

ORIGINAL ARTICLE

Study of Left Ventricle Ejection Fraction and Natriuretic Peptides in patients with heart failure treated with systemic medical ozone.

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ABSTRACT

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SUMMARY

Heart Failure (HF) is a prevalent disease and is a frequent reason for consultation. It is a complex entity that presents multiple pathophysiological aspects, and it is sometimes difficult to establish an adequate diagnosis, since its signs and symptoms may overlap with those of other diseases. For a better diagnosis and control of this pathology, it is currently essential to follow-up through echocardiography and the determination of natriuretic peptides. Natriuretic peptides increase significantly in patients with heart failure, having a negative predictive value for these patients. This study evaluates the effects of rectal ozone treatment on cardiac contractility and natriuretic peptides in patients with heart failure.

We conducted a study with two groups of 6 patients each, who had a diagnosis of Class II-III Chronic HF according to the functional classification of the New York Heart Association (NYHA) and the American Cardiology College / American Heart Association (ACC/AHA), Echocardiogram with a Left Ventricular Ejection Fraction (LVEF) less than 50% and elevated natriuretic peptides. We administer ozone rectally through insufflation, with a 20-session protocol (increasing concentration and volume every 5 sessions until reaching 300 ml), performing the following treatment scheme: 5 sessions with 25 µg/ml concentration and 200 ml volume, 5 sessions with 30 µg/ml and 250 ml, 5 sessions with 35 µg/ml and 300 ml and the last 5 sessions with 40 µg/ml and 300 ml volume.

As a result, it was obtained that ozone treatment through rectal insufflation, through its anti-inflammatory and immunomodulatory effects, was able to improve the clinical status of the study group. Significantly reducing below 50% the values of the natriuretic peptide that was elevated at the beginning of the study. In addition the ejection fraction of the left ventricle was significantly increased. Concluding in this way that ozone administration by rectal route as complement to conventional treatment, significantly increased the ejection fraction of the left ventricle, and decreased the values of natriuretic peptide, significantly improving the quality of life of these patients.

Keywords:

Heart failure, left ventricular ejection fraction, natriuretic peptide, rectal insufflation, ozone treatment

INTRODUCTION

Heart failure (HF) is a prevalent disease and is a frequent reason for consultation. It is a complex entity that presents multiple pathophysiological aspects, and it is sometimes difficult to establish an adequate diagnosis, since its signs and symptoms may overlap with those of other diseases. For a better diagnosis and control of this pathology, it is currently essential to follow-up through echocardiography and the determine the levels of natriuretic peptides. Natriuretic peptide levels increase significantly in patients with heart failure, having a negative predictive value for these patients.

Natriuretic peptides are hormones found in different tissues, but they are mainly synthesized and stored in atrial and ventricular myocytes. Of the three known forms of natriuretic peptides: ANP (atrial natriuretic peptide); BNP (brain natriuretic peptide) and CNP (natriuretic peptide type-C), BNP being the most clinically relevant. BNP is a 32-amino acid peptide secreted primarily by ventricular myocytes in response to increased ventricular filling pressure and myocardial stretch. It is stored in the form of pro-BNP and at the time of its excretion it is divided into two molecules: the inactive N-terminal portion (NT-ProBNP) and active BNP (1).

NT-Pro BNP is produced predominantly by cardiac ventricular myocytes and is released in response to myocardial stress and filling pressure and participates in the maintenance of intravascular volume homeostasis (2, 3). When cardiac cells are stimulated, natriuretic peptides are produced as prohormones (Pro BNP) and are cleaved into two fragments that are secreted into the bloodstream as the 32 amino acid active BNP and the 76 amino acid N-terminal fragment designated NT-Pro BNP. Measurements of BNP and NT-Pro BNP are currently used as a diagnostic and prognostic marker of the severity of HF (4, 5, 6, 7).

Several researchers have described the correlation between the plasma concentration of natriuretic peptides, specifically BNP and NT-Pro BNP, with the systolic function index in patients with HF.

During the last 3 decades, the mechanisms of action of ozone in the blood have been clarified, making explicit its modulation of multiple functions through metabolic pathways such as that of Nrf2. Among them the anti-inflammatory effect, on the metabolism of oxygen (such as changes in the rheological properties of the blood and the increase in the rate of glycolysis of the erythrocyte), the modulation of the biological oxidative stress and of the immune system, the synthesis and/or release of autacoids (endogenous substances with diverse physiological and pharmacological actions) as well as their hemodynamic effect, vasodilator and cardioprotective (8, 9, 10, 11, 12, 13).

Given the biological effects of ozone, which have been demonstrated in multiple studies, we can use ozone as an adjunct therapeutic option to the treatment of HF, since a notable improvement in clinical stage and left ventricular systolic function is evident in patients treated with ozone (14).

Based upon the current science, our team decided to carry out a study not only measuring the clinical and echocardiographic status of patients with heart failure, but also analysing the behaviour of NT-Pro BNP, which is the diagnostic and prognostic marker with the highest fidelity in heart failure nowadays of this

pathology and observe the response of the same in patients to whom ozone will be applied rectally.

Hypothesis: Considering the effects of ozone on ischemia reperfusion phenomena, its effects on the modulation of endogenous antioxidant defence and inflammatory processes, we believe that this treatment has a role in the quality of life of patients ICC carriers.

OBJECTIVE: To analyse the clinical, echocardiographic (LVEF) and NT-Pro BNP effects of ozone applied via rectal insufflation in patients with HF.

METHODS AND MATERIALS

A prospective cross-sectional study was carried out at the Cardiozono Medical Center located in Luanda, Angola, the sample was made up of 12 patients from both sexes who presented a clinical, echocardiographic and humoral diagnosis through the determination of Chronic HF natriuretic peptide, referred from our Cardiology consultation, in the period between March 2020 and July 2020. (Two study groups were randomly performed)

The sample was randomly divided into two groups of 6 patients:

Control Group: Those who received the established conventional treatment for heart failure, non-pharmacological treatment (nutritional advice, diet, suspension of alcoholic beverages) and pharmacological treatment. Medications used Diuretics: Hydrochlorothiazide 25 mg 1 tablet daily or Furosemide 40 mg 2 tablets daily, ACEI Enalapril 20 mg 1 tablet daily, ARA II Losartan 50 mg 1 tablet daily, B-Blockers Carvedilol 25 mg 1 tablet daily, Platelet Antiaggregant Aspirin 100 mg 1 tablet daily, Cardiotonic Digoxin 0.25 mg half a daily tablet.

Study Group: They received the conventional treatment in conjunction with ozone with the following treatment protocol:

20 sessions (a daily session) of ozone (gas mixture of oxygen and ozone) by rectal route.

1st week 5 sessions: 25 µg/ml concentration (mg/l) and 200 ml volume.

2nd week 5 sessions: 30 µg/ml concentration (mg/l) and 250 ml volume.

3rd week 5 sessions: 35 µg/ml concentration (mg/l) and 300 ml volume.

4th week 5 sessions: 40 µg/ml concentration (mg/l) and 300 ml volume.

A German-made Humazon Promedic (Humares GMBH) medical ozone generator was used, which emits a gas flow of 600 ml/minute.

The control group was made up of 6 black patients, 4 men and 2 women, the age ranged between 35 and 65 years of age (35 to 40 years a man, 40 to 50 years 2 men, 50 to 60 years 2 women, 60 to 65 years a man), the study group was made up of 6 patients also of the black race, 4 women and 2 men, with an age ranging from 40 to 80 years (40 to 50 years a man and a woman, 60 to 70 years old 2 women, 70 to 80 years old a woman and a man).

The determination of the NT-proBNP, was performed using the Ichroma™ NT-proBNP method, which is a fluorescence immunoassay (FIA) for the quantitative determination of NT-proBNP in whole blood/serum/plasma humans (15). This peptide was determined in all patients of both study groups at the beginning and 10 days after the last ozone session, the determination time was the same for both groups.

The inclusion criteria were: Patients with a diagnosis of chronic HF with class II-III of the functional classification of the New York Heart Association (NYHA) and American Cardiology College / American Heart Association (ACC/AHA), previous echocardiogram with an Ejection Fraction of the Left Ventricle (LVEF) between 35 and 50%. Determination of elevated NT-Pro BNP, patients who were undergoing treatment for a minimum period of 6 months and complied with the treatment protocol during the period analysed.

The exclusion criteria were:

Patients who did not meet the inclusion criteria.

The parameters evaluated were:

Functional Classification of the HF NYHA (New York Heart Association).

| CLASS | CHARACTERISTICS | DEFINITION |
|-------|---|---|
| I | No limitation: normal physical exercise does not cause fatigue, dyspnea, or palpitations. | Asymptomatic Left Ventricular Dysfunction |
| II | Mild limitation of physical activity: No symptoms at rest, normal physical activity causes fatigue, palpitations, or dyspnea. | Mild Heart Failure |
| III | Marked physical limitation: no symptoms at rest, any physical activity causes symptoms to appear. | Moderate Heart Failure |
| IV | Inability to perform physical activity: the symptoms of heart failure are present even at rest and increase with any physical activity. | Severe Heart Failure |

Ejection Fraction Classification according to the American Heart Association.

Ejection Fraction NORMAL \approx 50–70% is ejected during each contraction (Usually there is a feeling of comfort during physical activities.)

Ejection fraction BORDERLINE \approx 41–49% is ejected during each contraction (symptoms may be more noticeable during physical activity.)

REDUCED Ejection Fraction \leq 40% is ejected during each contraction (Symptoms may be more noticeable at rest.)

It was used to perform an echocardiogram. Mindray DC 60 equipment.

Natriuretic peptide (NT-Pro) normal value up to 300 pg/ml, a Korean Kit from Boditech, IChroma II, was used.

Statistical Processing.

To evaluate the behaviour of the results obtained from the descriptive-observational method.

RESULTS AND DISCUSSION

In the analysed parameters, we observed that the group that received double therapy presented favourable results in all the parameters compared to the control group.

In the control group we observed that before starting the study most of the patients were in class III for 66.7%, 30 days after starting we see that it remained the same, there was no variation in this parameter. (Table 1).

TABLE 1: Behaviour of the Functional Classification of HF in the Control Group.

| CLASS | Before starting the study | 30 days before starting the study |
|-------|---------------------------|-----------------------------------|
| I | 0 | 0 |
| II | 1 (16,6%) | 1 (16,6%) |
| III | 5 (83,3%) | 5 (83,3%) |
| IV | 0 | 0 |

In the study group before starting treatment, the highest percentage of patients was in class III for 66.7%, 30 days after starting treatment a significant change was seen, with 16.6% being in Class I and 83.3% in Class II. (Table 2)

This process suggests that the body's response to Rectal Insufflation with the doses used was favourable, although it is not capable of eradicating the disease, it tends to significantly improve the functional limitations of HF, which is consistent with similar studies.(16) It has been shown that ozone treatment increases levels of erythroid nuclear transcription factor, activating first-line enzymes against oxidative stress, it has an immune modulating effect by

inhibiting certain proinflammatory interleukins (TNF α , IL-1 β , IL-6), ozone treatment decreases the activation of intercellular adhesion molecules (ICAM), all this gives ozone treatment a role in endothelial protection against ischemic damage and inflammatory damage (17, 18, 19, 20, 21) , on the other hand in the pathophysiology of the chronic HF, the inflammatory response and oxidative stress play a fundamental role in Endothelial Dysfunction and Myocardial Dysfunction (22) , we think that the due to its beneficial effects on the protection of the vascular endothelium, ozone treatment is acting favourably on the quality of life in these patients with chronic HF (Table 2).

TABLE 2: Behaviour of the Functional Classification of HF in the study group.

| CLASS | Before starting the treatment | 30 days before starting the treatment |
|-------|-------------------------------|---------------------------------------|
| I | 0 | 1 (16.6%) |
| II | 2 (33.3%) | 5 (83.3%) |
| III | 4 (66.7%) | 0 |
| IV | 0 | 0 |

Ejection Fraction is the measurement of the percentage of blood ejected by the heart each time it contracts. In the control group at the beginning of the study we see that 16.6% of the patients had a LVEF between 30-35, 33.3% had an LVEF between 35-40, another 33.3% had a LVEF between 40-45 and the remaining 16.6% of the sample had a LVEF between 40-45. At 30 days of the study, we were able to observe this parameter getting worse since the patients with LVEF between 35-40 increased to 50.0%, maintaining the same percentage in the LVEF between 40-45 but there were two patients who worsened, one going from a LVEF between 40-45 to 35-40 and the other one with 45-50 went to 40-45. (table3).

TABLE 3: Behaviour of the Ejection Fraction in the Control Group.

| FEVI | Before starting the study | 30 days after the beginning of the study |
|---------------|---------------------------|--|
| 30-35 | 1 (16,6%) | 1 (16,6%) |
| 35-40 | 2 (33,3%) | 3 (50,0%) |
| 40-45 | 2 (33,3%) | 2 (33,3%) |
| 45-50 | 1 (16,6%) | |
| Older than 50 | | |

In the study group before starting treatment, a larger number of patients had a LVEF of 40-45 for 50.0%, presenting 16.6% respectively for LVEF between 30-35, 35-40 and 45- 50. At 30 days we can see that this changes favourably, we

can observe a LVEF between 35-40 16.6%, LVEF between 40-45 33.3%, LVEF between 45-50 16.6%, LVEF greater than 50 33.3%. (Table 4).

We attribute this result, as in our previous studies, to the effects of ozone on the contractile function of the myocardium, which improves cardiac muscle metabolism, increases circulating serotonin and causes a cardioprotective effect already mentioned in previous studies such as Borroto et al. (13,16)

TABLE 4: Behaviour of the Ejection Fraction in the Study Group.

| FEVI | Before starting the treatment | 30 days after the beginning of the treatment |
|---------------|-------------------------------|--|
| 30-35 | 1 (16,6%) | |
| 35-40 | 1 (16,6%) | 1 (16,6%) |
| 40-45 | 3 (50,0%) | 2 (33,3%) |
| 45-50 | 1 (16,6%) | 1 (16,6%) |
| Older than 50 | | 2 (33,3%) |

As we can see in Table 5 of the control group, which was treated with the conventional drug treatment for this type of pathology, there was no evidence of a decrease in the values of natriuretic peptides, not coinciding with Salomone (1), this could be due to that the time under study was not long enough for these levels to drop.

TABLE 5: Behaviour of the Natriuretic Peptide in the Control Group.

| NT-PRO | Before starting the study | 30 days after the beginning the study |
|----------------------|---------------------------|---------------------------------------|
| 300 pg/ml or less | | |
| 301 to 1000 pg/ml | | |
| 2000 to 3000 pg/ml | 2 (33,3%) | 1 (16,6%) |
| 3000 to 4000 pg/ml | 2 (33,3%) | 1 (16,6%) |
| 4000 to 6000 pg/ml | 1 (16,6%) | 2 (33,3%) |
| 10 000 pg/ml or more | 1 (16,6%) | 2 (33,3%) |

The behaviour of the peptide in the study group (table 6), we see that it decreased to more than 50% of the initial value after finishing the treatment, which gives a better prognosis and better quality of life to these patients. These results show that the use of ozone as a coadjuvant treatment in a short time helped to reduce plasma levels of natriuretic peptides.

TABLE 6: Behaviour of the natriuretic peptide in the study group.

| NT-PRO | Before starting the study | 30 days after the beginning of the study |
|----------------------|---------------------------|--|
| 300 pg/ml or less | | |
| 301 to 1000 pg/ml | | 4 (66,6%) |
| 2000 to 3000 pg/ml | 1 (16,6%) | 1 (16,6%) |
| 3000 to 4000 pg/ml | 2 (33,3%) | 1 (16,6%) |
| 4000 to 6000 pg/ml | 2 (33,3%) | |
| 10 000 pg/ml or more | 1 (16,6%) | |

There are three fundamental pathways from the pathophysiological point of view in CHF, these are: neurohormonal activation, sympathetic nervous system with attenuation of the baroreceptor reflex, modification of the ADH hormone, pathological increase in natriuretic peptides and activation of the Renin, Angiotensin, Aldosterone System and increase of Endothelin. The aforementioned inflammatory response and oxidative stress; these pathways lead to myocardial hypertrophy, myocardial apoptosis, depression of myocardial contractility, fibrosis, and cardiac remodelling with the consequent decrease in FEVI (24) . Among other effects of ozone is the decrease in NLP3-proteosome (inflammatory protein platform and apoptosis activator) and the decrease in interleukin 17 (interleukin related to chronic inflammatory processes). The study suggests that ozone treatment, rectal route, could be acting by inhibiting the inflammatory pathway and the oxidative stress pathway in these patients with CHF. In this way, ozone treatment will reduce myocardial dysfunction, improve the contractile capacity of the cardiomyocyte, thus increasing the efficiency of the heart as a pump. This resulted in an increase in FEV-I in patients in the study group. On the other hand, preload in these patients, distention and pathological dilation of the cardiac cavities will be reduced, thus reducing the stimulus for brain natriuretic peptide secretion (Table 4 and Table 6) (23,24).

CONCLUSIONS

Ozone treatment contributes to improving the quality of life of patients with heart failure by improving the ejection fraction of the left ventricle and reducing natriuretic peptide values, which are the current prognostic parameters for patients with this pathology.

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