Ketogenic diet for high partial pressure oxygen diving

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ABSTRACT

Introduction: A ketogenic diet (KD) may decrease central nervous system oxygen toxicity symptoms in divers, and in view of this implication a feasibility/toxicity pilot study was performed to demonstrate tolerance of KD while performing normal diving profiles. The exact mechanism of neuroprotection from the KD remains unknown; however, evidence to support the efficacy of the KD in reducing seizures is present in epilepsy and oxygen toxicity studies, and may provide valuable insight in diving activities.

Methods: Three divers (two males and one female ages 32-45 with a history of deep diving and high pO_2 exposure) on the KD made dives to varying depths in Hawaii using fully closed-circuit MK-15 and Inspiration rebreathers. These rebreathers have an electronically controlled set point, allowing the divers to monitor and control the oxygen level in the breathing loop, which can be varied manually by the divers. Oxygen level was varied during descent, bottom depth and ascent (decompression). Divers fasted for 12-18 hours before diet initiation. The ketosis level was verified by urinating on a Ketostix (reagent strips for urinalysis).

Results/Summary: Ketosis was achieved and was easily monitored with Ketostix in the simulated operational environment. The KD did not interfere with the diving mission; no seizure activity or signs or symptoms of CNS toxicity were observed, and there were no adverse effects noted by the divers while on the KD.

INTRODUCTION

The United States Special Operations Forces (SOF) conduct specialized overt and covert missions dedicated to the protection of nations throughout the world. For many of the underwater phases of these operations a decompression obligation is best avoided. The best tool for insertion and extraction into hostile waterborne territory and for avoiding detection is thought to be the closed-circuit rebreather (CCR). The oxygen delivered by CCR and open circuit is limited in functionality because oxygen delivered to the diver below 20 fsw (6.14 msw) may lead to central nervous system (CNS) oxygen toxicity [1].

All divers are physiologically required to limit exposure to oxygen and balance the risk of CNS oxygen toxicity with decompression sickness. CNS oxygen toxicity may cause convulsions similar to epileptic seizures, with sudden loss of consciousness that can lead to death while diving [2]. Other symptoms such as nausea, vomiting, palpitations, visual field constriction, tinnitus and auditory hallucinations can also lead to significant morbidity while underwater [3].

Although the exact mechanism is unknown, the high-fat, low-carbohydrate ketogenic diet (KD) has been effective in reducing the incidence of seizures in patients since the 1920s [4]. More recently, the diet has been shown to be useful in the management of other neurodegenerative disorders involving ischemia, trauma, free radical injury, neuronal excitotoxicity and apoptosis. The proposed protective effects of the

KD include antioxidant activity, prevention of mitochondrial damage, and activation of anti-inflammatory mechanisms [5-8].

Conventional anticonvulsant drugs are ineffective against central nervous system oxygen toxicity, as their mechanisms are primarily based on ion channel regulation and GABA enhancement and do not reduce oxidative stress.

In this study, we demonstrate feasibility that divers using a CCR can tolerate a KD while reaching ketosis with no adverse effects on diving activities.

METHODS

IRB approval was obtained for this study. A group of three divers – two males and one female, ages 32-45, with a history of deep diving and a high partial pressure of oxygen (pO_2) exposure – were observed for a period of four days during an initial dietary intake period prior to undertaking a protocol of four dives to varying depths using CCR (the Inspiration and MK-15 type apparatus). During this time, food was portioned into appropriate caloric and ketogenic portions by the study kitchen. Subjects were instructed to try to consume all the food provided, and were required to show their meal tray to the study assistant after each meal. All remaining food was subsequently weighed and recorded.

Subjects were required to consume at least 95% of the prescribed diet. During this time, subjects were restricted to no aerobic activity save the activity on the dives. Informed consent for each diver was obtained to perform these dives while ingesting the KD.

Prior to commencement of the ketogenic diet, subjects underwent a 12-18 hour fast to stimulate ketosis more rapidly. A KD comprised of a 1.3:1 ratio was then implemented, after the initial pre-diet fast. At the 48-hour mark, measurements of the ketone body acetoacetate in urine were taken using urine Ketostix (reagent strips for urinalysis). Ketosis measurements were compared within 15 seconds to the chart on the side of the bottle. Divers were instructed to err on the side of conservative interpretation, *i.e.*, if the measurement was almost a "mild," it was dropped down to "trace." Measurements of blood glucose levels were also performed twice daily to ensure that subjects were not becoming hypoglycemic. Glucose levels between 50-75 mg/dL are typical during ketogenic diet therapy; therefore, if glucose level were below 50 mg/dL, 15 mL of apple juice would have been given and a follow-up glucose check would have been administered after one hour.

Table 1. 1.3:1 and 2:1 ratio ketogenic diets

	1.3:1 ketogenic diet	2:1 ketogenic diet
Kcal	2000	2000
Fat (gm)	154	181
Protein (gm)	93	65
Carbohydrates (gm)	61	26

If the subject did not reach a state of ketosis within 24 hours following the initiation of the 1.3:1 diet, his/her diet was switched to a 2:1 ketogenic diet for the subsequent 24 hours (Table 1). Measurement of acetoacetate was repeated. While on the ketogenic diet, subjects were instructed to drink a minimum of 2L of fluid daily. A sample diet for the ketogenic ratio of 1.3:1 is shown in Table 2.

During the dive mission, the subjects used the aforementioned CCR with manually variable set point. The rebreather pO_2 was varied during descent, at the bottom depth, and during ascent (decompression) ranging from 1.5-1.6 atmospheres absolute (atm abs) while using a mixture containing helium = 45%, nitrogen = 35%. The water temperature was 72°F fixed, with no thermocline. Diver tasks included swimming briskly and skills such as stage bottle removal and replacement while swimming, removing and replacing gear and lift bag deployment. Following the mission, the subject was permitted to immediately resume a normal diet, but was instructed to avoid sweets and simple sugars for a few days to prevent peripheral edema, which can manifest after low-carbohydrate diets.

Throughout the study, subjects were evaluated for tolerance of the ketogenic diet, level of possible interference with diving mission, evidence of seizures or CNS oxygen toxicity signs/symptoms and presence of ketogenic diet side effects.

RESULTS

The three divers (two males and one female) successfully completed the study. Activity was limited to that performed during the dives, and a minimum of two liters of fluid was consumed daily. A ketogenic diet with fat-to-protein and -carbohydrate ratio of 1.3:1 was established. After 48 hours, testing using Ketostix reagent strips revealed that all subjects had achieved ketosis (Table 3).

Table 2. Sample three-day diet for 1.3:1 ketogenic ratio

	Day 1	Day 2	Day 3
Breakfast	· 2 eggs, fried in butter · 1 oz. of chopped onion, or other low-carb vegetable · 1 oz. of full-fat cheese · 4 slices bacon · Coffee with 1 oz. heavy cream	· 4 oz. ground beef, mixed with spices, 1 oz. of chopped onion, 1 oz. of low-carb vegetables, fried in butter · 1 oz. of full fat cheese · Unsweetened spiced tea with	· Protein shake made with chocolate whey protein powder · 16 oz. unsweetened almond milk · 2 oz. heavy cream
Lunch	· 3 cups of salad greens · 6 oz. chicken breast strips, cooked in butter or olive oil · 4 T high-fat, low-carb salad dressing · 1 oz. of full-fat cheese · 1 celery stalk with 1 oz. cream cheese · Water or unsweetened flavored sparkling water or other unsweetened beverage	· 6 oz. baked halibut with dill butter sauce · 1 cup cauliflower, chopped and sautéed in butter or olive oil · 1 cup of salad greens sprinkled with blue cheese and dressed with 1 T of full-fat dressing · Water or unsweetened flavored sparkling water or other unsweetened beverage	· 6 oz. smoked ham · 1 cup sliced summer squash, sautéed in butter or olive oil · 1 oz. of parmesan cheese, sprinkled over squash · 1 celery stalk stuffed with a mixture of blue cheese and cream cheese · Water or unsweetened flavored sparkling water or other unsweetened beverage
Dinner	· 6 oz. grilled or pan-fried steak · Mushrooms sautéed in butter · Broccoli or other low-carb vegetable · Water or unsweetened flavored sparkling water or other unsweetened beverage · Coffee with heavy cream	· 6 oz. pork chop baked in garlic cream · 2 cups shredded cabbage sautéed in butter with caraway · Salad greens with low-carb, high-fat dressing · Water or unsweetened flavored sparkling water or other unsweetened beverage · Coffee with heavy cream	· 6 oz. salmon topped with parmesan cream sauce and baked · 2 cups spinach sautéed with onions and garlic · Salad greens with low-carb, high-fat dressing · Water or unsweetened flavored sparkling water or other unsweetened beverage · Coffee with heavy cream

Table 3. Results of ketosis testing* during the study period

	DAY 1		DAY 2		DAY 3		DAY 4
Diver	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**
1 (45 y/o male)	trace	moderate	small	moderate	moderate	moderate/ large	moderate
2 (43 y/o male)	negative	trace	small	moderate/ large	small/ moderate	small	small
3 (32 y/o female)	negative	moderate	moderate	trace	large	small/ moderate	moderate

* (utilizing Ketostix reagent strips)

Repeat testing while maintaining this diet showed sustained ketosis (see Table 1); KD modification (*i.e.*, increasing the ratio to 2:1) was not needed. Twice-daily blood glucose checks were normal, with no findings of hypoglycemia (defined as blood glucose lower than 50 mg/dL). The diet was well tolerated, and subjects denied any untoward side effects; specifically, members did not experience nausea or any gastrointestinal symptoms during the protocol. Two divers experienced a small amount of weight loss (3 pounds each).

The diving mission was uncompromised throughout the study (see Table 4 for dive profiles). One dive was performed each day without incident. None of the subjects experienced seizures, nor any signs or symptoms of central nervous system (CNS) oxygen toxicity. At the conclusion of the study, all subjects promptly resumed a normal diet (*i.e.*, non-ketogenic) without difficulty. There were no apparent sequelae resulting from administration of the KD and study implementation.

Table 4. Dive profiles during the study period

	DAY 1	DAY 2	DAY 3	DAY 4
time (hours)	3+	3+	3+	3+
maximum pO_2 (ata)	1.5	1.6	1.6	1.6
maximum depth (fsw)	160	200	160	110

DISCUSSION

The outcome of this feasibility study was that a well-tolerated, quickly implemented and easily maintained diet that sustained ketosis was achievable. The implementation of the KD resulted in ketosis obtained within the allotted 48 hours in the study's three subjects. This rapid entrance into ketosis makes for a favorable effect of providing potential extra neuronal protection, especially in specific diving profiles exposed to high partial pressures of oxygen. No significant gastrointestinal symptoms were noted during this study. Of interest, the 45-year-old male subject who was eating a low-carbohydrate, gluten-free diet, due to confirmed celiac disease, did not achieve large amounts of ketosis on the prescribed diet; however, he was still able to reach the desired outcome of a moderate amount within 24 hours.

In a larger study, close attention should be given to the diet routine of each individual prior to participation. A dietician to closely monitor intake before and during the study would be beneficial to maintain standardization throughout the trial. Significant ketosis on testing may be more difficult to attain in individuals who regularly consume a ketogenic type of diet; however, the protective mechanism may be the same or greater. In one particular study, rats maintained on a KD for at least four weeks were discovered to have significantly more mitochondria in their hippocampi when compared with controls. This suggests that mitochondrial biogenesis is stimulated by consumption of a KD, therefore showing the potential benefits of extended time consuming the diet [9].

While the exact mechanism of CNS oxygen toxicity remains unknown, it has been postulated that oxidative stress and reactive oxygen species (ROS) play a significant role. The KD, which is easily tolerated and well established in the treatment of intractable epilepsy, has been proposed to act through these mechanisms in reducing seizure activity. Data indicates that the KD, whether through ketone bodies or polyunsaturated fatty acids, can exert neuroprotective actions through preserving mitochondrial integrity by reducing mitochondrial free radical production thereby leading to a decrease in oxidative stress and potentially, neuronal injury [10].

Substantial energy is utilized during a strenuous dive, and a KD may limit the amount of carbohydrates available for rapid consumption. However, none of the subjects in this study experienced significant hypoglycemia and had no perceived decreased level of performance while diving.

One must also consider the length of time it takes to reach ketosis after diet initiation, and the time period that SOF personnel are often allotted in preparation and initiation of a mission.

It may be beneficial to incorporate SOF personnel into the studies themselves, as this could lead to a more accurate simulated mission environment.

CONCLUSION

This study showed that is it is feasible to induce ketosis via dietary manipulation over a period of 48 hours and that such a diet does not appear to interfere with light diving activity. Given operational requirements of the U.S. military, as well as the continued drive in the commercial and civilian communities to continually explore the depths of our oceans, the extremes of diving limits are often pushed and occasionally exceeded. Equipment failure and human error, while rare, can prove catastrophic to not only an individual but to the entire mission, and any added benefits to ensure a safe and successful operation are continually sought after. Reducing the potential of CNS oxygen toxicity that could lead to a seizure, drowning and, ultimately, death in a diver should remain a topic of significant importance in the hyperbaric community.

The KD was tolerable and compatible with diving without incident. All divers in our study achieved ketosis. Our feasibility study utilizing the KD holds the potential for making a larger impact on increasing the level of safety and limits for one diving at high partial pressures of oxygen. A larger study using the KD in the future may show compelling results in favor of decreasing CNS oxygen toxicity. The authors believe the best path forward is to evaluate KD on exercise tolerance at both atmospheric and raised pressure.

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Conflict of interest

The authors have declared that no conflict of interest exists with this submission. ■

REFERENCES

1. Butler FK. Closed-circuit oxygen diving in the US Navy. UHM. 2004; 31(1): 4-20.

2. Eynan M, Ertracht O, et al. Prolonged Latency to CNS-O_2 toxicity induced by heat acclimation in rats is associated with increased antioxidative defenses and metabolic energy preservation. J Appl Physiol. 2012; 113(4): 595-601.

3. Clark J, Whelan H. Chapter 4. Oxygen toxicity: In: Kindwall E, Whelan H, eds. Hyperbaric Medicine Practice. 3rd Edition. Flagstaff, AZ: Best Publishing Company. 2008; 69-82.

4. Wilder R. The effects of ketonemia on the course of epilepsy. Mayo Clin Proc. 1921; 2: 307-308.

5. Veech R. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance and mitochondrial metabolism. Prostaglandins Leukot Essent Fatty Acids. 2004; 70: 309-319.

6. Sullivan P, Rippy N, Dorenbos K, et al. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. Ann Neurol. 2004; 55: 576-80.

7. Maalouf M, Sullivan P, Davis L, et al. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excito-toxicity by increasing NADH oxidation. Neuroscience. 2007; 145: 256-264.

8. Cullingford T. The ketogenic diet: fatty acids, fatty acid-activated receptors and neurological disorders. Prostaglandins Leukot Essent Fatty Acids. 2004; 70: 253-264.

9. Bough K, Wetherington J, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann Neurol. 2006; 60: 223-235.

10. Kim D, Rho J. The ketogenic diet and epilepsy. Curr Opin Clin Nutr Metab Care. 2008; 11: 113-120.

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