

# Influence of hyperbaric oxygenation treatment (HBOT) on clinical outcomes (recurrent myocardial infarction and survival rate) during five-year monitoring period after acute myocardial infarction

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## ABSTRACT

Surgical treatments of acute myocardial infarction (MI) possess a high clinical effectiveness, but there are fixed limitations, related to the patient's state, which are limited by medical resources and organizational problems. The development of new medical technologies provides a better and effective non-surgical treatment of acute MI and increases long-term prognosis in this category of patients. The study aims to investigate the influence of hyperbaric oxygenation treatment on clinical outcomes (survival rate and recurrent myocardial infarction (rMI)) during the five-year period of monitoring. The study involved 697 patients who suffered from acute MI, having undergone the standard treatment. The patients were randomly divided into two groups: Group 1 (reference, n = 363); Group 2 (test, n = 334). Patients of Group 2 were given the traditional treatment, accompanied with HBOT (isopression for forty minutes at a working pressure of 0.03 MPa). HBOT was applied first through the fifth day following MI. The treatment course included six cycles, once per day. The clinical assessment was focused on clinical outcome: rMI and mortality related to cardiovascular events. HBOT application that accompanied the acute MI with traditional pharmacotherapy has been proved to reduce rMI within five years following inpatient discharge (rMI rate was 14% in the reference group and 5.4% in the test

group,  $\chi^2 = 13.3$ ,  $p < 0.05$ ). The combination of HBOT with traditional methods in treating acute MI makes it possible to raise the five-year survival rate from 84.4% up to 95.9%.

## KEYWORDS

Hyperbaric Oxygenation Treatment; Myocardial Infarction; Recurrent Myocardial Infarction; Clinical Outcomes; Mortality Rate; Survival Rate

## 1. INTRODUCTION

Myocardial infarction (MI) is still considered one of the most dangerous complications of atherosclerosis, causing high mortality rates in several groups of patients [1-5]. Several bodies of evidences indicate a decrease in cases of cardiovascular mortality in developed countries in the last decade. Approximately 20% - 30% accounting for this decrease is due to the better quality of medical measures, while the remaining 70% - 80% reflects the effectiveness of rehabilitation program on primary prophylactics of atherosclerosis [6-8]. However, the effectiveness of the secondary prophylactics of atherosclerosis is lower and, particularly, the post-MI survivors retain the risky "hallmark" for recurrent myocardial infarction (rMI) and cardiovascular related mortality [9,10]. Moreover, while acute MI inpatient treatment methods can be assumed to have progressed immensely, the MI outpatient treatment achievements are still much to be desired.

Retrospective studies of over 5000 acute MI hospital patients in the USA for two decades (1975-1995) con-

firmed that rMI eventuality and mortality within a year following inpatient discharge did not tend to change in any way since the late 80s of the last century [11]: the first-year mortality rate was limited to 10% - 13%, the second-year mortality rate—17% - 19%. As reported [12], the total mortality rate of Scottish post-MI patients within the first year counted 31.4%, reaching 64.0% within a 10-year period. In a study of Swedish MI patients, the frequency of rMI within a 5-year period was 28%, and reaching 37% within a 10-year period [13]. The total mortality within a 5-year period was 19%, and within a 10-year period—33% [14]. Launbjerg *et al.* reported similar results in a Danish population [10]. According to Madsen *et al.* [15], the frequency of rMI after medication was 10.5% (during a 2.4-year observation time), which corresponds with the results obtained in the American population [16]. The findings of Vaccarino *et al.* indicate that in USA, mortality within a 2-year period after MI was 28.9% among females and 19.6% among males [16]. The situation in developed countries has markedly improved in the new millennium. However, the problem of rMI eventuality and cardiovascular mortality in patients with acute rMI remains relevant.

The post-infarction period is influenced by a number of factors, including clinical peculiarities of each acute MI case, risk factors (if any), patient's adaptability to the treatment etc. However, there is an unshakable dogma for early myocardial ischemia treatment to be a prerequisite for more favorable clinical course. In this regard, the use of oxygenation technology has gained an increasing prominence [17-19].

The oxygenation technology applied for ischemic heart therapy is based on the idea that blood oxygen partial pressure increase provides elimination of tissue hypoxia [18,19]. Starting from the 1940s, patients were efficiently treated with normobaric oxygenation; a bit later hyperbaric oxygenation (HBOT) technology was introduced [20-22]. The technology of hyperbaric medicine is effective for the treatment of ischemic brain damage [23,24], carbon monoxide poisoning [25], and a number of other clinical conditions [26,27]. Unfortunately, the technology failed to be widely used for some reasons. Firstly, HBOT does not provide "on-the-spot" clinical effect, as compared to drug therapy. Besides, our medicine is traditionally oriented on giving more rest for MI patients, thus, protecting them from any outer impacts, including equipment-related manipulations. Finally, we have no established clinical practice of long-term monitoring for MI-suffered patients and for those treated with HBOT [28,29]. Nowadays, oxygen therapy (of any variant) is regarded more like a tradition, well-founded by pathophysiologicals rather than clinical practitioners.

The aim of this study was to investigate the influence of hyperbaric oxygenation treatment on clinical out-

comes (recurrent myocardial infarction and survival rate) during a 5-year monitoring period.

## 2. SUBJECTS AND METHODS

The study was open, prospective, and randomized. It was conducted during 2005-2009 years in the cardiology hospital of Gomel region. The commission for medical ethics found no inconformity to the medical ethics and morality standards.

**Inclusion criteria:** The first myocardial infarction diagnosed verified by clinical, ECG and biochemical analyses [30-32]; MI of at least one-day history and at most five days history; age of patients between 30 and 75 years; informed consent to participate in the study; approval by the commission for medical ethics. **Exclusion criteria:** MI after 5-day history; right ventricular infarction; claustrophobia; oncology anamnesis; psychic disturbances; alcohol and/or drug abuse; refusal to participate; acute ear, nose, throat diseases; unstable hemodynamics (persistent pain syndrome, negative dynamics in ECG and laboratory analyses).

The study involved 697 MI patients. Treatment regimen of MI-patients corresponded to standard recommendation [33] and included the myocardial revascularization technique according to indications (thrombolysis, angioplasty, coronary stenting and coronary artery bypass surgery) and drug therapy. The standard drug therapy included aspirin, heparin, beta-blockers, ACE inhibitors, nitroglycerin, some patients were additionally treated with antiarrhythmic and hemodynamic preparations [33]. The patients were randomized into two groups: Group 1 (reference,  $n = 363$ ; 274 males and 89 females, mean age of  $56.4 \pm 11.7$  years); Group 2 (test,  $n = 334$ ; 266 males and 68 females, mean age of  $55.5 \pm 8.2$  years) (**Tables 1-3**). Patients of Group 2 were given the traditional treatment, accompanied with standard HBOT using the BLKS-307 (Russia, Moscow) single-seat apparatus (isopression for 40 minutes at a working pressure of 0.03 MPa). HBOT commenced on the first through the fifth day (average—2.3 days) following the MI; the treatment course included 6 cycles, once per day.

The groups were homogeneous in both socio-demographic parameters (**Table 1**) and clinical characteristics (**Table 2**). Thus, Q-wave-MI in Group 1 and 2 amounted to 71.4% and 79.3% respectively, anterior MI localization was found in 52.6% and 48.8% of patients, and thrombolysis was applied to 17.9% and 21.6% of the

**Table 1.** Gender and demographic characteristics of MI investigated patients,  $n$  (% ,  $M \pm m$ ).

	Males	Females	Age (years)
Group 1, $n = 363$	274 (75.5 $\pm$ 2.3)	89 (24.5 $\pm$ 2.3)	56.4 $\pm$ 11.7
Group 2, $n = 334$	266 (79.6 $\pm$ 2.2)	68 (20.4 $\pm$ 2.2)	55.5 $\pm$ 8.2

**Table 2.** Clinical peculiarities of diseases, concomitant pathology among MI investigated patients, n (% , M ± m).

	Group 1	Group 2
Non-Q-wave-MI	104 (28.6 ± 2.4)	69 (20.7 ± 2.2)
Q-wave-MI	259 (71.4 ± 2.4)	265 (79.3 ± 2.2)
Localization		
Anterior MI	172 (47.4 ± 2.6)	171 (51.2 ± 2.7)
Inferior MI	191 (52.6 ± 2.6)	163 (48.8 ± 2.7)
Myocardial revascularization, including:	138 (38.0 ± 2.6)	141(42.2 ± 2.7)
Coronary artery bypass surgery	49 (13.5 ± 1.8)	49 (14.7 ± 1.9)
Stenting	33 (9.1 ± 1.5)	62 (18.6 ± 2.1)
Thrombolysis	65 (17.9 ± 2.0)	72 (21.6 ± 2.3)
Concomitant pathology		
Arterial hypertension	242 (66.7 ± 2.5)	214 (64.1 ± 2.6)
Diabetes mellitus	59 (16.3 ± 1.9)	44 (13.2 ± 1.9)
Dislipidemia	212 (58.4 ± 2.6)	230 (68.9 ± 2.5)

**Table 3.** Frequency of complications of MI investigated patients, n (% , M ± m).

MI complications	Group 1	Group 2
Heart rhythm disturbance	40 (11.0 ± 0.7)	34 (10.2 ± 0.7)
Conductivity disturbance	36 (9.9 ± 0.4)	30 (9.0 ± 0.5)
Formation of aneurysm	19 (5.2 ± 0.2)	13 (3.9 ± 0.1)
Acute left ventricular failure	14 (3.9 ± 0.3)	11(3.3 ± 0.3)
Cardiogenic shock	3 (0.8 ± 0.2)	5 (1.5 ± 0.2)
Ventricular fibrillation	2 (0.6 ± 0.2)	1 (0.3)
Pulmonary embolism	2 (0.6 ± 0.2)	2 (0.6 ± 0.2)
Apparent death	1 (0.3 ± 0.1)	6 (1.8 ± 0.2)

cases respectively (**Table 2**).

The clinical assessment was focused on rMI and cardiovascular related mortality rate, as referenced by medical histories, outpatient cards, and death certificates. Monitoring duration was 5 years. Statistical data processing was carried out by nonparametric methods using the Pearson criterion,  $\chi^2$  and Fischer's exact test.

### 3. RESULTS

When applying HBOT, no substantial or life-menacing complications were observed in Group-2 patients. Post-MI patients of both groups were discharged in good state of health to follow their sanatorium and spa treatment. Forty two (n = 42) patients from the first group and 18 patients from the second group were excluded from the study due to the absence of information concerning their life-status (dead/alive) after 5 years of beginning the research (see **Table 4** for the clinical history during the 5-year monitoring period). Thus by the end of the study, we had information on 321 patient from reference group and 316 patients from the test group.

rMI was reported mainly in male patients (86% and 75% of reference and test groups respectively), having anterior MI localization (86% of the reference group, 75% of the test group). Male mortality also prevailed

**Table 4.** The rate of clinical outcome in the study groups.

Parameters	Group 1 (reference)	Group 2 (test)
	n	n
Included	363	334
Excluded (after 5 years)	92 (No data - 42; M - 50 <sup>*</sup> )	31 (No data - 18; M - 13)
rMI	45 <sup>*</sup>	17

Nota Bene: n—number of participants; <sup>\*</sup>Differences are valid for the 5-year monitoring,  $\chi^2$  criterion being applied. Among the excluded after 5 years, there was no data for 42 in the reference group and 18 in the test group. Mortality (M) was higher in the reference group ( $\chi^2 = 13.3$ , p = 0.00). The cases of recurrent myocardial infarction (rMI) were higher in the reference group, compared to the test group ( $\chi^2 = 13.3$ , p = 0.00).

(75% and 50% of reference and test groups respectively), with MI anterior localization (75% of the reference group, 50% of the test group). Eighty three percent (83%) of the patients of both groups were deceased within the first 12 months of monitoring. Our results are similar to the data previously reported by Goldberg *et al.* [11] and Capewell *et al.* [12].

Overall, the 5-year outcome is rather contrasting: rMI was reported in 45 patients of the reference group (14.0%), as compared to 17 patients of the test group (5.4%). The  $\chi^2$  criterion was applied to prove statistically, the considerable decrease in rMI eventuality in HBOT-treated patients during the 5-year period following acute MI ( $\chi^2 = 13.3$ , p = 0.00).

As we have shown earlier the rate of rMI in patients, who received HBOT as additional treatment, was significantly lower, than those, who did not. At the same time, rMI within the 2-year period was remarkably unbalanced: the first 6 months following acute MI is found to be the most unfavorable [34]. The results of this present research confirm our previous data [34], but with a very much higher statistical significance.

Similarly, during the study period, 50 MI-suffered patients of the reference group were deceased due to comorbidity (from total causes) (survival rate—84.4%).

When treating with HBOT, 13 patients were deceased during 5 years, also from total causes (survival rate—95.9%). In the previous study [34], the 2-year survival rate was 86.2% for the reference group and 94.7% for the test group. However, the difference was found to be statistically invalid ( $p > 0.05$ ). This was probably due to uneven distribution of mortality cases within the 2-year monitoring period. In the present study, statistical power was much higher; we managed to gain statistical difference ( $\chi^2 = 23.1$ ,  $p < 0.05$ ). However, we should mention that time inequality had played a role: mortality was at its peak during the first 6 months after the MI.

#### 4. DISCUSSION

In general, application of hyperbaric oxygen to acute MI treatment provides for rMI reduction (by ~8%) and 5-year survival rate increase (~11%) in post-MI patients. In discussing the study outcome, it is essential to pay special attention to some conditions. First, rMI eventuality and post-MI mortality rate in the reference group patients are similar to the generally known information [7,10,12,16]; some differences may be found due to peculiarities of the group organized, which is subject to exclusion criteria. The first half-year following acute MI attack is also well known to be the most life-dangerous period.

Presently, the question about hyperbaric oxygenation application for the treatment of MI remains controversial [21]. Our results confirm the point of view, that early HBOT application in MI patients, results in faster eradication of misbalanced oxygen myocardial need and delivery, which contributes to MI area reduction, scar healing with “softer” collagen tissue, aneurysm prevention [28,35]. It has been demonstrated in an experimental condition that the influence of hyperbaric oxygenation prevents the development of hypercoagulation syndrome [36], HBOT application immediately after coronary occlusion reduces myocardial necrosis and acute mortality in rats [37]. The beneficial effects of HBOT in treating ischemia-related wounds may be mediated by stimulating angiogenesis [27]. In addition, HBOT effects are characterized with concentration reduction of adrenaline, norepinephrine, biogenic amines, by myocardial electric homogeneity stabilization, by increased antioxidative protection followed by lipid reduced peroxidation and cytoprotection in early monitoring period [15,18,19,28,38]. On the other hand, results of experiment reveal that the use of HBOT induces catalase-activity and reduces infarct size in ischemic rat myocardium [39]. After 6 - 8 months, HBOT adaptation effects fade, and HBOT-treated post-MI patients' rMI and survival rate tend to demonstrate similar characteristics, as compared to patients treated with traditional pharmacotherapy.

In other words, HBOT is indispensable for the first half-year following MI to reduce rMI and increase the survival rate. We have used HBOT at a pressure lower than in traditionally applied ones (0.03 MPa). We opine that use of excessive dosage of oxygen (0.1 MPa) is irrelevant, in particular due to the activation of lipoperoxidation [40].

Ultimately, we are unable to make the decisive assessment on the data obtained by this study. However, the test group patients' lives actually saved can serve a good recommendation to introduce HBOT therapy, at least to treat acute MI, subject to patients' strict selection. Any further investigations might benefit specific clinical practice and experience in this issue.

A systematic review of hyperbaric oxygen therapy for acute coronary syndrome in the Cochrane Database showed that HBOT followed by an episode of acute coronary syndrome reduces the risk of death, re-infarction, dysrhythmias. However, the small number of studies, the modest numbers of patients, and the methodological and reporting inadequacies of the primary studies demand a cautious interpretation. Thus, the adjunctive application of HBOT in these patients cannot be recommended to be introduced into routine clinical practice [41].

#### 5. CONCLUSION

In conclusion, the present study showed that HBOT application that accompanied the acute MI traditional pharmacotherapy was proved to reduce rMI within 5 years following inpatient discharge (rate of rMI was 14% in the reference group and 5.4% in the test group,  $\chi^2 = 13.3$ ,  $p < 0.05$ ). Therefore, the joint application of HBOT and traditional method in treating acute MI makes it possible to raise the 5-year survival rate from 84.4% up to 95.9%.

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