

Hyperbaric Oxygen and Vitamins C and E on Receptors AT In A Myocardial Infarction Model

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ABSTRACT

Background: The renin-angiotensin system participates regulating the development of cardiovascular pathologies, AT1 and AT2 receptor participates in cardiovascular remodeling, the expression of these receptors and their ratios under different cardiac pathological conditions may be important in determining myocardial function and structure. The use of hyperbaric oxygenation therapy (HBO) is a coadjuvant treatment combined with antioxidant vitamins (C and E). The mechanisms that cause these effects are not entirely clear, so this study seeks to examine whether the concomitant use of these therapies results in the down regulation of the expression of AT1 receptors and increases the expression of AT2 receptors.

Methodology: It was used a model of myocardial infarct (AMI) in Wistar rats in which they are used and exposed from 1 to 3 sessions of HBO with concomitant administration of vitamins C and E, and afterwards expression of AT1 and AT2 receptors were measured in the heart. The obtained.

Results: Suggest that after administration of 3 sessions of HBO and Vitamins C and E the expression of AT1 receptors significantly reduces while the expression of AT2 receptor dramatically increases, so we can inferred that this coadjuvant treatment is beneficial for patients with AMI.

Introduction

Myocardial infarction (AMI) is a major cause of mortality and disability worldwide. The term AMI reflects cell death of cardiac myocytes because the supply of oxygen may be exhausted and an imbalance between supply and demand occurs which is translated into ischemia [1]. The renin-angiotensin system (RAS) is well known to play a central role in the pathophysiology of hypertension, vascular thickening, atherosclerosis, glomerulosclerosis, as well as in the post infarction and its sequels as cardiac hypertrophy and remodeling, heart failure [2]. In the heart AT1 receptor induces hypertrophy and apoptosis in post infarcted ventricular myocytes [3,4] and mediate vascular smooth muscle cell proliferation [5], while AT2 receptor activation inhibits cell proliferation [6,7] and remodeling independently of hemodynamic changes. Myocardial-

specific overexpression of the human AT1 produced initially cardiomyocyte hypertrophy followed by interstitial collagen deposition, myolysis, and cardiac remodeling. This in turn was accompanied by increased incidence of premature death caused by congestive heart failure [8]. In the other hand the AT2 receptors has also been implicated in pathological conditions associated with cardiovascular remodeling through its antiproliferative effect, a vasopressor response [9] and protective functions [10,11].

This receptor is up-regulated during ischemic cardiovascular injury [12,13]; this means that the AT2 receptor maybe play a potential role in regulating adaptive cardiovascular repair. The density of the myocardial AT2 receptor was shown to be increased in experimental myocardial infarction 1 day after infarction in

the affected portion, and AT2 receptor expression was further upregulated 7 days after infarction in both, infarcted and non infarcted portions, further in the hypertrophied rat heart, the ratio of AT2 to AT1 receptor densities is increased [14,15]. In the Infarction model the AT1 and AT2 receptors exert antagonistic action on myocardial biology, the expression of these receptors and their ratios under different cardiac pathological conditions may be important in determining myocardial function and structure [14]. Currently treatments by hyperbaric oxygenation have been reported, defined for the Hyperbaric Medical Society (UHMS) which settle hyperbaric oxygen (HBO2) as an intervention in which an individual breathes near 100% oxygen intermittently while being inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute, or ATA). For clinical purposes, the pressure must equal or exceed 1.4 ATA while breathing near 100% oxygen.

Some mechanisms of action about how the hyperbaric oxygenation works have been described, but this information doesn't explain its total benefits in all the systems. Hyperbaric oxygenation has been reported to promote cell replication, collagen formation, and mechanisms of homeostasis, such as active membrane transport,

e.g. the sodium-potassium pump. In addition, inhibits induction leukocyte adhesion to endothelium, diminishing tissue damage, and enhances leukocyte motility, resulting in improved microcirculation, stimulates neo-angiogenesis [16], therefore we can propose that such benefits may be beneficial to the post infarct heart.

It has been suggested that increased intake of various antioxidant vitamins reduces the incidence rates of cardiovascular disease, cancer, and other adverse outcomes [17] as well as the main antioxidants that are prescribed are vitamins C and E. The first one is the main water-soluble antioxidant in human plasma and is hypothesized to have a protective role in the development of atherosclerotic heart disease by inhibiting low-density lipoprotein oxidation. Oxidized low-density lipoprotein has been identified in atherosclerotic lesions and may be atherogenic in the vessel wall through several mechanisms [18,19], besides highlights its function as a co-factor for a number of enzymes, most notably hydroxylases involved in collagen synthesis, and as a water-soluble antioxidant. Vitamin C can also function as a source of the signaling molecule, hydrogen peroxide [20-22]. On the other hand, it has been shown that ascorbic acid dose affects the decrease of the binding affinity of the AT1 receptor without modifying its level of expression at the cell surface suggesting that ascorbic acid is may be involved in the regulation of vascular tone, and therefore, cardiovascular function [22].

The vitamin E or α -tocopherol's is a peroxy radical scavenger. The importance of this function is to maintain the integrity of long-

chain polyunsaturated fatty acids in the membranes of cells and thus maintain their bioactivity. These bioactive lipids are important signaling molecules and that change in their amounts, or in their loss due to oxidation, are the key cellular events that are responded to by cells [20,22]. The effect of vitamin E has been studied in an experimental myocardial infarction and the results suggest that prolongs survival in patients and animals after myocardial infarction because it is associated with arrhythmia and heart dysfunction, by reducing oxidative stress in acute myocardial infarction [19]. Vitamins C and E function as water-soluble and lipid-soluble chain-breaking antioxidants, respectively, and protect lipids, proteins, and membranes from oxidative damage. Vitamin C scavenges oxygen radicals in the aqueous phase, whereas vitamin E scavenges oxygen radicals within the membranes. Vitamin C regenerates vitamin E by reducing vitamin E radicals formed when it scavenges the oxygen radicals. This interaction between vitamin C and vitamin E radicals can take place not only in homogeneous solutions but also in liposomal membrane systems where vitamins C and E reside separately outside and within the membranes respectively, and vitamin C can act as a synergist [23-25]. Combined treatment with vitamins C and E suppressed neutrophil-mediated free radical production and lowered blood lipid peroxidation product in patients with acute myocardial infarction, an also is described that the use of antioxidant vitamins in patients with recent acute myocardial infarction may be protective against cardiac necrosis and oxidative stress, and could be beneficial in preventing complications and cardiac event rate in such patients [25].

Materials and Methods

Male Wistar rats weighing 300 +/- 50 g were used and kept in cages at room temperature, exposed to a cycle of 12 hours of light for 12 hours of darkness, and maintained with water and feed ad libitum. All animals will be used in accordance with the ethical standards established by the IPN High School of Medicine and comply with the requirements determined in the subject NOM-062-ZOO-1999 TECHNICAL SPECIFICATIONS FOR THE PRODUCTION, CARE AND USE OF ANIMALS LABORATORY, SAGARPA, and the GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS, National Research Council. To perform the infarction model, the technique of occlusion of the proximal anterior descending artery was used. The rat is pre-anesthetized with Xylazine dosed of 8 mg/kg and Ketamine 100 mg/kg body weight. Once anesthetized, thoracic trichotomy is performed and under asepsis and antisepsis conditions, rat was placed supine position in the surgical table, then the orotracheal intubation was performed with 16G catheter which was connected to a Harvard rodent ventilator 683 ventilator at a frequency of 60 ventilations per minute to provide ventilatory support during surgery with 2.5 to 3ml ambient air insufflations. Subsequently the fourth intercostal space was anatomically located and an incision was made in the skin, then dissection was performed

intercostal muscles, in which myotomy allowing access to the intrathoracic cavity approximately at the origin of the aorta artery, then a total anterior pericardiotomy was done, and after the left atrium is located, it is subtly separated, allowing the visualization of the anterior descending artery which is ligated with a 5-0 nylon suture, cardiac hemostasis was corroborated and the thoracic cavity is closed with a nylon suture 4-0 corroborating hemostasis and ensuring the maintenance of the intrathoracic negative pressure in order to avoid tension pneumothorax, the pectoral muscles are confronted again by facing them with 4-0 nylon suture and finally the skin was faced, once the surgical procedure is finished, the rat was placed in an artificial warmth area and was monitored to detect post-surgical alterations opportunely.

After a period of 10-20 minutes the rat was extubated and then administered with buprenorphine at a dose of 0.2 mg / kg subcutaneously, a dose that will be repeated daily to maintain animals under conditions of adequate postsurgical analgesia. It should be clarified that a group called SHAM was formed, which corresponds to simulated surgery, in which the same procedure was performed, however, after performing the pericardiotomy, the thorax was closed. Eight study groups were conformed considering n=5 randomly selected rats as will be described below (Table 1).

Table 1: Experimental groups, n=5.

Without Hyperbaric Oxygenation	With Hyperbaric Oxygenation
Healthy	Healthy
Myocardial infarction	Myocardial infarction
Myocardial infarction + C and E vitamins	Myocardial infarction + C and E vitamins
SHAM	SHAM

The groups conformed with rats to be treated with the antioxidant therapy were dosed with D-alpha-Tocopherol acetate (Vitamin E- gel caps at 25mg/kg/d) and ascorbic acid at a dose of 20 mg/kg/d were administered by orogastric route, after the first 24 postoperative hours. The rats were dosed in the same way for 3 consecutive days, simultaneous to exposure to HBO for the corresponding groups. The HBO groups were pressurized at two atmospheres of pressure for one hour, in a chamber for experimental use with a session per day for 3 days with the following specifications, the pressurization is carried out in a period of 15 minutes, one hour of isopression to 2 ATA, after the exposure time, the depressurizing is performed in the next 15 minutes, after this period the animals were removed from the chamber and placed in their respective cage, after completing the 3 sessions, rats shall be slaughtered by decapitation with prior anesthesia with sodiumpentobarbital at a dose of 60 mg/kg intraperitoneally and after that a total thoracotomy shall be performed to obtain the full heart and stored at REVCO in a -70°C of temperature, to finally analyze the tissues modifications with western blot transfer technique.

Western Blot

The expression of AT1R and AT2R was determinate by Western blotting. For Western Blotting, the heart was homogenized in the buffer containing (in mM) Tris 50nM, EDTA, Triton 1%, 1mM 0, NaCl 150mM, cocktail of protease inhibitors (pancreas extract and pronase inhibitor, thermolysin, chymotrypsin and papain inhibitor) (Roche Diagnostics). Homogenates proteins were determined using the Bradford assay kit (Bio Rad Protein Assay; Bio-Rad Laboratories) to each 30 µL of dilute extract or PBS (three replicates) in microplate. Polyacrylamide gels were used for electrophoresis with 30 mg of protein and transferred to polyvinylidene difluoride membrane (Hybond-P, Healthcare, GE, Amersham, UK). Membranes were blocked with 6% of nonfat milk in 20 mM Tris buffer pH 7.4, 0.1% Tween 20 (TBS-T) for 2 hours at room temperature. The blots were incubated with primary polyclonal antibodies for the AT1 (Cat. SC-31181, Santa Cruz Biotechnology, Santa Cruz, CA) and, AT2 (Cat.SC-7420, Santa Cruz Biotechnology, Santa Cruz, CA) receptors overnight at 4 oC in a 1:100 dilution for membranes. Secondary antibody donkey anti-goat IgG HRP (Cat. SC-2020, Santa Cruz Biotechnology, Santa Cruz, CA) was incubated for three hours at room temperature in a dilution of 1:1500.

Then, for the reveal, the membranes were incubated with the chemiluminescent substrate using luminol (western Blotting Luminol Reagent (sc-2040) from Santa Cruz biotechnology) following the manufacturer's instructions. After that procedure, they were placed in the amplification chamber for 15 min in direct contact with light sensitive film (Amersham hyperfilm ECL from GE healthcare limited). Subsequently the films were submerged in revealing liquid (professional Kodak d-19) for 30 seconds and in fixative, allowed to dry and labeled appropriately for future reading and analysis. The intensity of the bands detection was measured by scanning the bands with a scanner (HP Scanjet G3110), and densitometry was performed using Image Analysis Software (BioRad). The presence of proteins was normalized with reference protein beta-actin and quantified by densitometry with Image J 1.44 p program (National Institutes of Health, Bethesda, MD).

Electrocardiogram (EKG)

Electrocardiograms were performed in the pre surgical, immediate postsurgical period and after the corresponding days of treatment. The animals were anesthetized with Xylazine at a dose of 8 mg / kg and Ketamine at a dose of 100 mg/ kg body weight, an electrocardiogram (Contec) was used and it was calibrated at a speed of 50 mm / s and a voltage of 20 mm / mV. Once anesthetized, the extremities were cleaned with 70% alcohol, conduction gel was placed and the electrodes were placed and the electrocardiographic data corresponding to aVF, aVL, aVR, DI, DII, DIII, were taken. V1, V3 and V6 to assess the electrical conduction, corroborate the infarction in the corresponding groups, detect cardiac arrhythmias, determine the cardiac rhythm and calculate the heart rate.

Blood Pressure

At the same time that the rats were anesthetized for taking the EKG, the blood pressure was indirectly measured in the tail of the

rat by using the Harvard Bioscience equipment, indirect rat tail blood pressure system. The pressure transducer was placed on the tail of the animals in order to detect the pulse of the caudal artery and therefore determine systolic BP.

Results

Western Blot

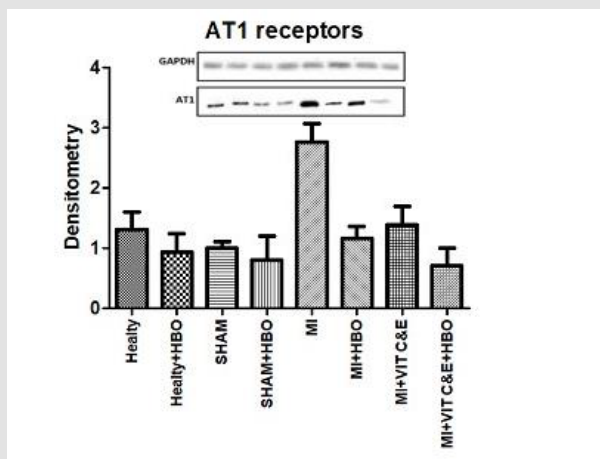


Figure 1: Expression of At1 receptor in a myocardial infarct in rats with hyperbaric oxygen therapy and vitamin C and E treatment. n=5, *p>0.05 +EEM.

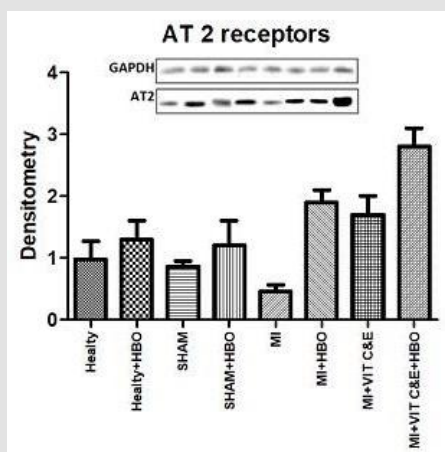


Figure 2: Expression of At2 receptor in a myocardial infarct in rats with hyperbaric oxygen therapy and vitamin C and E treatment. n=5, *p>0.05 +EEM.

Figure 1 shows how monotherapy with OHB in an infarcted heart dramatically decreases the expression of the AT1 receptor, an effect that is enhanced by the concomitant administration of vitamins C and E. Interestingly, we can observe that the administration of vitamins per se induces the increase in the expression of the AT2 receptor Figure 2, similar results are obtained in the group treated with HBO alone, however this cardioprotective effect is enhanced with the joint administration of both therapies, demonstrating an important synergistic effect.

EKG

In order to corroborate the infarction in the corresponding groups, determine the heart rate and calculate the heart rate, the

EKGs were performed. In the EKG of the rat with a 24-hr infarction Figure 3 with treatment, it can be observed that compared to the aberrant conduction of the infarcted heart without treatment, in that line a more homogeneous pattern can be observed in the complexes, in addition a significant decrease in heart rate, which can be translated into a decrease in cardiac work, thus decreasing its oxygen requirement, this in order to preserve the cardiac tissue hibernating. Afterwards, we found the electrocardiogram of the infarcted heart of 3 days of evolution Figure 4, changes that reflect in general an improvement in the electrical conduction of the heart, which could be reflecting an enhancement in the potentially fatal sequelae of myocardial infarction, meliorating the quality of life of patients who suffer from this pathology.

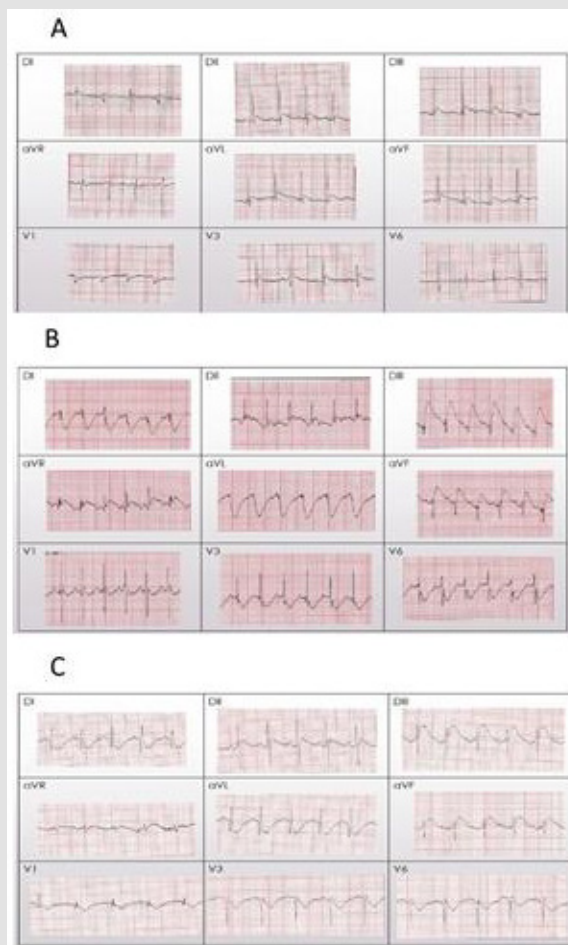


Figure 3: Electrocardiogram in control rats (a), myocardial infarct (b), myocardial infarct 24hr (c), myocardial infarct 24hr with treatment (d). n=5, *p>0.05 +EEM.



Figure 4: Electrocardiogram in myocardial infarct 3days (a) and myocardial infarct 3days with treatment (b). n=5, *p>0.05 +EEM.

Heart Rate

In Figure 5 it can be observed the heart rate taken from the electrostatic devices in a group without infarction and with the different treatments. The rhythm is unusual and has an average

frequency of 336 bpm in the control rats, interestingly found that the heart rate tends to decrease with the different treatments, being significantly noteworthy in the group where a combined treatment of HBO + vitamins C and E has been received, effect that is dependent on exposure time. On the other hand, pertaining to the myocardial

infarction group, as can be seen Figure 4, left anterior descending coronary artery ligation surgery causes a significant increase in heart rate in the postoperative period, and interestingly, after the corresponding days of evolution, in the groups without treatment, a considerable decrease in this parameter can be appreciated, which can be translated into data sequelae of myocardial infarction, in particular, heart failure. However, in the groups corresponding

to the combined treatment of vitamin C and E and hyperbaric oxygenation, a recovery is observed in the heart rate figure, and more markedly in the group of 3 days of treatment, which could be translated into said synergy is involved in the preservation of cardiac function, and could potentially participate by limiting the life-threatening sequelae of myocardial infarction Figure 4.

Blood Pressure (AT VALUES)

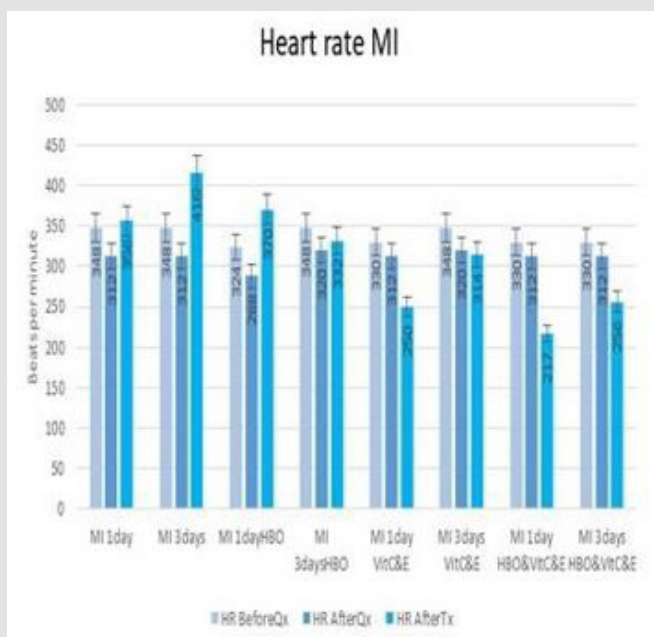


Figure 5: Heart rate in rats with and without myocardial infarct with hyperbaric oxygen and vitamin C and E. n=5, *p>0.05 +EEM.

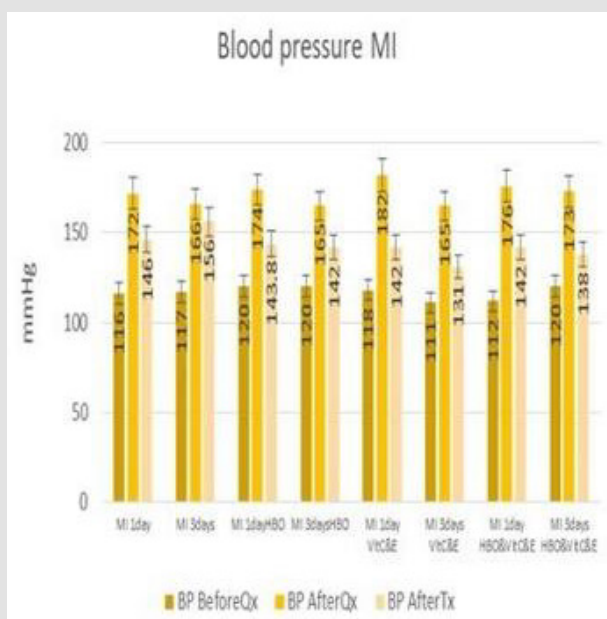


Figure 6: Blood pressure in rats with and without myocardial infarct with hyperbaric oxygen and vitamin C and E. n=5, *p>0.05 +EEM.

In the group of healthy rats, it was found that this parameter decreased in the groups with combined treatment Figure 6, however this decrease in blood pressure does not come to be considered hypotension, in addition this effect in the post infarction period could potentially become beneficial as will be mentioned later. In the SHAM group, blood pressure behaved similarly to healthy rats according to the different days of treatment, presenting a slight decrease in blood pressure in the immediate postoperative period, which may be related to the same surgery, the manipulation of the pericardial structures, the bleeding, and even the anesthetic may be causing this decrease, however this alteration reverted to the 24 hours of evolution. Figure 6. In the group of rats with AMI, it can be observed Figure 6 that in the immediate postoperative period blood pressure increases significantly modifying the cardiac physiology of the experimental model from the first post infarction minutes. Subsequently, it can be observed that in groups of 1 and 3 days without treatment, the arterial pressure continued high persistently. Regarding the treatments, we can observe that the synergic treatment of vitamin C and E with hyperbaric oxygenation provides a significant improvement in blood pressure figures, presenting a tendency to normal pressure, which can translate into a limitation of myocardial tissue damage in the post-infarction period.

Statistical Analysis

Data were expressed as the mean \pm SEM. Comparisons among the groups of data were carried out using the one-way ANOVA followed by Tukey's post hoc test. Significance was accepted at $*p < 0.05$.

Discussion

Statistics indicate that in the last decades cardiovascular diseases have been increasing in such an important way that currently occupy the first place of global morbidity and mortality [26], and although there are clinical guidelines for acute management and chronic of patients with AMI [27], is required to continue innovating in the investigation of adjuvant therapeutic options that improve the quality of life of patients with this pathology. HBO therapy has begun to be studied because, in the few reports that exist, beneficial effects have been found in a large number of pathologies. However, until now there is very little literature regarding cardiovascular pathologies, hence the importance of the present work. In this case, when evaluating the modification of the expression of AT1 and AT2 receptors, which have a great importance in cardiovascular diseases [28], we can also clarify which are the ways that can be silencing or stimulating after sessions of HBO and the administration of vitamin C and E. Our results indicate that HBO significantly modifies the expression of both AT1 and AT2 receptors, so offering monotherapy is a viable therapeutic option for patients who have had an AMI and; this coincides with investigations that have been carried out with

members and collaborators of our work team, in lines of research parallel to this work. As an interesting aspect, we can point out that vitamin C and E, antioxidant vitamins par excellence, have been administered jointly, which in experimental models of infarction have been used to reduce the area of infarction, decrease cardiac arrhythmias after infarction, and stabilize ROS [19-21,29], in the process of cardiac tissue necrosis, allowing to limit the sequelae that characterizes the natural history of this disease, aspects that we consider important and, coupled with a reduction in In the infarction zone, we can observe in our results that the angiotensin AT1 receptors are not statistically modified by the administration of monotherapy with vitamins C and E.

However, the AT2 receptors do show significant differences, which may justify their beneficial effect on the patients who suffer from this pathology. Interestingly, this study allowed us to realize that when applying both therapies there is a synergy between its beneficial effects, decreasing the harmful effects of the AT1 receptor and increasing the cardio protective effects of the AT2 receptor, in addition to being a viable and accessible therapy for any patient, aspect that has not been described in the literature. Having found all these effects, it is necessary to continue researching to continue providing knowledge that validates the use of the hyperbaric chamber concomitantly with vitamin C and E.

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