https://doi.org/10.23934/2223-9022-2020-9-3-356-362

The Influence of Verticalization on the Dynamics of the Energy Demand at Rest in Patients with Unresponsive Wakefulness Syndrome

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RELEVANCE For the acute phase of cerebral insufficiency (ACI) analysis of energy demand at rest (EDR) using indirect calorimetry method is effective to evaluate the level of hypermetabolism and selection of optimal nutritional support. In patients with chronic impairment of consciousness (CIC) the reasonability of such an approach is shown, but in this category of patients the influence of rehabilitation measures on energy demand is not taken into account. Verticalization is a routine method of prevention and treatment of immobilization syndrome in patients with ACI and its consequences today.

AIM OF STUDY To determine the effect of the verticalization procedure on the turntable on the dynamics of resting energy expenditure (REE) index in patients with unresponsive wakefulness syndrome (UWS).

MATERIAL AND METHODS A prospective, comparative, non-randomized study was conducted in 136 patients in the neuro-intensive care unit of the Brain Institute Clinic. The REE index was determined using the method of indirect calorimetry without load and during verticalization in 75 patients with UWS and in 51 patients of the intensive care unit, who also underwent ACI, but were clearly conscious.

RESULTS In patients with clear consciousness during verticalization REE increased by an average of 300 kcal (20%) from the initial values. The energy value of verticalization was about 5 kcal/kg. On the contrary, in the group of patients with UWS, the verticalization procedure practically did not increase the energy consumption, and the energy value of verticalization slightly exceeded 1 kcal/kg.

CONCLUSION Patients with UWS have a special metabolic status, probably due to a decrease in the functional activity of the brain. This can be confirmed using indirect calorimetry.

Keywords: acute cerebral insufficiency, chronic impairment of consciousness, energy exchange, indirect calorimetry

For citation Leiderman IN, Belkin AA, Rakhimov RT, Belkin VA, Zhiguzhevsky RA. The Influence of Verticalization on the Dynamics of the Energy Demand at Rest in Patients With Unresponsive Wakefulness Syndrome. Russian Sklifosovsky Journal of Emergency Medical Care. 2020; 9(3):356–362. https://doi.org/10.23934/2223-9022-2020-9-3-356-362 (in Russ.)

Conflict of interest. Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship. The study had no sponsorship

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BMI – body mass index
ICU – intensive care unit
ACI – acute cerebral insufficiency

UWS – unresponsive wakefulness syndrome
CDC – chronic disturbances of consciousness
CNS – central nervous system
CMRGlc – центральный метаболизм глюкозы
PVS – Persistent Vegetative State
REE – Resting Energy Expenditure

INTRODUCTION

Advances and advances in the intensive care of critical conditions, in particular neuroresuscitation, in the past two decades have led to an increase in the number of patients who survive after acute cerebral lesion. Some of these patients fully recover within the first days after the development of acute cerebral insufficiency (ACI), others – over a longer period of time go through various stages before they fully or partially recover consciousness (for example, small consciousness, vegetative state) or permanently lose all brain functions (brain death). Clinical practice shows how difficult it is often to recognize reliable criteria for conscious perception of the environment in these patients. These problems are reflected in the frequent misdiagnosis of locked-in syndrome, coma, small consciousness and vegetative state.

In 1972 B. Jennett and F. Plum [1, 2] defined the vegetative state as a clinical state of “wakefulness without awareness”. They cited an article from the Oxford English Dictionary to clarify their choice of the term "vegetative": "to vegetate is simply living a physical life, devoid of intellectual activity or social life". The term proposed not so long ago to designate a persistent vegetative state – unresponsive wakefulness syndrome (UWS) [3] – allows to more correctly denote the patient's social status, which is of great psychological importance for the patient's family.

According to the consensus “Multi-Society Task Force on PVS (1994)”, the formulation of the diagnosis “persistent vegetative state” is possible if the following criteria are met:

— lack of signs of awareness of oneself or the environment and an inability to interact with others;
— lack of evidence of sustained, reproducible, targeted, or voluntary behavioral responses to visual, auditory, tactile, or pain stimuli;
— lack of recognition and response to speech;
— intermittent wakefulness is manifested by the presence of sleep-wake cycles;
— sufficiently preserved autonomic functions of the hypothalamus and brainstem to ensure survival with adequate patient care;
— lack of control of urination and defecation;
— preserved reflexes from the cranial nerves and spinal reflexes [3].

Positron emission tomography showed a significant decrease in global brain metabolism in vegetative patients. Recently, studies have shown a decrease in total brain metabolism in the range of 50-60% in a vegetative state of various etiology and duration. In patients with “locked in syndrome”, total supratentorial cerebral metabolism was preserved partially or completely, while in comatose patients there was a 45% decrease [4–7]. As shown in studies by M. Buchsbaum et al. and P. Maquet et al., in conditions of slow wave sleep, total brain metabolism is reduced by 44% below the normal values corresponding to full wakefulness [8, 9].

Another example of transient metabolic depression is seen during general anesthesia. Thus, it was found that when different anesthetics are titrated to the point of no response to pain stimulus, the resulting decrease in glucose metabolism in the brain is comparable to that observed in vegetative patients [10, 11].

The results of scanning of patients with UWS and after recovery of consciousness showed that the rate of glucose oxidation in the gray matter after recovery did not significantly increase (4.5 mg / 100 g / min versus 4.7 mg / 100 g / min) [12].

It remains controversial whether the observed metabolic disorder in the vegetative state reflects functional and potentially reversible damage or irreversible structural neuronal loss. J. Rudolf et al. spoke in favor of the latter, using 11C-flumazenil as a marker of neuronal integrity in assessing the state of acute and vegetative patients who underwent hypoxic damage to the central nervous system (CNS) [13].

The first functional studies using the xenon 133 isotope and a scintillation chamber have already demonstrated a significant diffuse decrease in cerebral blood flow in patients with UWS, which correlated with neurological outcome and level of consciousness: the recovered patients had higher mean values of cerebral blood flow than patients with residual deficiency or those who died [16]. These results were confirmed by single-photon emission tomography, suggesting that a global decrease in cortical blood flow is a reliable predictor of poor long-term outcome. That is why further research has focused on studying brain metabolism in the early stages, assessing signs of neuronal integrity, or demonstrating sensitivity to external stimuli [17].

Cerebral glucose metabolism (CMRGlc) at 75% of the normal range, measured 1 month after an episode of CNS hypoxia, may be a predictor of coma recovery, but a clear association between CMRGlc and clinical outcome has not been established. In some studies, CMRGlc was associated with level of consciousness, and clinical recovery was accompanied by an overall increase in glucose metabolic rate. In SBP, total cortical metabolism is usually between 40% and 50% of the normal range, but in rare cases with residual cerebral activity, CMRGlc may be in the normal range. With an increased duration of SBP, that is, during the transition from an acute vegetative state to a persistent one, there is a further decrease in glucose metabolism to 30-40% [14, 15, 18].

Differences in metabolic pattern can be seen in accordance with the underlying cause of the disease: in the hypoxic brain, supratentorial glucose hypometabolism was generally homogeneous, but may be enhanced in borderline zones. Patients with traumatic UWS often exhibit heterogeneous metabolic patterns with a deficit or severely reduced metabolism at sites of primary tissue injury and varying degrees of decreased glucose metabolism in the remaining cortical and subcortical structures. Several studies of post-traumatic as well as post-anoxic UWS have reported that glucose metabolism in the cerebellum is less impaired (18-30% lower than normal) [19].

Verticalization is a therapeutic strategy for ensuring the normal functioning of the body in a natural upright position, a method for the prevention and treatment of immobilization syndrome in patients of any profile. The goal of verticalization is to maintain or restore the maximum value of the gravitational gradient (at least 80 °) as a prerequisite for the functioning of the patient during the rehabilitation process. It is achieved in the course of

orthostatic training, which ensures the preservation (restoration) of adequate afferentation from the articular and muscle-tendon receptors when the joints of the lower extremities and the spine are closed, the preservation of the proper influence on the poznotonic and dynamic activity of vestibular and postural reflex reactions and automatisms, improvement of respiratory function, and also preservation of the reflex mechanism of bowel and bladder emptying [20].

Objective: to determine the effect of verticalization on a turntable on the dynamics of resting energy expenditure (REE) in patients with UWS.

MATERIAL AND METHODS

A prospective comparative non-randomized study was carried out in 136 patients of the neuro-intensive care unit of the Clinic of the Brain Institute between January 2016 and December 2018. Also included in the study were 21 healthy volunteers. All patients were admitted to the intensive care unit (ICU) of the CBI during routing to the stages of medical rehabilitation after the completion of the intensive stage of treatment in the ICU of the Sverdlovsk region. The severity of the condition corresponded to 5 points on the modified Rankin scale. All patients received standard rehabilitation according to the regulations of clinical recommendations "ReabIT" [21] for at least 3 hours a day, including verticalization on a turntable (20-60 minutes a day).

The inclusion criteria were:

— age 18-75 years;

— critical condition caused by primary ACI;

— persistent vegetative state (UWS) after suffering a critical state as a result of acute cerebral failure.

Exclusion criteria:

— spontaneous vegetative crises 2 or more times a day;

— hyperthermia;

— decompensated chronic kidney and liver pathology;

— chronic heart failure IV functional class according to NYHA;

— duration of a chronic critical condition more than 6 months.

The study was divided into two stages.

At the first stage, 21 healthy volunteers were assessed for energy demand at rest and real energy demand during verticalization. The determination of the patient's energy demand was carried out using the method of indirect calorimetry (metabolic monitoring system in the bedside monitor MPR 6-03 (Triton Electronics, RF)) by direct gas analysis of the inhaled and exhaled mixture and the separate determination of oxygen consumption and carbon dioxide excretion during inhalation and exhalation.

The so-called energy price of verticalization was also calculated. To do this, the increase in real energy consumption in comparison with the energy consumption at rest during verticalization was divided by the patient's body weight (kcal / kg):

Energy cost of verticalization = (energy consumption during verticalization, kcal / day) - (energy demand at rest, kcal / day) / (body weight, kg)

At the second stage of the study, indirect calorimetry at rest and during verticalization was performed in 75 ICU patients with UWS. A similar assessment of energy exchange was carried out in 51 ICU patients who also underwent ACI, who were in clear consciousness but had severe neurological deficit.

All patients received standard nutritional support in the form of enteral nutrition via a nasogastric tube or gastrostomy tube. The average daily volume of introduced energy substrates ranged from 1800-2000 kcal per day.

Verticalization was performed on a turntable in accordance with the clinical guidelines of the Russian Union of Rehabilitation Therapists (https://rehabrus.ru/materialyi/klinicheskie-rekomendaczii.html).

Statistical analysis of the research results was carried out using the Statistica 10.0 program and the statistical add-in for the Excel application for Windows 10. For quantitative features, the data were given as the arithmetic mean (M) and borders (in brackets) 95% confidence interval (CI) as median (Me) and the boundaries of the interquartile range (in brackets) Percentile 25–75%. For qualitative features, the percentage was given. Comparative analysis of qualitative features was performed using the Mann-Whitney test. For all statistical tests, the type I error was set equal to 0.05. The null hypothesis (no difference) was rejected if the probability (p) did not exceed a type I error.

RESULTS OF THE STUDY

A study of the characteristics of energy metabolism in healthy volunteers showed that when verticalization is performed on a turntable (gravitational gradient of 80º), there is a moderate (by an average of 250–300 kcal) increase in the indicator of real energy demand compared to the energy demand of rest with the head end of the bed raised to 20º. Thus, we found that in a healthy person, the increase in real energy consumption against the background of verticalization reaches an average of 20%, and the energy cost of verticalization fluctuates in a wide range of 1-6 kcal / kg (Table. 1).

Table 1
Energy value of verticalization in healthy volunteers (n=21)

#	Energy requirement at rest, kcal / day	Energy requirement for verticalization (gravitational gradient 80º), kcal / day	Energy value of verticalization, kcal / kg
1	1667	1747	0.99
2	1834	1990	1.88
3	1753	2279	6.26
4	817	1268	8.2
5	1166	1428	3.08
6	992	1059	1.16
7	1853	2208	4.61
8	1248	1258	0.17
9	1349	1828	6.94
10	1123	1468	7.34
11	1956	1978	0.29
12	1782	1788	0.8
13	1277	1665	6.36
14	748	807	1.02
15	770	970	3.2
16	1687	1827	1.75
17	1566	2327	10.3
18	1892	2345	5.7
19	986	1195	4.01
20	1211	1392	3.4
21	1403	1561	3
Mean value, standard deviation	1384.76 ± 393.66	1632.05 ± 455.29	3.83 ± 2.89

At the second stage of the study, the assessment of the indicators of energy demand at rest and real energy demand against the background of verticalization was carried out in 75 patients with UWS and 51 patients who were in clear consciousness. Body mass index (BMI), body weight, daily energy requirement calculated using the Harris-Benedict formula, as well as indicators characterizing the state of the visceral protein pool (serum levels of transferrin and albumin), did not differ significantly in the compared groups (Table. 2).

Table 2
Main indicators of nutritional status and protein metabolism depending on the level of wakefulness

	Unresponsive wakefulness syndrome, n = 75. Average value, error mean	Clear consciousness, n = 51. Average value, error mean	R
Body mass index, kg/m2	18.25 ± 2 11	21.31 ± 3.07	> 0.05
Body weight, kg	55.86 ± 3.76	61.1 ± 4.65	> 0.05
Albumin, g / L	29.86 ± 4.63	29.91 ± 3.89	> 0.05
Transferin, g / L	1.77 ± 0.23	1.61 ± 0.46	> 0.05
Energy demand according to the Harris-Benedict formula, kcal / day	1412.44 ± 189.11	1417 ± 212.21	> 0.05

A comparative analysis of the energy needs of lucid patients and patients with UWS at rest and against the background of verticalization revealed a number of fundamental differences and certain patterns (Table. 3).

Table 3

Energy consumption at rest without load and during verticalization. The energy value of verticalization at different levels of consciousness

	Unresponsive wakefulness syndrome, n = 75. Average value , error mean	Clear consciousness, n = 51. Average value , error mean	R
Energy consumption at rest without load, kcal / day	1156.41 ± 156.23	1425.63 ± 132.16	0.032
Energy consumption at rest during verticalization , kcal / day	1174.23 ± 106.55	1728.37 ± 124.31	0.02 4
Energy value of verticalization, kcal / kg	1.08 ± 1.01	4.92 ± 0.95	0.029

As can be seen from Table 3, in patients with clear consciousness during verticalization on the table, there was an increase in the indicator of true energy consumption by an average of 300 kcal, which corresponds to an average increase of 20%. At the same time, the energy price of verticalization was about 5 kcal / kg. On the contrary, in the group of patients with UWS, the verticalization procedure practically did not increase energy consumption, and the energy cost of verticalization slightly exceeded 1 kcal / kg.

THE DISCUSSION OF THE RESULTS

Evaluating resting metabolism in a horizontal position using indirect calorimetry, we saw a difference between healthy people and patients who underwent ACI, which was not when calculated using the Harris-Benedict formula. After analyzing the situation, we suggested that cerebral metabolism should be activated with a standardized test that activates interneuronal connections. For this, a verticalization maneuver was chosen, physiologically provoking the activity of the thalamus, the "switch" of proprioception, and an obligatory component of the rehabilitation process. It turned out that the profile of energy consumption in patients with UWS differs from patients who underwent ACI, but retained a clear consciousness. When comparing the energy balance of a group of healthy and conscious patients, no statistically significant difference was found. A similar result was obtained when comparing the indicator of the energy cost of verticalization – patients with UWS spend less energy on verticalization. The patterns of vegetative support of the verticalization process were clearly manifested: the transition to a vertical position up to the level of 80° of the gravitational gradient is accompanied by an increase in energy consumption. Based on an understanding of the physiological mechanisms of verticalization, such dynamics corresponds to the implementation of the algorithm for providing a gravitational gradient, which is based on the centralization of blood circulation and cerebral vasodilation, initiated by the neuroendocrine reaction of the hypothalamic-pituitary-adrenal system in response to proprioceptive activation of the thalamus. The identity of the direction of the change in energy consumption in all studied groups may mean the independence of the verticalization mechanism from the state of the cerebral hemispheres. Considering that no intergroup difference in nutritional status was obtained, it is tempting to attribute the differences in the metabolic balance to the cerebral fraction of energy consumption. But this is hindered by the heterogeneity of the group of patients with UWS in terms of nosology and the severity of the syndrome of the consequences of intensive care [22], which have an unconditional effect on the vegetative status. Moreover, without parallel analysis of the parameters of the functional activity of the brain, for example, electroencephalography or microdialysis, it is difficult to prove the cerebral "trace" in the dynamics of metabolism. Nevertheless, in the course of the study, we found that indirect calorimetry makes it possible, during a standardized verticalization maneuver, to register an increase in energy consumption, probably associated with an increase in the activity of the diencephalic region, aimed at implementing the mechanism for providing a gravitational gradient.

Disadvantages of research: a single fixation of calorimetry data only at two points of the gravitational gradient without synchronized monitoring of neurophysiological parameters is not sufficient to reflect the whole picture of metabolic changes during verticalization and to reveal the training effect of this procedure, which may take place during the rehabilitation process in patients with chronic impairments of consciousness.

CONCLUSION

Patients with chronic disorders of consciousness, apparently, have a special metabolic status, presumably due to a decrease in the functional activity of the brain, and this can be confirmed using the method of indirect calorimetry.

FINDINGS

1. The increase in real energy consumption against the background of verticalization in a healthy person reaches 20% on average, and the energy cost of verticalization ranges from 1 to 6 kcal / kg.

2. In patients who underwent ACI, in a clear consciousness during verticalization, the true energy demand increases by an average of 300 kcal, and the energy cost of verticalization is about 5 kcal / kg.

3. In patients with UWS, the verticalization procedure practically does not increase energy consumption, and the energy cost of verticalization is slightly higher than 1 kcal / kg.

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Received on 24.01.2020

Accepted on 06.03.2020