CASE REPORT

Rectal Ozone therapy role in the quality of life of a Heart Failure patient.

Javier Cespedes Suarez [1], Pedro Conde Pérez [1], João Sanchez Arnot [1], José Luís Calunga Fernandez [2], Yisel Rodriguez de Celis [1], Carmen Luísa Rodriguez [1].

[1] Cardiozono Medical Center, Luanda, Angola, [2] Integrative Medicine Mexico-Cuba Medical Clinic

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Authors information
docj09@gmail.com

ABSTRACT

Heart failure (HF) is a nosological entity with multiple pathophysiological aspects including the phenomenon of ischemia-reperfusion (I/R). It is reported to be a heterogeneous syndrome resulting from structural damage to the myocardial fiber which occurs through various mechanisms. On the other hand, ozone therapy has shown a protective role against I/R phenomenon observed in clinical situations such as HF and circulatory shock. On this point, our objective was to evaluate rectal ozone therapy effect in a patient with decompensated heart failure and diabetes mellitus type 2 treated in our Medical Center.
Variables to be measured before and after rectal ozone therapy were: functional classification, biochemical parameters and left ventricular ejection fraction. As a result, rectal ozone therapy was able to improve the clinical condition of our patient, the renal and hepatic function tests were also improved and the ejection fraction of the left ventricle was significantly increased. As a result rectal ozone therapyis provento be complementary to conventional treatment, improved the quality of life of this patient, as well as, the ejection fraction of the left ventricle was significantly increased, reflecting the cardioprotective effect of rectal ozone therapy.

Key words:
Heart failure, phenomenon of ischemia-reperfusion, rectal ozone therapy, ejection fraction of the left ventricle.

OBJECTIVE

To assess the effect of rectal ozone therapy in a patient with decompensated heart failure and diabetes mellitus type 2, treated in our Medical Center on April 2020.

INTRODUCTION

From the chemical point of view ozone (O_3) is a molecule made up of three oxygen atoms (O_2), this element is considered an oxidizing agent capable of reacting with certain biomolecules, within which polyunsaturated fatty acids occupy the first position in terms of chemical reaction against ozone.

It has been demonstrated that when ozone makes an electrolytic attack to the carbon-carbon double bonds present in the polyunsaturated fatty acids, some compounds are originated, such as: ozonides, alpha hydroxy-hydroperoxides, hydrogen peroxide (H_2O_2) and aldehydes, considered as the second messengers of the ozone therapy.

These second messengers are the ones that generate the biological effects of this therapy such as: increase of the oxygen metabolism, broad spectrum germicidal effect, increase of vasodilating agents such as prostacyclines, immunomodulatory effect and in the regulation of the metabolism (1,2).

It is reported that long term ozone therapy is able to form lipid oxidation products that at low concentrations have anti-inflammatory effects and stimulate enzymatic and non-enzymatic antioxidant defense (2,3). In addition, ozone therapy has an effect on tissue protection against ischemia-reperfusion (I/R), a phenomenon that occurs in various clinical situations such as circulatory shock, myocardial ischemia, organ transplant, renal failure, among others. Preclinical studies have been published where ozone therapy has shown a protective role of organs such as kidneys and liver against I/R (4,5).

On the other hand, it is known that heart failure (HF) is a nosological entity that, within its multiple physiopathological aspects, there is the phenomenon of I/R (6). It is reported that HF is a heterogeneous syndrome resulting from structural damage to the myocardial fiber through various mechanisms such as idiopathic cardiomyopathy, acute myocardial infarction, systemic arterial hypertension or valvular heart disease, among other reasons. The prevalence of HF has increased significantly as current therapy has reduced the mortality of ischemic heart disease, particularly acute myocardial infarction (AMI) (7).

The prevalence increased in many patients is often harmful, it significantly affects quality of life (7).

Currently there are more than one reports related to the cytoprotective effects of ozone therapy in myocardial disease. In 2016 Borroto and collaborators demonstrated that ozone therapy improved the quality of life of patients with heart failure and, years later, Cespedes and his group showed that the major auto hemotherapy with ozone significantly increased the ejection fraction in patients with heart failure (8,9). Therefore objective of this study is to assess the effects of rectal ozone therapy as a complementary treatment in a heart failure patient case.

MATERIALS AND METHODS

Black male patient, 58 years old, with current clinical and echocardiographic diagnosis of HF associated with systolic dysfunction of the left ventricle grade III according to the classification of the New York Heart Association (NYHA)[7]. The patient, with a history of arterial hypertension, was treated with levofloxacin 500 mg once a day for 10 days, digoxin 0.25 mg, 1 tablet at 8 am daily, rivaraxaban 10 mg, 1 tablet at 9 pm, enalapril 20 mg per day, bisoprolol (5 mg) 1/2 tablet

per day. Also, the patient suffers from diabetes mellitus type 2, for more than 10 years, which was treated with metformin (850 mg) 1 tablet at lunch and 1 tablet at dinner and accompanied with dopaglifozin (10 mg) 1 tablet per day. He also suffers from hypertensive heart disease and severe ischemic heart disease, which led the patient to angioplasty in two occasions, the first on March 2nd, 2016 and the second on December 2019, both of them performed without complications.

The patient arrives at our Cardiozono Medical Center after having presented a cardiovascular decompensation that led him to several hospital admissions under the diagnosis of AMI, performing the second angioplasty referred to, above. Later, he was admitted to another hospital center under the diagnosis of left-sided heart failure, dilated cardiomyopathy and pulmonary embolism, all between December 2019 and February 2020. At the beginning of April 2020, the patient came to our service with a significant loss of general condition with marked dyspnea at medium and small efforts and with significant weight and muscle loss that made it considerably difficult for him to walk, despite this, his neurological status remained stable.

The patient was given the functional classification made by the NYHA for patients with heart failure (10) (Table 1) and it is worth to mention that our patient arrived in group 4 before starting ozone therapy.

Table 1. Functional Classification for Patients with Heart Failure (NYHA)

Classes	Clinical Data
Class 1	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or angina.
Class 2	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or angina.
Class 3	Marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea or angina
Class 4	Unable to carry on any physical activity without discomfort. Symptoms of heart failure or angina may be present even at rest. If any physical activity is performed, discomfort increases.

Once in our center the patient is re-evaluated by a multidisciplinary team formed by cardiology, intensive therapy, radiology and nephrology. Before starting the complementary ozone therapy treatment, the following laboratory tests such as blood chemistry and blood biometry are performed (Table 2).

Table.2. Laboratory studies before treatment with ozone therapy

Studies	Result	Reference
Hemoglobin	10.3 g/L	13,5-17,5
Hematocrit	32.1%	41.0-53.0
Erythrocytes	4.23 million/mm^3	4.50-5.90
Leukocytes	14.210/mm^3	4.000-11.000
Glycemia	187 mg/dL	60-115
Hemoglobin Glycosylated	9.9%	< 6.4
Platelets	268.000 mm3	150.000-450.000
TGP	939.3 U/L	≤ 40.0 U/L
TGO	501 U/L	≤41.0 U/L
Urea	123 mg/dL	16.6-48.5
Creatinine	1.60 mg/dL	0.72-1.25
Triglycerides	164 mg/dL	< 150
LDL-Cholesterol	340 mg/dL	0-120

During this period the patient also required an echocardiogram dated April 11th, 2020 which confirmed: severe pulmonary hypertension, severe left ventricular systolic dysfunction, grade III diastolic dysfunction, segmental disorders of the anterior descending artery (ADA) area, circumflex artery (ACX) and 22% ejection fraction. The patient had a reduced left ventricular ejection fraction (LVEF) according to the LVEF classification for heart failure (Table 3) (11).

Table 3. Classification of the Ejection Fraction according to NYHA

Left Ventricular Ejection Fraction (LVEF)	Characteristics
LVEF= Normal	50-70% volume is ejected at each contraction; the patient feels comfortable during physical activity.
LVEF= Bordering	41-49% volume is ejected during each contraction, here the symptoms of heart failure are noticeable during physical activity
LVEF= Reduced	≤ 40% is ejected during each contraction, here the symptoms of heart failure are noticeable at rest.

After discussing the case the patient's treatment was readjusted as follows: hygienic-dietary treatment, rivaraxaban 10 mg 1 tablet at 9:00 pm, digoxin 0.25 mg 1 tablet 8:00 am daily, spironolactone 25 mg 1 tablet every 12 hours, sildenafil 50 mg 1/2 tablet every 8 hours, furosemide 40 mg 1/2 tablet 8:00 am and 1/2 tablet at 4:00 pm, enalapril 5 mg 1/2 tablet at 8:00 am, dopaglifoxin 10 mg 1 tablet before lunch, metformin 850 mg 1 tablet at lunch and dinner, allopurinol 100 mg 1 tablet in the morning. In addition to this treatment, the medical team decided to use rectal ozone therapy as adjuvant treatment.

For this purpose, a cycle of 20 sessions of rectal ozone therapy was indicated. The dose of ozone in the the first 5 sessions were 5000 micrograms (200 mL of ozone/oxygen mixture at 25 µg/mL), from the sixth to the tenth session 7500 micrograms (250 mL of ozone/oxygen mixture at 30 µg/mL), from the eleventh to the fifteenth was 10500 micrograms (300 mL of ozone/oxygen mixture at 35 µg/mL) and the ozone dose of the last five sessions, 12000 micrograms (400 mL of ozone/oxygen mixture at 40 µg/mL).

The treatment frequency was one session per day (from Monday to Friday). The duration of the treatment was four weeks.

As variables measuring the quality of life of our patient, we evaluated before and after the treatment with Rectal Ozone Therapy: the functional classification for patients with heart failure - (NYHA), evolution of biochemical parameters before and after rectal ozone therapy, evolution of the left ventricular ejection fraction according to the classification made by the NYHA (6).

STATISTICAL PROCESSING

Contingency tables were used to describe the evolution of the results, in addition the statistical package SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) was used, applying the chi-squared statistic for the numerical significance of biochemical parameters before and after ozone treatment, as well as the changes at the level of the ejection fraction before and after ozone therapy treatment.

RESULTS

Before receiving rectal ozone therapy treatment, our patient arrived in class 4, according to the functional classification made by the NYHA. After receiving rectal ozone therapy, as adjuvant treatment to the pharmacological prescription, he showed clinically significant improvements going from class 4 to class 2, according to such functional classification (Table 1). It is important to highlight that in the case of biochemical variables measured at the blood level, before receiving rectal ozone therapy, the patient showed pathologically low figures of hemoglobin, hematocrit, erythrocyte count as well as pathologically high figures of leukocytes, glycemia, glycosylated hemoglobin, transaminases (TGP, TGO), urea, creatinine, triglycerides, and low-density lipoprotein (LDL) cholesterol (Table 2).

According to the evolution of these biochemical parameters, there is a normalization of them observed after the patient received the rectal ozone

therapy treatment, this normalization was characterized by a significant increase in hemoglobin, hematocrit, erythrocyte count as well as a significant decrease in blood leukocyte count, basal glycemia, glycosylated hemoglobin, TGP, TGO, urea, creatinine, triglycerides and LDL cholesterol (Table 4).

Table 4. Evolution of biochemical parameters before and after the treatment with Rectal Ozone Therapy. Different letters (a, b) mean significant differences. Chi-square test (X^2). p< 0.05.

Studies	Before Ozone Therapy	After Ozone Therapy	Reference
Hemoglobin	10.3 g/L a	13,7 b	13,5-17,5g/L
Hematocrit	32.1% a	41.8 % b	41.0-53.0%
Erythrocytes	4.23 million/mm^3 a	4.50 million/mm^3 b	4.50-5.90.Million/mm^3
Leucocytes	14.210/mm^3 a	10.000/mm^3 b	4.000-11.000 mm^3
Glycemia	187 mg/dL a	115 mg/dL b	60-115 mg/dL
Glycosylated Hemoglobin	9.9% a	6.3 b	< 6,4 %
Platelets	268.000 mm3 a	250.000 b	150.000-450.000.Mm3
TGP	939.3 U/L a	40.0 U/L b	≤ 40.0 U/L
TGO	501 U/L a	41.0 U/L b	≤41.0U/L
Urea	123 mg/dL a	48.5 mg/dL b	16.6-48.5 mg/dL
Creatinine	1.60 mg/dL a	1.20 mg/dL b	0.72-1.25 mg/dL
Triglycerides	164 mg/dL a	145 mg/dL b	< 150 mg/dL
LDL-Cholesterol	340 mg/dL a	120 mg/dL b	0-120 mg/dL

Regarding the evolution of the echocardiogram, the first one performed before starting the treatment with rectal ozone therapy (April 11th, 2020) showed severe pulmonary hypertension, severe systolic dysfunction of the left ventricle with an ejection fraction of 22%, diastolic dysfunction grade III, segmental disorders of the anterior descending artery (ADA) and circumflex artery (ACX) area. A second echocardiogram is performed (April 13th, 2020) coinciding with the beginning of the rectal ozone therapy treatment which reports: global dilated cardiomyopathy, mild capillary vein pulmonary hypertension, type II diastolic dysfunction, severe left ventricular dysfunction with ejection fraction of 28. 2%. However, in the third echocardiogram performed to the patient on June 13th, 2020 after the end of the rectal ozone therapy treatment showed: dilated cardiomyopathy, mild pulmonary hypertension, moderate systolic dysfunction of the left ventricle, type III diastolic dysfunction and an ejection fraction of 43%. The fourth echocardiogram, performed 21 days after the ozone therapy cycle, was as follows: dilated cardiomyopathy, mild pulmonary hypertension, mild systolic dysfunction of the left ventricle, type III diastolic dysfunction (restrictive) and an ejection fraction of 49.08%. Analyzing these results, a significant increase of the left ventricular ejection fraction is observed after the cycle of 30 sessions of rectal ozone therapy (Table 5).

Table 5. Evolution of the left ventricular ejection fraction (LVEF) before, during and a month after rectal Ozone therapy. Chi-square test (X^2), different letters mean significant differences. $p<0.05$.

LVEF (%)	DATE: April 11 2020	DATE: April 13 2020 (Beginning of ozone treatment)	DATE: May 13 2020 (End of ozone treatment)	DATE: Jun 8 2020 (21 days after the ozone treatment)
30-35	22% a	28.2% a		
35-40				
40-45			43% b	
45-50				49.08% b
> 50	0	0	0	0

DISCUSSION

As we can see in these results, ozone therapy showed an improvement in the quality of life of our patient. Other authors have already reported the beneficial effects of ozone therapy on heart failure (8,9). HF is a heterogeneous syndrome resulting from structural damage of the myocardial fiber through various mechanisms such as idiopathic cardiomyopathy, acute myocardial infarction, systemic arterial hypertension or cardiac valvulopathy, among other causes. In the pathophysiology of HF there are two important mechanisms: progressive loss of contractility and progressive loss of myocardial cells through apoptosis, on the other hand ozone therapy through its anti-apoptotic effect could, somehow, prevent apoptosis at the level of cardiomyocytes and thus improve cardiac contractility, based on the fact that some authors have shown ozone therapy capacity to inhibit NLRP3 inflammasome (caspase-1, proinflammatory cytokines and chronic inflammatory processes activating protein complex) (12). Hypoxia and the phenomenon of I/R are present in HF affecting heart activity as a bomb, several studies highlight the role of ozone therapy in the attenuation of I/R (4,5). This, somehow explains the improvement of our patient after the 20 sessions observed in the evolution of Functional Classification for patients with HF (Table 1), where our patient passed from class 4 to class 1. In the case of Table 4, an increase in hemoglobin, red blood cell count and decreased leukocytes occurred in this patient with diabetes mellitus, decompensated heart failure, pulmonary hypertension who also presented a picture of inflammatory lung consolidation, related to bacterial inflammatory pulmonary disease. In these parameters previously exposed, there was a positive evolution after ozone therapy. We believe it is due to the ozone therapy has an indirect germicidal effect mediated by the activation of immune-competent cells (1,3).

Continuing with the analysis in Table 4, normalization of basal glycemia, glycosylated hemoglobin, triglycerides and LDL-cholesterol was also observed. This effect is due to the physiological mechanisms of ozone therapy in the diabetic patient (13,14). Oxidative stress (OS) and inflammation in heart disease lead to cardiac remodeling phenomena, with structural and functional changes, closely related to chronic inflammatory states provoking severe damage to heart tissue (15).

OS plus calcium accumulation affects the selective permeability of the internal mitochondrial membrane provoking opening of the mitochondrial pore with cytochrome C release, producing the caspases 3,6,7 and 9 activation; all this activates apoptosis in myocardial cells injuring himself the contractility of the cardiac muscle (15).

The mechanism of protection induced by ozone therapy by rectal insufflation in organs under ischemia/reperfusion (I/R) syndrome has been shown for differents authors (16,17). The ozone pre and postconditioning may be linked to NRF2/ EpRE (nuclear factor erythroid 2/electrophile-responsive element) activation pathway in vivo. Levels of NRF2 in peripheral blood mononuclear cells (PBMC) were found to increase immediately after ozone/oxygen exposure (35 mg/ ml, prior to reinfusion) (16,17), ozone can increase the level of nuclear translocated NRF2, which is associated with an increase in NRF2 protein translocation from the cytoplasm to the nucleus, increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) among others (18), decreasing the OS, achieving a protective effect on cardiac muscle (16,17). Recently, Weixin and cols. showed that ozone therapy protects rat heart against I/R injury mediated it by local activation of NRF2 in the rat heart (16,17).

Such biological effect indirectly protects the function of the GLUT-4 transporter, attenuating the insulin resistance reflected by our patient and thus normalizing triglyceride levels, glycosylated hemoglobin, LDL-cholesterol results (Table 4).

Decompensated HF creates ischemic hepatitis (19) that sometimes leads to hepatocyte necrosis with transaminase elevation and alteration of liver function in general. After rectal ozone therapy our patient improved levels of transaminases (Table 4). In our opinion this is related to the hepatoprotective effects of ozone therapy. It has been confirmed that ozone therapy stimulates adenosine A1 receptor activity, stimulates antioxidant activity at hepatocyte level, increases ATP levels in the hepatocyte and has an anti-inflammatory effect mediated by the decrease at hepatic level of proinflammatory cytokine (TNF-α) (5).

In Table 5, our patient showed a significant increase in the left ventricle ejection fraction after rectal ozone therapy, this has already been reported by other authors but applying ozone therapy via major autohemotherapy (8,9). In HF, the loss of cardiocytes due to necrosis is largely due to hypoxia. Ozone therapy increases levels of 2-3 dysphoglyceraldehyde (2-3 DPG), which causes hemoglobin to lose affinity for oxygen and increase oxygen sessions to tissue subjected to hypoxia (14). This would protect our patient's heart tissue after ozone therapy, increasing contractility and thus increasing LVEF (Table 5). It has been found that patients with HF show severe OS, which is capable to interrupt the process of coupling excitation-contraction, severely affecting cardiac contractility and LVEF 7. We already explained that ozone therapy decreases OS (1,2,3,4,14,18,19), this could favor the recovery of LVEF in our patient (Table 5). Regarding the improvement of renal function parameters (urea-creatinine) observed in our patient (Table 4), we proposed that in HF there is a drop in renal blood flow leading to renal ischemia with an overproduction of renin, activating the renin-angiotensin-aldosterone systema. This worsens the ischemic renal picture, decreasing the intensity of glomerular filtration and increasing blood levels of

creatinine and urea. Ozone therapy has local and systemic anti-inflammatory effects (20), it also has documented protective effects against renal reperfusion ischemia, it improves glomerular filtration intensity and stimulates renal blood flow in kidneys exposed to ischemia (4,21). This effect could be acting on our patient (Table 4).

CONCLUSION

We can conclude what has already been reported in scientific literature related to ozone therapy and heart failure. Rectal ozone therapy improved the quality of life of our patient and, as an adjuvant treatment, it significantly increased left ventricular ejection fraction, without side effects.

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