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Resting energy expenditure in brain death

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Abstract *Objective*: To evaluate resting energy expenditure (REE) in brain dead patients and to investigate the hypothesis that the reduction in REE results from a decrease in cerebral blood flow.
Design: Prospective, open labeled, control study.
Setting: General intensive care unit of a tertiary referral teaching hospital.
Patients: 30 critically ill patients with isolated head injury divided in two groups: group 1 patients ($n = 10$) with a Glasgow Coma Scale (GCS) score of 4 to 8 and group 2 patients ($n = 20$), in whom the final outcome was brain death (GCS = 3). Group 2 patients were divided into two subgroups: Group 2 a ($n = 11$) were admitted as brain dead (GCS = 3) and group 2 b ($n = 9$) were admitted with a GCS > 3 and progressed to brain death.
Interventions: Clinical and instrumental, using transcranial Doppler sonography (TCD), diagnosis of brain death. Cerebral blood flow studies of the middle cerebral artery bilaterally by bidimensional TCD and measurement of REE using indirect calorimetry.
Measurements and results: Measurements of REE and TCD studies were performed simultaneously on admission and after hemodynamic and neurologic stabilization. In cases with progressive neurologic deterioration, serial measurements were performed REE values were expressed as percentage of basal metabolic rate (% BMR), which were estimated according to each patient's gender, age, height, and weight. Group 1 patients, had normal TCD patterns throughout their hospitalization and their REE value was 21 ± 11 % higher than BMR. Group 2 patients demonstrated TCD patterns compatible with brain death and their REE value was 24.5 ± 11 % lower than BMR ($p < 0.01$). Group 2 a patients, who were admitted as brain dead and remained brain dead, had REE values 30 ± 11 % lower than BMR ($p < 0.01$). Group 2 b patients, who were not brain dead on admission but progressed to brain death, in serial measurements revealed a significant relationship between REE and TCD findings ($R = –0.77$, $p < 0.0001$). In this subgroup of patients, with multiple regression analysis a significant relationship was found only between REE and the TCD pattern, but not with body temperature.
Conclusions: In brain dead patients, REE decreases to values lower than BMR. This can be attributed to the cessation of cerebral blood flow and consequently cerebral metabolism and not to hypothermia.

Key words Brain death · Head injury · Resting energy expenditure · Basal metabolic rate · Transcranial Doppler sonography

Introduction

The diagnosis of brain death is based on a series of clinical as well as instrumental criteria. The clinical criteria rely on the findings of absent brain stem reflexes and a positive apnea test. Besides the clinical criteria, some authors advocate an isoelectric electroencephalogram [1]. However, in cases of hypothermia or overdose with central nervous system depressant drugs, these criteria are unreliable and considered insufficient. Therefore, other confirmatory tests are required to establish accurately the diagnosis of brain death, tests that can either document the absence of neuronal activity or the absence of cerebral blood flow or perfusion. Abolition of neuronal activity in brain death can be documented with brain stem auditory evoked responses [2–4]. The absence of cerebral blood flow/perfusion can be documented via selective cerebral angiography, radionuclide computed tomography (CT), xenon CT measurements, radioisotope bolus technique, as well as transcranial doppler sonography (TCD), [5–8]. In certain countries, such as Norway and Switzerland, clinical criteria alone are considered insufficient to diagnose brain death and therefore cerebral angiography is required as the final confirmatory test, especially if these patients are considered for organ procurement [1, 9].

Basal metabolic rate (BMR) represents the metabolic rate of the patient while awake, at rest, without physical or psychological stress, and at least 12 h after the last meal. It is dependent on age, weight, height, and sex. Resting energy expenditure (REE) represents the metabolic rate of the patient while awake, at rest, and in the postabsorptive state. Various disease processes influence the REE, modifying the patient's metabolic requirements. Traumatic brain injury induces a hypermetabolic-hypercatabolic state, with an increase in REE up to 125–165 % of the predicted BMR [10–12]. On the contrary, several investigators have reported a reduction in the REE in brain dead patients [13–16]. This reduction in REE is considered by some to be due to hypothermia [13, 16]. We designed this study in order to investigate whether, once brain death is established, REE is indeed reduced to values lower than BMR, and whether this reduction is mainly due to decreased cerebral blood flow, and consequently decreased cerebral metabolism, and not to hypothermia.

Patients and methods

Patients

We included 30 patients admitted to the intensive care unit of our institution over a period of 2 years with the diagnosis of isolated traumatic brain injury. All patients were under controlled mechanical ventilation in order to maintain normal arterial carbondioxide tension ($PaCO_2$) and arterial oxygen tension (PaO_2). Patients were divided into two groups according to their initial Glasgow Coma Scale score (GCS), and the evolution of their neurologic state and TCD pattern during hospitalization. Group 1 consisted of 10 patients with severe head injury (GCS 4–8), clinically confirmed neurologic activity, and normal TCD findings after hemodynamic stabilization. Group 2 consisted of 20 patients in whom the final outcome was brain death. This group was further divided into two subgroups. Group 2 a ($n = 11$) consisted of patients who, on admission, met the clinical criteria and TCD findings of brain death (GCS = 3) as well as after 24 h of resuscitation. Group 2 b ($n = 9$) consisted of patients who, on admission, had a GCS of 4–8; however, despite medical and/or surgical treatment, they progressed to brain death. Medical treatment in both groups consisted of hemodynamic support with fluid administration and inotropic drugs to preserve the cerebral perfusion pressure, treatment of intracranial hypertension with mannitol and/or hypertonic saline (7.5 %), and treatment of hyperthermia with cooling blankets. Mild hypothermia ≥ 35 °C presenting on admission was considered therapeutic and not treated, since hypothermia decreases the cerebral metabolic needs. Midazolam and fentanyl were administered to groups 1 and 2 b to keep them sedated while on the ventilator. Group 2 a was neurologically unresponsive on admission and therefore did not require sedation.

In all patients, the following parameters were continuously monitored: heart rate, invasive blood pressure, arterial oxygen saturation via pulse oximetry, central body temperature, and intracranial pressure (ICP) where applicable. Postcraniectomy patients did not receive an ICP device because the validity of the measurements are questionable. Central body temperature was recorded with a temperature probe inserted into the esophagus or via the thermistor of the pulmonary artery catheter which was inserted in some patients with hemodynamic instability for guidance of hemodynamic support.

The diagnosis of brain death was established clinically (based on absent brain stem reflexes and a positive apnea test) as well as on their TCD flow patterns (see below). These patients had no major metabolic disorder, no major hypothermia (temperature ≥ 35 °C), and were hemodynamically stable for at least 24 h and after cessation of sedation for at least 48 h.

Methods

In all patients, estimation of BMR and measurements of REE and cerebral blood flow velocities in the middle cerebral artery (MCA) were performed as described below.

BMR

BMR was estimated according to the Harris-Benedict equation [17]. Men: BMR(kcal) = 66.5 + (13.75 × weight) + (5.003 × height) – (6.775 × age). Women: BMR (kcal) = 655.1 + (9.63 × weight) + (1.50 × height)–(4.76 × age)

REE

REE was measured by indirect calorimetry using the Deltatrac II metabolic computer (Datex, Finland) connected to the ventilator. This method calculates REE based on the measurement of oxygen consumption (VO_2) and carbondioxide production (VCO_2) in the expired gases, according to the Weir equation [18].

$$REE = (3.14 \times VO_2) + (1.106 \times VCO_2) \times 1.44$$

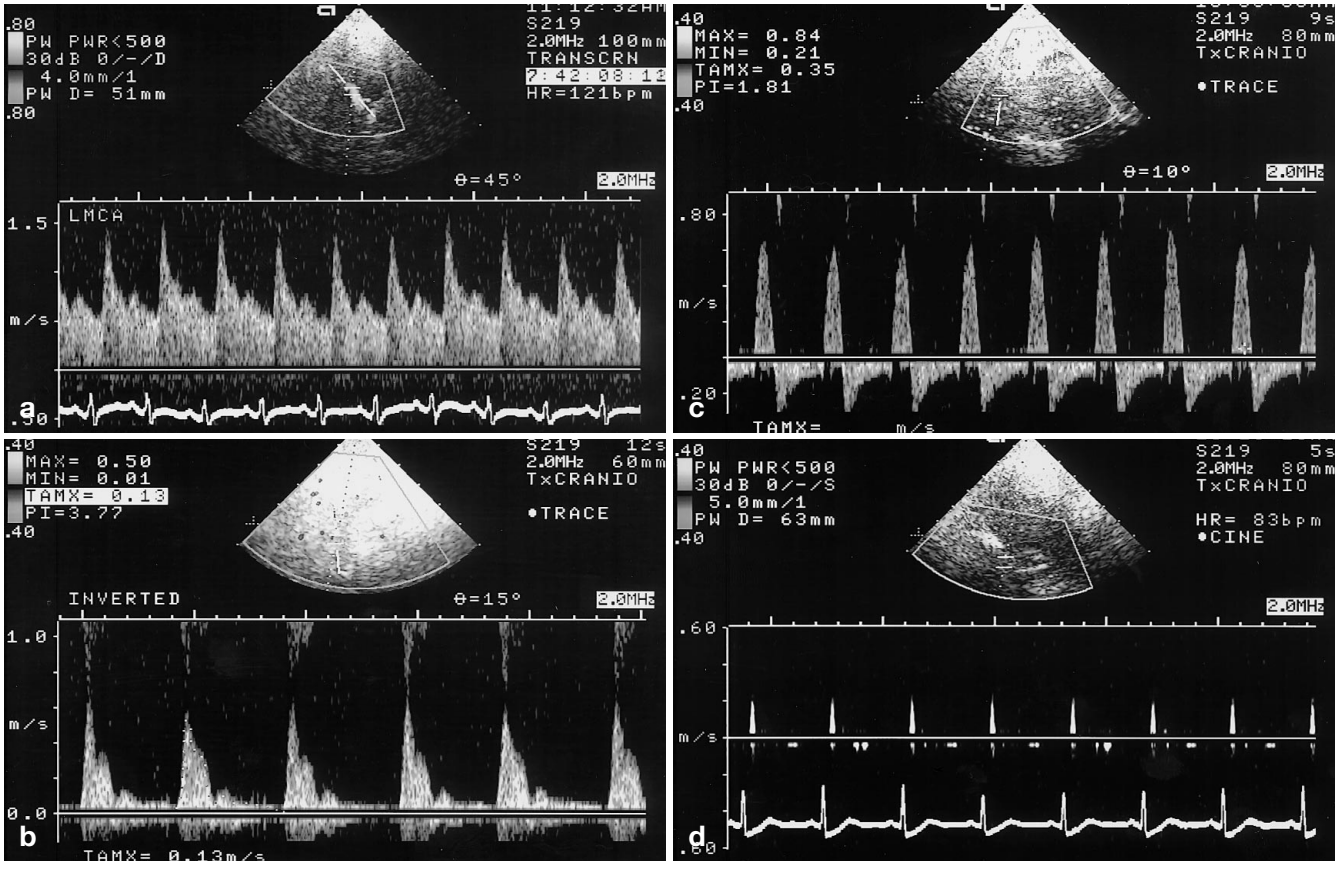

Fig. 1 From top to the bottom: TCD patterns showing a progressive decrease in cerebral blood flow. **a** Normal pattern, **b** ischemic pattern, **c** flow reversal, **d** early systolic spikes

Before each REE measurement, the metabolic computer was calibrated for 30 min. After this calibration period, 28 measurements of VO_2 and VCO_2 were performed at 1 min intervals for each patient using the formula above; we obtained 28 serial measurements of REE. The mean value of these 28 serial measurements represents the REE for each patient. The overall standard deviation in REE measurements for the entire series of patients was $4.29 \pm 1.8\,\%$ (Table 2). Each patient's calculated REE value was compared to his other BMR and expressed as a percentage of BMR (% BMR).

TCD

TCD was performed simultaneously with REE measurements over a period of 30 min using a 2-MHZ 2D ultrasound probe (Computer Sonography Accuson 128 XP/10c, USA). MCAs were identified bilaterally with the two-dimensional color-flow mapping, and pulse-wave Doppler signals with angle correction obtained using the transtemporal approach and insonating to a depth of between 40 and 60 mm. Early systolic spikes, and loss of a preexisting TCD signal are findings which were considered compatible with brain death if they persisted for more than 24 h (Fig. 1). These findings are typical when the ICP exceeds the arterial blood pressure, resulting in cessation of cerebral blood flow and perfusion. Patients with no TCD signal on admission were excluded from the study, since this absence cannot be attributed to the inability to obtain an acoustic window or loss of cerebral blood flow.

All groups had one set of TCD and REE measurements on admission, which were not taken into account for statistical analysis because on admission patients were hemodynamicaly and neurologically unstable; however, they were used to guide medical treatment. Group 1 patients had a second set of measurements within 48 h (10 patients:10 paired REE and TCD measurements, Table 1), once hemodynamic stabilization was obtained. Group 2a patients also had a second set of measurements within 48 h (11 patients: 11 paired REE and TCD measurements, Table 2), once brain death was confirmed (based on clinical and TCD criteria). We chose these sets of measurements for statistical analysis because they were performed after hemodynamic and neurologic stabilization and before other factors, like nosocomial infection, could influence REE. Group 2b patients, despite medical and/or surgical treatment, clinically deteriorated from an initial GCS of 4–8 to brain death. These patients had multiple REE and TCD measurements (once on admission, after hemodynamic stabilization, and after deterioration of the neurologic status). Of these multiple measurements, we used for statistical analysis those which corresponded to the TCD patterns compatible with a graded reduction in cerebral blood flow. The TCD patterns which we took into account were: (1) normal pattern (pulsatility index: $0.8 < PI < 1.6$), (2) high resistance pattern ($PI > 1.6$), (3) diastolic flow reversal pattern, and (4) early systolic spikes or absence of flow signal (Fig. 1). The total number of paired REE and TCD measurements in this group (2b) was 34 because of two missing REE data (Table 4).

Table 1 Demographic and measurement data for group 1 (non-brain dead) patients. Values are means
Group No 1

Patient No.	Sex	Age (years)	BMR	REE	REE (% BMR)	% of increase	Temperature (°C)
1	M	25	1790	2420	1.35	35.2	39
2	M	31	1790	2100	1.17	17.3	37.5
3	M	45	1530	1620	1.06	6	38
4	F	45	1760	2130	1.21	21	39.3
5	M	18	1880	2400	1.27	27.6	36
6	M	23	1930	2540	1.31	31.6	38.6
7	M	69	1610	2240	1.39	39	37.9
8	F	56	1460	1580	1.08	8.2	38
9	M	72	1380	1610	1.16	16.6	39
10	M	66	1600	1870	1.17	16.9	38.5
Mean ± SD		45 ± 20	1673 ± 184	2051 ± 361	1.21 ± 0.11	21 ± 11	38.18 ± 0.95

It is well recognized that there is no absolute correlation between cerebral flow velocities (measured with TCD) and cerebral blood flow. This lack of absolute correlation can be attributed to the possible changes in cerebral blood vessel diameter or changes in $PaCO_2$. In our study, $PaCO_2$ was kept within the normal range during the TCD measurements. In addition, when there was deterioration of the normal TCD pattern (high resistance, flow reversal, or absence of flow), we assumed this to be due to a relative decrease in cerebral blood flow. Mean velocity, pulsatility index, and other TCD findings were not used for statistical analysis, because these findings are considered meaningless when the TCD pattern shows diastolic flow reversal or early systolic spikes.

Statistics

Data were expressed as mean ± SD. The Kolmogorov-Smirnov Goodness of Fit test was used for normal distribution pattern analysis of age, REE, BMR, and temperature for all patients as well as between group 1 and 2, and between group 2a and 2b. Data analysis between groups 1, 2, 2a and 2b was performed using the one way analysis of variance with the Duncan test. One-way ANOVA, simple regression with the Spearman test for nonparametric data, and multiple stepwise regression analysis were also used for the serial measurements of temperature, REE, and TCD patterns in patients in group 2b. A p value < 0.05 was considered significant. For statistical analysis, the SPSS for windows (Student's version) software was used.

Results

The Kolmogorov-Smirnov Goodness of Fit test indicated a normal distribution pattern for all variables. Table 1 summarizes the individual data and the mean values ± standard deviation for age, temperature, BMR, REE, and REE expressed as a percentage of BMR in group 1. Table 2 summarizes these data for group 2 as well as for subgroups 2a and 2b.

There was no significant difference in age or BMR between group 1 and group 2 (45 ± 20 vs 47.8 ± 18 years, and 1673 ± 184 vs 1561 ± 206 kcal, respectively) (Table 3). Group 1 patients had a higher body temperature than those in group 2. (38.2 ± 0.9 vs 36.5 ± 1.37 °C, $p <$ 0.01). Group 2a had a significantly lower temperature than groups 1 and 2b (35.8 ± 1.1 vs 37.2 ± 1.2 °C and 38.18 ± 0.95 °C, respectively, $p < 0.01$). Furthermore, REE values were higher in group 1 than in group 2 patients (2051 ± 361 vs 1170 ± 193 kcal/day, or 121.5 ± 11 vs 75 ± 11 % of BMR ($p < 0.01$) (Table 3).

All group 1 patients had normal TCD patterns of the MCA bilaterally, on admission, and during their hospitalization. Among group 2 patients, 11 (group 2a) had on admission a TCD pattern compatible with brain death and 9 (group 2b) were admitted with a normal TCD pattern but became brain dead during hospitalization. Serial TCD studies in group 2b patients revealed TCD patterns compatible with progressive deterioration of cerebral perfusion. In this last group of patients we observed a significant decrease in REE ($p < 0.01$, ANOVA) as the TCD pattern deteriorated from normal to early systolic spikes or no flow (Table 4). In addition, a highly significant correlation was found between REE values (expressed as % BMR) and TCD findings ($R = –0.77$, $p < 0.0001$) (Fig. 2). Concerning the relationship between TCD pattern, REE, and temperature, multiple stepwise regression analysis revealed a strong relationship only between the worsening of the TCD pattern and the decrease in REE (multiple $R = 0.77$, $F = 46.5$, $p < 0.01$). On the contrary, no relationship was found between TCD patterns and temperature, or REE and temperature (Table 4).

Discussion

The metabolic changes accompanying brain death have not been studied extensively. Pevsner et al. [14], were the first to indicate that cerebral metabolism decreases in brain death and suggested that this could be a reliable prognostic finding. Subsequent studies reported that in brain death REE is decreased to levels ranging from 50

Table 2 Demographic and measurement data for group 2 (brain dead) patients. Values are means

Patient No.	Sex	Age (years)	BMR	REE	REE SD (%)	REE (% BMR)	% of decrease	Temperature (°C)
Group 2a								
1	M	37	1820	1110	3.6	0.61	39	35
2	M	47	1910	960	4.4	0.502	49.7	35
3	M	15	1420	860	4.6	0.605	39.4	35.8
4	M	43	1450	1000	6.2	0.689	31	37.5
5	M	73	1440	1150	3.7	0.798	20.1	35
6	F	64	1360	990	3.7	0.727	27.2	36
7	F	32	1510	1110	4.9	0.735	26.5	35
8	M	60	1720	1310	2.4	0.761	23.8	38
9	F	56	1330	950	1.5	0.714	28.5	35.2
10	F	48	1500	1390	2.2	0.926	7.33	37
11	M	65	1600	990	2.3	0.618	38.1	35
Mean ± SD (n = 11)		49 ± 16	1550 ± 190	1074 ± 160	3.5 ± 1.4	0.7 ± 0.1	30 ± 11	35.8 ± 1.1
Group 2b								
12	M	17	1850	1460	7.5	0.789	21	38.6
13	M	32	1830	1490	8	0.814	18.5	37.8
14	F	61	1330	1140	2.3	0.857	14.2	35.7
15	F	34	1230	1150	4.4	0.935	6.5	35.6
16	M	17	1860	1430	3.9	0.768	23.1	36
17	M	68	1660	1240	4	0.746	25.3	37.5
18	M	56	1500	1340	5	0.893	10.6	39.3
19	M	66	1470	990	3.7	0.673	32.6	37.3
20	M	65	1440	1340	7.5	0.93	6.94	37.8
Mean ± SD (n = 9)		46.2 ± 21	1574 ± 235	1286 ± 168	5.14 ± 2	0.82 ± 0.08	17.68 ± 8.8	37.2 ± 1.2
Mean ± SD (n = 20)		47.8 ± 18	1561 ± 206	1170 ± 193	4.29 ± 1.8	0.75 ± 0.11	24.5 ± 11.8	36.5 ± 1.37

Table 3 Statistical analysis by one-way ANOVA with the Duncan test between groups 1, 2, 2a, and 2b. Values are means ± SD

	Group 1	Group 2	Group 2a	Group 2b	
Age (years)	45 ± 20	47.8 ± 18	49 ± 17	46.2 ± 21	NS
BMR	1673 ± 184	1561 ± 206	1550 ± 191	1574 ± 235	NS
REE	2051 ± 361	1170 ± 193*	1074 ± 160*	1286 ± 168* $	$p < 0.01$
REE (% BMR)	1.21 ± 0.11	0.75 ± 0.11*	0.7 ± 0.1*	0.82 ± 0.08* $	$p < 0.01$
Temperature (°C)	38.18 ± 0.95	36.5 ± 1.37*	35.8 ± 1.1*	37.2 ± 1.2* $	$p < 0.01$

* Significant differences between groups 2, 2a, 2b and group 1
$ Significant difference between groups 2a and 2b

to 80% of BMR [13, 15, 16, 19]. After head injury, REE usually increases [10, 11], and this is mainly attributed to high levels of endogenous catecholamines. However, the decrease in REE during brain death remains unclear. Few investigators have addressed this issue, and the decrease in REE has been attributed to hypothermia [13, 16]. Dominguez-Roldan et al. [13] observed a significant correlation between REE and temperature, thus emphasizing the influence of core temperature on REE values.

Body temperature is considered normal in the range 36.5–37.5 °C. Usually within 24 h after head injury, the body temperature increases, probably as a result of a change in the hypothalamic thermoregulatory set-point, mediated by interleukin-1, a product of macrophages after tissue damage [20]. This was also the case in our patients in group 1 in whom the temperature increased to 38.1 ± 0.95. There is a positive correlation between temperature and REE in non-brain dead, head injured patients [20]. Sztark et al. [21] demonstrated a 10% increase in REE per 1 °C increase in body temperature. An increase in REE up to 21 ± 11% was also found in our group 1 patients, and this increase was in accordance with the increase in body temperature up to 38.18 ± 0.95 °C. Although the effect of increased temperature on REE is proven, there are conflicting data

Table 4 Statistical analysis of group 2b patients by one-way ANOVA with Duncan test between REE values (expressed as % of BMR) and temperature, as TCD pattern worsens from the normal to now-flow conditions

Patient No.	TCD 1: Normal pattern		TCD 2: Ischemic pattern		TCD 3: Reverse flow		TCD 4: Systolic spikes or absence of flow	
	REE (% BMR)	Temp. (°C)	REE (% BMR)	Temp. (°C)	REE (% BMR)	Temp. (°C)	REE (% BMR)	Temp. (°C)
12	Missing	Missing	– 4	38	– 16	38.6	– 22	38.6
13	31	36.8	8	36.6	– 10	35.8	– 18.5	37.8
14	– 1	35	– 1	35.7	– 4	36	– 14.2	35.7
15	16	36	8	35.8	– 1	35.8	– 7	35.6
16	Missing	Missing	– 1	36	– 8	35.8	– 23	36
17	14	37.5	2	37.3	– 12	37	– 25	37.5
18	15	38.8	– 4	38	– 15	36.2	– 11	39.3
19	18	37.9	12	37.8	– 16	37.3	– 33	37.3
20	65	39	35	39	4	37.8	– 7	37.8
Mean ± SD	22.5 ± 20	37.2 ± 1.4	6.1 ± 12.2*	37.1 ± 1.1	– 8.6 ± 7* $	36.7 ± 1	– 17.68 ± 8.8* $	37.2 ± 1.2

* Significant differences in REE between normal TCD pattern and the other TCD patterns ($p < 0.01$)
$ differences between TCD patterns 3 and 2 as well as 4 and 2 ($p < 0.05$)

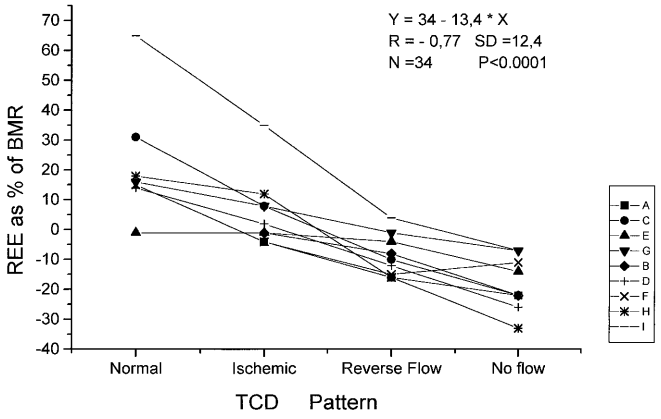

Fig. 2 Individual REE changes as TCD pattern deteriorates from normal to no-flow pattern. Letters *A–I* represent the 9 patients in group 2b reported in Table 4. The equation represents the linear correlation between TCD pattern and REE

concerning the influence of hypothermia. Some investigators have demonstrated a decrease in cerebral metabolic rate of oxygen and REE during hypothermia [20, 22–24], while others have found an increase in REE and suggested that this may be due to either catecholamine-mediated non-shivering thermogenesis or hypothalamus-mediated shivering thermogenesis [24]. A significant but transient increase in catecholamine levels has been demonstrated during brain death [25]. However, it remains unknown if catecholamine-mediated non-shivering thermogenesis ceases immediately after the onset of brain death. Hypothalamic, mesencephalic, and bulbar failure result in cessation of central temperature regulation, leading to poikilothermy [26]. This could possibly explain the low temperatures observed in most of the brain dead patients. In the context of our results, as well as in the above mentioned reports, we believe that hypothermia must be considered very carefully as being the major determinant of a decrease in REE during brain death.

In our study, in 20 brain dead patients (group 2) we found that REE decreases to a mean value of 24.5 % lower than BMR when brain death is established. This decrease in REE correlates with the reduction of cerebral blood flow as indicated by TCD patterns. Of the 20 brain dead patients, 11 met the clinical and TCD criteria of brain death on admission and after 24 h of resuscitation (group 2a) and their REE values were 30 ± 11 % lower than BMR. Furthermore, 9 patients (group 2b), who were admitted as non-brain dead and became brain dead during hospitalization, had REE values that gradually decreased from 22.5 ± 20 % above BMR to 17.68 ± 8.8 % lower than BMR. This REE decrease was in accordance with the cerebral blood flow changes indicated by the TCD pattern (Fig. 2 and Table 4) which evolved from normal to ischemic, to reverse flow, to early systolic spikes, or to a no-flow pattern (Fig. 1). In this group of patients (2b), multiple regression stepwise statistical analysis demonstrated that between TCD pattern, temperature, and REE, only the TCD pattern was responsible for the decrease in REE. Given the coupling of cerebral blood flow and metabolism, these findings suggest that the decrease in REE is the result of the reduction of cerebral metabolism. Approximately 20 % of cardiac output is directed to the brain, which, despite its small volume, has high energy requirements, consuming up to 20 % of the total body REE [13–15]. Therefore, we can assume that during brain death, the arrest of cerebral blood flow is accompanied by a drop in cerebral energy consumption. This most likely accounts for a significant proportion of the 24.5 % decrease in REE we observed. However, the decrease in REE beyond the

level expected to result from lack of cerebral perfusion, observed in patients in group 2 a (30 ± 11 % of BMR) could be attributed to other factors, such as mild hypothermia (35.8 ± 1.1 °C), absence of regulatory/anabolic functions of the brain, hormonal changes, and the lack of specific dynamic action of food.

Other factors, such as hypermetabolic hormones (thyroid hormones and catecholamines), have been analyzed in brain death. Low levels of triiodothyronine are a common finding [27]. In addition, in an experimental study Cooper et al. [28] showed that 3 h after the onset of brain death adrenaline and dopamine levels were normal and only noradrenaline levels were significantly below normal values. Consequently, the early decrease in energy expenditure observed in brain dead patients cannot be attributed to low thyroid hormones or catecholamine levels.

We conclude that the onset of brain death is accompanied by a decrease in REE to values lower than BMR. This is mainly due to the decrease in cerebral blood flow and, consequently, metabolism. However, in some cases variations in temperature may influence this decrease in REE to levels higher (patients 1, 2, 3, 5, 7, 11, Table 2) or lower than can be expected (patients 12, 13, 18, 20, Table 4). Further, larger scale studies are required to confirm and validate our findings and to clarify the time-course between brain death and changes in REE due to changes in cerebral metabolism.

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