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Speckle Tracking Evaluation of Mild Hyperbaric Oxygen Effects on Myocardial Contractility and Ejection Function in a Patient with Severe Ischemic Cardiomyopathy: A Case Report and Physiological Discussion

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ABSTRACT

Introduction: This case report focuses on the effects of mild hyperbaric oxygen therapy (mHBOT) in an over 70 years old female patient with symptomatic ischemic cardiomyopathy, severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aorta-coronary bypass surgery due to coronary anatomical characterizations. The patient suffered repeated episodes of heart failure resistant to pharmacological therapy (currently the patient is at the maximum anti-ischemic therapy), having an ejection fraction (EF) pre-mHBOT protocol severely reduced, seen also at speckle tracking with a marked depression of the systolic function due to marked global hypokinesis and severe dyskinesia of the antero-lateral myocardial walls, especially the apical segments.

Methods: The mHBOT was performed with a medical hyperbaric chamber using the following protocol: 1.45 atm, 96 % O2, 75 min sessions, three times a week for three months. Pre- and post-mHBOT clinical values which were compared are the following: Bull's eye speckle tracking echocardiography with longitudinal strain and color pattern, EF, Angina scale.

Results: Post-mHBOT recordings showed massive improvement of myocardium contractility, from a severely dyskinetic and hypokinetic contractility to a normal kinetics, with a color shift from "blu" to "red" in the anterior and lateral segment at the bull's eye representation accompanied by normalization of the longitudinal strain values globally and especially on the severely dysfunctional lateral and anterior segments. EF also went from being severely depressed to normality range and angina symptoms disappeared.

Conclusions: The mHBOT protocol has been shown in this case report to improve myocardial function, contractility and symptomatology of the patient. Post-protocol EF dramatically increased with improvement of myocardial functions as seen with speckle tracking recordings at ultrasound examination of the myocardium, with normalization of kinetics of the myocardial segments. The improvements remained at the 6 months post-HBOT follow-up cardiac check. This case report highlighted the importance and possible future application in patients with ischemic cardiomyopathy of mHBOT, a replicable, low cost and highly efficacious therapy.

Keywords: mHBOT, Ischemic Cardiomyopathy, Speckle Tracking

Introduction

History of hyperbaric medicine

It was 1662 when the English Henshaw built the first hyperbaric chamber mechanism, named the "domicillium" [1]. The machine was powered by organ bellows and equipped with valves to control air flow. This marked the beginning of what is now a over than 340 years old history of hyperbaric and more in general terminology recompression chambers technology. This "domicilium" was a sealed chamber which functioned to both create hyperbaric (above normal) and hypobaric (below normal) conditions. Henshaw believed that acutely ill patients benefited from increased air pressure, while chronically ill patients benefited from a more tenuous environment. At his time Henshaw had no scientific basis for his theory. He suggested that hyperbaric therapy was "an excellent remedy that aids digestion, promotes insensible breathing, promotes respiration and excretion, and is therefore excellent in the prevention of

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most lung diseases." Since Dr Henshaw's times, hyperbaric medicine (Hyperbaric Oxygen Therapy-HBOT) has become an ever-increasing important field in medical research, applying this technology in a wide range of pressures, which led to the birth of mild-HBOT (mHBOT), a lower cost, easily applicable and replicable protocol and medical therapeutic technology.

Mechanisms of action of HBOT, mHBOT and physiological discussion on its effects in body and cardiac system

Many mechanisms through which HBOT achieves the several therapeutic goals are not completely understood and neither are the exact mechanisms through which hyperoxygenation and hyperoxia affect cellular and DNA components. What is known is that HBOT has a strong clinical outcome through regeneration of tissues. Regenerative medicine has as its main goal the repairment and replenishment of damaged tissues (tissue which has been altered due to extrinsic or intrinsic - ie aging-related processes - factors). This is achieved through a plethora of mechanisms which include cellular, genetic and micro-environmental factors. The mechanisms of actions of HBOT are various and of dramatic impact. With little side-effects (granted the patient is cleared to undergo such a therapy), HBOT could be of immense impact to some of the most complex pathologies us medical doctors face as a community. This is also applied to what is known as mHBOT, working at lower pressures compared to the standard HBOT (starting from 2.0 atm), it works in the range of pressures below 1.5 atm, granting this protocols lower side-effects and easier systems and replicable protocols applications. In fact, several studies revealed the beneficial effects of these levels of hyperbaric pressures, such as the fact that at hyperbaric conditions of 1 to 2 atm there may be the most favorable for enhancement of cell count in chondrocytes [2]. A recent study on mice, highlighted the protective effects of mHBOT (1.5atm) during ischemia and reperfusion phases and its effects on vascular relaxations showing increased sensitivity to acetylcholine, increased levels of plasma nitrates, and reduced infarction size [3]. Mild HBOT can truly be a precious tool for medical doctors, as shown in recent research, it was revealed that mHBOT at pressures as low as 1.3 ATA with oxygen supplementation, it induced oxygen saturation levels nearest to 100%, demonstrating how therapeutic levels of oxygen saturation in the blood can be brought by mHBOT [4]. Mild hyperbaric environment per se holds strong effector power on the body, as shown by a further study showing a three-fold 72 hours post completion of a protocol in which a subject underwent mild hyperbaric condition (1.27 atm) at normo-air.

Research has shown how at mHBOT, a lower cost and highly replicable technology, important clinically relevant effects on the body occur. For instance, in a study after mHBOT (with a protocol at 1.4 atm of pressure and just 35-40 % of O2) there was a successful increase of Natural Killer cells by the regulation of the activity of the parasympathetic activation through the increased oxygen activity [5]. Similarly, in a different research group where they used a similar protocol as the one mentioned before, mHBOT increased the flow of blood in the capillary system, by regulatiing the parasympathetic system through increased oxygen delivery of oxygen bound to hemoglobin and through the oxygen directly dissolved in the plasma [6].

New interest has sparked in the last years over the effects of both HBOT and mHBOT in cardiac function. Recently, a group over sixty-years old patients were enrolled in a HBOT protocol which results showed that HBOT indeed helped enhance the patients' physical performance. The improvements that have been noted included gains in cardiopulmonary functions, with improved maximal oxygen consumption (VO2Max) and increased myocardial perfusion brought on by HBOT, with both cardiac blood flow (MBF) and cardiac blood volume (MBV) exhibited significant increase when compared to the control group (cardiac improvement measured with cardiac magnetic resonance imaging and cardiopulmonary maximal exercise test) [7].

At pressures above 1.0 atm, oxygen (normally solely bound to hemoglobin in the blood) directly diffuses into the blood. This hyperoxygenation of blood has a plethora of effects. First, it is the most intuitive one which is the oxygenation of the tissues. Areas of inflammation, edema and tissue alterations will have a diminished blood flow, therefore not being the 96-99 % oxygenation seen at the pulse oximeter in "healthy" individuals and thus not detectable by such devices when these areas are not in the section measured by these oximeters. These hyper-oxygenations will cause a decrease in hypooxygenation in pathological areas, stimulation of the microvasculature, and a consequent reaction of redox enzymes and antioxidants in response to this oxidative stress much greater than the oxidative stress itself, following the hormesis theory. Tissue hypoxia is one of the leading causes of pathological status of organs and tissues, leading to cell suffering and an etiological contributing factor to degeneration, tumor genesis, and apoptosis. Different mechanical and biochemical protective effects are witnessed in different type of tissues. Taking as example the neurological organs, HBOT has been shown to have a neuroprotective effect by stimulating mitochondrial transfer between microglia and neurons, increasing the CNS perfusion and stimulating the microcirculation (also connected to the increased of HIF in between the patient's status in the chamber of an hyperoxic and hyperbaric and the patient outside the chamber, where it is in a state of what we can name "hypoxic mirage") [8]. This improvement in perfusion is seen at functional perfusion magnetic resonance images (MRI) scans. The neuro-protective effect is seen also due to the stimulation of stem cells, both in tissue and in blood. Hippocampal improvement has been seen in animal models while a significant increase in circulating stem cells has been recorded in patients 'undergoing HBOT protocols [9,10]. These effects are then translated into the clinics, where we see incredible functional and organic-based recoveries in the patients, for the neuroprotective and neuro-regenerative effects seen for instance in post-Traumatic brain injury patients [11].

For a further understanding of the effects of HBOT in the human body, a detour deep into the epigenetics and genetics effects of hyperoxygenation at hyperbaric pressures and even the change in oxygen concentrations must be done, exempli gratia: the hypoxichyperoxic paradox. Recent studies shed new light on the regenerative and anti-aging properties of HBOT. Aging markers have been re-winded in patients undergoing HBOT protocols, specifically telomeres, which are caps at the end of the human chromosomes keeping the DNA intact and stabilizing it (metaphorically compared to shoelaces caps, keeping the laces from unfolding into disarray) [12]. Second marker are senescent cells, aging and dying cells which create inflammation and burden the organs. After HBOT protocols these cells have reduced in combination with a reduction in clusters of inflammation markers found and measured in the blood. Furthermore, recent study showed modulating properties of the physiopathology of skin aging, whence by analysis histologically skin samples of patients who underwent HBOT protocol, it has been shown that it restored the elastic properties of the skin [13]. Many in the scientific community have started to define HBOT as also being a gene therapy, as it affects the epigenetic landscape and thus the actual effector portion of the genes themselves. By specifically changing the three-dimensional conformation of the genetic portion of the cell, genes can be shut down or turned on accordingly, this being the epigenetic aspect of HBOT effects.

Joint and osteo-muscular pathologies also have been recorded and studied in terms of their reactions to HBOT protocols. HBOT effects on joints mobility and inflammation has been compared to be as effective as the one of patients under acetylsalycilic-acid therapy, revealing the strength in terms of anti-inflammatory and regenerative capacity of HBOT.

An important factor to consider when discussing the effects of HBOT is that changes in oxygen concentrations are one of the most important biochemical triggers in human homeostasis and physiology. This leading to the concept of the hyperoxic-hypoxic paradox [12]. This hyperoxygenation of tissues and hyperbaric environments will then lead to a before-mentioned "hypoxic mirage" where the body is tricked into believing that it is in a hypoxic stage and therefore will release several chemical reactions such as Hypoxic-inducible factor (HIF) and Vascular-endothelial growth factor (VEGF). This reaction does not have negative impact to the tissues compared to a similarly mediated biochemical reactions which are carried out under true pathological hypoxic situations. Several studies have also explored the effects on tumor genesis and progression of HBOT. Not only it has been shown not to increase tumor genesis and progression, but it has been shown to act as an anti-tumoral therapy by several mechanisms, such as inhibiting the Epithelial-to-mesenchymal (EMT) and pushing it to Mesenchymal-to-Epithelial (MET) path in case of subtypes of carcinomas [14]. Over 29 million people in the United States suffer from Diabetes, and with it a greater risk for cardiac diseases, which could require heart surgery. Studies have shown how even two HBOT sessions pre-heart surgery reduced cognitive deficits by thirty percent [15]. Furthermore, hospitals have reported that HBOT will help heal heart surgery scarring and tissue healing in post-op setting [15].

Patient's clinical background

This paper aims at presenting an at increasing awareness on the need for increasing understanding and use of mHBOT and the unexpected highly efficacious results of mHBOT in a geriatric patient with severe ischemic cardiomyopathy.

This case report focuses on the effects of mHBOT in an over 70 years old female patient with ischemic cardiomyopathy, severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aorta-coronary bypass surgery due to coronary anatomical characterizations (figure 1).

The patient suffered repeated episodes of heart failure resistant to pharmacological therapy (currently patient is at the maximum anti-ischemic therapy), having an ejection fraction (EF) pre mHBOT protocol severely reduced, seen also at speckle tracking with a marked depression of the systolic function due to marked global hypokinesis and severe dyskinesia of the antero-lateral myocardial walls, especially the apical segments. The patient was under the maximal protocol in terms of pharmacological therapy and has been under this therapy since before the mHBOT protocol started. During the protocol no changes in pharmaceutical therapy were made. The patient underwent a coronary angiography procedure resulting in a positive result for a severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aorta-coronary bypass surgery due to coronary anatomical characterizations (figure 1).

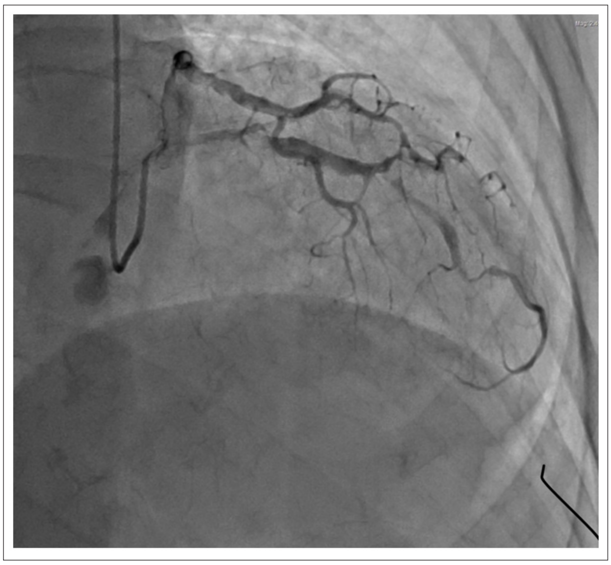

Figure 1: Image of coronaries with diffuse narrowing and atheromasia (left coronary circulation shown in the image during coronary angiography)

The patient had marked asthenia with a speckle tracking myocardial results at speckle tracking. The EF pre-mHBOT protocol of the patient was severely reduced and being 24 %, therefore the patient had a severely reduced ejection fraction with an ischemic cardiomyopathy.

Speckle tracking echocardiography

Lately, speckle tracking echocardiography (STE) has become a popular quantitative method for precise cardiac function estimation. This method provides an objective, nonDoppler angle independent study of myocardial deformation by analyzing the mobility of speckles in a two-dimensional ultrasonic image. In the last years speckle tracking has been proved to be a highly precise parameter for evaluating the function of the myocardium and quality of contraction [16]. It also allows one to quantify the dynamics of cardiac thickening, shortening, and rotation. Since Doppler imaging is not needed for this method, the analysis is mostly independent of angle and only slightly impacted by artefacts related to cardiac in-plane motion. In speckle tracking echocardiography, the operator gets a Bull's eye display of segmental and global/ segmental peak-systolic longitudinal strain.

Regarding speckle tracking results interpretation, it is worth to note that normal individual has a with normal value of −16% to −24% in terms of global and/or segmental longitudinal strain (GLS) of left-ventricle, while on the color scale of the speckle tracking bull's eye representation normal kinesis is depicted towards the color "red" [17]. Whilst, going towards the color "blue" longitudinal strain values being less negative signify hypokinetic myocardial contractility. Positive values of longitudinal strain signify myocardial contractility being dyskinetic. Public discussion of clinical cases like this one are a fundamental stepping stone to a future where HBOT is applied to a wider range of pathologies and all the while raising awareness on the potential benefits which this therapy could bring to the patients.

Methods

This case report focuses on an over 70 years old female patient coming to the Olimpia Medical Center (Vicenza, Italy) where she was enrolled in a mHBOT protocol to ameliorate the condition of severe myocardial function depression, ischemic cardiomyopathy, severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aortacoronary bypass surgery due to coronary anatomical characterizations. The patient suffered repeated episodes of heart failure resistant to pharmacological therapy (currently patient is at the maximum anti-ischemic therapy), having an ejection fraction (EF) premHBOT protocol severely reduced, seen also at speckle tracking with a marked depression of the systolic function due to marked global hypokinesis and severe dyskinesia of the antero-lateral myocardial walls, especially the apical segments. The parameters used to assess the myocardial function of the patient were:

- Primarily, the main parameter used was Speckle tracking for segmental myocardial contractility function (comparing both segmental longitudinal strain values and bull's eye color)
- Ejection Fraction measurement
- Angina scale
- These parameters were assessed pre- and post- mHBOT protocol.
- The clinical and detailed informations were collected from 2nd October 2023 to 2nd August 2024.
- Full written consent was collected after full explanation of the data collection and aim was explained to the patient.
- The methodology used to measure the effect of mHBOT on the patient was:
- Measurement of Cardiac speckle tracking ultrasound and ejection fraction measurement.
- The Ultrasound machine used for the cardiac measurements is the GE Vivid E9 with both 2D and 3D probes with piezoelectric probes.
- The HBOT chamber used was a medical "Biobarica" hyperbaric chamber.
- The patient also filled the 5-grade angina scale, Guidelines for Cardiac Rehabilitation,
- Sixth Edition, pre- and post-mHBOT protocol.
- The mHBOT Protocol consisted:
- 1.45 atm at 96 % Oxygen for 75 minutes - 3 months protocol - 3 times a week

Results

This case report focuses on the effects of mild hyperbaric oxygen therapy (mHBOT) in an over 70 years old female patient with ischemic cardiomyopathy, severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aorta-coronary bypass surgery due to coronary anatomical characterizations. She underwent three months of mHBOT protocol.

The patient was under the maximal protocol in terms of pharmacological therapy and has been under this therapy since before the mHBOT protocol started. During the protocol no changes in pharmaceutical therapy were made.

The patient had an angina grade of 3/5 before undergoing the HBOT protocol (patient underwent a coronary angiography procedure resulting negative but with a positive result for a microvascular coronary angiography). The patient had marked asthenia with a speckle tracking myocardial results at speckle tracking. The Ejection Fraction (EF) pre-HBOT protocol of the patient was severely reduced and being 24 %, therefore the patient had a severely reduced ejection fraction with a hypertensive cardiomyopathy. As seen also at speckle tracking, before the HBOT protocol the patient had a marked depression of the systolic function due to hypokinesis and dyskinesis of the antero-lateral myocardial walls, especially the apical segments.

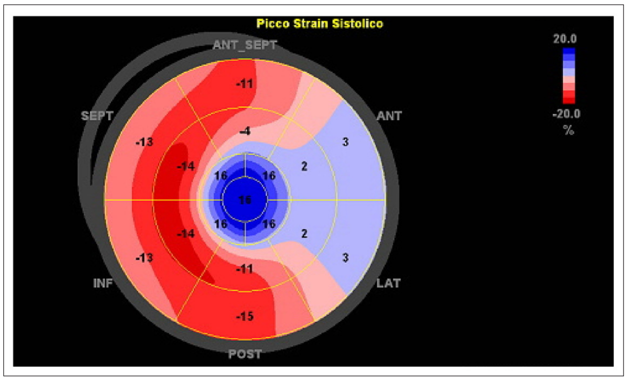

Figure 2: Pre-therapy Bull's eye Speckle tracking of the myocardium

In figure 2 it can be noted severely dyskinetic anterior and lateral myocardium strains with reduced hypokinetic overall myocardial segments peak systolic strains. Longitudinal strain values on the lateral and anterior segments being positive indicate dyskinesis of the myocardial wall (color tending to the light blue).

At pre-HBOT speckle tracking analysis it can be noted a hypokinetism of the septal, inferior and posterior segments of myocardium with dyskinetism of the antero-lateral segments.

Then the speckle tracking analysis was performed on the patient post-HBOT protocol .

In figure 3, it can be seen that the overall systolic peak strain improvement across all myocardial segments. At clinical analysis, reduced asthenia and improvement in cognitive functions. Longitudinal strain values on the lateral and anterior segments went into the normality range in almost all segments, including the previously severely dyskinetic anterior wall, with a major improvement of the lateral myocardial wall (color red in all segments). Post-protocol EF increased to 60 % with improvement of myocardium functions as seen with speckle tracking recordings at ultrasound examination of the myocardium. The speckle tracking echocardiography showed a normal segmentary contractility of the left ventricle. Normalization of kinetics in terms of longitudinal strain but also seen at the bull's eye analysis, with improvement especially at the anterior and lateral LV myocardial segments contractility.

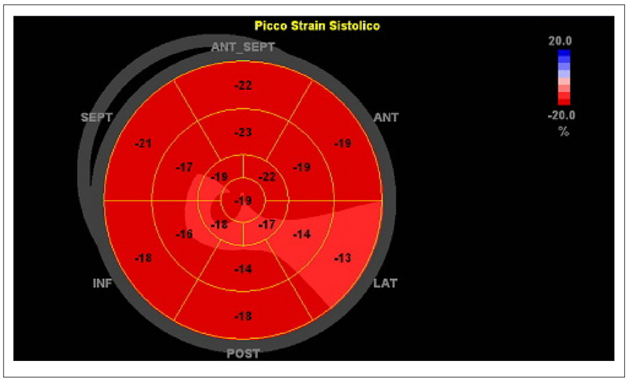

Figure 3: Post-therapy Bull's eye Speckle tracking of the myocardium

The grading of angina severity post-protocol immediately after the two months period went from 3/5 to a 0/5. These improvements remained at the 6 months post-HBOT follow-up check.

Conclusions and Discussions

Several studies in the last decade have brought to light a quite under-discussed medical therapy, the HBOT, holding an intrinsic potential therapeutical clinical prowess to be applied in a plethora of medical fields to achieve the ultimate goal for any professional in the medical field, the improvement of the patient's life. Especially in the last years, several studies have revealed the regenerative power of HBOT, which acting at the gene level is able to target several hallmarks of biological aging and regenerative medicines, such as working on senescent cells and telomere length but also HIF-1 levels and wound recovery [18].

This case report focuses on the effects of mild hyperbaric oxygen therapy (mHBOT) in an over 70 years old female patient with ischemic cardiomyopathy, severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aorta-coronary bypass surgery due to coronary anatomical characterizations. She underwent three months of mHBOT protocol.

The patient had a symptomatic ischemic cardiomyopathy with an angina grade of 3/5 before undergoing the mHBOT protocol.

The patient had marked asthenia with a speckle tracking myocardial results at speckle tracking. The Ejection Fraction pre-HBOT protocol of the patient was severely reduced and being 24 %, therefore the patient had a severely reduced ejection fraction with an ischemic cardiomyopathy. As seen also at speckle tracking, before the HBOT protocol the patient had a marked depression of the systolic function due to hypokinesis of the anterolateral myocardial walls, especially the apical segments (reduced anterior and lateral myocardium strains with reduced overall segments peak systolic strains).

At pre-HBOT speckle tracking analysis it can be noted a hypokinetism of the septal, inferior and posterior segments of myocardium with dyskinetism of the antero-lateral segments. Longitudinal strain values on the lateral and anterior segments being positive indicate dyskinesis of the myocardial wall (color tending to the light blue).

Post-protocol EF increased to 60 % with improvement of myocardium functions as seen with speckle tracking recordings at ultrasound examination of the myocardium. It can be seen that the overall systolic peak strain improvement across all myocardial segments. At clinical analysis, reduced asthenia and improvement in cognitive functions. Longitudinal strain values on the lateral and anterior segments went into the normality range in almost all segments, including the previously severely dyskinetic anterior wall, with a major improvement of the lateral myocardial wall (color red in all segments). The speckle tracking echocardiography showed a normal segmentary contractility of the left ventricle. The speckle tracking echocardiography showed a normal segmentary

contractility of the left ventricle. Normalization of kinetics in terms of longitudinal strain but also seen at the bull's eye analysis, with improvement especially at the anterior and lateral LV myocardial segments contractility. Therefore, post-mHBOT recordings showed massive improvement of myocardium contractility with a shift from "blu" to "red" in the anterior and lateral segment at the bull's eye representation accompanied by normalization of the longitudinal strain values globally and especially on the severely dysfunctional lateral and anterior segments. EF also went from being severely depressed to normality range and angina symptoms disappeared.

The grading of angina severity post-protocol immediately after the two months period went from 3/5 to a 0/5. These improvements remained at the 6 months post-HBOT follow-up check.

This case report reveals the potential use of mHBOT, a low cost and highly reproducible in terms of clinical applications technology, in an over 70 years old female patient with ischemic cardiomyopathy, severe diffuse coronary atheromasia not revascularizable by coronary angioplasty nor by aorta-coronary bypass surgery due to coronary anatomical characterizations. The patient suffered repeated episodes of heart failure resistant to pharmacological therapy (currently patient is at the maximum anti-ischemic therapy), having an ejection fraction (EF) pre-mHBOT protocol severely reduced, seen also at speckle tracking with a marked depression of the systolic function due to marked global hypokinesis and severe dyskinesia of the antero-lateral myocardial walls, especially the apical segments.

The mHBOT protocol has been shown in this case report to improve myocardial function, contractility and symptomatology of the patient. Post-protocol EF dramatically increased with improvement of myocardial functions as seen with speckle tracking recordings at ultrasound examination of the myocardium, with normalization of kinetics of the myocardial segments. The improvements remained at the 6 months post-HBOT follow-up cardiac check.

This case report highlighted the importance and possible future applications in patients with ischemic cardiomyopathy of mHBOT, a replicable, low cost, low side-effects and highly efficacious therapy and the usefulness of speckle tracing in assessing improvements in myocardial function in research focused on the improvement of myocardial contractility while revealing the need for bigger research studies assessing the applicability of mHBOT in severe ischemic cardiomyopathy patients of the severity, which could reveal that indeed this technology could prove as a very effective, easy to apply with low side-effects for the patient and low-cost in terms of therapeutic delivery in the management of this complex category of patients.

Declarations

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interests: The authors do not have any ownership in any hyperbaric chamber manufacturers nor other related companies. No conflict of interests.

Ethics statement: The studies involving human participants were reviewed and approved by Olimpia Medical Center Board of Directors. The patients/participants provided their written informed consent to participate in this study.

Consent: Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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