Lung (2015) 193:939–945
DOI 10.1007/s00408-015-9806-7

RESPIRATORY PHYSIOLOGY

Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects

Rubini Alessandro[1] · Bosco Gerardo[1] · Lodi Alessandra[1] · Cenci Lorenzo[1] · Parmagnani Andrea[1] · Grimaldi Keith[2] · Zhongjin Yang[3] · Paoli Antonio[1]

Received: 30 June 2015 / Accepted: 21 September 2015 / Published online: 26 September 2015

Abstract
Purpose The effects of the ketogenic diet (KD) on weight loss, metabolic, and respiratory parameters were investigated in healthy subjects.
Methods Thirty-two healthy subjects were randomized into two groups. The KD group followed a ketogenic diet for 20 days (KD t_0–t_{20}), then switched to a low-carbohydrate, no-ketogenic diet for 20 days (KD t_{20}–t_{40}), and finally was on a Mediterranean diet (MD) for 2 more months (KD t_{40}–t_{2m}). The MD group followed a MD for 20 days (MD t_0–t_{20}), then followed a MD of 1400 kcal over the next 20 days (MD t_{20}–t_{40}), and completed the study with the MD for 2 months (MD t_{40}–t_{2m}). Body weight, body fat, respiratory rate, and respiratory gas parameters (including respiratory exchange ratio (RER) and carbon dioxide end-tidal partial pressure ($PETCO_2$), oxygen uptake (VO_2), carbon dioxide production (VCO_2), and resting energy expenditure (REE)) were measured at each point.
Results A significant decrease ($p < 0.05$) in RER was observed after 20 and 40 days in the KD group, but not in the MD group. In the KD group, significant reductions were observed for both carbon dioxide output and $PETCO_2$, however, there was no significant change in VO_2, VCO_2, and REE. While both diets significantly decreased body fat mass, the KD diet overall proved to have a higher percentage of fat loss versus the MD diet.
Conclusion The KD may significantly decrease carbon dioxide body stores, which may theoretically be beneficial for patients with increased carbon dioxide arterial partial pressure due to respiratory insufficiency or failure.

Keywords Ketogenic diet · Respiration parameters · Metabolism · Resting energy expenditure

Introduction

The ketogenic diet, which is of a high-fat, adequate-protein, low-carbohydrate content, is originally designed to treat refractory epilepsy in children. Though underlying mechanisms are not fully understood, systemic acidosis, electrolyte changes, and hypoglycemia induced by the ketogenic diet have all been suggested to be responsible for its therapeutic effects [1]. Recent studies have suggested that the ketogenic diet may be used as an adjunctive therapy in many other pathological conditions such as diabetes mellitus, polycystic ovary syndrome, acne, neurological diseases, cancer, and the amelioration of respiratory and cardiovascular disease risk factors [2, 3]. Moreover, very low-carbohydrate ketogenic diets are more effective for body weight reduction and fat loss compared to balanced or low-calorie Mediterranean diets, at least in the short-medium term [4, 5]. Despite the widespread use of the ketogenic diet, its effect on respiratory parameters is still not well investigated. One of the metabolic effects of the ketogenic diet is the higher than usual oxidation of fats, which reduces the respiratory exchange ratio (RER) values [6, 7]. Measured RER can be used to estimate the respiratory quotient (RQ), an indicator of which fuel

✉ Zhongjin Yang
Yangz@upstate.edu

[1] Department of Biomedical Sciences, University of Padova, 35131 Padua, Italy

[2] Biomedical Engineering Laboratory, University of Athene, 15773 Athens, Greece

[3] The Institute for Human Performance, SUNY Upstate Medical University, Syracuse, NY 13210, USA

(carbohydrate or fat) is being metabolized to supply the body with energy. Metabolic carbon dioxide output (VCO_2) can be calculated as the product of alveolar ventilation times alveolar fractionalcarbon dioxide content. A recent study suggests that administering the ketogenic diet for 6 months in patients with medically refractory epilepsy increased fat oxidation, and decreased RER and the RQ, without appreciable changes in resting energy expenditure (REE) [7]. Theoretically, the ketogenic diet decreases RER and metabolic carbon dioxide production, therefore, may lead to a decreased arterial carbon dioxide partial pressure ($PETCO_2$) and decreased pulmonary ventilation. These effects may be useful as an adjunctive therapy in managing patients with respiratory failure. However, this respiratory aspect of the ketogenic diet has not been previously investigated. In the present report, we studied the effect of the ketogenic diet on metabolic and respiratory parameters, including RER, $PETCO_2$, and pulmonary ventilation in healthy subjects, during and after the ketogenic diet period, and we compared these effects with the results obtained during and after a Mediterranean diet protocol. The effects of the ketogenic diet and Mediterranean diet protocol on body weight and fat mass (FM) have also been investigated.

Materials and Methods

Subjects

Participants were recruited via advertisement placed in two pharmacies located in the province of Vicenza (Veneto, Italy). Primary eligibility criteria included being 18–65 years old, BMI 25 to 30 kg/m^2, currently on a diet with normal to high amount of carbohydrate (>55 %)/compatible to a modified ketogenic diet i.e., a Mediterranean ketogenic diet with phytoextracts (KD) [8–10]. The subjects had normal renal function and no diabetes, nor were they pregnant or lactating. Changes of habits, like starting a new exercise program or taking new drugs during experimental period, would be excluded from final analysis. Forty female subjects were initially recruited in this study; six were excluded for medical reasons, one was following a low-carbohydrate diet already and 1 refused to participate after the first interview, thus 32 subjects participated in the study and were randomized into two groups ($n = 16$ for each group): MD (age 44.7 ± 13.9, BMI 27.5 ± 2.8, weight 77.2 ± 9.8 kg) and KD (age 51.4 ± 12.4, BMI 29.3 ± 2.8, weight 82 ± 12.4 kg). The study was approved by the Ethical Board of the University of Padova, Department of Biomedical Sciences, and conformed to standards for the use of human subjects in research as outlined in the current Declaration of Helsinki. Investigators explained the purpose of the study, the protocol to be followed, and the experimental procedures to be used prior to allowing participants to enter the study. Subjects received no monetary compensation for their participation and signed a voluntary consent before initiating the diet.

Diet

During a preliminary meeting, diets were explained and each participant received a detailed menu containing permitted and non-permitted food. The KD subjects were followed for 20 days on a ketogenic diet (KD t_0–t_{20}) with extremely low carbohydrate (<30 g/day). The diet used meals that mimic the aspect and the taste of carbohydrate, but with virtually zero carbohydrate, and added with phytoextracts (Tisanoreica® by Gianluca Mech SpA, Asigliano Veneto, Vicenza, Italy). The permitted food during the ketogenic diet phase was cooked or raw green vegetables (200 g/meal); meat, fish, or eggs (1 time/day); and olive oil 30 g/day. Allowed drinks were water, infusion tea, Mocha coffee, and specific herbal extracts (Estratti Decottopia Tisanoreica® by Gianluca Mech SpA, Asigliano Veneto, Vicenza, Italy). The diet was also integrated with four PATs® per day (PAT is the acronym for Porzione Alimentare Tisanoreica = Tisanoreica Nutritional Portion), which is composed of high-quality proteins (each PAT is equivalent to 18 g of protein) and virtually zero carbohydrates. After the ketogenic diet phase, the subjects were followed on a low-carbohydrate no-ketogenic diet over the next 20 days (KD t_{20}–t_{40}). During this period, complex carbohydrates (50–80 g/day) and cheese (60 g/day) were introduced and the number of permitted PATs was reduced to two, while the other indications remained unchanged. The distribution of nutrients (proteins, carbohydrates, and fats) in terms of percentage of total caloric intake was 43, 14, and 43 % during the ketogenic phase, and 27, 34, and 39 % during the next stage, respectively. Throughout the ketogenic period, all subjects consumed 30 ml of extract A and 30 ml of extract B diluted in 1.5 l water, daily. They also consumed 15 ml of extract C before breakfast and lunch, diluted in one glass of water. Following 20 days, after dinner, 20 ml of extract D diluted in one glass of warm water was added. The diet protocols have been tested in our previous researches [5, 9, 10].

The MD group followed a Mediterranean diet, consuming 1200 kcal/day for 20 days (MD t_0–t_{20}), and it was then followed with another set of Mediterranean diet consisting of 1400 kcal/day over the next 20 days (MD t_{20}–t_{40}). The macronutrient percentage during the Mediterranean diet consisted of 15 % protein, 60 % carbohydrate, and 25 % fat for the total daily caloric uptake.

After the initial 40 days, both the KD and MD groups were followed on a Mediterranean diet with a total daily caloric uptake of 1400 kcal. The Mediterranean regime consisted of a balanced diet, in which the use of whole grain pasta, bread, and rice was permitted, mainly at breakfast and lunch, but in a smaller quantity at dinner. Raw and cooked vegetables were prescribed at lunch and dinner; fruits were permitted as snacks in the morning or in the afternoon; and proteins (meat/fish/cheese/eggs/bean curd, etc.) were provided only at dinner. Sweets, pizza, and alcoholic drinks were allowed once a week and the accepted dressings were olive oil, salt, spices, and vinegar. Moderate physical activity and the use of infusions during the daytime were also suggested.

Detailed composition of the diet is listed in Tables 1, 2, and 3.

Measurements

Subjects were invited to the Laboratory of Physiology, Department of Biomedical Sciences, University of Padua, where measurements were performed. REE and RR and body weight were measured in the morning after overnight fasting at the start of the study (t_0), after 20 days (t_{20}), at the end of the diet-period (t_{40}), and 2 months after the end of the study (t_{2m}). Subjects were weighed at the same time of the day at the start (t_0), at t_{20}, t_{40}, and t_{2m} using the same weighing scales (Digital Scale Joycare® Jc431). Body composition analysis was performed using the Akern STA-BIA instrument, which provided us with the following information: fat free mass (FFM), FM, total body water (TBW), and muscular mass. REE was analyzed using oxygen uptake (VO_2), carbon dioxide production (VCO_2), and RER measurements with a Vmax® Encore 29 System (Vmax) (Viasys Healthcare, Inc., Yorba Linda, CA). Vmax used a mixing chamber and generated VO_2 and VCO_2; those data were converted to REE expressed in Kcal/d using appropriate RR values and established tables based on the Weir equation [10]. The device was calibrated with reference gases prior to each participant. Oxygen uptake was measured (ml/min) and also normalized to body weight (ml/kg/min), and the respiratory RR was determined. After resting for 15 min, the data were collected for 30 min, and only the last 20 min were used to calculate the respiratory gas parameters [9].

All tests were performed in the morning before breakfast (7–8 am), while the subjects were seated. The room was dimly lit, quiet, and approximately 24 °C. Subjects were requested to abstain from caffeine or alcohol consumption for 24 h prior to the measurement.

Statistical Analysis

The data were expressed as mean and standard deviation. Bland–Altman plots and comparison of the test–retest measurements performed in our laboratory confirmed good reproducibility of the measurements for RR and VO_2 (ICC >0.85 and >0.9, respectively, with $p < 0.05$). A one-way ANOVA for repeated measurements was used (GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego, California USA). Tukey's post hoc test was used. $p < 0.05$ was considered significant. Normality of the data was checked and subsequently confirmed using the Shapiro–Wilk test. The present sample size was selected based on a power analysis. Body weight and body FM data were analyzed using two-way ANOVA test for repeated measures, and unpaired t-tests with Welch's correction were performed when appropriate.

Results

Respiratory Gas Analysis

As shown in Fig. 1, the KD group showed a significant decrease ($p < 0.05$) in the mean value of RER after 20 days of ketogenic diet. The RER was maintained at lower levels even after 40 days (t_{40}), when subjects were no more in ketosis. The reduction in $PETCO_2$ (Fig. 2) was observed after both the ketogenic diet and Mediterranean diet. There were no significant changes in VO_2 (Fig. 3), VCO_2 (Fig. 4), and VE (Fig. 5).

The MD group did not show any significant difference (data not shown).

As shown in Fig. 6, a significant body weight loss was noticed in both groups between t_0 and t_{20} ($p < 0.01$), the body weight loss was more significant in the KD group than in the MD group. The mean values of body weight in both groups are as follows:

Table 1 Diet composition in KD diets (values are expressed in mean per day)

	KD t_0–t_{20}	KD t_{20}–t_{40}	KD t_{40}–t_{2m}
Daily energy, Kcal/day	848	938	1400
Protein, g/day (% daily energy)	92 (43.4)	64.4 (27.5)	52.5 (15)
Carbohydrate, g/day (% daily energy)	30 (14.1)	80 (34.1)	210 (60)
Fat, g/day (% daily energy)	42 (42.4)	42 (38.4)	54.4 (35)

Table 2 Plant extracts during the KD group's diet (from)

Plant extracts	ml/day	Composition
Extract A	30	Durvillaea Antarctica, Black Radish, Mint, Liquorice, Artichoke, Horsetail, Burdock, Dandelion, Rhubarb, Gentian, Lemon Balm, Chinaroot, Juniper, Spear Grass, Elder, Focus, Anise, Parsley, Bearberry, Horehound
Extract B	30	Serenoa, Red Clover, Chervil, Bean, Elder, Dandelion, Uncaria, Equisetum, Horehound, Rosemary
Extract C (only during the first ketogenic phase)	30	Eleuthero, Eurycoma Longifolia, Ginseng, Corn, Muira Puama, Grape, Guaranà, Arabic Coffee, Ginger
Extract D (only during the second non-ketogenic phase)	20	Horsetail, Asparagus, Birch, Cypress, Couch Grass, Corn, Dandelion, Grape, Fennel, Elder, Rosehip, Anise

Table 3 Main active ingredients of phytoextracts and their reported beneficial effects (from)

Extract	Main active ingredients	Reported beneficial effects
A	Mint	Indigestion
	Black radish	Antioxidant
	Burdock	Choleretic, increases bile secretion helping digestion
B	Serenoa Repens (Saw Palmetto)	Hormonal regulating effect
	White bean	Alpha-amylase inhibitory properties have been reported to aid weight loss and glycemic control
C	Ginseng	Ameliorate the commonly reported symptoms of weakness and tiredness during 1st phase of ketosis (1/2 weeks)
	Muira puama	
	Guaranà	
D	Equisetum	
	Dandelion (Taraxacum officinale)	

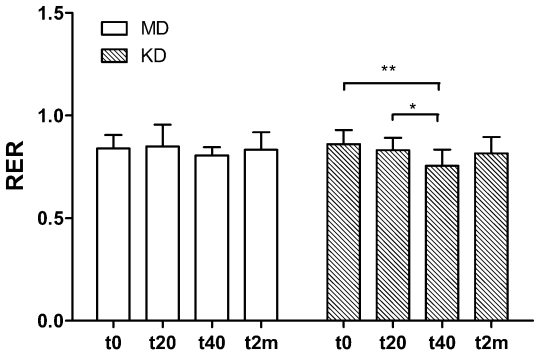

Fig. 1 The effect of ketogenic diet on respiratory exchange ratio (RER) measured at different time points during the diet period. Ketogenic diet significantly decreased the respiratory exchange ratio as measured on day 20. RER continues to decrease as measured on day 40, and returned to the baseline as measured in 2 months. t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. $^{**}p < 0.01$. Values are shown as mean and SD

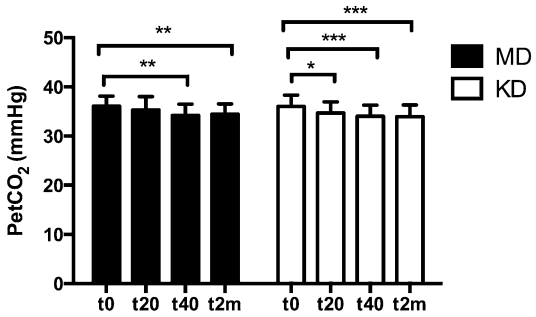

Fig. 2 The changes of carbon dioxide end-tidal partial pressure ($PETCO_2$) measured at different time points during the diet period. Comparing with the baseline of $PETCO_2$ at the start of the study (t_0), significant decrease ($p < 0.05$) was observed after 20 days (t_{20}) of ketogenic diet, at the end of the diet-period (t_{40}), and 2 months after the end of the weight reduction program (t_{2m}). t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. $^{**}p < 0.01$. Values are shown as mean and SD

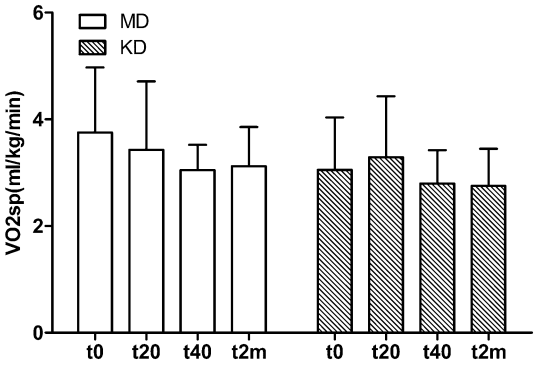

Fig. 3 The changes in oxygen uptake (VO2) measured at different time points during the diet period. There was no significant change in VO2 during the entire diet period. t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. Values are shown as mean and SD

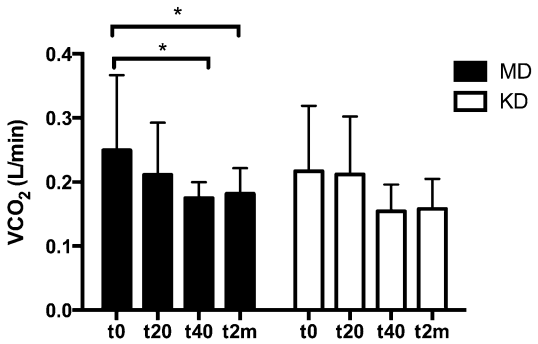

Fig. 4 The changes in carbon dioxide production (VCO2) measured at different time points during the diet period. There were no significant changes observed during the diet period. t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. Carbon dioxide output relies largely on the amount of energy your body is using. Values are shown as mean and SD

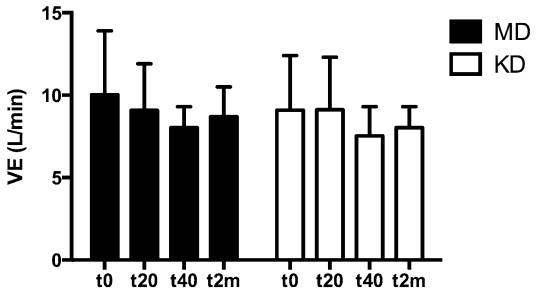

Fig. 5 The changes in expired total ventilation (VE) measured at different time points during the diet period. There were no significant changes observed during the diet period. t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. Values are shown as mean and SD

- KD: t_0 82.0 ± 12.4; t_{20} 77.8 ± 12.0; t_{40} 74.8 ± 11.7; t_{2m} 73.5 ± 12.6

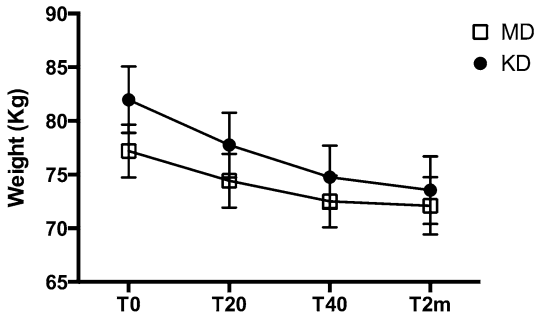

Fig. 6 The effect of ketogenic diet on body weight measured at different time points during the diet period. Significant body weight loss was observed in both diet groups. t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. No significant differences were detected between treatments. Values are shown as mean and SD

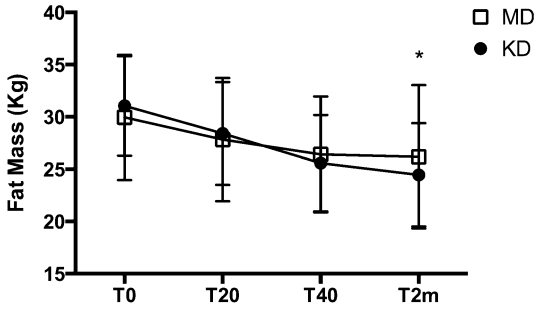

Fig. 7 The effect of ketogenic diet on body fat mass measured at different time points during the diet period. Significant body fat mass loss was observed in both diet groups. t_0 day 0, the value as baseline; t_{20} as measured on day 20; t_{40} as measured on day 40; t_{2m} as measured in 2 months. At t_{2m}, KD group showed significant decrease ($*p < 0.05$) compared to MD group. Values are shown as mean and SD

- MD: t_0 77.2 ± 9.8; t_{20} 74.4 ± 10.0 t_{40} 72.5 ± 9.6; t_{2m} 72.1 ± 10.7

The average weight loss was 8.4 kg for the KD group and 5.1 kg for the MD group at t_{2m}.

As shown in Fig. 7, both groups showed a good drop in FM between t_0 and t_{20}, although it was more significant for the KD group (p value MD $t_{20} < 0.01$; p value KD $t_{20} < 0.001$). The average of the FM lost in this group between t_{40} and t_{2m} is 1 kg in KD and 0.2 kg in MD group.

All subjects completed the experimental trial.

Discussion

The main findings in the present study are that (1) the ketogenic diet significantly decreased the value of RER; (2) the ketogenic diet significantly decreased carbon dioxide end-tidal partial pressure ($PETCO_2$); (3) the ketogenic diet

had no significant effect on REE, oxygen consumption (VO_2), carbon dioxide production (VCO_2), or expired total ventilation (VE); (4) the ketogenic diet significantly decreased body mass and body FM.

The RER is the ratio between the amount of CO_2 produced and molecules of O_2 consumed in one breath. A RER of 0.70 indicates that fat is the predominant fuel source, a RER of 0.85 suggests a mix of fat and carbohydrates, and a value of 1.00 or above is indicative of carbohydrates being the predominant fuel source. Deceased RER seen in the present study reflects fat as the predominant fuel source during consumption of the ketogenic diet. This is in agreement with our previous study [6] and others [7].

Oxygen consumption is linearly related to the workload; consumption of different diets should not significantly change REE. A recent study showed that administering the ketogenic diet for 6 months in patients with medically refractory epilepsy increased fat oxidation without changing REE [7]. Our data are in agreement with their findings that KD did not change REE. As pointed out by Tagliabue et al. the body has a great capacity to adjust substrate oxidation to substrate intake after approximately 1 week of carbohydrates and fats. Fat oxidation increased in our study as an adaptation to the high-fat intake, typical of the KD. The consequence of an isoenergetic exchange of fat for carbohydrate is that the results can also be interpreted as being an adaptation to a low-carbohydrate intake [11, 12].

We have previously demonstrated that using KD for 30 days can decrease body weight and body FM without negative effects on strength performance in high level athletes [9]. The data from the present study validate the weight reduction effect of KD. We previously suggested that KD reduced body weight and FM loss and it may be due to reduced REE in elite artistic gymnasts caused by gluconeogenesis and the thermic effect of proteins [9]. In the present study, in healthy subjects the reduced body weight and FM were not associated with reduced REE. The possible mechanisms may be due to reduction in lipid synthesis and increased lipolysis mechanisms, reduction in at rest RQ and, therefore, an increase in fat metabolism for energy use.

High-fat content in the ketogenic diet causes ketosis and metabolic acidosis, which leads to a reduction in carbon dioxide metabolic production for a given oxygen consumption. As shown in the present study, REE was not changed; therefore, the total oxygen consumption was not altered by the ketogenic diet. The carbon dioxide metabolic production should decrease as the present study demonstrated. As a consequence, decreased pulmonary ventilation parameters values should be expected. Expired minute volume is an important parameter in respiratory medicine due to its relationship with blood carbon dioxide levels. Blood carbon dioxide levels generally vary inversely with minute volume. For example, a person with increased minute volume should demonstrate a lower blood carbon dioxide level. The healthy human body will alter minute volume in an attempt to maintain physiologic homeostasis. However, our data do not follow this principle; reduced carbon dioxide metabolic production is not associated with increased expired total ventilation. This phenomenon suggests that reduced carbon dioxide output may be due to a decreased carbon dioxide body store. This may be partially caused by reductions in body mass and FM, and/or, greater oxygen uptake necessary to obtain the same energy yield as on a mixed diet due to increased fat oxidation after the ketogenic diet. According to the definition of carbon dioxide store, the amount of CO_2 contained in the body as a gas and in the form of carbonic acid, carbonate, bicarbonate, and carbaminohemoglobin, during a steady state of ventilation and aerobic respiration, the rate at which CO_2 leaves the body equals the rate at which it is produced, and CO_2 store remains constant. The ketogenic diet decreases the production of CO_2, and since the rate of CO_2 leaving the body does not change (no change in expired volume), the CO_2 store consequently decreases.

Few studies have described the consequent changes in pulmonary ventilation and/or arterial carbon dioxide partial pressure during high fat metabolism. For example, Sabapathy et al. examined the relationship between minute ventilation, CO_2 production, and blood lactate concentrations during incremental exercise performed with reduced muscle glycogen stores [13]. Peak oxygen uptake was unchanged with glycogen reduction. Peak blood lactate decreased significantly. At any percentage of peak oxygen uptakes, O_2 uptake and minute ventilation were similar for both treatment conditions, whereas VCO_2 and RER values were lower during the reduced glycogen trial than under normal glycogen conditions. Therefore, VE/VCO_2 tends to be higher and end-tidal CO_2 partial pressure tends to be lower during exercise performed in the reduced glycogen state. Minute ventilation was significantly correlated with CO_2 production under both treatment conditions. Minute ventilation during exercise was similar under both treatment conditions. This suggests that factors other than CO_2 delivery to the lung and metabolic acidosis play an important role in regulating minute ventilation during exercise. Similar results were also reported [14]. Cai et al. evaluated the efficacy of feeding a high-fat, low-carbohydrate (CHO) nutritional supplement as opposed to a high-carbohydrate diet in COPD patients on parameters of pulmonary function. They found that lung function measurements decreased significantly and forced expiratory volume increased significantly in the high-fat, low-carbohydrate diet group. Their study demonstrates that pulmonary function in COPD patients can be significantly improved with a high-fat, low-CHO oral supplement as compared with the traditional high-CHO diet. These

findings suggest that factors other than CO_2 delivery to the lung and metabolic acidosis play an important role in regulating ventilation during ketogenic diet. The present study supports their findings that the high-fat diet may decrease the carbon dioxide store, and therefore, improve pulmonary ventilation. In this preliminary study we tested healthy subjects; it is reasonable to suppose that the variations of blood gases during a ketogenic diet follow the same trend in normal subjects and in respiratory compromised patients. The ketogenic diet has been described to be associated with an increased leptin blood concentration [15], and leptin has been recognized as an effective ventilation stimulant [16, 17]. Thus, the ketogenic diet-induced reduction in carbon dioxide metabolic load is coupled with a reduced carbon dioxide partial pressure value, with maintained pulmonary ventilation.

Hypercapnic respiratory failure (type II) is characterized by an increased carbon dioxide arterial partial pressure values higher than 50 mm Hg. Through the specific treatment on the etiology of respiratory failure, the ketogenic diet may provide the potential useful effects because it lowers carbon dioxide arterial partial pressure values. In our opinion, it is not possible to definitely state that the observed changes in $PETCO_2$ may be clinically relevant in all conditions. Such a little change may reveal not to be decisive in some clinical settings, but even such minor changes may have clinically relevant consequences in border-line patients with risk of respiratory failure.

One limitation of our study was the relative low number of subjects and the heterogeneity of sample (even though the differences of investigated variables at the start of the study was not statistically significant). Further studies are needed to verify this working hypothesis. In particular, it would be of interest to verify that the constancy of pulmonary ventilation is associated with a lack of any significant changes in the mechanical work of breathing. This would suggest that respiratory failure patients undergo reduced arterial carbon dioxide partial pressure values without an incremented risk of respiratory failure on a mechanical basis because of respiratory muscle fatigue.

Acknowledgments We wish to thank Kim Hare and Marcelyn Cook for their English editorial assistance.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Hartman AL, Vining EP (2007) Clinical aspects of the ketogenic diet. Epilepsia 48:31–42
2. Paoli A, Rubini A, Volek JS, Grimaldi KA (2013) Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr 67:789–796. doi:10.1038/ejcn.2013.116
3. Cross JH, McLellan A, Neal EG, Philip S, Williams E, Williams RE (2010) The ketogenic diet in childhood epilepsy: where are we now? Arch Dis Child 95:550–553. doi:10.1136/adc.2009.159848
4. Volek JS, Sharman MJ (2004) Cardiovascular and hormonal aspects of very-low-carbohydrate ketogenic diets. Obes Res 12:115S–123S. doi:10.1186/1475-2891-10-112
5. Paoli A, Cenci L, Grimaldi KA (2011) Effect of ketogenic Mediterranean diet with phytoextracts and low carbohydrates/high-protein meals on weight, cardiovascular risk factors, body composition and diet compliance in Italian council employees. Nutr J 10:112
6. Langfort J, Pilis W, Zarzeczny R, Nazar K, Kaciuba-Uscilko H (1996) Effect of low-carbohydrate-ketogenic diet on metabolic and hormonal responses to graded exercise in men. J Physiol Pharmacol 47:361–371
7. Tagliabue A, Bertoli S, Trentani C, Borrelli P, Veggiotti P (2012) Effects of the ketogenic diet on nutritional status, resting energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: a 6-month prospective observational study. Clin Nutr 31:246–249. doi:10.1016/j.clnu.2011.09.012
8. Perez-Guisado J, Munoz-Serrano A, Alonso-Moraga A (2008) Spanish Ketogenic Mediterranean Diet: a healthy cardiovascular diet for weight loss. Nutr J 7:30. doi:10.1186/1550-2783-9-34
9. Paoli A, Grimaldi K, D'Agostino D, Cenci L, Moro T, Bianco A, Palma A (2012) Ketogenic diet does not affect strength performance in elite artistic gymnasts. J Int Soc Sports Nutr 9:34. doi:10.1186/1550-2783-9-34
10. Paoli A, Moro T, Marcolin G, Neri M, Bianco A, Palma A, Grimaldi K (2012) High-intensity interval resistance training (HIRT) influences resting energy expenditure and respiratory ratio in non-dieting individuals. J Transl Med 10:237. doi:10.1186/1479-5876-10-237
11. Schrauwen P, van MarkenLichtenbelt WD, Saris WH, Westerterp KR (1997) The adaptation of nutrient oxidation to nutrient intake on a high-fat diet. Z Ernahrungswiss 36:306e9
12. Schrauwen P, van MarkenLichtenbelt WD, Westerterp KR (2000) Fat and carbohydrate balances during adaptation to a high-fat diet. Am J Clin Nutr 72:1239e44
13. Sabapathy S, Morris NR, Schneider DA (2006) Ventilatory and gas-exchange responses to incremental exercise performed with reduced muscle glycogen content. J Sci Med Sport 9:267–273
14. Cai B, Zhu Y, Ma Y, Xu Z, Zao Y, Wang J, Lin Y, Comer GM (2003) Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. Nutrition 19:229–232
15. Srivastava S, Kashiwaya Y, King MT, Baxa U, Tam J, Niu G, Veech RL (2012) Mitochondrial biogenesis and increased uncoupling protein 1 in brown adipose tissue of mice fed a ketone ester diet. FASEB 26:2351–2362. doi:10.1096/fj.11-200410
16. Malli F, Papaioannou AI, Gourgoulianis KI, Daniil Z (2010) The role of leptin in the respiratory system: an overview. Respir Res 11:152. doi:10.1186/1465-9921-11-152
17. Makinodan K, Yoshikawa M, Fukuoka A, Tamaki S, Koyama N, Yamauchi M, Tomoda K, Hamada K, Kimura H (2008) Effect of serum leptin levels on hypercapnic ventilatory response in obstructive sleep apnea. Respiration 75:257–264