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Ozone Preconditioning in Viral Disease

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Abstract

Introduction: The purpose of this manuscript is to provide a narrative review of the literature and the basis of ozone therapy to treat viral illnesses including COVID-19 therapy.

Methods: We performed a narrative review of 239 relevant publications and present new data not previously published from our group.

Result: Ozone, a tri-atomic oxygen molecule is a natural substance made by the human white blood cells and metabolized into hydrogen peroxide and many lipo-peroxidases. Ozone is one of the most important modulators of the human immune system. Many investigators purport multiple potential mechanisms by which ozone treats a variety of viral and other illnesses at the atomic and cellular levels. While these mechanisms are operative, they represent passive events resulting from the ozone's impartation of resonant energy to the human energetics' fields. We present data demonstrating that the basis of most all human disease results from specific organ energetic deficiencies. Ozone may be one of the most potent preconditioning agents yet discovered in the human body. We discuss ozone dynamics, the vascular/blood connection, ozone preconditioning, and ozone therapy for specific viral diseases. Our review of the literature uncovered a spate of case reports describing beneficial outcomes with ozone treatment in diverse viral syndromes including Human Immunodeficiency Virus (HIV), Human Papillomavirus (HPV), hepatitis C, herpes zoster, ebola, and SARS-CoV-2. Additionally, we found *in vitro* studies describing inactivation of herpes and HIV by ozone treatment. We reviewed our successful use of ozone as an adjuvant and/or primary agent for the successful treatment of COVID-19. We report two cases of very successful use of ozone therapy in the maternal-fetal dyads in the severely infected/affected fetuses with CMV; this has never been reported in the medical literature.

Conclusion: Ozone is an effective primary or adjuvant therapy for COVID-19 and for many other viral illnesses. Most all disease processes represent an energy deficient state and we have shown that the primary mechanism of ozone is to impart and restore energy deficiencies.

Keywords: Ozone therapy • Viral diseases • Immune system • COVID-19

Introduction

Reports of disease-modifying properties of ozone in the 1970s spurred interest among researchers in further exploring its potential. In the 1980s physicians reported beneficial results with ozone in HIV patients. Later studies indicated that ozone enhances immune function. The list of disorders that responded favorably to ozone continued to grow: autoimmune conditions, peripheral vascular disease, fibromyalgia, neurodegenerative diseases, renal and gastrointestinal disorders, various cancers, healing of wounds and more. Recent studies have found beneficial effects in COVID-19 pneumonitis.

Such results seem paradoxical given that ozone is widely regarded as a toxic environmental substance. When in excess in atmospheric air it produces difficulty in breathing, cough, nasal congestion, chest discomfort and, in susceptible individuals, predisposes to asthma attacks, angina pectoris and occasional heart attack. A powerful oxidant, ozone impairs mitochondrial function resulting in diminished ATP synthesis, production of reactive oxygen species and a host of toxic intermediary compounds.

How can ozone on the one hand be a potent toxin and yet, on the other, confer beneficial effects in various disease states? Emerging recognition of ozone's vast disease-modifying potential is tied into three seemingly unrelated discoveries in recent decades.

The first concerns the recognition of biphasic medicinal effects based purely on dosage, known as hormesis, in which substances induce paradoxically distinct effects at different concentrations. This dynamic is now recognized to be at play many widely employed therapeutic substances.

The second was the chance discovery of the Preconditioning (PC) phenomenon by Murry et al. in 1986 who found that application of one or more of 'sublethal' amounts of physiologic stressors like ischemia, hyperthermia, or toxins induce a powerful counter-response that confers body-wide protection to subsequent insults acutely and for up to 72 h afterward. The PC phenomenon is now recognized to be the most powerful form of endogenous protection ever discovered.

The third discovery was the recognition of an organized blood-borne energy field, electromagnetic in nature, generated by the contraction and dilation of the heart. The diastolic phase of the cardiac cycle, long held to be a period of relaxation, is the primary determinant of cardiac function, a period during which electromagnetic energy is infused into the blood engendering the active outward movement of the cardiac and arterial

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walls. Impairment of this vital phase of cardiac function, known as diastolic dysfunction, is now recognized as a primary feature of a host of acute and chronic disease syndromes.

In this paper we examine the science behind the ozone phenomenon. As we will see ozone activates this energy field in a dose-dependent manner and asserts its effects *via* the PC phenomenon.

Literature Review

Ozone dynamics

In the 1880s German pharmacologist Hugo Schulz examined the effects of toxic substances on yeast cultures. Using a variety of compounds over a broad range of concentrations, and expecting to find progressive dose-dependent toxicity, Schulz was taken aback to observe that while all agents produced toxic effects at high doses they paradoxically stimulated fermentation in yeast cultures at low concentrations [1]. He advanced the general axiom that at low doses toxins stimulate functions while at high doses they inhibit. Such biphasic effects were widely accepted among 20th century homeopathic physicians but roundly rejected in scientific circles.

In recent decades the biphasic dose-response effect has reemerged and become more widely acknowledged in scientific discourse due in large part to the writings of toxicologist Edward Calabrese. Beginning around 2000 he published a series of papers on hormesis documenting the rise, fall and eventual revival of this ubiquitous phenomenon. He cites many scientific articles confirming such biphasic dose effects [2-7]. Such paradoxical biphasic activity forms the basis of ozone's effects.

Rats exposed to higher concentrations and/or longer exposure periods of ozone developed brain dysfunction manifesting in cognitive and motor impairment. Other reports found that ozone inhalation induced pathological neuronal alterations in the brainstem, basal ganglier and hippocampal regions which would seem to explain the various functional impairments [8-11]. It is well-established that elevated ozone levels in inspired air are associated with increased incidence of ischemic stroke in humans [12-15].

On the other hand, an increasing number of studies support the beneficial role of ozone in the treatment of various neurological conditions. Ozone has been used for decades in acute and chronic neuropathic pain syndromes with reduction in subjective pain scores as well as analgesic requirements [16-25]. Sporadic reports suggest its potential to reduce the size of the ischemic penumbra in acute stroke and thus limit the severity of long-term functional deficits [26-29].

Recent studies point to its clinical utility in neuro-inflammatory conditions like multiple sclerosis. In addition to symptomatic improvement effects include reduction of oxidation markers, prionflammatory T-cells and cytokines and increased anti-oxidant levels, regulatory T-cells and anti-inflammatory cytokines [30-35]. As we will see, modulation of the inflammatory response plays a major role in the induction of ozone's effects including those involving viral pathogens. But through what means are such effects mediated? This is where the PC phenomenon comes into play.

Murry et al. [35] designed their PC experiment in order to study mechanisms at play in myocardial infarct. They tested whether intermittently reopening the coronary arteries to allow for brief return of blood flow altered the course of cellular injury [36]. In a control group of dogs a coronary artery was clamped for 40 minutes to assess the extent of infarct damage. Another group underwent a series of four 5-minute arterial occlusions interrupted by 5-minute intervals of reperfusion. Afterward the artery was clamped for 40 minutes. To their complete surprise, animals that received PC pulses had only about 25% of damage as the control group.

The protection afforded by the PC phenomenon has been substantiated in many human and animal studies. When the PC sequence is applied prior to a prolonged ischemic episode a period of protection ensues that lasts about 2-3 hours during which ischemia-mediated damage is markedly reduced. Biochemical analysis suggests that PC slows the rate of ATP consumption, anaerobic glycolysis, lactate accumulation, and development of tissue acidosis. Surprisingly, cardiovascular functions like endothelial dependent vasodilation are preserved and the myocardium becomes resistant to potentially lethal arrhythmias. Researchers are at a loss to explain the various effects but suggest that PC pulses somehow slow the metabolism and diminish energy demand [37-46].

A 1993 study found that preconditioning pulses applied to one vascular territory of the heart protected the rest of the heart from prolonged arterial occlusion [47]. Several years later another study found reduction in myocardial infarct size in rabbits after administration of PC pulses to skeletal muscle [48]. Reports soon followed describing protection in organs besides the heart after PC pulses in distant vascular territories. Remote PC effects involving brain, liver, intestines, kidneys, stomach and lungs were described [49-62].

The PC response originates in the cardiovascular system and blood and spreads throughout the body. PC pulses applied to any vascular bed confer systemic resistance to prolonged ischemia. Remote PC induced by serial inflation-deflation of a blood pressure cuff in the extremities is now used prior to various surgical procedures to limit operative and postoperative injury [63]. Reports suggest beneficial effects are transferable from one animal to another by transfusion of blood or bodily fluids [64-66]. It became recognized that the PC response could be induced by different means other than ischemia: hyperthermia, exercise, cardiac pacing, ethanol, volatile anesthetics, and a host of others include ozone [67-85].

A 1996 study ascribing a complex temporal signature to the PC phenomenon complicated the picture even further [86]. The initial period of heightened resistance to ischemic injury disappears after about 2-3 hours but then protective effects recur in echo-like fashion about 24 hours later and persist for up to 48-72 hours; this is called the second window of protection. Researchers remain baffled as to its basis [87, 88]. As effects are associated with appearance of different mediator substances in the blood it appears to involve gene transcription.

PC is now regarded as the most powerful form of body-wide protection. It has been 35 years since its discovery and 10,000's of reports in the literature have detailed its various aspects. Molecular biologists have identified dozens of potential chemical mediators and various mechanisms-heat shock proteins, adenosine, various neurotransmitters, erythropoietin, nitric oxide, oxygen-derived free radicals, ATP-sensitive potassium channels to name a few-but to date no convincing molecular explanation for the PC phenomenon has come to light [89-96].This is where recognition of the blood-borne energy field provides crucial insight.

The vascular/blood connection

Around the time Murry and colleagues stumbled upon preconditioning the world of cardiology was in seismic transition. For most of the 20th century the heart had been conceived as a mechanical pump which propelled blood forward through the arteries during the systolic phase of its cycle. Diastole, in turn, was regarded as a period of passive relaxation. In the early 1980s reports surfaced describing negative intraventricular pressures in early diastole which researchers soon realized must account for diastolic filling and the forward movement of blood [97,98].

A 1986 article in Scientific American entitled “The Heart as a Suction Pump” advanced a new model of cardiac function [99]. A spate of articles followed in support of active dilation and by the late 1980s researchers had coined the term ‘diastolic dysfunction’ to designate a growing number of disease conditions associated with impaired outward movement of the ventricle [100-102]. In the mid-1990s a paper refuted the propulsion theory of heart function [103]. By the 1990s imaging studies described spiral arterial flow currents which can only be explained on the basis of an energy-derived suction force [104-107].

Deterioration of the heart-blood energy field forms the basis of numerous

acute and chronic diseases. A plethora of reports link diastolic dysfunction to coronary artery disease, chronic heart failure and other cardiac conditions; diastolic dysfunction is associated with metabolic syndrome X, first described in the 1980s, and the cluster of associated disturbances including hypertension, insulin resistance, diabetes, and obesity [108,109]. Such chronic conditions reflect impaired energy generation in the blood and it is on this basis that the effects of ozone PC are mediated.

By the same token the functional disturbances associated with COVID-19 infection are mediated in large part by diastolic dysfunction and inflammatory changes originating in the cardiovascular system and blood. Studies indicate that vascular endothelial cells become infected by SARS-CoV-2, and widespread endothelial injury and inflammation is present in advanced COVID-19 cases leading some to question whether the cardiovascular system plays a primary role in the systemic manifestations of the syndrome [110-117].

The endothelium forms a vital interface between the blood and all bodily tissues, orchestrating a wide range of functions including vasomotor, vessel permeability, hemostasis, coagulation and fibrinolysis, all of which are energy-driven. Diastolic and endothelial dysfunction is widely believed not only to impair organ perfusion but to facilitate the systemic pro-thrombotic state resulting in macro and micro thrombi in arteries and veins. The ubiquitous distribution of the vascular tree accounts for the wide range of symptoms and functional deficits from person to person with apparent random involvement of multiple organs like the lungs, heart, kidneys and brain [118-129]. Equally, diastolic dysfunction is the common link among comorbid states like hypertension, diabetes, chronic heart and kidney disease as well as obesity, all of which increase the risk for severe COVID-19.

The presence of widespread inflammation involving large and small vessels, endothelitis, points to a more than causal relationship between runaway inflammation and impaired energy-generation by the vascular compartment. Inflammation represents a cellular response to deficient energy flow across the cell membrane. Diminished intracellular energy induces mitochondrial dysfunction with a shift from aerobic to less efficient metabolic pathways that result in generation of Reactive Oxygen Species (ROS), accumulation of acidic metabolic by-products, as well as altered membrane potentials of intracellular organelles including mitochondria and lysosomes [130-136].

Not only does generation of ROS induce structural damage by denaturation of proteins but also triggers formation of the cellular stress-related structure known as the NLRP3 inflammasome which, secondarily, is responsible for induction of the pro-inflammatory milieu and the cytokine storm that accompanies runaway inflammation in COVID-19.Blood analysis of COVID-infected patients has shown increased TNF-αand inflammatory interleukins including IL-1α, IL-2, IL-6, and IL-10 which amplify the already existing endothelial dysfunction. As others have pointed out, there are not one but two storms, the cytokine storm, secondary to widespread mitochondrial dysfunction and a primary, equally impactful ROS storm [137-145].

The global energy deficit has a profound impact on immune cell function. In recent decades impaired autophagy, i.e., intracellular digestion, has been associated with a large and growing number of acute and chronic disease states involving inflammation like autoimmune and infectious diseases including COVID-19 [146-158]. Autophagy, which involves intra-lysosomal concentration of acid and activation of acid-based enzymes, forms the cornerstone of the cellular immune response and the primary defense against infection. Scientific articles thus suggest autophagy-enhancing substances to treat COVID-19 [159-163]. But autophagy, like maintenance of trans-membrane voltage gradients, is an energy-dependent process and most symptomatic COVID-19 cases already have impaired mitochondrial function [164-170]. Such conjoined cellular energy defects involving mitochondria and lysosomes in cells throughout the body, including immune cells are, in fact, precisely what drives inflammation [171-182].

Ozone preconditioning

PC comprises two opposing aspects: the immediate consequences of the toxic assault and the protective response initiated by the body to counteract its noxious influence. A dramatic display of this PC effect is seen with ozone, possibly the most powerful PC agent yet discovered.

Erythrocytes (RBCs) are the first to experience the oxidative effects of ozone and to mount a response. Upon contact with ozonated tissue fluid, RBCs undergo a transient dose-dependent decrease in energy flux, estimated to be in the 5-25% range over a period of 15-20 minutes, and then respond with a rebound surge of heightened metabolism and energy release along with outpouring of antioxidants. Ozone induces up-regulation of glycolytic enzymes in RBCs with activation of the Krebs cycle, enhanced ATP synthesis, and production of NADPH reducing equivalents which spill into the blood and neutralize the oxidizing effects of ozonated water [183-187].

Heightened energy output by the RBC mass translates directly into increased blood flow and energy delivery to peripheral tissues. RBCs possess the enzyme Nitric Oxide (NO) synthase and generate large amounts of NO in response to oxidative stress that not only increases RBC hardiness and deformability but interacts with endothelial-generated NO to maintain active vasodilation (a reliable proxy for blood energy content) [188-199]. Ozone-related oxidative stress triggers activation of Hypoxia Inducible Factor-1 (HIF-1) which, in turn, augments release of Vascular Endothelial Growth Factor (VEGF) and Erythropoietin (EPO) which stimulate angiogenesis, blood flow and oxygen delivery to peripheral tissues [200].

The first phase of the PC response, aimed at generating increased blood energy levels, mediates subsequent events at the cellular level. Energy currents, carried in the interstitial fluid space, enter cells *via* ion channel mechanisms and, in short order, enhance mitochondrial function and intracellular energy metabolism as well as inducing a plethora of genes that actively counteract oxidative stress. The second window of protection is driven primarily by events at the cellular level as a result of gene induction. Critical response pathways include Nuclear Factor Erythroid 2-related Factor 2 (Nrf2) and the Heme Oxygenase-1 Enzyme (HO-1) system.

The powerful antioxidant and anti-inflammatory effects unleashed throughout the body by low dose ozone administration are mediated through activation of the transcription factor Nrf2. Nrf2, master regulator of redox balance, binds to over 200 different genes, known as the Antioxidant Response Element (ARE), and effects transcription of cytoprotective substances like heat shock proteins, antioxidant and detoxification molecules, enzymes involved in synthesis of glutathione, a host of growth factors like VEGF and EPO, and more. The Nrf2-driven battery of gene products also effects breakdown and/or refolding of misfolded proteins, DNA repair, mitochondrial rebuilding, autophagy regulation, as well as intracellular metabolism. Impaired Nrf2 function is a hallmark of many chronic disease conditions [201-207].

The most striking downstream effect of ozone PC is mitigation of the inflammatory response *via* suppression of NLRP3 inflammasome activity. This effect can only be explained on the basis of energy infusion into the cell and reversal of mitochondrial dysfunction. Since abnormal inflammasome activation is a prominent feature of various chronic conditions like Alzheimer's, autoimmune disorders, cardiac and renal disease, as well as acute inflammatory syndromes like COVID-19, it has been suggested that ozone PC could modulate disease activity in these circumstances as well [208-223].

Ozone in viral disease

Our review of the literature uncovered a spate of case reports describing beneficial outcomes with ozone treatment in diverse viral syndromes including Human Immunodeficiency Virus (HIV), Human Papillomavirus (HPV), hepatitis C, herpes zoster, ebola, and SARS-CoV-2 [223-228]. Additionally we found *in vitro* studies describing inactivation of herpes and

HIV by ozone treatment [229-230]. Controlled clinical studies were only reported in HIV and SARS-CoV-2.The 1991 HIV study, based on a small number of patients, found negligible outcomes. By far largest number of reports has emerged during the ongoing COVID-19 pandemic which is why it became a main focus of our paper [231-237].

Before describing our experiences several qualifying comments regarding ozone PC are necessary. All current medical treatments for viral diseases are specific in nature and based on targeting specific structural or functional attributes of the viral agent. Ozone therapy, on the other hand, through its stimulation of energy generation *via* the PC response, augments cell metabolism and general immune functions like autophagy. For this reason we regard ozone as a non-specific function enhancer that can (and should) be used alongside other modalities.

Secondly, given that all the various viral syndromes are, in essence, primary energy deficiency states, the timing of ozone PC with respect to the infective process is a crucial determinant of outcome. In the 1991 failed HIV ozone study no mention is made as to the disposition of the subjects and the duration of their infective process. By the same token, several recent controlled clinical studies cited above involved hospitalized COVID-19 patients with advanced disease in which only modest beneficial outcomes were reported in the ozone groups. Because ozone PC stimulates energy production by RBCs it is axiomatic that once cellular metabolism deteriorates beyond a certain point beneficial effects cease. It is well known that the PC response is blunted or absent in advanced chronic conditions like diabetes and the metabolic syndrome.

Another important consideration involves mode of delivery. Various avenues of administration have been described: autohemotherapy, which involves removing a small aliquot of venous blood, exposing it to ozone, and reinjecting it into the vein; rectal or vaginal insufflation of ozone gas; direct Intravenous (IV) injection of ozone gas; IV infusion of ozonated saline solution; topical administration of ozonated oil preparations. All of the various approaches are safe and side effects virtually non-existent. Most of our experience has been with IV infusion of ozonated water and topical oils [238].

In the spring of 2021 we developed a new technique for infusion of ozone into drinking water. With the exception of ozonated oil, all the other approaches are hampered by instability and volatility of the preparation and must be administered straight away. Using our infusion method we have shown stability of drinkable ozonated water up to at least 4 weeks. Two of the authors (KT and ET) have used the oral route exclusively since June, 2021, and have observed no significant differences compared with the intravenous infusion method. We have started small-scale production operation (Soma Energetics) for local distribution of water and oil preparations. This method allows for daily, non-invasive ozone PC over weeks to months at a small fraction of the cost of other methods like autohemotherapy.

Collectively we have treated over 500 COVID-19 patients with ozonated-saline in an outpatient setting the majority by one author (DDV). Many of these cases had multiple comorbidities and presented with moderate-to-advanced disease including respiratory difficulty and low oxygen saturations. The first wave (229 patients) was treated between March 2020 through May 2021.The second wave (252 patients) was during the outbreak of predominantly delta and lambda variants. In both waves the preponderance of individuals had improved symptoms within 24-48 hours. During the first wave, 38 patients required multiple treatments (299 total infusions), 16 had clinical or radiological evidence of COVID-19 pneumonia, 5 required hospitalization, and 3 died after prolonged hospital stays [239-242].

The variant wave was more severe with 66 presenting with pneumonia, 59 required multiple treatments (344 total infusions), 6 were hospitalized, and 4 died. In both waves, average duration of symptoms before receiving treatment was one week. No complications related to ozone PC occurred. Intravenous ozonated-saline combined with other adjuvant therapies proved to be an effective treatment to relieve the symptoms, lessen morbidity, and shorten the course of the disease in an out-patient setting especially for those presenting early in the course of disease. Ozone PC proved to be an effective treatment even for those presenting in later stages of the illness with compromised lung function.

Discussion

Two of the authors used ozone PC to treat severe in-utero Cytomegalovirus (CMV) infections *via* maternal administration of ozonated water and oil. In the first case (JAT and DDV) there was marked thrombocytopenia, anemia and neutropenia with over 2 million viral copies/ml of fetal blood. A local maternal fetal medicine specialist had recommended termination of pregnancy which the parents declined and, instead, pursued ozone PC therapy. The child was born entirely healthy with no stigmata of CMV infection. At the time of this report, she is 7 months of life, had a zero CMV viral load and continues to be in good health and has reached all developmental milestones well in advance.

In the second case (KT and JAT), there was marked fetal intrauterine growth restriction with a head circumference at the first percentile; termination of gestation had been advised. Within 2 weeks after initiation of maternal ozone therapy with oral ozonated water and topical oil over the ventral abdomen an explosive acceleration of fetal brain growth occurred. At the time of this writing, 3 months later, the infant is healthy and has reached all his milestones well in advance. In both cases, ozone therapy was well tolerated by the two mother-fetus dyads and coincided with improvement of fetal disease. To our knowledge, these cases represent the first reports in the medical literature describing ozone PC for intra-uterine CMV disease (Reports currently in preparation).

Our final example involves a 56 year-old woman who presented with 6-week history of severe, disabling shingles (herpes zoster) over her left back and ventral chest wall which was refractive to multiple courses of antiviral treatment with valacyclovir. Within days of initiating ozonated water orally and oil topically over the chest wall pain and inflammation began to subside and by 10 days had completely resolved. Neither the oral and topical approaches were associated with side effects (Figures 1and 2).

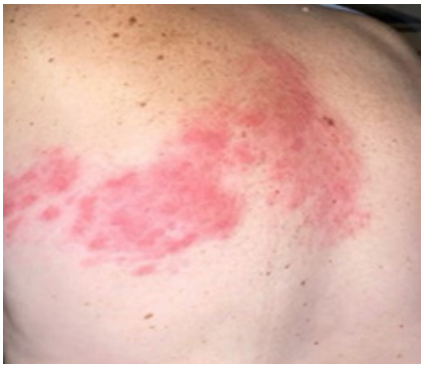

Figure 1. A 56 year-old woman who presented with 6-week history of severe, disabling shingles (herpes zoster) over her left back and ventral chest wall which was refractive to multiple courses of antiviral treatment with valacyclovir.

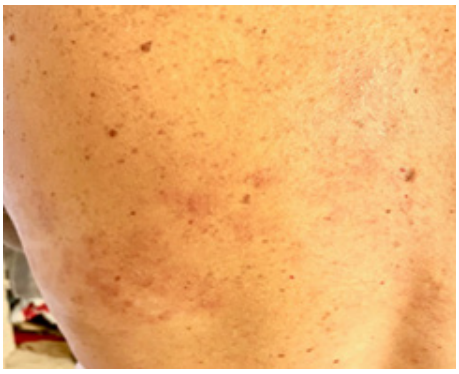

Figure 2. Within days of initiating ozonated water orally and oil topically over the chest wall pain and inflammation began to subside and by 10 days had completely resolved.

Conclusion

In this review we have examined the physiology and mechanism of action of ozone PC and highlighted its application in a handful of viral diseases. Ozone is a safe, low-cost, widely available and highly effective adjunct in the treatment of a multitude of inflammatory conditions. Based on the evidence we have presented its implementation into widespread clinical practice is warranted and, further, systematic study of its effects in other disease complexes recommended.

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