

# Improvement of Ischemic Non-Healing Wounds Following Hyperoxygenation: The Experience at Rambam-Elisha Hyperbaric Center in Israel, 1998–2007

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**ABSTRACT:** **Background:** Wounds of the lower extremities are a significant public health problem, being severe and costly to treat. Adjunctive treatment with hyperbaric oxygenation (HBOT) has proven to be a useful and cost-effective means of treating ischemic wounds, mainly in diabetic patients.

**Objectives:** To describe patients with ischemic wounds treated at the Rambam and Elisha Hyperbaric Medical Center and their wound improvement following HBOT.

**Methods:** We conducted a retrospective cohort study of all patients (N=385) treated in the center during 1998–2007 for ischemic non-healing wounds in the lower extremities.

**Results:** The mean age of the patients was 61.9 years (SD 13.97). Most of them were diabetic (69.6%) and male (68.8%). Half of the subjects had a wound for more than 3 months prior to undergoing pre-HBOT transcutaneous oximetry (TcPO<sub>2</sub>) testing. Most of the wounds were classified as Wagner degree 1 or 2 (39.1% and 46.2% respectively). The median number of treatments per patient was 29. Only 63.1% of patients had continuous treatments. Approximately 20% of patients experienced mild side effects. An improvement occurred in 282 patients (77.7%) following HBOT: 15.2% fully recovered, 42.7% showed a significant improvement (and were expected to heal spontaneously), and 19.8% a slight improvement.

**Conclusions:** HBOT can benefit the treatment of non-healing ischemic wounds (especially when aided by pretreatment TcPO<sub>2</sub> evaluation; data not shown). Our experience shows that this procedure is safe and contributes to wound healing.

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**KEY WORDS:** hyperbaric oxygenation, ischemic wound, non-healing wound, diabetic wound, transcutaneous oximetry

elderly populations (aged > 65) are increasing, and range from 3% to 5% [2]. In 1998, the long-term cost of treating a patient with an ischemic wound was \$27,203. The estimated resultant rates of amputation – a procedure associated with high mortality – ranged from 2.8 to 43.9 per 100,000/year [1].

Hyperbaric oxygenation treatment involves the use of 100% oxygen breathed in a chamber with ambient pressure above 1 atmosphere absolute (ATA). The beneficial effects of HBOT include intermittent correction of wound hypoxia, reduction of tissue edema, enhanced host immune response, improved wound metabolism, prevention of re-perfusion injury, and induction of cytokine and cytokine receptors [3]. Since tissue hypoxia is the key feature in many patients with non-healing wounds, the marked increase in tissue oxygen gradient from blood to ischemic tissue under hyperbaric oxygen conditions is the main mechanism whereby HBOT can improve cellular oxygenation. This occurs even when the tissue perfusion rate is low. Thus, HBOT can make a major contribution to the treatment of non-healing wounds. Detailed descriptions of HBOT and its rationale for treating non-healing wounds have been reported previously [4,5].

Complications of HBOT are minor when trained personnel are involved; they include ear barotrauma, transient myopia and claustrophobia. Central nervous system oxygen toxicity is very rare. The only absolute contraindication for HBOT is tension pneumothorax [3].

Adjunctive HBOT has been demonstrated to be useful and cost-effective mainly in diabetic patients [6,7]. It has been recommended by health agencies and organizations worldwide and has been included in Israel's 'basket of health services' since 1986 [8,9]. The present article describes the patients with ischemic wounds who were treated at the Rambam and Elisha Hyperbaric Medical Center and their wound improvement following HBOT.

HBOT = hyperbaric oxygenation treatment

**W**ounds in the lower extremities represent a significant problem, with implications for both the individual and the health care system [1]. Prevalence rates among western

**PATIENTS AND METHODS**

We conducted a retrospective cohort study at Rambam and Elisha Hospitals' Hyperbaric Medical Center. This center is the only facility in northern Israel that treats patients with chronic indications for HBOT. Candidates for HBOT undergo large vessel assessment, physical examination by a physician at the center, and an assessment of wound ischemia by transcutaneous oximetry. Patients receive daily HBO treatments 5 days a week. Each treatment takes 90 minutes after which a nurse dresses the wound. The number of HBO treatments is determined for each patient individually based on clinical findings and progress, usually after 15 treatments. In addition, patients are examined by a plastic surgeon once a week and the wounds are photographed and sketched.

The study group comprised all 385 patients with lower extremity ischemic non-healing wounds who were treated in our center during a 10 year period: 1 January 1998 to 1 March 2007. The study was approved by the ethics committee of Rambam Medical Center, the largest university-affiliated hospital in northern Israel.

**DATA COLLECTION AND VARIABLES DEFINITION**

Data collection was based on the patients' medical and nursing records in the hyperbaric center. Records were reviewed by one of the study investigators (Y.F.I.), a nurse from the center, who used a specifically designed study questionnaire.

**DEMOGRAPHIC FACTORS**

Data on age, gender, ethnicity, socioeconomic status and employment status were gathered. Socioeconomic status was determined using the Israel Bureau of Statistics classification of local authority clusters [10]. Clusters 1–5 were considered low socioeconomic status, 6–7 moderate and 8–10 high. Employment status was based on whether the patient was documented as employed or not.

**CLINICAL FACTORS**

Clinical variables included documentation of diabetes, its duration (long/short) and treatment (diet/medication/insulin). The duration was considered short if the patient had diabetes for less than 5 years or if no complications were documented. In cases where a patient received more than one type of diabetes therapy, the more invasive one was recorded.

Additional factors were presence or absence of neuropathy, hypertension, heart disease, previous stroke, hyperlipidemia, peripheral artery disease, kidney disease, hypercoagulability, anemia, pain and mobility. Smoking status was categorized as never smoked, formerly smoked, or currently smoked. Body mass index was calculated based on weight and height (kg/m<sup>2</sup>).

**WOUND ASSESSMENT**

- Ischemic non-healing wound was defined as a radionecrosis wound or a wound with osteomyelitis, or if the patient had TcPO<sub>2</sub> values < 40 mmHg while breathing air at sea level. If the patient had more than one wound, the most severe one was selected.
- TcPO<sub>2</sub> was measured by a Novametrix 860 device with a single electrode attached near the patient's wound [Figure 1]. The values were recorded in three consecutive conditions: breathing air at sea level, breathing oxygen at sea level (10 min) and breathing oxygen at 2 or 2.4 ATA (at 0, 5, 10 and 15 min after reaching that pressure).

The following wound characteristics related to the period beginning 2 weeks before the first HBOT administration and ending 1 week thereafter:

- Wound infection was noted if antibiotics were taken following signs of infection or positive culture results
- Wound osteomyelitis was defined based on the presence or suspicion of bone infection or positive biopsy, bone scan, X-ray or magnetic resonance imaging findings
- Wound appearance was classified based on the plastic surgeon's examination: a) wound covered with scar, b) wound covered with good granulation tissue, c) partial granulation, d) no granulation and/or wound covered with fibrin, e) necrosis at the base of the wound or wound covered with an eschar
- The depth of the wound was determined according to the Wagner grading scale of six categories: 0 – no open wound,

TcPO<sub>2</sub> = transcutaneous oximetry

**Figure 1.** TcPO<sub>2</sub> criteria for HBOT in the Rambam and Elisha Hospitals' Hyperbaric Center



Breathing air at sea level: TcPO<sub>2</sub> < 40 mmHg  
 Breathing 100% oxygen: 10% increase in TcPO<sub>2</sub> values after 10 min  
 Breathing 100% oxygen at 2–2.4 ATA: TcPO<sub>2</sub> > 200 mmHg

ATA = atmosphere absolute

1 – superficial involving skin only, 2 – involving bones or tendons, 3 – involving bones or tendons with infection, 4 – necrosis at digit or foot requiring local amputation, 5 – extensive gangrene requiring amputation below the knee. The depth of the wound was used to determine wound severity

- Surface area of wounds was the sum of all the patient's wounds (cm<sup>2</sup>) measured at admission and based on medical data
- Additional wound parameters documented were: wound location, presence of edema, secretion, duration of wound until TcPO<sub>2</sub> testing (months), history of past wounds (yes/no), number of wounds, amputation and vascular surgery.

#### TREATMENT CHARACTERISTICS

The number of treatments and continuity of treatments were recorded. Treatments were defined as non-continuous when the following interruptions occurred: the patient missed 5 consecutive days of HBOT or the patient received fewer than four treatments per week for two or more consecutive weeks [11].

#### OUTCOME MEASURES

- Wound improvement was determined at the end of the HBO treatments (a week before and up to 2 weeks after the last treatment). Wound improvement was classified as 'full recovery', 'significant improvement', or 'slight improvement'. Full recovery was documented when the wound was completely epithelialized or had been successfully closed with a skin graft. Significant improvement was documented when the wound was covered with granulation tissue or had a demarcation line, and a physician's note stating that it was expected to heal spontaneously. Another scenario included a note that it was expected to heal completely following a skin graft. Slight improvement was documented when there had been an improvement in the wound's characteristics (i.e., depth, appearance, area, secretion), when the wound was partially closed by a skin graft, or when a demarcation line was present but the wound was not expected to heal spontaneously. Wounds described as 'no change', 'worsened' or 'amputated' were classified as 'not improved'.
- Direct side effects of the HBO recorded during a treatment session included barotrauma, oxygen poisoning, hypoglycemia, lung edema, sinus crush, visual disturbances, anxiety and arrhythmia.
- Outcomes related to the lower extremities included the occurrence of new wounds, infections or osteomyelitis a week after starting HBOT and up to a week following its completion.

#### STATISTICAL ANALYSIS

A pretest was initially conducted on 30 randomly selected records. After completing the data collection, logic and reliability tests were run. Reliability was checked by a blinded data collection of nine randomly selected records. Kappa

and intra-class correlation was calculated for categorical and continuous variables respectively.

Categorical data are presented by numbers and percentages, and continuous variables by range, mean and standard deviation. The median is presented when appropriate. Analyses were performed using SPSS, version 13.0.

## RESULTS

The study population treated in our facility (1998–2007) and who met our research criteria numbered 385 patients. The mean age of the population was 61.9 years (SD=14.0) and most of them were males (68.8%). Additional sociodemographic characteristics are shown in Table 1.

The majority of patients were diabetic (69.6%), had long disease duration (63.8%), and were treated with diet (5.7%), hypoglycemic agents (50.9%) and insulin (43.4%). About half the patients had peripheral artery disease (45.5%) and most of them were either non-smokers or former smokers (43.4%, 38.2% respectively). Most of the patients were overweight (29.5%) or obese (28.5%). Almost half the patients (45.5%) needed assistance in mobility and 60.0% reported pain. Additional clinical characteristics are presented in Table 2.

At admission the total number of lower extremity wounds for each patient was one or two (a median of one wound). The surface area of wounds per patient ranged from 0.25 to 187 cm<sup>2</sup> (median 9.5 cm<sup>2</sup>). In about 85% the wounds were classified as Wagner grade 1 or 2. In half the patients the most severe wound prevailed for at least 3 months prior to TcPO<sub>2</sub> testing. At admission, a third of the patients (32.3%)

**Table 1.** Sociodemographic characteristics of the study population (N=385)\*

Variable	Category	No.	%
Age (yrs)	< 50	67	17.4
	50–64	118	30.6
	65–74	139	36.1
	≥ 75	61	15.8
Gender	Male	265	68.8
	Female	120	31.2
Ethnicity	Jewish and other	334	86.8
	Arab	51	13.2
Socioeconomic status**	Low	194	50.7
	Moderate	180	47.0
	High	9	2.3
Employment**	Employed	96	25.4
	Unemployed	282	74.6

\*Missing values are excluded

\*\*See definitions in study methods

**Table 2.** Medical conditions of the study population (N=385)\*

Variable	Category	No.	%
Diabetes	Yes	268	69.6
	No	117	30.4
Hypertension	Yes	279	72.5
	No	106	27.5
Heart disease	Yes	191	49.6
	No	194	50.4
Previous stroke	Yes	54	14.0
	No	331	86.0
Hyperlipidemia	Yes	161	41.8
	No	224	58.2
Peripheral artery disease	Yes	175	45.5
	No	210	54.5
Kidney disease	Yes	84	21.8
	No	301	78.2
Hypercoagulability	Yes	19	4.9
	No	366	95.1
Anemia	Yes	156	40.5
	No	229	59.5
Neuropathy	Yes	79	20.5
	No	306	79.5

\*Missing values are excluded

had a history of amputation at the lower extremity with the most severe wound (the index extremity). Approximately a quarter (21.4%) of the patients underwent vascular surgery in the index extremity, 34.3% had an infection and 16.1% had osteomyelitis.

Most of the TcPO<sub>2</sub> measurements were conducted near a foot wound (78.1%), whereas the rest of the measurements were conducted near a leg wound. The median value of TcPO<sub>2</sub> near the wound, with the patient breathing air at sea level, was 20.0 mmHg, and while breathing pure oxygen at 2 or 2.4 ATA, after 10 min, was 515 mmHg. Other wound characteristics are shown in Table 3.

The number of treatments ranged from 1 to 115. The median number of treatments was 29 per patient. Only 63.1% of patients had continuous treatments.

Overall, 363 of 385 patients (94.3%) had a documented outcome: 282 (77.7%) showed improvement following HBOT, of whom 15.2% fully recovered, 42.7% showed a significant improvement and 19.8% a slight improvement. The rest of the patients had no change (6.1%), a worse outcome (4.1%), or underwent an amputation (12.1%). Most of the patients did not exhibit any side effects of HBOT (79.2%) and did not develop any new infection, wound or osteomyelitis (60.5%) during the treatment course.

**Table 3.** Clinical characteristics of wound and extremities at admission (N=385)\*

Variable	Category	No.	%
Wound appearance**	Good granulation	19	5.1
	Partial granulation	132	35.1
	No granulation and/or the wound is covered with fibrin	153	40.7
	The base of the wound is full with necrotizing tissue	72	19.1
Wound depth**	Superficial, without subcutaneous tissue	148	39.1
	Involvement of tendons or bones	175	46.2
	Involvement of tendons or bones with infection	45	11.9
	Digit gangrene with digit requiring local amputation	11	2.9
	Foot gangrene requiring below-knee amputation	0	0
Edema**	Yes	251	79.7
	No	64	20.3
Secretion**	No	7	2.6
	Low	51	19.2
	Moderate	121	45.7
	High	86	32.5
Past wounds	Yes	156	45.5
	No	187	54.5
Amputation**	Yes	124	32.3
	No	261	67.8
Amputation (other extremity)	Yes	63	16.4
	No	322	83.6
Vascular surgery**	Yes	82	21.4
	No	301	78.6
Infection**	Yes	132	34.3
	No	253	65.7
Osteomyelitis**	Yes	62	16.1
	No	323	83.9

\*Missing values are excluded

\*\* At the index extremity

## DISCUSSION

The present study describes the characteristics of Israeli patients who underwent HBOT for ischemic non-healing wounds in our facility during a 10 year period. The advanced age of the population (mean 61.9 years) receiving therapy is due to the higher incidence and prevalence rates of wounds in older people [2]. Similarly, in other studies on ischemic non-healing wounds, the age range was 60–68.9 years [8,12-14]. This finding mandates that the medical staff at the center address the special needs of older patients, such as improving accessibility, adjusting the medical and nursing care to patients' chronic illnesses and medications, providing clear guidance and careful monitoring with regard to side effects, assessing self-efficacy and giving emotional support.

The proportion of women receiving HBOT was significantly lower ( $P = 0.000$ , binomial test) than the proportion of women aged 50+ in the general population (31.2% vs. 54.3%, respectively) [15]. This lower proportion of women on HBOT was also reported elsewhere, with Fife et al. [11] documenting 42% and Faglia et al. [16] 27%. This finding is surprising given the known higher rates of chronic lower extremity wounds in women [17]. It might be the result of different medical care given to women (resulting in higher recovery rates, or higher amputation or death rates) and/or the result of different accessibility to HBOT.

As shown in Table 2, more than 70% of our patients suffered from various chronic illnesses that are known to affect wound healing. Artery and vein diseases, hypertension, hyperlipidemia, heart disease, diseases of lung, liver and kidney, hematologic and rheumatologic diseases, malignancies, immune deficiencies and drugs (chemotherapy) are documented risk factors for impaired healing [18]. Some of these factors are modifiable, such as anemia and smoking, and should be considered by primary care physicians prior to HBOT. It is not surprising that diabetic patients constitute the majority (69.6%) of our sample, since HBOT was previously demonstrated to be effective for ischemic non-healing wounds primarily in diabetic patients [12,19].

Our patients underwent on average 33.5 (SD 22.5) HBO treatments. Despite the similarity to findings and recommendations in the literature, our range of treatments was much wider (1–115), although a similar treatment range (15–108) was found by Wattel et al. [14]. This finding could be attributed to the different insurance policies in various countries. The optimal number of HBO treatments for ischemic non-healing wounds remains to be determined [3].

A large number of treatments is usually associated with a high risk of side effects, mainly transient myopia. Nevertheless, no such relationship was found in our study ( $P = 0.142$ , Mann-Whitney), with only 20.8% of patients demonstrating HBOT side effects, the most common being hypoglycemia (14.9%), barotrauma (12.5%, mostly very mild), anxiety (2.9%) and worsening of heart failure (2.1%, not related to hyperoxygenation). Only two patients (0.5%) had seizures, one due to hypoglycemia and the other to oxygen poisoning. The latter occurred when 2.4 ATA pressure was used; today the pressure employed at our facility is only 2 ATA. In other studies seizures were reported in up to 10% of patients [20]. In our study barotrauma was found in the lower limit of the range reported in other studies (3.8–37%) [12,21]. Other studies reported pneumothorax, vision disturbances and death due to seizures or lung edema, side effects that were absent in our patients [20]. It is important to note that the side effects of HBOT have a similar prevalence to that of other procedures [22]; of the 57 studies reporting serious side effects of therapy only 9 (15.8%) described wounds treated

with HBOT [20]. Some researchers reported absence of side effects [19]. Overall, HBOT is considered a safe procedure.

TcPO<sub>2</sub> values and their rate of increase under hyperbaric conditions are routinely used in our center to predict the response to HBOT since these measures reflect the microcirculatory support at the tissue level [23]. TcPO<sub>2</sub> values that do not reach 200 mmHg within 10 minutes of administering HBOT (a median value of 515 mmHg in the study) indicate insufficient microcirculatory support. It is difficult to compare our TcPO<sub>2</sub> results with those reported elsewhere, since many studies reported TcPO<sub>2</sub> values after their stabilization regardless of the time it took to reach these values. The high TcPO<sub>2</sub> values at entry are expected to predict healing success, and indeed, about 78% of our patients showed improvement.

Improvement following HBO treatments occurred in 282 (77.7%) of 363 patients with available outcome data. This positive outcome, manifested by slight improvement up to full wound recovery, relates, however, also to 20 patients with TcPO<sub>2</sub> values below 200 mmHg (after 10 minutes under hyperbaric conditions). According to the literature the latter patients are not candidates for HBOT since their chance of healing following treatment is relatively low [11]. They were given HBOT in an attempt to prevent amputation of the remaining leg (after a previous amputation). Only 12 (60%) of these 20 patients showed improvement. HBOT tends to be beneficial after at least 10 treatments. Twenty-seven of our patients received fewer than 10 treatments. Since these patients discontinued HBOT before achieving the beneficial effect, it is not surprising that only 15 (40.7%) improved. In a univariate logistic regression model, a one unit increase in the number of treatments was associated with a 1.04-fold increase in the rate of wound improvement ( $P = 0.000$ ). The improvement rate among patients (N=261) who had TcPO<sub>2</sub> values above 200 mmHg and who had at least 10 HBO treatments was 81.2%.

We found two studies, similar in methodology to ours, that reported slightly lower rates of wound improvement (73.8%, 70.4%) [8,13]. However, there are differences in the populations studied that make the comparison between improvement rates difficult.

It should be noted that wound severity in our study was relatively low in comparison to wounds described by others: wounds with Wagner grade 1 and 2 were prevalent in 39.1% and 46.2% of our patients, respectively. The parallel proportions among patients described by Fife and co-authors [8] were 60.1% and 16.8%. We believe, however, that ischemic wound, as proven by TcPO<sub>2</sub> values, will probably not heal spontaneously, regardless of its Wagner grade. Ischemia that is corrected in the early stage may prevent further wound deterioration. Our analysis shows that the median pre-entry wound duration was 3 months. The Israel Ministry of Health recommends treating non-healing wounds within 2 months

of standard therapy failure [9]; we posit that ischemic wounds be treated with HBOT as soon as possible, especially when using TcPO<sub>2</sub> results.

Although the present study was not a randomized controlled clinical trial on the effectiveness of HBOT, it seems that patients undergoing this adjunctive therapy have a good chance for wound improvement. Additional adjunctive therapies are suggested in the literature, such as ultrasound, electric stimulation, shock wave therapy, hydrotherapy, macrophages and vacuum-assisted closure [4,24,25]. The only adjunctive therapy that was reported to be effective in a randomized controlled clinical trial was vacuum-assisted closure [25]. Since the various studies on these therapies were conducted in different populations, on different types of wounds and used different definitions of healing or improvement, comparing their effectiveness is difficult.

**LIMITATIONS**

This study was based on good quality data, indicated by high Kappa and intra-class correlation values when reexamining records. It should be mentioned that in order to achieve accurate TcPO<sub>2</sub> measurements using one electrode only, the participation of clinically experienced professionals was required. The external validity of the study is compromised because the study was conducted in one center only.

**CONCLUSIONS**

HBOT can make a major contribution to the treatment of ischemic non-healing wounds (especially when aided by pre-treatment TcPO<sub>2</sub> evaluation; data not shown). Our experience demonstrates that this procedure provides a good chance for wound improvement and is safe.

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**“Parkinson's Fourth Law: The number of people in any working group tends to increase regardless of the amount of work to be done”**

C. Northcote Parkinson (1909-1993), British historian and author