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Case Report

Role of ozone therapy in the treatment of hypertensive ischemic heart disease. Review and case presentation

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ozone, ozone therapy, ozonized saline solution, micro bubbling, ischemic heart disease, hypertension, oxidative stress.

Abstract

Cardiovascular diseases continue to be the leading cause of death in most Western countries. According to the World Health Organization, ischemic heart disease generally refers to conditions involving narrowing or blockage of blood vessels, caused by damage to the heart or blood vessels by atherosclerosis.

The present case presents hypertensive ischemic heart disease with a background of Diabetes Mellitus 2, uncontrolled dyslipidemia and obesity.

Since ozone therapy can activate the antioxidant system, improve blood circulation and oxygen supply to tissues, the patient was treated from the beginning with Ozonated Saline Solution (SSO3) under micro bubbling, for 5 consecutive days with the aim of stabilizing the patient as soon as possible and establishing the therapeutic efficacy of ozone combined with antithrombotic and antihypertensive therapy.

The patient debuted with chest pain, intense front-occipital headache and significant dyspnea. He was admitted to intensive care where, by means of an angio-CT and echocardiography, he was diagnosed with ischemic and hypertensive heart disease, concentric hypertrophy of the left ventricle, mitral aortic sclerosis and calcification, and hypokinesia of the distal third of the septum and tip.

The patient responded favorably to the combined therapy, and was transferred to the ward after 48 hours with oxygen support saturating normally. There he continued with his treatment for 15 days. He was discharged after 15 days of hospitalization under strict outpatient treatment and medical follow-up.

It was established that the Ozonated Saline Solution under micro bubbling as a complement to the basic therapy was safe and effective in this patient..

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1. Introduction

Cardiovascular disease remains the leading cause of death in most Western countries.[1] Coronary artery disease is the most common cause of sudden death and death in people between 30 and 85 years of age.[2]
According to the World Health Organization (WHO) and the Pan American Health Organization (PAHO), ischemic heart disease generally refers to conditions involving narrowing or blockage of blood vessels, caused by damage to the heart or blood vessels by atherosclerosis.[3]

Risk factors that are widespread across all ethnicities and regions of the world (Yusuf et al., 2004)[4] include smoking, dyslipidemia, obesity, diabetes, and hypertension that have been gradually increasing (Gupta et al., 2008),[5] and are believed to be the driving influence behind the heart disease epidemic we face today (Franco et al., 2011).[6]

The etiology of hypertension involves complex interactions between genetic, environmental, and pathophysiological factors that influence many regulatory systems. Hypertension is classically associated with vascular dysfunction, cardiovascular remodeling, renal dysfunction, and stimulation of the sympathetic nervous system. These processes have in common oxidative stress, defined as an imbalance between oxidants and antioxidants in favor of oxidants that leads to disruption of oxidation-reduction state (Redox) signaling control and molecular damage.[7]
In hypertension, oxidative stress promotes post-translational modification of proteins and aberrant signaling with consequent cellular and tissue damage. Many enzymatic systems generate reactive oxygen species, but nicotinamide-adenine dinucleotide phosphate (NADPH) oxidases are the main sources. The expression and activity of nitrogen oxides are increased in hypertension and are the main systems responsible for oxidative stress in cardiovascular disease.

The use of ozone gas as a therapy in complementary medicine has been met with skepticism due to its unstable molecular structure. However, a great number of research has provided evidence that the dynamic resonance structures of ozone facilitate useful physiological interactions to treat a wide variety of pathologies.[8] Specifically, ozone therapy induces moderate oxidative stress by interacting with lipids. This interaction increases endogenous antioxidant production, local perfusion and oxygen delivery, as well as enhancing immune responses.[9] Despite compelling evidence supporting oxidative stress as the unifying cause of hypertension and the use of ozone as a way to counteract the deleterious vascular effects of oxidative stress, further studies are essential to mark it as a viable and gold-standard treatment option for hypertension and ischemic heart disease.

Hypertension affects 1 in 3 adults worldwide. This common and deadly condition leads to stroke, heart attack, heart failure, kidney damage, and many other health problems.[10] Hypertension is a complex, multifactorial, and multisystem disorder, as originally described by Irvine Paige in his mosaic theory when he proposed that high blood pressure involves the interplay among many elements, including genetic, environmental, anatomical, adaptive, neural, endocrine, humoral, and hemodynamic factors.[11] Then, in 2013, David Harrison revised Paige's mosaic theory, highlighting common molecular mechanisms, specifically oxidative stress and inflammation, as the primary drivers coordinating diverse cellular events and dysfunction in organ systems in hypertension.[12]

Oxidative stress is characterized by excessive production of reactive oxygen species (ROS) and altered oxidation-reduction (redox) status. These molecular events induce protein oxidation and deregulated cell signaling, leading to inflammation, proliferation, apoptosis, migration, and fibrosis, which are important processes contributing to impaired vascular function, cardiovascular remodeling, renal dysfunction, immune cell activation, and sympathetic nervous system excitation in hypertension. A major source of cardiovascular ROS is a family of non-phagocytic NADPH oxidases (Nox1, Nox2, Nox4, and Nox5 in humans).[13] Expression and activation of Nox isoforms are increased in hypertension and are a likely cause of oxidative stress in cardiovascular, renal, and immune cells in hypertension-associated target organ damage. Other enzymatic sources of ROS include mitochondrial oxidases, xanthine oxidase, endoplasmic reticulum oxidases and uncoupled nitric oxide synthase (NOS) (Fig 1).[10]

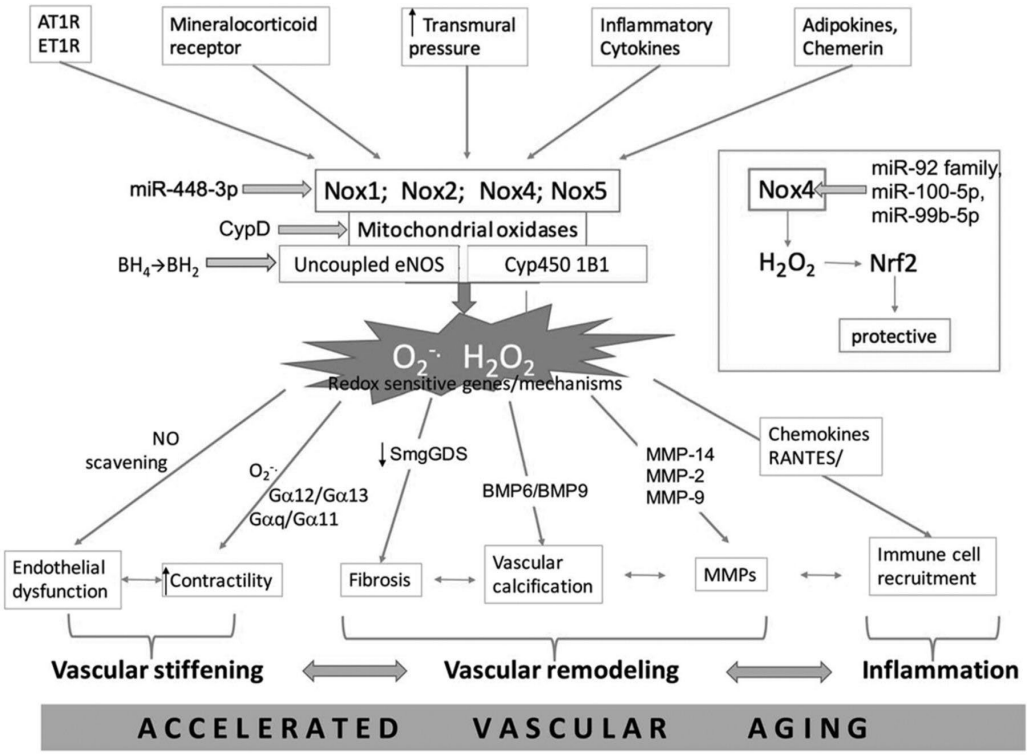

Fig 1. *Central role of oxidative stress in accelerated vascular aging in hypertension. AT1R indicates angiotensin II receptor type 1; BH_2, dihydrobiopterin; BH_4, tetrahydrobiopterin; BMP, bone morphogenic protein; CypD, cyclophilin D; eNOS, endothelial NO synthase; ET1R, endothelin 1 receptor; H_2O_2, hydrogen peroxide; MMP, matrix metalloproteinase; Nox, NADPH oxidase; O_2^-, superoxide anion; RANTES, regulated on activation, normal T cell expressed and secreted chemokine; and SmgGDS, GTP-binding protein dissociation simulator*[5]

Nitric oxide synthase enzyme (NOS) possesses the unique ability to be "uncoupled" to produce superoxide anion (O(2)(-)) instead of nitric oxide (NO). Reduced NO bioavailability as a result of NOS uncoupling has been speculated to play an essential role in cardiovascular pathologies including dilated cardiomyopathy, ischemia reperfusion injury, endothelial dysfunction, atherosclerosis, hypertension and diabetes mellitus.[13]

A major effect of these ROS is the promotion of inflammation, in part by activating redox sensitive transcription factors. In particular NFκB activation is potently stimulated by increased cellular levels of ROS.[14] In turn, the transcription factor NF-κB regulates multiple aspects of innate and adaptive immune functions and serves as a pivotal mediator of inflammatory responses. NF-κB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation. This process, left unchecked by an unhealthy redox response, continues to perpetuate a vicious disease cycle.[15,16]

Oxidative stress and altered redox signaling have emerged as major pathogenic factors in hypertension. This review and case presentation examines the role of ozone therapy in the treatment of ischemic cardiovascular disease and hypertension, with a focus on oxidative stress as a common molecular process in its pathogenesis and it will discuss how ozone induces its regulation of redox balance and may act as a therapy in hypertension.

Novel Treatment Strategy: Ozone Therapy.

Ozone therapy has been studied for more than a century,[17] and even longer. Its effects are proven, consistent and with minimal side effects. Medical ozone (O3) was initially used to disinfect and treat diseases and has been used for over 150 years. Medical ozone toxicity does not apply when its administration is controlled and appropriated. Numerous studies have shown that the effects of ozone therapy are consistent and that the therapy is safe and does not cause side effects if properly applied.[18]

The ozone therapy mechanism of action is based on the formation of reactive oxygen species (ROS) and lipids oxidation products (LOP). Fortunately, ROS disappear quickly, as they are short-term acting particles. LOPs are distributed throughout the tissues; therefore, instead of causing harm, these particles stimulate antioxidant defense, as well as modify the immune system.[15,18,19]

Moderate oxidative stress caused by O3 increases activation of the transcriptional factor mediating nuclear factor-erythroid 2-related factor 2 (Nrf2). Nrf2's domain is responsible for activating the transcription of antioxidant response elements (ARE). Upon induction of ARE transcription, an assortment of antioxidant enzymes gains increased concentration levels in response to the transient oxidative stress caused by O3. The antioxidants created include, but are not limited to, superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), catalase (CAT), heme oxygenase-1 (HO-1), ADPH-quinone-oxidoreductase (NQO-1), heat shock proteins (HSP), and phase II enzymes of drug metabolism. Many of these enzymes act as free radical scavengers clinically relevant to a wide variety of diseases, including hypertension.[20]

The oxygen-ozone therapy also results in the rise of adenosine triphosphate (ATP) and 2.3-diphosphoglycerate content in the red blood cells. Ozone also promotes pentose phosphate pathway reactions that result in the release of nicotinamide adenine dinucleotide phosphate. This molecule is crucial for erythrocyte membrane integrity. Moreover, ozone lowers blood viscosity and stimulates hydrogen dioxide release that breaks down thrombus, thus microcirculation may be improved.[9,18] The O2-O3 therapy has been shown to down-regulate oxidative stress and inflammatory processes Redox bioregulation through oxidative preconditioning by ozone at low concentrations is the basic mechanism of ozone.[19,23]

According to Crigee,[21] a primary ozonide is formed, and in the second step, a secondary ozonide. This is cleaved and reacts with water to form “ozone peroxide”, which is understood as the pharmacologically active substance. The “ozone peroxide” behaves as a second messenger and a regulatory molecule transducing its information via the GSH reaction to nuclear factors, mainly NFkB, which is responsible for immunomodulation, among other factors, and Nrf2, which is responsible for the regulation of antioxidants.

The first step seems to be an inflammatory response to the low and specific oxidative stress of “ozone peroxide” via NFkB and in the second step, the anti-inflammatory response via Nrf2 regulating the enzymatic antioxidant system. Redox bioregulation will be blocked with using high peroxide concentrations and dosages; this is the situation in patients under high oxidative stress and chronic inflammatory diseases,[15,18] such as hypertension. Redox regulation can only take place at low ozone concentrations and doses; low concentrations induce, high concentrations block.[23,24]

On this basis, the low-dose ozone concept was developed; it is suitable for prevention and management of chronic inflammatory disease and disease caused by excess, unregulated oxidative stress, such as hypertension. Low-dose ozone will modulate the immune response and protect cells from oxidative stress and free radical damage through building a strong antioxidant system.[9,15,18,19]

Another mechanism of action of ozone is the activation of NO-synthetase, which stimulates the production of NO by the vascular endothelial cells and, consequently, the vasodilator effect.[7,15,18] In the treatment of hypertension, ozone therapy has been shown to be effective when used independently, as well as combined with other medications.
The systemic route chosen for this case was Ozonated Saline Solution (O3SS) under micro-bubbling because it is a fast, safe and effective route.[25,26]

4. Method and Materials

This clinical case was approved by an institutional review committee (Scientific and Ethics Committees of the Institution, Hospital del Seguro Social de San Pedro Sula-Honduras and Clínica Fiorela Honduras) in accordance with the principle of the Declaration of Helsinki (AMM, 2004).

The Ozonobaric P® (Sedecal®) ozone generator was used, registered in Spain by the AEMPS and the European Union as a medical device. CE 1639 certified (MDD class llb), RoHS, CSA
The device for administering O3SS was the ASSO3® glass device with a microbubble plate. The method used was O3SS under continuous flow micro-bubbling, 0.9% Saline Solution 250 mL was used.

Initial ozone dose: 1 µg/kg (2.0 µg/NmL); flow rate at 200 mL/min, continuous flow to saturation, for 5 min. Bubble-free administration. In parallel, the patient maintained his basic treatment.

5. Case Presentation

68-year-old male patient, diabetic and hypertensive, medicated, obese. He arrived to the emergency service on 05/26/2023 with a feeling of chest pain, intense front-occipital headache, difficulty of breathing, swelling of the feet, general fatigue, not being able to sleep lying down, need to urinate a lot especially at night.

On examination he had PO2 90%, Heart rate 85 per min BP 135/90 mm. Hg; Weight 124.7 kg.

Laboratories: Negative PCR for SARS-Cov-2 Covid 19; NT-proBNP 199 pg/mL, INR 1.85; TPT 35.5; PT 14.5; Hb 19.50; Hct 57.40; Leukocytes 11,500; Lymphocytes 14.6; HDL 21 mg/dL; LDL 155 mg/dL; Triglycerides 250; Creatinine 1.55 mg/dL; Urea 56.45 mg/dL; D-dimer 3.5 ug/ml; Fibrinogen 350 mg/dL; CPK-MB 50 U/l; LDH 515 U/L; GOT and GPT normal; Fasting glucose 153; Glycosylated Hb 6.8%.

Angio CT and echocardiography revealed: ischemic and hypertensive heart disease, concentric hypertrophy of the left ventricle, sclerosis and calcification of the mitral aorta, and hypokinesia of the distal third of the septum and the tip.

The following treatment is started: O2 support 3L/min; Enoxiparin 40 mg; Acetylsalicylic acid 100 mg; Candesartan 32 mg; Furasemide 40 mg; Sildenafil 50 g; Dopagliflozin 10 mg; Nifedipine 20 mg; Clindamycin 300 mg; Apixaban 5 mg; Atorvastatin 80 mg.

In parallel, the following protocol was administered: During the first week, five sessions of O3SS were administered, one per day. Dose 1.0 µg/kg.(2.0 µg/NmL)

Glutathione 1200 mg IV, Carzilase 12.5 mL IV (20 mg) three times a week on alternate days. During the second week, the same regimen was applied, but in alternating sessions of O3SS (three times a week) followed by Glutathione 1200 mg IV, Carzilase 12.5 mL IV (20 mg). Strict hypocaloric diet.

The patient evolved very well. PO2 97% All serological parameters begin to decrease rapidly. BP (blood pressure) normalized within 24 hrs. and coagulation values drop to low-risk values after five days. With these values already at low risk, the patient was discharged after ten days of hospitalization (on June/06/2023), under multidisciplinary outpatient follow-up with strict rest and a low-calorie diet.

At the third week and already under outpatient follow-up, the ozone dose was increased to 2 µg/kg (4.0 µg/NmL) two sessions per week. 4th, 5th, 6th and 7th week, same regimen, once a week. Glutathione 1200 mg IV, Carzilase 12.5 mL IV (20 mg) once a week. Total: 15 sessions of O3SS received.

Additionally, the patient was given: Omega 3 EPA 6 mg/day and Probiotics.
At one month of follow-up (June/27th/2023) the examination and laboratories were as follows: PO2 97%, Heart rate 80 per min, BP 120/75 mm. Hg; weight 106.4 kg, He has lost 18.3 kg.

Negative PCR for SARS-Cov-2 Covid 19; NT-proBNP 117 pg/mL, INR 1.0; TPT 15.5; PT 12.5; Hb 19.50; Hto 45.30; Leukocytes 10,000; Lymphocytes 15.8; HDL 30 mg/dL; LDL 107 mg/dL; Triglycerides 139; Creatinine 1.35 mg/dL; BUN 21 mg/dL; Urea 50.01 mg/dL; D-dimer 2.5 ug/ml; Fibrinogen 350 mg/dL; CPK-MB 35 U/l; LDH 250 U/L; GOT and GPT normal; Fasting glucose 98; Glycosylated Hb 5.8%.

The patient is currently being monitored on an outpatient basis, with a low-calorie diet, moderate exercise (walking 30 minutes a day) and with the following medication: Co-Diovan 80/12.5; Eliquis 5 mg; Controlip 160 mg; Furosemide 40 mg; Atorvastatin 40 mg; Omega 3 EP 600 mg/day; Probiotics; Co-Enzyme Q-10 300 mg/day; Berberine 500 mg/day; Ashwaghanda 1000 mg.
The patient is receiving an average dose (2 µg/kg) of O3SS (4.0 µg/NmL) once every 15 days, followed by Glutathione 600 mg and Carzilase 10 mL IV.
The patient feels well and has resumed his daily life with a good quality of life. Pacemaker implantation is being studied.

6. Discussion

Accumulating evidence once again demonstrates that O3SS is effective, rapid and safe, but further studies are needed to corroborate this.

Hypertension is a chronic inflammatory disease that involves the migration, accumulation and activation of immune cells and the production of ROS (Reactive Oxygen Species).[27] These processes have in common oxidative stress with an associated abnormal redox state and altered redox signaling.[28,7] Inflammatory and oxidative stress can damage vascular endothelial cells and cause microcirculation remodeling.[18]

Although there are many drugs that can treat hypertension, a deeper understanding of the mechanism of high blood pressure and the discovery of more action targets will be more conducive to early prevention and treatment of hypertension and therefore significantly reduce the occurrence of cardiovascular adverse events.[27]

As highlighted in this review, hypertension is complex. However, this complexity seems to have a common pathway. Strengthening the immune system and enhancing cell protection mechanisms through redox bioregulation will help protect patients from elevated oxidative stress. Redox regulation occurs at low concentrations and doses of ozone.[15,16,18] This is perfectly achieved with the use of O3SS which works at low and personalized doses, i.e. per kg of patient weight, this alone makes it very effective and safe.[25,26]

Ozone therapy can alter the natural history of several diseases and disorders, including hypertension and diabetes. A large number of laboratory studies have provided evidence of the antioxidant capabilities of O3, as well as its vascular, hematological and immune system modulations.
O3 therapy has proven especially beneficial in the diabetic foot, ischemic wounds, and peripheral vascular disease, areas in which O3 use is most prevalent[15]. Despite the presently compelling evidence, future studies should include more double-blind, randomized clinical trials, to determine the longevity in benefits produced, as well as, the degree of benefit observed.

7. Conclusions

O3 therapy has been shown to be particularly beneficial in diabetic foot, ischemic wounds, and peripheral vascular disease, areas where O3 use is most common.[18,29-31] The case presented is an example of the effectiveness of this therapy. Despite the current evidence, future studies should include more randomized, double-blind clinical trials to determine the longevity of the benefits produced, as well as the degree of benefit observed.

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