Factors influencing the outcome of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy

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ABSTRACT

The objectives of this study were to report outcomes of a large number of patients receiving hyperbaric oxygen therapy (HBO_2T) for diabetic lower-extremity ulcers, and to identify likely outcome predictors. Five hyperbaric facilities supplied data on 1,006 patients. A sixth clinic served as a validation sample for the regression-based prediction model, and later additional data from Memorial Hermann Hospital were added. The severity of lower-extremity lesions was assessed upon initiation of HBO_2T using the Modified Wagner scale, and the outcome described as healed, partially healed, not improved, amputated, or died. Overall, 73.8% of patients improved (granulated or healed). Factors significantly related to outcome included renal failure, pack-year smoking history, transcutaneous oximetry, number of HBO_2T treatments, and interruption of treatment regimen. Number of treatments per week and treatment pressure (2.0 vs. 2.4 atmospheres absolute) were not significant factors in outcome. Concomitant administration of autologous growth factor gel did not improve outcome. A multiple regression model was fitted to the data that can be used to predict the outcome of diabetic patients undergoing HBO_2T. Given the high cost of amputation and rehabilitation, these data suggest that hyperbaric oxygen treatment should be an important adjunctive therapy to heal lower-extremity lesions, especially those with a Wagner grade of 3 or higher.

Hyperbaric oxygen therapy (HBO_2T) is the administration of oxygen at pressures greater than sea level and is administered by placing the entire patient inside a pressure vessel and allowing them to breathe oxygen. At a pressure of 2 atmospheres absolute (ata) the increase in plasma-dissolved oxygen from about 20 to 24 vol% results in an arterial pO_2 rise to about 1,400 mmHg, with soft tissue and muscle pO_2 levels correspondingly elevated. Tissue oxygen tensions are dose dependent on oxygen pressure and persist for several hours, which can instigate wound healing in hypoxic tissues by a variety of mechanisms, the most important of which is angiogenesis.[1–5] Stimulation of vascular endothelial growth factor (VEGF) is believed to be one of the factors that contributes to the initiation of angiogenesis.[6]

Many other processes are promoted by HBO_2T, including fibroblast replication, collagen synthesis, and the processes of neovascularization and epithelialization.[7–10] HBO_2T has been shown to up-regulate gene expression of platelet-derived growth factor (PDGF)-β receptor.[11] Finally, enhancement of oxygen levels at the cellular level improves leukocyte bactericidal activity against aerobic Gram-positive organisms, such as *Staphylococcus aureus*, aerobic Gram-negative organisms, and is cytotoxic toward anaerobic bacteria.[12–14] As a result, HBO_2T has found increasing use as a primary or adjunctive treatment in a number of wound-related conditions, including clostridial myositis and myonecrosis, necrotizing soft tissue infections, compromised skin grafts and flaps, crush injury, compartment syndrome, and other acute ischemias, soft tissue radionecrosis, and refractory osteomyelitis.

One specific application for which HBO_2T is particularly useful is the healing of high Wagner grade diabetic foot ulcers and prevention of lower extremity amputation. Several randomized, controlled trials have shown the benefit of HBO_2T in diabetic foot ulcer outcome,[15–20] for which Medicare and other third-party carriers will provide compensation. The economic and emotional costs of amputation and rehabilitation easily exceed the cost of HBO_2T when it is successful,[1] and the cost-benefit of HBO_2T is enhanced when patients who are unlikely to respond to it are excluded.

Transcutaneous oximetry appears to be the best procedure in selecting patients most likely to benefit from HBO_2T,[21] and works by noninvasively measuring the partial pressure of oxygen ($P_{tc}O_2$) through intact skin using a modified Clark electrode and a heated thermistor. Because the instrument cannot be used in the ulcer bed, adjacent measurements must be taken, and although these

are inexact, they can be useful in assessing the vascular supply to the area.

In a previous retrospective study reported in this journal,[22] we described the relationship between the measurement of transcutaneous oxygen tension under several conditions and the outcome of HBO_2T in the treatment of lower-extremity wounds in diabetic patients. We have now extended that study by segregating the patients by comorbidity factor, and further analyzed outcome, and outcome predictors using multivariate analysis.

MATERIALS AND METHODS

Patients and settings

Over a 7-month period, a single physician observer reviewed 1,006 diabetic patient records from five Texas hyperbaric facilities. All the charts in each facility were reviewed for details of medical history, treatment, outcome when HBO_2T was discontinued, and status at follow-up where available. Permission for the study was obtained from the Committee for the Protection of Human Subjects at The University of Texas Health Science Center (Houston) and from other participating units: the Southeast Texas Center for Wound Care and Hyperbaric Medicine, Conroe; the Jefferson C. Davis Wound Care and Hyperbaric Medicine Center at Methodist Hospital, San Antonio; the Wound Care and Hyperbaric Medicine Facility at Nix Medical Center, San Antonio; The University of Texas Medical Branch Hyperbaric Medicine Center, Galveston; and the Memorial Hermann Hospital Center for Hyperbaric Medicine at the University of Texas Health Science Center, Houston. In a separate data collection, a single nurse observer reviewed data from the Hyperbaric Medicine Department at Travis AFB in California.

Wound classification

The immediate cause of each of the three largest lesions was recorded, and categorized as follows: (1) spontaneous or not known, (2) postoperative, and (3) trauma. The severity of each lower extremity wound was assessed using the Wagner grading scale as modified by Kominsky[23]: Grade II—superficial ulcer; Grade III—deep ulcer to tendon, capsule, or bone; Grade IV—deep ulcer with abscess, osteomyelitis, or joint sepsis; Grade V—localized gangrene of forefoot or heel; and Grade VI—gangrene of the entire foot. If a Wagner grade was not designated in the record, the reviewer studied the description of the wound and photographs taken at the time the patient was initially evaluated—photographs taken at the time of consultation were available in over 99% of patients—and determined it. The outcome was similarly determined and assigned to one of four categories: (1) amputated, (2) not improved, (3) partially healed, and (4) healed. The category of *healed* was used only for complete epithelialization, while the category of *partially healed* represented a broad range of response, from minimal granulation to almost completely healed.

Treatments and transcutaneous oxygen measurement

In terms of standard care, the practices were similar at all clinics with the following exceptions: (1) at Hermann Memorial the hyperbaric treatment pressure was 2 vs. 2.4 ata for all others; and (b) the use of Procuren was a standard care practice at Conroe, whereas at the other clinics it was not used. However, the majority of patients at Conroe did not receive Procuren because they did not meet the minimum transcutaneous oxygen value of 30 mmHg.

Patients usually underwent HBO_2T at least 5 days a week. An interruption in treatment was arbitrarily defined as receiving three or fewer treatments per week for 2 or more weeks, or missing five consecutive treatments.

Transcutaneous oxygen was measured next to the wound and recorded under three conditions: while breathing air at sea level ($P_{tc}O_2$ [Air]; available in 84% of patients), while breathing oxygen at sea level ($P_{tc}O_2$ [O_2]; available in 65% of patients), and while breathing oxygen in the hyperbaric chamber ($P_{tc}O_2$ [HBO_2]; available in 16.8% of patients). When multiple $P_{tc}O_2$ measurements were recorded, the value obtained closest to the lesion was selected. If there were two immediately adjacent values, the lowest value was selected.

Multivariate analysis

Individual categorical factors believed to be clinically important to the outcome were initially evaluated by tabulating the factor vs. outcome, and assessing significance by χ^2 tests. Factors with p-values ≤ 0.10 were passed onto a second stage in which the factors were evaluated concurrently with regard to their influence on outcome through multivariate analysis. In the multivariate analysis, the outcome category (1=amputated, 2=no healing, 3=some healing, and 4=complete healing) did not provide the best method of scoring the outcome. One reason is that the use of the numbers 1–4 implies equal distance between categories. Clearly the categories of *some healing* and *complete healing* are much better than *amputation* or *no healing*. In addition, patients classified into category 3 (some healing) were nonhomogenous; some were closer to no healing and others were closer to complete healing. As a consequence, the score used in the regression analysis was revised to employ the natural logarithm of the category rank, which also made it congruent with the statistical practice of constructing log–linear, log–log, and logistic regression response models. The logarithmic transformation makes *partially healed* [3] closer to *completely healed* [4] than *no healing* [2], and far away from *amputated* [1]. The score was used to define the outcome response in regression, and the other variables were used to "explain" the numerical level of the score.

RESULTS

General

In the initial 5-clinic data set, the outcomes of 35 patients were not verbally recorded in the charts, nor were their discharge photos available. Nine people also died during the course of treatment. Although none died from their wounds, because we could not determine if the cause of death influenced the wound healing process, these patients were deleted from the database, as this was a small number in comparison with *N*. This left 971 patients whose

outcome responses could be analyzed, with an overall 73.8% (717/971) of the patients being improved.

There were no differences in outcomes between males and females. Women constituted 41.7% of the total population, and this percentage was virtually constant across all admitting centers. Racial and ethnic percentages, however, differed widely among the five facilities. Hispanics, known to have a predisposition for diabetes, comprised a large subgroup (43%) in this study, primarily because 53% of the patients were from San Antonio, where the population is predominantly Hispanic. Nevertheless, there were no differences in the number of wounds per patient, in wound severity, or in the propensity to have an interrupted treatment program (12% overall) that could be ascribed to racial factors. In addition, the treatment outcome was not significantly different among racial groups.

Follow-up information was available on 602 patients whose treatment ended with either no healing, partial healing, or complete healing. These follow-up studies were encouraging, but the follow-up time (median=3 weeks) was too soon after discharge to be a convincing predictor of outcome stability. Nevertheless, during this brief period, there was a high rate of death or amputation among those with no healing (45%), and a low rate among those who were healed or partially healed at discharge (3.7%).

Patients who improved after hyperbaric oxygen therapy received a mean of 34 treatments, whereas those who did not received a mean of 24. This probably was a result of early HBO_2T discontinuation in those patients who did not appear to be improving.

It should also be noted that for many parameters in this study that the number of patients for which these parameters were recorded differs slightly, as is reflected in the results.

Screening for factors related to outcome

Renal failure (RF)

There was a large difference in the patterns of initial conditions and outcome between the group with renal failure (n=136) whose patients were receiving dialysis or had kidney transplants (RF), and the nonrenal failure (NRF) group (n=835). These differences are summarized in Table 1.

Although the percentage of transplant patients that improved was higher (74%) when compared with patients undergoing dialysis (58%), this result was not significant. If the numbers of transplant patients had been higher, however, the result would likely have been significant.

Only 79 of 136 (58%) RF patients improved after HBO_2T treatments compared with 638 of 835 (76%) for the NRF patients. This difference was found to be significant using the t-test of differences in proportions ($p < 0.00001$). The number of lesions was highly correlated with outcome among RF patients: in patients with one lesion, 65 of 91 (71%) were improved, whereas in patients with two or more lesions, only 14 of 45 (30%) were improved. Among the NRF patients there was no such striking pattern, although as the number of lesions increased, the likelihood of improvement tended to be reduced. The influence of the maximum modified Wagner score from the worst three wounds was significantly related to outcome in both groups with p-values of < 0.001, but was more pronounced among RF patients. The effect of an interrupted treatment regimen was also more pronounced among RF patients, but this could be a spurious artifact of a small sample size as only 19 of the 136 RF patients had an interrupted regimen. The interruption rate was similar in both groups (14% RF; 12% NRF).

Because the differences between the two groups were so pronounced, the RF patients were removed from the subsequent statistical analyses to avoid confounding the results of the NRF patients who form the focus of the study. In addition, the RF group did not constitute a sufficiently large sample to be analyzed separately in the multivariate models.

Table 1. Metric averages for the renal failure and non-renal failure groups

Category	Metric	Patients in RF[1] group (sample size)	Patients in NRF[2] group (sample size)
Healed	Age	51.10 (17)[5]	64.57 (128)[5]
	Duration of diabetes	23.67 (6)	17.17 (46)
	$P_{tc}O_2$ (Air)[3]	27.62 (13)	21.94 (90)
	$P_{tc}O_2$ (O_2)[4]	53.53 (13)	85.52 (86)
Partially healed	Age	58.14 (62)[5]	62.29 (510)[5]
	Duration of diabetes	21.32 (62)	16.63 (263)
	$P_{tc}O_2$ (Air)[3]	24.45 (51)	24.32 (374)
	$P_{tc}O_2$ (O_2)[4]	93.49 (39)	105.82 (322)
No healing	Age	55.79 (16)[5]	65.51 (53)[5]
	Duration of diabetes	26.22 (9)	18.07 (30)
	$P_{tc}O_2$ (Air)[3]	25.91 (11)	19.62 (42)
	$P_{tc}O_2$ (O_2)[4]	45.20 (10)	98.21 (29)
Amputation	Age	59.32 (41)[5]	64.53 (144)[5]
	Duration of diabetes	22.31 (27)	19.05 (75)
	$P_{tc}O_2$ (Air)[3]	17.36 (28)	16.96 (120)
	$P_{tc}O_2$ (O_2)[4]	64.96 (24)	54.60 (93)

[1]Renal failure.
[2]Nonrenal failure.
[3]Transcutaneous oxygenation breathing air.
[4]Transcutaneous oxygenation breathing O_2.
[5]N for each category of patients; duration of diabetes, and $P_{tc}O_2$ (air or O_2) are only available for some patients; age and duration of diabetes values are in years; $P_{tc}O_2$ (Air) and $P_{tc}O_2$ (O_2) values are in mmHg.

Insulin dependency

Of the 866 NRF patients, 69.8% were insulin dependent. The failure rates of both groups were similar to the average

failure rate of 23.6%, and hence there was no significant difference in the outcome based upon this characteristic ($p=0.79$).

Autologous growth factor treatment

Autologous growth factors, manufactured from the patient's own blood (''Procuren,'' available at the time from Curative Technologies Inc, Minneapolis, MN), were employed in some of the patients at Conroe. Of the 866 patients without RF, 194 had growth factors. Eighty-four percent of patients having HBO_2T plus Procuren were designated as having improved or healed at the time HBO_2T was discontinued, compared with 74% of the patients who were not treated with growth factors. Further analysis, though, showed that the two patient populations differed: patients receiving Procuren had baseline transcutaneous oximetry measurements that were 19% higher than patients who did not have growth factors. This finding is consistent with protocols for the use of growth factors, which recommend a minimum transcutaneous value of 30 mmHg before initiation of Procuren. However, patients treated with Procuren received 53% more hyperbaric treatments for the same outcome compared with patients who did not receive autologous growth factor gel. When Procuren patients were compared with the other patients with similar transcutaneous values, wound severity, and other factors, there was no difference in the outcome between the two groups, suggesting that Procuren had no beneficial effect on the outcome. Because patients receiving Procuren received significantly more hyperbaric treatments, they were removed from the database to avoid confounding the results for ''standard care'' patients. Procuren patients represented 23% of the data, but their removal did not adversely affect the quality of the results because 641 patients remained for analysis.

Lower extremity neuropathy

Lower extremity neuropathy was recorded for 355 patients in the NRF group. Only 22.5% were deemed ''normal''; 68.2% were classified as decreased sensation; and 9.3% were classified as insensate. The correlation with outcome was not statistically significant ($p=0.16$), but the insensate category had twice the amputation rate of the other two categories (30.3 vs. 15%).

Treatment frequency

Of the 835 NRF patients, only 6.7% received more than one treatment per day. The frequency of treatment was moderately related to the outcome ($p=0.07$) in such a manner that those who received twice-a-day treatments fared worse. It is very likely that the increased frequency was a reaction to a condition perceived as more serious, or to a deteriorating condition.

Smoking

Data regarding smoking were available in 604 NRF patients. Within this group, 281 patients had never smoked, 276 were former smokers, and 47 were current smokers. The failure rates were 21.4, 26.4, and 23.4%, respectively, and were not significantly different ($p=0.38$). Patients who had a >40 pack-year history had a significantly worse outcome than patients with <40 pack-years, or those who had never smoked. Computer modeling showed that the effect of 10 or fewer pack-years was indistinguishable from the nonsmoking group with regard to outcome score, whereas for 10–100 pack-years, the effect was linear, and above 100 it was flat. This observation has been published in detail.[24]

Transcutaneous oximetry

The details of the transcutaneous oximetry findings have been previously published.[22] Experience showed that 25 mmHg was the best breakpoint to discriminate between patients who improved and those who did not improve, using either χ^2 tests or odds ratios. One-dimensional analysis does not yield adequate guidance. However, improvements can be made by adding other factors, such as the amount of increase in the sea-level oxygen challenge, Wagner grade of the wound, or in-chamber $P_{tc}O_2$. For example, our data indicated that if the baseline $P_{tc}O_2$ (Air) was 25 mmHg or less, and the transcutaneous values did not increase by more than 20 mmHg while breathing pure oxygen at sea level, the failure rate was 42.9% (54/126), while those patients outside of this window had a much smaller failure rate of 20.9% (78/373). But the false-negative rate is too large (57.1%) for this result to be useful, and if one tries to develop simple cutoff scores from more than two dimensions, both the analysis and application become more difficult.

Figure 1 shows the distribution of $P_{tc}O_2$ (Air) measurements (in air at sea level, mmHg) for 516 patients. However, a value of 25 mmHg would prove inadequate as a filtering criterion for HBO_2T in this data set as 61.8% of the patients in this study had values of 25 mmHg or lower. Indeed, the median value was 18 mmHg. Instead, in-chamber transcutaneous oximetry proved the most accurate single factor in predicting outcome. Thus, patients with an in-chamber $P_{tc}O_2$ (HBO_2) <100 mmHg had a

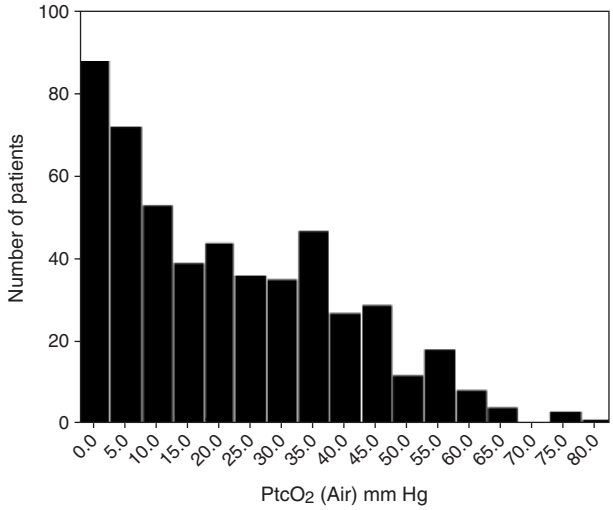

Figure 1. Transcutaneous oxygenation adjacent to the lesion ($P_{tc}O_2$ [Air] measurements). Mean=21.3; SD=17.9; $N=516$.

14% likelihood of benefit while patients with an in-chamber $P_{tc}O_2$ (HBO_2) > 200 mmHg had an 84% chance of benefit. However, it must be stated that the accuracy of these values as predictors of outcome was only 75%.

Wound severity and number

The number of wounds being treated concurrently was not related to the outcome recorded for the worst wound in standard care patients (no RF and no Procuren), but was correlated with treatment failure for RF patients. The modified Wagner score was the primary measure of wound severity in this study, and this was also a highly significant factor in determining the outcome ($p < 0.001$). Table 2 shows the results for standard care patients.

Prior amputations

Of the 641 standard care patients, 57.6% had at least one prior amputation, but there was no significant difference in outcome compared with the group with no prior amputation ($p=0.48$).

Other factors

Other potentially important outcome determinants, such as osteomyelitis, whether the affected extremity was offloaded, and retinopathy were inconclusive in this study, because they had too low a reporting rate.

Final data set

Table 3 shows the numbers for starting and final populations of the study, and the subpopulations that were removed.

Multiple regression analysis of outcome predictors

No single hospital recorded all 137 types of information. As a consequence, the data were highly unbalanced in the measurement of many potential indicators of outcome success, and this reduced the scope of multivariate analyses that could be conducted. While multivariate analysis allows the interactions between factors to be investigated and modeled, every factor entered into the analysis further decreases the number of patients in the surviving database. Thus, two multivariate methods were evaluated: ordered logistic regression and multiple regression. The ordered logistic regression preserved the categorical nature of the outcomes, but performed worse in predicting the outcome compared with multiple regression, which treated the outcome values as points on a continuous wellness scale. Consequently, the remainder of the models were developed using ordinary least-squares multiple-regression procedures.

The most important individual variables were the first to be included in the multiple regression model. The patient's age and the duration of diabetes were not significant when used separately and were highly correlated (older persons tend to have a longer history of diabetes). An improved model was constructed using a single variable (DURAGE) that was the sum of the two numbers. This was superior to the product of the numbers or using both variables plus interaction (the product), and which suggests the measurement of a physiological age. Other important variables were the maximal modified Wagner score over the worst three wounds, the number hyperbaric treatments administered, $P_{tc}O_2$ (Air), the ramp function for pack-years of smoking, and interruption of the treatment regimen (yes/no). Details of the regression equation and *p*-values are reported in Table 4. While all factors listed are statistically significant, the Wagner score and the number of

Table 2. Modified Wagner score effects for the standard care patients

Wagner score	Observations	% Helped[1]	HBO_2T (mean number)
1	3	100.0	10.0
2	130	83.8	26.4
3	465	77.2	27.4
4	138	64.5	29.0
5	38	28.9	23.9

[1]''Helped'' is defined as being healed or partially healed.

Table 3. Numbers of populations for starting and final datasets and subgroup populations removed

Description of population	*n*	*N* after population removal
Starting dataset	1,015	—
Patients who died during treatment	9	1,006
No outcome record	35	971
Renal failure patients	136	835
Growth factor patients	194	641
Final dataset (standard care patients)	641	—

Table 4. Predicted outcome score

Coefficient	Variable	*p*-value
+0.2087	Ln (HBO_2Ts +1)[1]	0.0002
+0.0040	$P_{tc}O_2$ (Air)[2]	0.0152
−0.0035	Ramp10[3]	0.0175
−0.1527	WGMAX[4]	0.0003
−0.0041	DURAGE[5]	0.0295
−0.1907	Interrupted[6]	0.0267

Equation form=coefficient (variable)+0.98061; $N=180$; $R^2=22.8\%$; standard error=0.4095.
[1]HBO_2T function.
[2]Transcutaneous oxygen in air.
[3]Function for pack-years of smoking.
[4]Maximal Wagner grade.
[5]Age+duration of diabetes.
[6]Interruption of the treatment regimen.

hyperbaric treatments had the smallest *p*-values and thus were the ones most highly related to healing. The HBO_2T factor was nonlinear and a logarithm transformation captured the fact that as the number of HBO_2Ts increased, the marginal benefit decreased.

The model performance was evaluated by how accurately the predicted outcomes matched the observed outcomes. The initial outcome number coding was scored so that an increasing number implied a better outcome. Therefore, scores 1 and 2 represented failures, three represented partial healing, and four represented complete healing. As the natural logarithm of 2 is 0.69, and that of 2.5 is 0.92, the predicted score was interpreted as predicting a failure if it was 0.69 or less; a possible success if between 0.69 and 0.91; and a probable success if 0.92 or greater. This was compared with the actual outcome coded as either success or failure (not helped). From Table 5 it can be seen that the model predicts success with greater reliability than it predicts failure. Nevertheless, the model does better at predicting failure than any other simple model that was tried.

Figure 2 shows the expected trajectory of a patient (characteristics are listed with the figure). Some improvement should be visible after 12 treatments, while the maximum number of treatments to effect significant healing should be 30–35 for this patient.

Figure 3 shows the effects of interrupted treatment based upon regression model results, while Table 6 compares the statistics of interrupted treatments with noninterrupted treatments.

Expanded database

After the regression model was fitted, a new database was created with the addition of 80 patient records obtained from Travis Air Force Base (AFB) and 59 patient records from Memorial Hermann Hospital. This new database consisted of 780 non-RF, standard care patients (641 standard care from the first five clinics+80+59). The patient data set from Travis AFB was collected specifically as a sample to validate the regression model by comparing the model prediction against the analysis of the Travis AFB data set. Several of the initial findings were revisited with the larger database.

X-ray confirmed osteomyelitis

A subset of 164 patients had radiographic evaluation, obtained to evaluate possible osteomyelitis. The rationale for HBO_2T in these patients was to increase bone oxygen levels as an adjunct to aggressive antibiotic treatment, rather than to reverse wound hypoxia. Although the x-ray results did not correlate with the ultimate outcome, they did exhibit a pattern of association with the $P_{tc}O_2$ (Air) measurements. Patients with radiographically confirmed osteomyelitis were more likely to have higher $P_{tc}O_2$ (Air) readings, thus exaggerating the prospect of healing ($p=0.064$).

Table 5. Multivariate model performance

Category	% correct	% misclassified
Probable failure	24/39=61.5	38.5
Possible success	41/65=63.1	36.9
Probable success	69/76=90.8	9.2
Overall	134/180=74.4	25.6

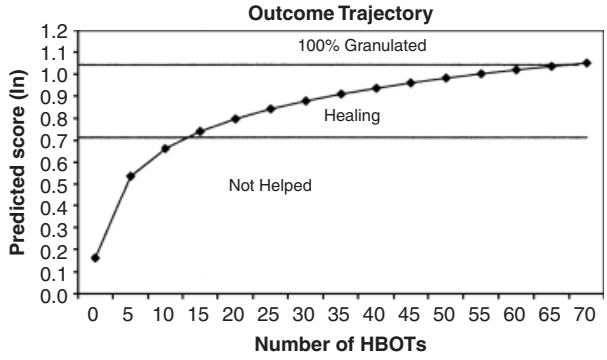

Figure 2. Outcome trajectory. Patient characteristics: age=60 years; diabetes=15 years; Wagner=3; $P_{tc}O_2$ (Air)=15 mmHg; nonsmoker.

In-chamber $P_{tc}O_2$ (HBO_2) and treatment pressure

The lower treatment pressure at Memorial Hermann appears to reduce the in-chamber $P_{tc}O_2$ (HBO_2) that can be attained. At Hermann the average $P_{tc}O_2$ (HBO_2) was 460 mmHg, compared with 802 and 870 mmHg at Conroe, and Travis, respectively. These are highly significant differences ($p < 0.001$) as illustrated in Figure 4. There were 221 patients with in-chamber $P_{tc}O_2$ (HBO_2) measurements and associated HBO_2T outcomes reported.

Figure 5 indicates that the greatest improvement occurs when the $P_{tc}O_2$ (HBO_2) exceeds 100 mmHg. Another, smaller drop in the failure rate occurs with an in-chamber $P_{tc}O_2$ (HBO_2) of 600 mmHg.

Our next evaluation compared the performance of the Memorial Hermann chamber (2.0 ata) (atmospheres absolute) with chambers from two other clinics that had treatment pressures of 2.4 ata. For the Memorial Hermann

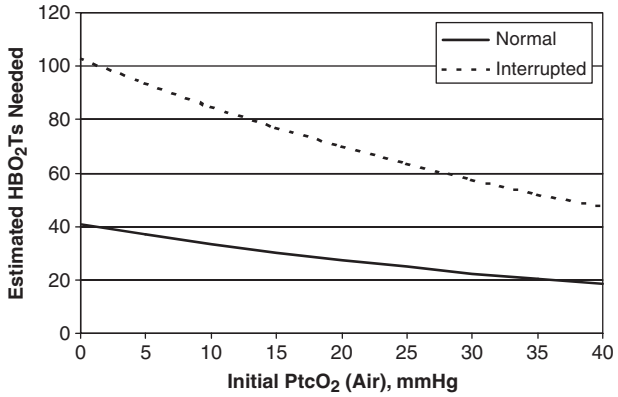

Figure 3. The effects of interrupted treatment on the number of HBO_2T treatments.

Table 6. Comparison of characteristics of interrupted and uninterrupted treatment patients

Item	Average for noninterrupted treatments	Average for interrupted treatments	*p*-value
Number of HBO_2Ts	25.98 (686)	34.61 (120)	< 0.001
Percent helped[1] by HBO_2T	76 (655)	63 (119)	0.004
Age (years)	62.9 (686)	61.8 (120)	0.355
Duration of diabetes (years)	16.9 (389)	17.7 (83)	0.506
Pack years of smoking	18.6 (414)	21.2 (93)	0.506
Wagner score	3.10 (686)	3.12 (120)	0.795
$P_{tc}O_2$ (Air) (mmHg)	24.3 (543)	26.7 (109)	0.246
$P_{tc}O_2$ (HBO_2) in chamber (mmHg)	733.3 (169)	727.3 (52)	0.919

[1]''Helped'' is defined as being healed or partially healed.

patients, 67.2% of the $P_{tc}O_2$ (HBO_2) values were $\leq$ 600 mmHg while only 25% of the values from the other two clinics were $\leq$ 600. Nevertheless, the Memorial Hermann failure rate was less than that of the other clinics in both $P_{tc}O_2$ (HBO_2) groups, although the sample sizes were relatively small. The *p*-values for the $\leq$ 600 and $>$ 600 mmHg groups were 0.368 and 0.249, respectively, which is not a statistically significant difference. Thus, there does appear to be a slight decrease in failure rate as the in-chamber $P_{tc}O_2$ (HBO_2) increases. At Memorial Hermann, where all of the patients were treated at 2.0 ata,

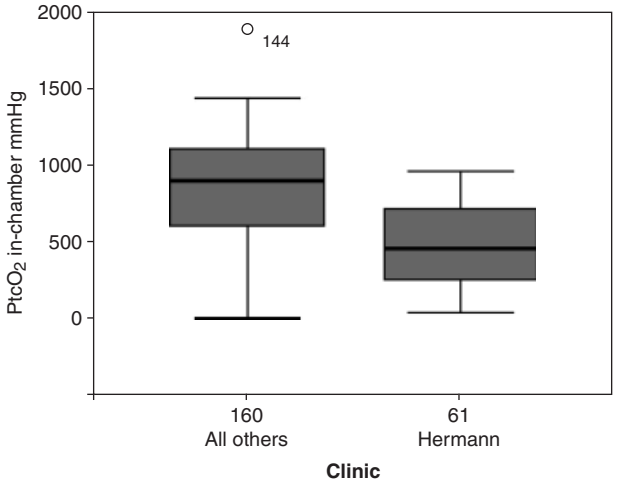

Figure 4. Box plot of in-chamber $P_{tc}O_2$ values obtained from Hermann Memorial compared with all other clinics.

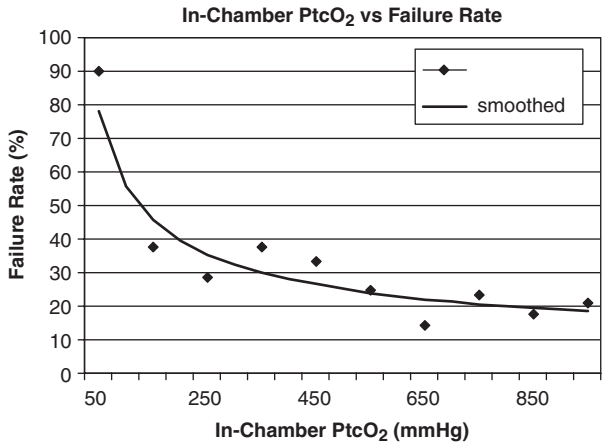

Figure 5. In-chamber failure rates vs. $P_{tc}O_2$ achievement.

the failure rate was lower in the in-chamber $P_{tc}O_2$ (HBO_2) group $<$ 600 mmHg. The 10 patients who had $<$ 100 mmHg were found to have a very high rate of interrupted treatments (40%) and that might have biased the apparent $P_{tc}O_2$ (HBO_2) effects.

Table 7 and Figure 6 show the in-chamber data with the $<$ 100 mmHg patients excluded. The Mantel–Haenszel method for combining different tables was used to obtain better estimates of the effects of each factor, treatment ata, and in-chamber $P_{tc}O_2$ (HBO_2). This showed that the effect of treatment pressure (adjusted for $P_{tc}O_2$) was not significant (p=0.113), and that the effects of $P_{tc}O_2$ (adjusted for treatment pressure) was not significant either (p=0.747). These results are astounding. The treatment pressure effect is near the level of being declared significant, while the $P_{tc}O_2$ result indicates that achieving a value over 100 mmHg is the critical issue. The data also suggest that 600 mmHg is a good minimum threshold if treatment is performed at 2.4 ata. These results are consistent with those of Wattel and Mathieu.[21]

DISCUSSION

The results of any retrospective study are largely dependent on the consistency of the observer in recording the

Table 7. Failure rates by in-chamber $P_{tc}O_2$ groups

$P_{tc}O_2$ (HBO_2) range	Not helped (%)	Helped[1] (%)	*N*
101–600 mmHg	32.4	67.6	71
2.0 ata	27.3	72.9	37
2.4 ata	38.2	61.8	34
$>$ 600 mmHg	20.7	79.3	140
2.0 ata	10.0	90.0	20
2.4 ata	22.5	77.5	120
Overall	24.6	75.4	211

[1]''Helped'' is defined as being healed or partially healed.
ata, atmospheres absolute.

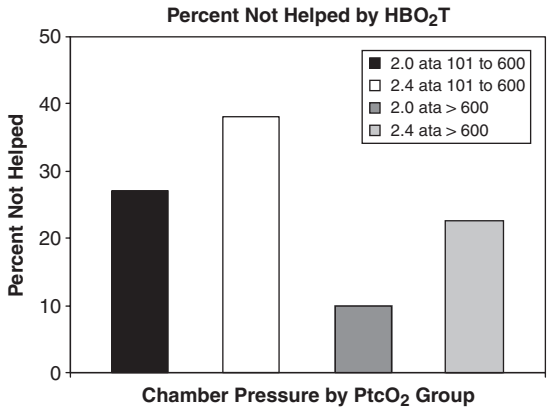

Figure 6. Failure rates for 2.0 vs. 2.4 ata by in-chamber $P_{tc}O_2$ group.

data and the accuracy and completeness of the available charts. The primary advantages of a multiinstitution database are that it permits a much larger sample size and reduces the chance of bias that might result from treatment practices at an individual facility. The principal disadvantages are that the evaluations and chart entries are performed by different people, and tests, such as transcutaneous oximetry, are carried out by different members of the medical staff according to varying protocols with instruments that have not been calibrated to a common standard. In addition, within a multiinstitutional database, the completeness and quality of the information varies among facilities and within the same facility over time, with older charts generally being less well documented than more recent ones. Moreover, the objectives of treatment have changed somewhat over the years during which these patients were seen. For example, rather than complete healing of a lesion, the objective today is more often a partial healing by granulation to the point that epithelialization can continue without further hyperbaric therapy. As a consequence, achieving the *complete healing* category might not be the best objective for cost-effective treatment of patients with hyperbaric oxygen therapy.

Many reviewers have commented on the possibility that different standards of care could have contributed to the outcome. It is certainly the case that care might have differed between facilities. However, the physicians had all received similar hyperbaric medicine training, followed similar treatment protocols, adhered to similar philosophies of care (hence their interest in pooling data) and operated similar types of equipment. We believe that with the exception of treatment pressure and the use of Procuren, which have already been discussed, there were no other major differences in practices of care that could have had a significant effect on the outcome of HBO_2T treatment.

Even patients with very low baseline oximetry values healed with HBO_2T. For this reason, baseline air values cannot be used as a predictor of whether HBO_2T will be successful, but only to screen out patients who might heal spontaneously and therefore do not need HBO_2T at all. Even a quadrupling of oximetry values with sea-level oxygen is not an accurate predictor of whether HBO_2T will be successful. In-chamber oximetry provides the single most accurate method for determining the likely benefit of HBO_2T, but as a single factor it is still less than 75% accurate. We measured in-chamber $PtcO_2$ in only 17% of our patients, and as a result must apply a caveat that this subset could have incorporated undetected bias. However, our analysis of the relationship between these values and outcome in this group is similar to those reported by Strauss et al.[25] There is an advantage, therefore, in using a model that incorporates multiple patient factors rather than focusing on only one.

The number of HBO_2T treatments is related to the outcome. For example, the model indicates little incremental increase in the outcome after the 40th treatment. For patients who failed to benefit, HBO_2T was usually discontinued after a mean of 24 treatments. Nevertheless, there were still some patients with treatment failure who received more than 50 treatments. Clearly, if there is no evidence of improvement, continuing HBO_2T beyond 20 or 30 treatments significantly diminishes its potential cost–benefit ratio.

Medicare treatment guidelines require documentation of improvement after a month of therapy if further treatments are to be covered, and this is a reasonable requirement. In this regard, the continuity of HBO_2T treatments affects the outcome: most patients received an average of five treatments per week, though the actual number of treatments per week was not found to be significant. However, patients with interrupted treatment had twice the amputation rate of patients with no treatment interruption (31.7%, 32 of 101 patients, compared with 15.3%, 112 of 734 with noninterrupted treatments). In addition, an interruption in treatment increased the number of total HBO_2Ts required for a given outcome, so the importance of regular treatments should be emphasized to patients.

The cost of care is presumably also increased in patients receiving autologous growth factor gel, because they were given an average of 45% more HBO_2T treatments than other patients. After controlling for their higher baseline transcutaneous oxygen values and greater number of HBO_2Ts, patients receiving Procuren had no improvement in outcome. Whether the higher number of HBO_2T treatments received was due to treatments given before Procuren was initiated remains unknown.

Renal failure patients with two or more lesions and a Modified Wagner score of 3 or higher are unlikely to improve following HBO_2T. In addition, their response patterns differ from patients without RF. Whether this is caused by a metabolic disruption from a lack of functioning kidneys in the dialysis group, the associated immunosuppressive medications in the transplant group, or that RF itself is an indication of advanced disease, is not clear. Although our database is too small to ascribe probabilities to failure events, it appears that the cost effectiveness of HBO_2T is limited in RF patients with high modified Wagner scores and multiple wounds. Unfortunately, these are also the very patients who are least likely to benefit from any other type of intervention.

The treatment pressure showed a tendency for better outcomes when patients were treated at 2.0 vs. 2.4 ata, although this was not statistically significant, and it should be pointed out that the 2.4 ata group was considerably larger than the 2.0 ata group. Patients subjected to higher treatment pressures were also more likely to have higher in-chamber oximetry values, but values > 600 mmHg did not necessarily correlate with an improved outcome. This

might be because after reaching a particular tissue oxygen threshold, which we currently do not know, further increases in tissue oxygen levels confer no additional benefit.

At present, our outcome data are insufficient to establish the durability of benefit from HBO_2T. Even in the brief follow-up time recorded (2–4 weeks), there were high amputation and death rates in patients who failed to benefit from HBO_2T. The reasons for subsequent amputation in those who benefited from HBO_2T include the diagnosis of osteomyelitis, which might result in limb loss despite an excellent wound response.

Although it is not possible to construct a description of patients who will universally fail to benefit from HBO_2T, it is feasible, however, to model the outcome using the significant variables described. The accuracy and potential value of these models should be prospectively assessed. The cost–benefit of HBO_2T can be maximized by limiting the number of HBO_2Ts in patients who fail to demonstrate improvement after a fair trial, recognizing that there are diminishing returns after a total of 35–40 treatments. Also, limiting the use of HBO_2T in patients with RF and who have high Modified Wagner scores and multiple lesions might be considered. Nevertheless, a significant number of patients with severe and multiple lesions did improve after HBO_2T treatment. Finally, the greatest benefit of HBO_2T appears to occur within the first 15 treatments (Figure 2), although this observation should not be misconstrued to indicate that it is not worthwhile continuing treatment beyond this number. Hopefully, in the future, indications such as an increase in $P_{tc}O_2$ associated with angiogenesis might prove useful in lieu of a specific number of treatments.

While the regression model calibrates the effectiveness of HBO_2T treatment and the diminishing returns to large treatment numbers, there are, unfortunately, no data available on a suitable control group to conduct a more traditional comparison of cohort groups. For many patients, though, it must be recognized that HBO_2T is the only alternative to amputation. The fact that a high correlation exists between the number of HBO_2T treatments and an improved outcome in this large and diverse data set, does suggest that HBO_2T is an effective medical procedure for these patients, and an important adjunct to healing of lower extremity lesions in this challenging population. With increased understanding of the underlying biochemical factors that hyperbaric oxygen treatment affects, it is hoped that likely candidates will be better defined, and treatments refined.

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