severe injury [6]. FT3 may fall abruptly as early as 4 h after brain injury in one patient while remaining normal 126 h in another. The importance of sedative drugs is less easy to establish because it is difficult to differentiate the role of sedation from that of time. The patients without any sedation are those who were injured too seriously for any improvement to take place; in these cases, brain death occurred soon after the initial accident. However, seven patients did not receive any barbiturate therapy. Six of them had normal FT4 in all samples, including the only two patients who had a normal FT4 in spite of a very low FT3 level. Morphine and opiate administration result in an increase in serum T3 and T4 concentrations [35]. On the contrary, thiopentone decreases thyroid hormone levels without any change in the plasma TSH concentration [4, 16, 29]. In fact, the real effect of barbiturate coma on thyroid function in man is not well known. The decrease in O_2 consumption induced by thiopental may interact with the cell requirement of thyroid hormones.

Is there a justification for treating brain-dead patients with T3? The acute depression of FT3 in 80% of all potential donors represents a state of sick euthyroid syndrome, whether due to brain injury or to brain death. The normal clinical findings and the changes in biological responses to hormonal levels argues against thyroid hormone treatment in patients with this syndrome [8, 12, 36]. In fact, raised intracellular thyroid hormone levels, secondary to catecholamine action on the cell membrane [18], may occur, and biological responses to T3 may be enhanced or depressed by cellular factors that affect postreceptor mechanisms [36]. Thus, hormonal level measurement is not valid for establishing the real thyroidal state of the entire individual. Moreover, this study and others [30, 37] failed to demonstrate any correlation between hemodynamic status of the brain-dead donor and the decrease in FT3 or T3. Blood pressure is not different at the time of sample collection, whether FT3 is very low or normal. Some patients with normal FT3 needed dopamine while donors with very low FT3 had a very good hemodynamic function without any inotropic drug. One out of the 20 patients was unsuitable for transplantation, owing to cardiac deterioration. However, cardiovascular collapse occurred quickly after a long sympathetic storm (6 h), and T3 replacement would have been difficult in this case. When brain death occurs, nearly all patients have a large decrease in blood pressure. This collapse cannot be attributed to a decrease in FT3 since this decrease does not occur at the same time.

The FT3 serum level of donors is not linked to immediate post-transplant graft function in this study, something which is in accordance with the findings of Gifford et al. [13] and Macoviak et al. [17]. Wahlers et al. [37] demonstrated that there is a relation between the T3 level of the donor and the amount and duration of dopamine support required in the postoperative period. However, mean dopamine concentrations remained lower than 3 μg/kg per minute, which does not represent a significant hemodynamic support. The epinephrine requirements of these patients did not differ with respect to the T3 levels of the donors. The real influence of this factor is very difficult to demonstrate because of the various clinical states of the recipients (in particular, the state of pulmonary circulation).

There is no endocrinological justification for T3 replacement based on an isolated low serum FT3; this does not represent a hypothyroid state and does not seem to be directly linked with the hemodynamic state of the patients. The question, then, is whether the case of brain-dead patients is different from sick euthyroid syndrome in other illnesses. Myocardial injuries in brain-dead donors have been demonstrated [9, 27]. Experimental and clinical data provide arguments for a beneficial effect of T3 therapy in brain-dead donors.

FT3 has a very important action upon cardiac cells [10, 34, 35]. Novitzky demonstrated that T3 therapy reverses the deterioration in cardiac function, the depletion in energy stores, and the K^+/Na^+ ratio of cardiac cells after induction of brain death in animals [25]. In an experimental study, T3 increased the K^+/Na^+ ratio in kidney, but decreased this ratio in liver slices. The ratio is unchanged in heart slices [39]. T3 replacement therapy in brain-dead pigs was found to have a beneficial effect on myocardial energy stores and functional testing of hearts [24] and to reverse deterioration in the function of kidney slices [38]. However, induction of brain death in animals is followed by a rapid loss of triiodothyronine, cortisol, and insulin [22]. There does not seem to be exactly the same pattern in brain-dead patients. The drop in T3 is not uniform, and cortisol and insulin levels remain normal in most cases [15, 30].

A decrease in the serum FT3 level is accompanied by a reduction in the number of hepatic nuclear receptor sites [33]. Montero et al. [20] found the same decrease in myocardial cells of heart donors, and there was a relation between the reduction of receptors and myocardial damage. This could be explained by a possible relationship between sick euthyroid syndrome and catecholamine secretion at the onset of brain death: the intensity of the sympathetic storm can be related to myocardial damage [27] as well as to the decrease in FT3 [19].

T3 therapy was administered to 21 potential organ donors in a first study [23] and to 116 consecutive donors in a more recent one [28]. It resulted in a significant improvement in their cardiovascular status and a decrease in the number of patients considered unsuitable for cardiac transplantation. However, these patients had a poor cardiovascular status when referred to the transplantation unit, and their need for inotropic support and bicarbonate administration was great. These studies were not randomized, and it is difficult to determine whether better hemodynamic management of these patients played a role in their improvement. Suitable dosage regimens have not yet been established. In the first study, Novitzky patients received 2 μg hourly, but in the following 70 patients the dosage regimen was not specified. In a recent controlled study, the effect of pretreating donors with T3, cortisol, and insulin was tested [9]. The dosage had to be raised to 4 μg/h in order to be efficient. However, in this latter case, a significant improvement was noted on heart biopsies. A T3 therapy for heart recipients has been proposed, but in these cases dosages have to be adjusted to be useful without creating a hyperdynamic state that may compromise cardiac function.

It must be kept in mind that T3 therapy is not harmless, and the proper dose must not be exceeded. This challenge may be difficult because the exact thyroid state of the patient is unknown. Exogenous thyroid administration may induce severe myocardial ischemia due to coronary artery spasm and increase in oxygen demand even in patients with normal coronary anatomy [1]. The risk of spasm is not linked to hormone serum levels [11]. Myocardial ischemia, associated with arythmia, may sometimes lead to sudden deaths. In these cases, focal myocarditis has been found; similar changes have been described after catecholamine storm [2]. Madsen et al. [19] emphasized the risk of thyroid hormone therapy in cases of abnormal catecholamine release. Sympathetic storm at the onset of brain death leads to elevated catecholamine levels, and T3 therapy should not be begun until these levels have returned to normal. On the other hand, this therapy must not be given too late. The effects

of thyroid hormones on oxydative phosphorylation are rapid [3]. However, effects on Ca + + and myosin synthesis have been demonstrated in longlasting experiences. In addition to cardiovascular problems, an increase in protein catabolism, observed with T3 treatment in the case of sick euthyroid syndrome [12], may be deleterious. Thyroid therapy may precipitate an acute adrenal crisis in the case of adrenal insufficiency [31], which may be present in these patients at risk for hypothalamic pituitary insufficiency. Lastly, the thyroid effect on brain-dead, multiorgan donors must be studied. In the hyperdynamic circulation of hyperthyroidism, splanchnic blood flow is not increased [21]. This leads to a reduction in hepatic vein oxygen levels, which may be deleterious before liver transplantation. The adverse effect of T3 on the K + /Na + ratio, demonstrated in liver slices, may also be deleterious.

This study confirms the decrease in FT3 levels in most brain-dead potential donors. This deterioration in hormonal levels is not constant and it is not possible to predict which patients will be affected. The FT3 decrease is accompanied by an increase in rT3, but FT4 may remain normal. Differences from one patient to another are difficult to understand. Hormonal depression may occur before or after brain death. We did not find any relation between these disorders and hemodynamic failure. Thus, T3 treatment is probably not to be considered a hormonal replacement. It is not certain that the low FT3 serum level is really correlated with a low intracellular level of this hormone, associated with a worse metabolic function in clinical conditions. However, T3 treatment may lead to an improvement in heart transplants in experimental and clinical conditions, either by an action on mitochondria and oxydative phosphorylation, by a permissive action on the biological responses to catecholamines, or by some other factor. Meticulous donor management must remain the first priority in a transplant unit. T3 therapy may be of value in difficult cases. Further controlled studies are necessary to confirm this beneficial action in all multiorgan donors, including liver donors, and to establish dosage regimens without harm to the donor.

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