

Optimizing Your Mitochondrial Function with Intermittent Hypoxia

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January 05, 2025

STORY AT-A-GLANCE

- › Hypoxic training is successfully being used in the treatment of diseases such as asthma, high blood pressure, chronic inflammation and chronic infections, all of which are rooted in mitochondrial dysfunction
- › The scientific application of intermittent hypoxic treatment started in Russia in the late 1970s. Early research showed it was radioprotective. When you reduce the partial pressure of oxygen in tissues that are being irradiated, there's a significant protective effect on healthy tissues. Tumors are not protected, however, because they're already hypoxic (hypoxic radioprotection)
- › Intermittent hypoxia takes place during embryonic development. Scientists now hypothesize that this is a powerful mechanism that may control the quality of mitochondria
- › One of the mechanisms that helps explain the benefits of hypoxia is that it raises your endogenous production of carbon dioxide (CO₂) which, in turn, increases the efficiency of oxygen transport and metabolism
- › One simple way to stimulate your mitochondrial function through intermittent hypoxia is to intermittently hold your breath. In clinical practice, oxygen-depleted air is intermittently administered using a hypoxic generator. The latest models include computerized biofeedback, and allow for all sorts of protocols to be administered

Editor's Note: This article is a reprint. It was originally published January 14, 2024.

The interview above features Dr. Arkadi Prokopov, a Russian integrative medicine physician who specializes in hypoxic training and mitochondrial medicine. Optimizing your mitochondrial function is, of course, one of the most important strategies you can do to optimize your cellular energy, so it's at the core of almost everything that you do to improve your health.

Prokopov graduated from Moscow Medical University in 1980. Most of his work has revolved around biomedical research, specifically research with professional divers. He did his postgraduate dissertation on the improvement of stress resistance in deep-sea divers.

After a decade of doing these kinds of studies, Russia started cutting research funding, so he returned to medical practice, where he began to apply his knowledge of diving physiology and controlled intermittent hypoxia (low oxygen) to the treatment of diseases such as asthma, high blood pressure, chronic inflammation and chronic infections.

"I was always interested, what is the best application of oxygen treatment to stimulate nonspecific, nonspecific [general] stress resistance?" he says. "And from many, many studies, it became clear, paradoxically, that the most efficient intervention is intermittent hypoxic treatment."

Intermittent Hypoxia Treatment

The scientific application of intermittent hypoxic treatment started in Russia in the late 1970s. Early research showed it was radioprotective. As explained by Prokopov, when you reduce the partial pressure of oxygen in tissues that are being radiated, there's a significant protective effect on healthy tissues. Tumors are not protected, however, because they're already hypoxic, so they're not affected by the small, physiological decrease of oxygen partial pressure.

Early pioneers also discovered that intermittent hypoxia takes place during embryonic development. So, in utero, there are significant variations of partial pressure of oxygen.

It was not clear what the physiological purpose of these oscillations was, but now, decades later, "we understand that this is a powerful mechanism to control the quality of mitochondria," Prokopov says. Intermittent hypoxia is also very common in other instances.

"For instance, when we have some physical activity, when we stress our muscles, when they are contracted, the circulation is blocked and the muscle experiences [mild] hypoxia. Then, during relaxation, blood delivery [resumes] and muscles become again [saturated with] oxygen and nutrients.

This is the universal mechanism which is providing continuous repair and recovery of the mitochondria and other cellular structures. So why not to use this natural mechanism for other purposes, like enhancement of endurance in athletes? Now, this is this very well known as altitude training. Thousands of athletes use altitude training."

As explained by Prokopov, one of the simplest ways to stimulate your mitochondrial function through hypoxia is simply to intermittently hold your breath.

Intermittent flow of oxygen-depleted air can also be administered via a face mask. These machines are known as hypoxic generators. The latest models also include computerized biofeedback, and allow for all sorts of protocols to be administered. I've been participating (involved?) in the development of such devices for the last two decades.

Basically, it cycles through the amount of oxygen you breathe, from the therapeutic low of 10% to 14%, to a high up to 21% to 34%.

Hypoxia and the Role of Carbon Dioxide

One of the mechanisms that helps explain the benefits of intermittent hypoxia training is that it raises your carbon dioxide (CO₂) which, in turn, increases the efficiency of oxygen transport and metabolism. The hypoxia also relaxes your capillaries. In your brain,

hypoxia increases blood perfusion up to 40%. This is a normal physiologic hypoxic response, and CO₂ plays a significant role.

If you routinely overbreathe (breathe too deeply or too rapidly, or both), you end up with lower CO₂ levels than are ideal. This kind of subclinical hyperventilation is frequently a learned response to stress, and needs to be unlearned — something we discuss in my interview with Peter Litchfield, which will be posted next week.

Interestingly, Prokopov claims that once people improve the quality of their mitochondria, they typically stop overbreathing automatically. He explains:

"Because where do we get carbon dioxide from? From the mitochondria. It's an element metabolite, the byproduct of oxidative phosphorylation. And if the mitochondria are not active enough, they just don't produce enough carbon dioxide."

Normally, the urge to breathe is stimulated and regulated by a slight increase in CO₂, which happens in any physical activity. But today, in stressful situations, we rarely switch on the "fight-or-flight" response that raves up metabolism and raises CO₂ production. Instead, we have only a fast increase of CO₂ removal by accelerated breathing, but without an increase of physical activity that would produce more CO₂ and would compensate for its drop.

Add stress, when you hyperventilate even more, which further reduces your CO₂ level. Before you know it, you're in a vicious doom loop that can send you to the emergency room.

One way to increase the amount of CO₂, thereby breaking this loop, is to **breathe into a paper bag**. That can reduce many symptoms of overbreathing and hyperventilating in just a couple of minutes. A hypoxia generator can also be used. The drawback of these kinds of tools is that they only offer temporary relief.

"It's just a symptomatic treatment if used only sporadically," Prokopov says. "As soon as you stop it, you overbreathe again and you have the same problems."

But if regenerate your mitochondria, if you make them work more efficiently, more economically, it produces a much better level of endogenous carbon dioxide.

Normal partial pressure of carbon dioxide in blood plasma is from 35 to 45 torr, but most people are below 35. If mitochondria are functioning optimally, it automatically [resets the partial pressure of CO₂] and we see reduction or complete elimination of all problems connected to overbreathing."

The Most Efficient Way to Optimize Mitochondrial Function

One simple and most useful strategy to optimize your mitochondrial function is to eat the right carbs, in optimal amounts; simultaneously limiting fats. The reason for this is because glucose metabolism, when it occurs in the mitochondria, optimizes CO₂.

As mentioned, virtually all the CO₂ is produced in the electron transport chain of your mitochondria. Fat metabolism reduces mitochondrial efficiency by 25% to 50%.

Glucose metabolism also increases structured water (mitochondria-produced water), also known as deuterium-depleted water, and reduces reactive oxygen species (ROS) production in the mitochondria. Naturally, oxidative damage is a major contributor to ill health and premature death, so you want to minimize ROS production as much as possible. Prokopov comments:

"First of all, I must say that if you don't load your mitochondria continuously, they automatically degrade. What do I mean by load? The mitochondria can feel only two interventions, two inputs – the amount of fuel, and the amount of oxygen.

If there is a continuous flow of fuel – nutrients – and a continuous, stable level of oxygen, the mitochondria undergo degradation, because during this ad libitum nutrition and ad libitum oxygen, oxidative damage in mitochondrial DNA results in a growing population of damaged mutated mitochondria, and mutated mitochondria have smaller DNA molecules.

Normal metabolism results in continuous mutation and it makes the mitochondrial DNA smaller, because mutations are repaired very insufficiently. In a stable situation, what molecules will reproduce faster?

The smaller molecule will make copies a little bit faster than the larger, therefore, if everything is stable, normal, the mutated disadvantaged mitochondrial DNA will dominate, and we see it with the normal aging process (as clonal expansion of mutated mtDNA).

We see it in some diseases also, especially in neurodegenerative diseases. And of course with chronic infection. So the task is to continuously eliminate, or help the natural process of elimination of mutated mitochondria. If we just help this natural process of mitochondrial regeneration, we prevent accelerated decline of mitochondrial quality.

And the best tool for this is intermittent hypoxic training, because ... the aged mitochondria are much more sensitive to O₂ oscillations. They don't have enough protective mechanisms because mitochondrial DNA protects itself, but mutated mitochondria don't have enough of these [protective] enzymes, so they are just killed by the oscillations [intermittent highs and lows of O₂]."

Why Intermittent Fasting Doesn't Always Work

So, to summarize, your mitochondria need fuel and oxygen, but both of these inputs are needed in a cyclical or intermittent fashion. Continuous fuel is a disaster and so is continuous oxygen. Both need to be augmented and throttled back at intervals. This would suggest that intermittent fasting is an ideal strategy. Or is it? Prokopov comments:

"What I see, and a lot of research and experience in the clinical field [shows], is that in the fasting state, when your ketone metabolism is much higher, the mitochondrial energy production is more optimal when we have healthy mitochondrial population.

But when the mitochondrial population is a mix of mutated and healthy mitochondria, [fasting] can cause problems. Many people cannot start fasting, they cannot start intermittent fasting or go on a ketogenic diet, because they have, let's say, 50% mitochondria that are dysfunctional.

As soon as we repair the mitochondria with gradually introduced intermittent fasting, gradually introduced ketones, and in parallel, intermittent hypoxic training, we see immense improvement of energy metabolism, we see improvement of OXPHOS and ATP production, and most interestingly, much more economical [energy production].

So, mitochondria in an idling state consume much less oxygen. On the other hand, they're much more efficient. So, we're improving quality of the mitochondria ... Most patients [with mitochondrial dysfunctions] show very low mitochondrial energy production."

Once your mitochondria are sufficiently healthy to handle intermittent fasting, Prokopov suggests an 8/16 schedule, where you eat all your meals within an eight-hour window, and fast for the remaining 16 hours.

As your metabolic flexibility improves, which is also wholly dependent on the functionality of your mitochondria, your eating window can be narrowed to six hours or even less. Prokopov personally eats all his meals within a four- to five-hour window. Intermittent fasting also works synergistically with hypoxic training.

Reconciling Seemingly Opposing Concepts

Now, I used to intermittently fast and eat a ketogenic diet until I discovered the work of the late Ray Peat, which convinced me the high-fat/low-carb science had it all backward. When you don't have enough glucose to fuel the mitochondria, when you deplete your glycogen level, then stress hormones — adrenaline and cortisol — are released to trigger endogenous production of glycogen.

Those stress hormones are pathologic, and if they're continuously released at high levels to compensate for insufficient glucose, it will accelerate disease and premature death. There's no question in my mind that these stress hormones are bad news. Cortisol, for example, drains the amino acids, the protein, from your tissues, thereby decreasing bone density and muscle mass, which is bad news.

But, if all of that is true, how do we reconcile that with the finding that intermittent fasting and ketone metabolism optimize mitochondrial energy production? Prokopov comments:

"This is a very important issue. First of all, gluconeogenesis is an extremely important evolutionary biological mechanism. If we take, let's say, an herbivore, a cow or deer, and we measure their glucose level, it's about 100. If we take a cat, or a lion, and if we measure their glucose level, it will also be about 100. Why? They don't eat any carbohydrates.

[The answer is] they get glucose from gluconeogenesis. And gluconeogenesis consumes amino acids. A normal liver produces about 180 grams of glucose a day. But you should be healthy enough. You should be metabolically flexible. You should have good mitochondria, then it functions better.

Our erythrocytes, red blood cells, survive exclusively from glucose. That's true. But, stress hormones, when they are continuously released, it's a catastrophe.

Endurance athletes, if they're overstressed, they get injuries and aerobic power will be reduced. But with properly organized training, they have recovery periods when they replenish all the exhausted hormones. So, it's the combination [intermittent inducement] of stress and relaxation, stress and relaxation [that brings benefit]. Any continuous stress depletes hormones, exhausts steroid hormones and induces oxidative stress."

So, to rephrase, a key part of the answer to this to-fast-or-not-to-fast dilemma is that your liver stores glycogen, and if you have sufficient glycogen stores, you can easily

intermittently fast for 16 hours and not activate your stress response hormones like glucagon, cortisol and adrenaline.

If you go for a lot longer, certainly after two or three days, then your glycogen stores will be completely depleted and your stress hormones will be activated, because that's the only route left to remain alive. The stress hormones will prevent your glucose level from dropping too low, as that could cause you to go into a coma and eventually die.

The problem is that **30% of adults in the U.S. have nonalcoholic fatty liver disease (NAFLD)**, which impairs your body's ability to produce glucose through gluconeogenesis. You also can't store as much. If your liver function is impaired, you will not be able to store as much glycogen in your liver. Then you have to be more careful about not letting your glucose level drop for too long, because then the stress response will kick in as there is less reserve glucose in your liver.

How CO₂ Affects Your Microbiome

There's no question intermittent hypoxia training works. I suspect one of the primary mechanisms, but certainly not the only one, is because it increases CO₂. CO₂ attaches to and forms an electric cloud over proteins, specifically lysine and histidine, which protects them from oxidative damage from LA metabolites like OXLAMs.

CO₂ also modulates the functional expression of the proteins. This is important as nearly all hormones are proteins, and their function can be modulated by CO₂ levels. So, you can activate and radically increase the efficiency of proteins and hormones in your body. Histones are proteins that surround nuclear DNA, and they modulate the expression of that DNA.

Akkermansia muciniphila, a specific type of anaerobic bacteria increases glucagon like peptide (GLP), which can be useful in the treatment of diabetes and obesity. Ideal levels of *Akkermansia* are about 10% of your microbiome. But most populations now have less than 1%, likely due to inadequate mitochondrial function and resultant oxygen leakage in the gut.

Akkermansia is a gram-negative bacterium, but it does not produce lipopolysaccharide (LPS) or endotoxin. In fact, if their population is increased, they will crowd out the endotoxin-producing gram-negative bacteria by competitive inhibition. Akkermansia also produces mucin, a thick, protective gel-like substance that lines the gastrointestinal tract.

Mucin forms a protective barrier on the gut lining, shielding the epithelial cells of the intestinal wall from mechanical damage, chemical irritation from stomach acids and digestive enzymes, and pathogenic organisms like bacteria and viruses.

Akkermansia probiotic supplement are available, but the good news is you can easily enhance the akkermansia levels in your gut through dietary interventions. Eating foods that support Akkermansia, such as polyphenol-rich fruit, and other beneficial bacteria, and avoiding processed foods and seed oils that contain **linoleic acid** will help to restructure your microbiome in a positive way. Other tips include:

- **Eating more fiber** – The short-chain fatty acids that form from fiber as it ferments in your intestines feed beneficial bacteria, including Akkermansia.
- **Increasing FODMAPs in your diet** – FODMAP refers to "fermentable oligo-, di- and mono-saccharides and polyols," which include fructose (found in fresh fruit) and lactose (found in milk and other dairy products).
- **Boosting intake of dietary polyphenols** – Black tea, red wine grape extract, cranberry extract and Concord grape, specifically, have all been shown to significantly promote growth of Akkermansia.
- **Avoiding alcohol and high-fat diets** – Several studies have shown a correlation between high-fat diets (60% fat or higher) and significantly reduced Akkermansia colonization. Ditto for alcohol consumption.
- **Supplementing with probiotics and prebiotics that promote Akkermansia growth in the gut** – Specific examples include Lactobacillus rhamnosus, Bifidobacterium animalis, Lactococcus lactis (probiotics) and oral fructo-oligosaccharides (oligofructose or FOS, a common prebiotic).

As noted by Prokopov, CO₂ also neutralizes peroxynitrite, one of the most damaging oxidants known. Peroxynitrite damages DNA, so CO₂ helps support genome stability and slows down the aging process. This is something I was unaware of and am certain it is a major reason why increasing CO₂ levels improves your biology.

More Information

To learn more about intermittent hypoxic training and Prokopov's work, visit his website, www.oxyesta.com, follow him on [Facebook](#), or subscribe to his [YouTube channel](#). You can also find more information on [cell-oxy.com's science](#) pages.

For those interested in using hypoxic training for Lyme disease, see his 2020 book, "[Undoing Lyme Disease: How to Make Your Mitochondria Fight Lyme Borreliosis by Surfing Oxygen Waves.](#)"