

## What is EBOO?

Extracorporeal Blood Oxygenation and Ozonation (EBOO) therapy is a medical procedure that involves using specialized equipment to infuse medical-grade ozone gas into a patient's blood outside of their body.<sup>1</sup> During EBOO therapy, a patient's blood is carefully removed, passed through a filter and exposed to a controlled mixture of ozone and oxygen. The EBOO machine also uses ultraviolet (UV) light to activate the ozone molecules. After treatment with the EBOO machine, the clean, ozonated blood is intravenously infused back into the patient. EBOO therapy can be applied in the treatment of chronic pain and inflammation, infections, circulatory disorders, fungal infections, and many other conditions.<sup>2,3,4</sup>

## What is Ozone?

Ozone (O<sub>3</sub>) is a molecule composed of three oxygen atoms with oxidative properties. Studies have demonstrated that EBOO therapy can elicit antioxidant effects<sup>5,6</sup>, potential prophylactic effects on reducing the age-related effects of oxidative stress<sup>7,8,9,10</sup>, improve blood circulation<sup>11</sup>, enhance oxygen delivery to ischemic (reduced blood flow) tissues<sup>12,13</sup>, boost

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<sup>1</sup> Tricarico, G., & Travagli, V. (2021). The Relationship between Ozone and Human Blood in the Course of a Well-Controlled, Mild, and Transitory Oxidative Eustress. *Antioxidants (Basel, Switzerland)*, 10(12), 1946. <https://doi.org/10.3390/antiox10121946>

<sup>2</sup> Sagai M, Bocci V. Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress?. *Med Gas Res.* 2011;1:29. Published 2011 Dec 20. doi:10.1186/2045-9912-1-29

<sup>3</sup> Serra, M. E. G., Baeza-Noci, J., Mendes Abdala, C. V., Luvisotto, M. M., Bertol, C. D., & Anzolin, A. P. (2023). The role of ozone treatment as integrative medicine. An evidence and gap map. *Frontiers in public health*, 10, 1112296. <https://doi.org/10.3389/fpubh.2022.1112296>

<sup>4</sup> Smith, N. L., Wilson, A. L., Gandhi, J., Vatsia, S., & Khan, S. A. (2017). Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. *Medical gas research*, 7(3), 212–219. <https://doi.org/10.4103/2045-9912.215752>

<sup>5</sup> Bocci V, Larini A, Micheli V. Restoration of normoxia by ozone therapy may control neoplastic growth: a review and a working hypothesis. *J Altern Complement Med.* 2005;11:257–265

<sup>6</sup> Travagli V., Zanardi I., Bernini P., Nepi S., Tenori L., Bocci V. Effects of ozone blood treatment on the metabolite profile of human blood. *Int. J. Toxicol.* 2010;29:165–174. doi: 10.1177/1091581809360069

<sup>7</sup> Mancuso C, Pistrutto G, Tringali G, Grossman AB, Preziosi P, Navarra P. Evidence that carbon monoxide stimulates prostaglandin endoperoxide synthase activity in rat hypothalamic explants and in primary cultures of rat hypothalamic astrocytes. *Brain Res Mol Brain Res.* 1997;45:294–300

<sup>8</sup> Onal O, Yetisir F, Sarer AE, et al. Prophylactic ozone administration reduces intestinal mucosa injury induced by intestinal ischemia-reperfusion in the rat. *Mediators Inflamm.* 2015;2015:792016

<sup>9</sup> Kal A, Kal O, Akillioglu I, et al. The protective effect of prophylactic ozone administration against retinal ischemia-reperfusion injury. *Cutan Ocul Toxicol.* 2017;36:39–47

<sup>10</sup> El-Sawalhi MM, Darwish HA, Mausouf MN, Shaheen AA. Modulation of age-related changes in oxidative stress markers and energy status in the rat heart and hippocampus: a significant role for ozone therapy. *Cell Biochem Funct.* 2013;31:518–525

<sup>11</sup> Madej P, Plewka A, Madej JA, et al. Ozonotherapy in an induced septic shock. I. Effect of ozonotherapy on rat organs in evaluation of free radical reactions and selected enzymatic systems. *Inflammation.* 2007;30:52–58

<sup>12</sup> Bocci VA, Zanardi I, Travagli V. Ozone acting on human blood yields a hormetic dose-response relationship. *J Transl Med.* 2011;9:66

<sup>13</sup> Bocci V, Zanardi I, Huijberts MS, Travagli V. Diabetes and chronic oxidative stress. A perspective based on the possible usefulness of ozone therapy. *Diabetes Metab Syndr.* 2011;5:45–49

intracellular oxygen levels which can improve the efficiency of cellular respiration<sup>14</sup>, enhances pathogen inactivation mechanisms<sup>15,16,17</sup>, and elicits immune system activation<sup>18,19,20,21,22</sup>.

### How does EBOO work?

EBOO is thought to work by eliciting controlled and acute “oxidative eustress,” a process that results in adaptive cellular responses with physiological benefits<sup>23</sup>.

Studies suggest that EBOO therapy may have antioxidant effects by eliciting transient and moderate oxidative stress, stimulating the activation of the transcriptional factor that mediates Nrf2. Upon activation, Nrf2 is responsible for increasing the transcription of antioxidant response elements (AREs). The transcription of AREs results in an increased production of antioxidant enzymes, thus eliciting downstream antioxidant processes<sup>24,25</sup>. Similarly, the potential prophylactic effects of EBOO therapy on age-related effects of oxidative stress may be attributed to its role in rebalancing the dysregulated redox state that accumulates as individuals age<sup>26</sup>.

EBOO therapy can modulate and improve vascular and hematological processes through myriad mechanisms. For example, EBOO therapy makes the mitochondrial respiratory chain more efficient by increasing intracellular oxygen<sup>27</sup>. EBOO therapy can elicit an increase in intracellular oxygen because ozone is a stimulator of the transmembrane flow of oxygen<sup>28</sup>.

In addition, EBOO therapy can boost immune processes involved in pathogen inactivation and may enhance the overall functioning of immune response processes. Studies have demonstrated that ozone can oxidize bacterial cell envelopes and fungal cell walls, leading to a reduction in cell envelope stability and cytosolic membrane stability, respectively<sup>29</sup>. These processes block enzymatic activity in these pathogens, resulting in bacterial mortality and

<sup>14</sup> Ajamieh HH, Menendez S, Martinez-Sanchez G, et al. Effects of ozone oxidative preconditioning on nitric oxide generation and cellular redox balance in a rat model of hepatic ischaemia-reperfusion. *Liver Int.* 2004;24:55–62

<sup>15</sup> Gulmen S, Kurtoglu T, Meteoglu I, Kaya S, Okutan H. Ozone therapy as an adjunct to vancomycin enhances bacterial elimination in methicillin resistant *Staphylococcus aureus* mediastinitis. *J Surg Res.* 2013;185:64–69

<sup>16</sup> Bocci V. Does ozone really “cure” cancer. *Int J Cancer.* 2008;123:1222. author reply 1223

<sup>17</sup> Caliskan B, Guven A, Ozler M, et al. Ozone therapy prevents renal inflammation and fibrosis in a rat model of acute pyelonephritis. *Scand J Clin Lab Invest.* 2011;71:473–480

<sup>18</sup> Orakdogan M, Uslu S, Emon ST, Somay H, Meric ZC, Hakan T. The effect of ozone therapy on experimental vasospasm in the rat femoral artery. *Turk Neurosurg.* 2016;26:860–865

<sup>19</sup> Sweet F, Kao MS, Lee SC, Hagar WL, Sweet WE. Ozone selectively inhibits growth of human cancer cells. *Science.* 1980;209:931–933

<sup>20</sup> Smith, N. L., Wilson, A. L., Gandhi, J., Vatsia, S., & Khan, S. A. (2017). Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. *Medical gas research*, 7(3), 212–219. <https://doi.org/10.4103/2045-9912.215752>

<sup>21</sup> Izadi M., Tahmasebi S., Pustokhina I., Yumashev A.V., Lakzaei T., Alvanegh A.G., Roshangar L., Dadashpour M., Yousefi M., Ahmadi M. Changes in Th17 cells frequency and function after ozone therapy used to treat multiple sclerosis patients. *Mult. Scler. Relat. Disord.* 2020;46:102466

<sup>22</sup> Tartari A., Moreira F.F., Pereira M., Carraro E., Cidral-Filho F.J., Salgado A.I., Kerppers I.I. Anti-inflammatory effect of ozone therapy in an experimental model of rheumatoid arthritis. *Inflammation.* 2020;43:985–993. doi: 10.1007/s10753-020-01184-2

<sup>23</sup> Smith NL, Wilson AL, Gandhi J, Vatsia S, Khan SA. Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. *Med Gas Res.* 2017;7(3):212-219. Published 2017 Oct 17. doi:10.4103/2045-9912.215752

<sup>24</sup> Bocci V, Larini A, Micheli V. Restoration of normoxia by ozone therapy may control neoplastic growth: a review and a working hypothesis. *J Altern Complement Med.* 2005;11:257–265

<sup>25</sup> Smith NL, Wilson AL, Gandhi J, Vatsia S, Khan SA. Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. *Med Gas Res.* 2017;7(3):212-219. Published 2017 Oct 17. doi:10.4103/2045-9912.215752

<sup>26</sup> El-Sawalhi MM, Darwish HA, Mausouf MN, Shaheen AA. Modulation of age-related changes in oxidative stress markers and energy status in the rat heart and hippocampus: a significant role for ozone therapy. *Cell Biochem Funct.* 2013;31:518–525

<sup>27</sup> Bocci VA, Zanardi I, Travagli V. Ozone acting on human blood yields a hormetic dose-response relationship. *J Transl Med.* 2011;9:66

<sup>28</sup> Bocci V, Zanardi I, Huijberts MS, Travagli V. Diabetes and chronic oxidative stress. A perspective based on the possible usefulness of ozone therapy. *Diabetes Metab Syndr.* 2011;5:45–49

<sup>29</sup> Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. *Arch Med Res.* 2006;37:425–435

inhibition of fungal growth. Further, EBOO therapy has been shown to interfere with virus-to-cell contact in lipid-enveloped viruses by oxidating (and therefore inactivating) molecules that are integral to successful viral reproduction<sup>30</sup>.

### **What does EBOO therapy involve?**

EBOO generally has three main steps: blood withdrawal, ozone infusion, and blood reinfusion<sup>31</sup>. In the blood withdrawal step, a specific volume of the patient's blood is withdrawn from their body using a sterile and closed system. In the ozone infusion step, the drawn blood is mixed with a precise concentration of medical-grade ozone. This mixture is then exposed to ultraviolet light to help activate the ozone molecules and create a combination of ozone and oxygen (O<sub>2</sub>/O<sub>3</sub>) known as an ozone-oxygen gas mixture or ozonated blood. In the last step, blood reinfusion, the ozonated blood is returned to the patient's body through the same closed system. The reinfused blood carries the ozonated blood to different tissues and organs.

An EBOO therapy session typically takes around 1 hr - 1.5 hr to complete.

### **What are the benefits and risks of EBOO therapy?**

The ozone component of EBOO therapy can stimulate the body's immune response, improve circulation, increase oxygen utilization, and potentially help with various medical conditions such as circulatory disorders, chronic infections, immune system dysfunction, and more. While EBOO therapy is generally considered very safe, side effects may include nausea, vomiting, headache, and dizziness<sup>32</sup>. In rare cases, EBOO may lead to more serious complications, such as seizures and heart problems<sup>33</sup>.

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<sup>30</sup> Gulmen S, Kurtoglu T, Meteoglu I, Kaya S, Okutan H. Ozone therapy as an adjunct to vancomycin enhances bacterial elimination in methicillin resistant *Staphylococcus aureus* mediastinitis. *J Surg Res*. 2013;185:64–69

<sup>31</sup> Di Paolo N, Gaggiotti E, Galli F. Extracorporeal blood oxygenation and ozonation: clinical and biological implications of ozone therapy. *Redox Rep*. 2005;10(3):121-130. doi:10.1179/135100005X38888

<sup>32</sup> Bocci V. The Potential Toxicity of Ozone: Side Effects and Contraindications of Ozonotherapy. *OZONE*. 2010;75-84. Published 2010 Sep 24. doi:10.1007/978-90-481-9234-2\_7

<sup>33</sup> Bocci V. The Potential Toxicity of Ozone: Side Effects and Contraindications of Ozonotherapy. *OZONE*. 2010;75-84. Published 2010 Sep 24. doi:10.1007/978-90-481-9234-2\_7