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ORIGINAL

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Eficiency of triiodothyronine treatment on organ donor hemodynamic management and adenine nucleotide concentration

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Abstract *Objective:* We compared hemodynamic values, oxygen utilization, and adenine nucleotide concentration in the extracted organs of brain-dead donors treated with triiodothyronine vs. standard support treatment. *Design:* Prospective, randomized, double-blind controlled study. *Patients:* We recruited 52 consecutive adult cadaveric organ donors. Inclusion criteria were diagnosis of brain-death, transplantation suitability [1], and family consent for donation; exclusion criterion was preexisting thyroid disease. *Interventions:* The treatment group (n=29) received an intravenous bolus of 1 μg/kg triiodothyronine followed by continuous perfusion at 0.06 μg/kg per hour, and controls (n=23) received 0.9% ClNa delivered over 270 min. Hemodynamics, tonometry, thyroid hormones, and serum lactate were measured every 90 min from brain death to extraction procedure. Biopsies were processed to determine adenine nucleotides concentration. *Results:* Hemodynamic measurements did not differ significantly in the two groups, and the inotrope dose could not be diminished after treatment. Thyrotropin levels increased from brain death to extraction procedure in controls. Thyrotropin measured 90 and 180 min after the beginning of the perfusion was significantly lower in the treatment group than controls. The Pco_2 gap increased in both groups from brain death to the extraction procedure. The lactate level of the treatment group was lower than in controls. Biopsy specimens were obtained in 19 controls and in 20 donors of the treatment group; the adenine nucleotides concentration did not show any significant difference. *Conclusions:* Triiodothyronine did not add any benefit over the standard management of the organ donor nor did it affect the adenine nucleotides concentration of any biopsied organs.

Keywords Brain-dead donor · Triiodothyronine · Nonthyroidal illness · Pco_2 gap · Adenine nucleotides

Introduction

Optimal care of the organ donor ensures organ viability on several recipients. The goals of triiodothyronine (T_3) treatment are improvement of hemodynamic parameters, restoration of anaerobic metabolism and organ donor presumably hypothyroidal state. Focusing on end-organ function, we used a gastric tonometer to guide the adequacy of aerobic metabolism in a tissue particularly vulnerable to alterations in perfusion and oxygenation [2].

As intensivists we focus on T_3 hemodynamic actions. Hemodynamic improvement after T_3 administration has been explained by direct effect on vasodilatation arterioles. T_3 also acts directly on myocardiocites through nuclear receptors and nonnuclear pathways [3, 4]. At the transcriptional level T_3 modulates synthesis of the Ca^{2+}-

ATPase of the sarcoplasmic reticulum and the Na^+/K^+ ATPase of the cell membrane. Regulation of cell membrane Na^+, K^+, and Ca^{2+} channels is a nonnuclear T_3 actions on myocardiocytes. These enzymes are crucial because they modulate the concentration of Ca^{2+} in the sarcolemmal and its reuptake into the sarcoplasmic reticulum. The velocity of myocardiocite diastolic relaxation and systolic contractility depends on the activity of these enzymes [5, 6]. The stunned myocardium (observed during cardiac surgery and heart transplantation) has diminished capacity to reuptake Ca^{2+}; Ca^{2+}-ATPase would be activated by T_3. Thus transplantation of hearts previously discarded [7, 8] was permitted after T_3 administration.

Reversion of anaerobic metabolism after T_3 has been reported by Novitzky and Cooper [9]. By acting on the mitochondria, T_3 would increase pyruvate, glucose, and palmitate use as well as normalize plasma lactate and free fatty acid metabolism. According to Novitzki and Cooper [9], T_3 induces activity of the adenine nucleotide translocase and ATPase systems, synthesizing adenine nucleotides. Although there is no in vitro test to predict function in vivo after transplantation of an organ, the organ's ability to synthesize ATP may be considered a good index of posttransplant function [10, 11] that is correlated to viability after storage, with adenine nucleotides concentration in that organ. Based on these data, we decided to measure the adenine concentration by performing a biopsy of the organs. We chose T_3 because of the controversial thyroid dysfunction in the donor. Some authors suggest that a hypothyroid condition of the donor would lead to deterioration of the organs and thus affect posttransplant graft function. Abundant literature can be found on T_3 benefits for donors, but most of the studies were nonrandomized and included only a small number of donors. Therefore we performed a randomized control study that would help critical care practitioners to make decisions about T_3.

Materials and methods

Between May 1997 and May 2000 we randomized 52 consecutive adult organ donors to either a treatment group (n=29, mean age 38.4±17 years) or controls (n=23, mean age 40.7±23.3 years). Inclusion criteria were diagnosis of brain death, suitability for transplantation according to the National Transplant Organization recommendations, and family consent for donation; exclusion criterion was any preexisting thyroid disease. Diagnosis on admission in the treatment group was 25 with intracerebral hemorrhage and 4 with subarachnoid hemorrhage; the corresponding figures in contols were 20 and 3. Mean time from admission at the intensive care unit to brain death diagnosis was 2 days (26 h–3 days in the treatment group; 32 h–3 days in controls). The Institutional Review Board approved the study, and written informed consent was obtained from the next of kin. The study was conducted in conformity with the Declaration of Helsinki.

A standard maintenance protocol was carried out in every case [12]. Central core temperature was maintained with a convective blanket above 35.5°C. Red blood cells were transfused if hemoglobin decreased below 10 g/dl, crystalloids were perfused to maintain pulmonary capillary wedge pressure was 0.79–1.99 kPa, and mean arterial pressure between 9.31–9.97 kPa. If this was not achieved by crystalloids, dopamine was infused at 2–8 μg/kg per minute for 270 min. A Servo 900 C ventilator (Siemens) parameters was programmed to maintain $PaCO_2$ at 4.8–5.9 kPa and PaO_2 at 11.3–13.3 kPa. Desmopressin (1 μg/8 h intravenously) was administered when neurogenic diabetes insipidus was detected. No enteral feeding or steroids were administered. Famotidine was infused intravenously at 20 mg/12 h. A thermodilution pulmonary artery catheter (Baxter), a gastric saline tonometer (Tonometrics, Trip), and an artery catheter were inserted once brain death was diagnosed. Basal measurements (t_0) were carried out once brain death was established, followed by randomization. From the beginning of T_3 or saline perfusion until retrieval, hemodynamic and tonometric measurements were made every 90 min as well as blood samples obtained, to determine thyroid hormones and lactate concentration. This time sequence is defined as the length of time (in minutes) after perfusion began (t_{90}, t_{180}, t_{270}). The donor was then transferred to the operating room for retrieval.

T_3 treatment consisted of an intravenous bolus of 1 μg/kg administered to saturate T_3 receptors followed by 0.06 μg/kg per hour perfused for 270 min. Maximal dose of T_3 was 100 μg.

Hemodynamic parameters were determined by a pulmonary arterial catheter inserted via the internal jugular vein. This was advanced while observing the pressure wave until pulmonary wedge pressure was obtained. A Vigilance Monitoring System (Baxter) was used for the continuous measurement of cardiac index, reference range (2.8–4.2 l min^{-1} m^{-2}). Arterial and pulmonary capillary gas samples were processed by an ABL520 Gas Analyzer (Radiometer Copenhagen). All data were computerized to obtain the systemic vascular resistance index (reference range 1760–2600 dyne s^{-1} cm^{-5}), pulmonary vascular resistance index (45–225 dyne s^{-1} /cm^{-5}), oxygen delivery index (520–720 ml min^{-1} m^{-2}) oxygen consumption index (100–180 ml min^{-1} m^{-2}), and oxygen extraction (20–30%).

Serum lactate was measured by a TDX Analyzer (Abbot; reference range 6–22 mg/dl). A gastric saline tonometer was used to determine gastric PCO_2. The position was checked by chest radiography. The tonometer was filled with 2.5 ml ClNa 0.9%, after an equilibration time of 90 min; 1 ml dead space volume was aspirated from the catheter and discarded. The remaining ClNa 0.9% solution was aspirated and analyzed for Pco_2 by a ABL 520 Gas Analyzer (Radiometer Copenhagen). The Pco_2 measurement was corrected according to the manufacturer's recommendation. The Pco_2 gap is the difference between gastric intramucosal Pco_2 and arterial Pco_2. Thyroid hormones were determined by radioimmunoassay in a laboratory at Alicante University General Hospital. Reference ranges in our laboratory are: thyroid-stimulating hormone (TSH) 0.3–4.8 mu/l, free thyroxine (fT_4) 10.3–25.8 nmol/l, free T_3 (fT_3) 2.3–4.9 pmol/l, and reverse triiodothyronine (rT_3) 258–645 nmol/l.

For intracellular adenine nucleotides biopsy specimens were obtained in the operating room before aortic cannulation. Pancreas, heart, lung, and liver were biopsied. All were stored immediately at −80°C and processed at the end of the study. The adenine nucleotides concentration was measured by HPLC using a 1100 Supercosil LC-18-T (Hewlett Packard). The adenine concentration was then calculated as energy charge (EC) ratio, according to the formula [13]: EC=[(ATP)+1/2(ADP)]/[(ATP)]+(ADP)+(AMP)). The term [(ATP)+(ADP)+)AMP)] was expressed in nanomoles per grams of protein.

Qualitative variables were analyzed by the absolute and relative frequencies. Quantitative variables were studied by Kolmogorov-Smirnov test. Thyroid hormone variables showed a nonparametric distribution and are reported as median and 25th–75th percentiles. We used the Mann-Whitney U test to compare thyroid hormones between treatment group and controls at t_0,t_{90},t_{180}, and t_{270} and the

Wilcoxon test to compare thyroid hormones within groups at t_0 and t_{270}. Hemodynamic, tonometric, and metabolic variables showed a normal distribution and are reported as mean ±SD. To compare hemodynamic and tonometric parameters and lactate values between treatment group and controls at t_0,t_{90},t_{180} and t_{270} we applied Student's t test. With the help of Student's t test for pairs we analyzed these variables within groups at t_0 vs. t_{270}. Student's t test was used to compare adenine nucleotide concentration between treatment group and controls. Differences at the level of $p<0.05$ were accepted as statistically significant.

Results

Mean dopamine dose was 5.66±3.7 μg/kg per minute in the treatment group and 5.33±2.6 in controls (n.s.). Systemic vascular resistance index at t_0 was 1590.3±662.8 in the treatment group and 1488.3±538.4 in controls (n.s.), considering 1760–2600 dyne s^{-1} cm^{-5}as the reference range. Findings regarding cardiac index, oxygen extraction, serum lactate, and Pco_2 gap are presented in Table 1, serum thyroid hormone concentrations in Table 2, and adenine nucleotide concentrations in Table 3.

Discussion

Hemodynamic parameters

Hemodynamic phenomena occurring after brain death have been described by studies performed on animal models [14]. Increased intracraneal pressure causes ischemia which, progressing through the medulla, results in a sympathetic storm. Increased heart rate, blood pressure, and peripheral vasculature vasoconstriction occur for 15 min. This phase is followed by one of decreased blood pressure, heart rate, and systemic and pulmonary vascular resistance indexes by 50% of baseline values. A signifi-

Table 1 Hemodynamic parameters and oxygenation measurements (*CI* cardiac index, *O_2E* oxygen extraction)

	t_0	t_{90}	t_{180}	t_{270}
CI (l min^{-1} m^{-2})				
Treatment	4.3±1.9	4.4±1.5	4.7±1.7	4.4±2.2
Control	4.5±1.5	4.8±1.8	4.6±1.3	4.7±1.7
O_2E (%)				
Treatment	18.7±6.0	18.3±7.2	17.8±4.8	18.4±5.6
Control	17.5±3.2	17.9±4.7	17.0±3.9	18.2±5.0
PCO_2 gap (kPa)				
Treatment	0.77±0.78	0.93±0.86	1.27±0.90	1.30±0.86*
Control	1.25±1.48	1.79±2.19	1.99±2.31	1.98±2.32**
Lactate (mg/dl)				
Treatment	20.2±10.6	16.3±7.0[4]*	14.7±4.8***	17.3±8.6***
Control	19.5±8.4	24.0±15.5	24.3±17.4	31.5±23.2

*$p<0.01$ vs. t_0, **$p<0.05$ vs. t_0, ***$p<0.01$ vs. control, [4]*<0.05 vs. control

Table 2 Thyroid hormones (*TSH* thyroid-stimulating hormone, *fT_4* free thyroxine, *fT_3* free triiodothyronine, *rT_3* reverse triiodothyronine, *parentheses* range)

	t_0	t_{90}	t_{180}	t_{270}
TSH (mu/l)				
Treatment	0.22 (0.1–0.4)	0.22 (0.0–0.3)	0.20 (0.1–0.4)[4]*	0.20 (0.1–0.6)[4]*
Control	0.28 (0.1–0.9)	0.38 (0.1–0.9)	0.45 (0.2–1.1)	0.44 (0.1–1.3)**
fT_4 (nmol/l)				
Treatment	12.5 (9.0–15.4)***	10.9 (5.1–12.9)	10.8 (7.7–14.1)	9.8 (6.4–14.1)*
Control	9.1 (6.4–10.3)	8.1 (6.4–10.3)	9.4 (6.4–11.6)	9.5 (6.4–12.4)
fT_3 (pmol/l)				
Treatment	1.5 (1.2–2.1)	19.5 (9.3–29.7)[5]*	20.4 (9.6–32.5)[5]*	18.86 (10.2–32.8)[5]*
Control	1.1 (0.7–1.9)	1.5 (0.7–1.9)	1.6 (0.7–2.1)	1.7 (0.9–2.1)
rT_3 (nmol/l)				
Treatment	555.9 (380.5–844.9)	477.3 (412.8–548.2)	570.1 (267.0–879.7)	455.3 (310.8–548.2)
Control	1001 (555.9–1328.7)	701.1 (460.5–1062.9)	770.1 (428.2–1130)	762.3 (340.5–1062.9)

*0.02 vs. t_0, **0.08 vs. t_0, ***$p<0.05$ vs. control, [4]*$p<0.01$ vs. control, [5]*$p<0.001$ vs. control

Table 3 Energy charge; the concentration of AMP, ADP, and ATP measured as nanomoles in relation to grams of proteins (*parentheses* range)

	Liver	Pancreas	Heart	Lung
Treatment	0.39 (0.3–0.6)	0.44 (0.3–0.5)	0.43 (0.3–0.4)	0.45 (0.3–0.5)
Control	0.45 (0.3–0.5)	0.38 (0.2–0.4)	0.38 (0.3–0.4)	0.38 (0.2–0.4)

cant decrease in myocardiac contractility has been reported 45 min after the brain injury. End-diastolic pressures in the right and left ventricles are increased by 50% and 300%, indicating biventricular impairment [15, 16].

We expected to find improved hemodynamic parameters based on nontranscriptional T_3 actions [6, 17], but neither our own findings nor those of Goaring et al. [18] or Randell et al. [19] confirm this hyphothesis. In our opinion, the loss of cardiovascular tone caused by rostral-to-caudal ischemia and the vasodilatation effect of dopamine explains the low systemic vascular resistance index and high CI observed. Reducing the inotrope dose is one of the arguments in favor of T_3 treatment. Novitzky and Cooper [9] suggest administering T_3 at 2 μg/h and successive bolus of 4–6 μg every 15 min until hemodynamic stability is attained to reduce the inotrope dose. Recently Wood et al. [20] recommended T_3 in unstable donors who require more than 10 μg/kg dopamine per minute or have an ejection fraction of less than 45%. However, we knew neither the optimal dose of T_3 nor the timing of its administration. The mean dopamine dose did not differ significantly between controls and the treatment group; thus hemodynamic stability was attained without any T_3 influence. We were able to reach hemodynamic goals in the donor with a Swan Ganz catheter.

We searched for a explanation for the surprisingly low oxygen extraction values. Some authors have addressed this issue by using direct and indirect calorimetry to measure the oxygen consumption in organ donors. Bitzani et al. [21] measured the resting energy expenditure and basal metabolic rate by direct calorimetry. The resting energy expenditure was decreased as below the basal metabolic rate. Up to 20% of the resting energy expenditure was consumed by the brain, but once brain death occurred, metabolic demands were minimal. The diminished resting energy expenditure observed could not be attributed to low levels of fT_3 or hypothermia but to lack of cerebral blood flow. Indirect calorimetry was used by Langeron et al. [22] to measure oxygen consumption in donors. They found it to be decreased by 25–30%, the same range observed in patients under general anesthesia. A high plasma lactate concentration despite adequate oxygen delivery was also detected. The authors' hypothesis was that brain death modifies the ratio of regional oxygen delivery index to oxygen consumption index, causing organ dysfunction. Based on the previous reports we conclude that the high cardiac index observed in our study oversupplied the donor's metabolic condition and resulted in a low oxygen extraction. On the other hand, the dopamine dose used is not known to have any effect on oxygen consumption.

Metabolic parameters

High lactate has been reported by Powner et al. [23] in donors with no hypoxemic or hypotensive events during maintenance. These authors did not find the cause of hyperlactatemia, but low fT_3, hypoxia, and hypotension were rejected. Our maintenance protocol ensured adequate PaO_2, Hb, and cardiac index; therefore hyperlactatemia would not be secondary to low oxygen delivery. We believe that dysoxia [24] might cause hyperlactatemia in organ donors. Even in a scenario of low metabolic demands, oxygen use may have been impaired at the tissue level. Another possible cause of hyperlactatemia has been suggested by Novitzky and Cooper [9]: a hypothyroid condition in the donor. T_3 would act on the mitochondrial redox system, favoring the aerobic metabolism thus reducing lactate. This hypothesis could not be confirmed as no locus for T_3 was isolated in the mitochondria [3].

Pco_2 gap

The Pco_2 gap (tonometer -blood Pco_2) was considered, for methodical reasons, the ideal parameter for monitoring splanchnic circulation. Kolkman et al. [25] considered 1.2 kPa the upper normal limit. When hypoperfusion was established, values greater than 1.2 kPa were reached. If anaerobic metabolism occurred, a critical gap of 3.3 kPa was detected. Subsequent reports have set a higher threshold gap. Uhlig et al. [26] proposed a threshold gap below 3.3 kPa to prevent hypoxia and 6.6 kPa to detect critical flow reduction in the splanchnic circulation. According to the Kolkman et al. [25] value, the critical gap was not reached in our study, but the Pco_2 gap of both groups increased between t_0 and t_{270}. We believe that the loss in vascular tone may cause regional flow mismatch and abnormal oxygen utilization. Dysoxia (the inability of tissues to metabolize oxygen adequately) may explain the Pco_2 gap behavior in the donor [27, 28]. Although the mechanisms that lead to dysoxia remain unknown, microcirculatory flow redistribution and impaired cellular oxygen use seem to be involved.

Thyroid hormones

We investigated whether thyroid hormones in the donor can be considered part of nonthyroidal illness. Therefore we measured fT_3, fT_4, TSH, and rT_3 from brain death to retrieval. We first determined TSH in the control group to assess its physiology after brain death. Within the first 270 min the value increased. Knowing that TSH half-life is 35-55 min, we can assume that TSH secretion was maintained even after brain death. Because the superior hypophyseal arteries (which have an extradural origin,

thus less affected by endocraneal hypertension) were supplying the anterior pituitary [29, 30].

We then examined whether TSH is sensitive to T_3 administration. Significantly lower TSH was observed in the treatment group than in controls at t_{180} and t_{270} due toT_3 administration. This negative feedback supports a normal pituitary-thyroid function in the donor. It might also contribute to the decreasing in fT_4 between t_0 and t_{270} in the treatment group but not in controls. Dopamine would have also contributed; all donors received it as a constant dose for 270 min. Although dopamine suppresses TSH, its effect would have affected both groups equally. We think that the TSH was suppressed by T_3, although dopamine also had a role.

Finally, we believe that low fT_4, low fT_3, normal TSH, and high rT_3 (in controls) may be considered a pattern of severe nonthyroidal illness. We agree with Gramm et al. [30]$^{\$}$, Powner et al. [23], Howlett et al. [31], and Masson et al. [32] that brain death per se did not cause dysfunction of the hypotalamic-pituitary axis. Our findings of increased TSH as well as its negative feedback after T_3 administration favor the hypothesis of a peripheral alteration in thyroid hormones. The preexisting condition leading to brain death might cause low FT_3 and FT_4. The physiology of the nonthyroidal illness is: a decreased activity of the 5′-deiodinase lowering T_3 so that T_4 is diverted from conversion to T_3 to other metabolic pathways. Normal to high rT_3 is due to the decreased 5′-deiodinase activity.

Intracellular adenine nucleotides

Guaranteeing graft viability after transplantation is the goal in caring for the donor. The capacity to generate adenine nucleotides is considered a parameter of cellular viability by some authors [33, 34]. Lanir et al. [35] demonstrated a direct correlation between high ATP content in the donor liver and good posttransplant graft function. Novitzky [36] suggest administering T_3 to the donor and the recipient to avoid a relapse of the anaerobic metabolism caused by a low T_3 state. Novitzky and Cooper [9] propose that T_3 "reactivates" the mitochondria by stimulating adenine nucleotide translocase system and ATPase systems. The physiology of T_3 nontranscriptional actions on the mitochondria system has not been described. The results of some of the studies made on animal models [37] do not support a causal correlation between T_3 administration and adenine nucleotides synthesis. A better knowledge of T_3 physiology is needed to clarify whether adenine nucleotides synthesis is induced in the mitochondria by T_3.

Conclusions

Hemodynamic goals are reached by the help of a Swan Ganz catheter. T_3 administration adds no benefit in attaining the stability for suppressing inotropes. The donor hemodynamic condition is not directly linked to thyroid hormone plasma levels. Although the gastric tonometer is a reliable instrument for determining splanchnic perfusion, the hypoperfusion threshold is still controversial, limiting the clinicians' decision making. Although the cause of hyperlactatemia in the donor is unclear, it has not been considered a clinical manifestation of hypothyroidism. Lactate is the only variable significantly affected by T_3. Therefore T_3 treatment is not considered useful to donors. We did not observe a causal correlation between T_3 cellular actions and adenine nucleotides synthesis. Should future investigations clarify this, as clinical decisions on the graft function will be reached.

The study has following limitations. The observation time was far too short, and the adenine nucleotides metabolites were extreme labile. In regard to the former, The National Transplant Organization and the legal requirements in our country permitted an average time of 5 h for organ donors to be maintained in the intensive care unit. Protein synthesis induced by T_3 may begin as early as 20 min after T_3 but will not reach its peak until about 4 h later [23]. The second limitation is the high lability of adenine nucleotides under normothermic conditions; biopsy specimens were therefore frozen immediately after their extraction, but we cannot rule out some loss of nucleotides while processing. Better knowledge of T_3 nonnuclear actions would help clinicians to find the optimum T_3 dose, the mean observation time needed to detect any effect, and a reliable parameter to measure the functional benefits on the organs to be transplanted.

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