Review articles

Transcutaneous oximetry, problem wounds and hyperbaric oxygen therapy

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Key words

Transcutaneous oximetry, wounds, chronic wounds, hyperbaric oxygen therapy, diabetes, review article

Abstract

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Introduction: Transcutaneous oximetry measurement (TCOM) is the process of measuring the partial pressure of tissue oxygen ($P_{tc}O_2$) via a heated electrode placed upon the skin.

Aim: We aim to describe the use of TCOM to define tissue hypoxia and normal ranges for $P_{tc}O_2$, and correlate TCOM with clinical outcomes for wounds treated with hyperbaric oxygen therapy (HBOT).

Methods: A structured literature search covering the past 25 years was performed using the MeSH terms: blood gas monitoring; transcutaneous; wound healing; peripheral vascular disease; diabetes; and hyperbaric oxygenation. We critically appraised all relevant papers and, using our synthesis of the data, present our recommendations for the use of TCOM in the assessment of problem wounds for HBOT, and for further research.

Results: Normal chest $P_{tc}O_2$ is 60–70 mmHg, which is similar to limb values. TCOM values do not change significantly with age in healthy individuals but limb values are reduced in diabetes, peripheral vascular disease and in limb elevation. TCOM has been validated in predicting wound healing, and successful vascular reconstruction and amputation level, as well as in confirmation of the need for amputation. TCOM is a more effective marker of disease than Doppler assessment or ankle-brachial indices. Thirty-eight studies since 1982 suggest that hypoxia is defined as $P_{tc}O_2$ = 10–40 mmHg. A single critical value for tissue viability has not been determined. $P_{tc}O_2$ increases with increasing partial pressure of inspired oxygen (P_IO_2), and is markedly elevated during HBOT. TCOM values progressively increase during a course of HBOT. While low $P_{tc}O_2$ values breathing air confirm wound hypoxia, they do not predict outcome with HBOT. Breathing 100% oxygen at ambient pressure is somewhat predictive of outcome – if wound $P_{tc}O_2 < 35$ mmHg, 41% fail to heal; while a $P_{tc}O_2 > 200$ mmHg breathing hyperbaric oxygen is the best single discriminator between success and failure of HBOT (74% reliable). Using the available data, we suggest clinical guidelines.

Conclusions: TCOM is useful to identify patients with problem wounds who may respond to HBOT. Poor quality of the available clinical studies limits the interpretation of the available evidence. A large, multicentre prospective study is required that correlates TCOM using a standard protocol with initial wound grades and clinical outcomes.

Introduction and aims

Oxygen plays a vital role in wound healing. Many cellular processes such as fibroblast replication, collagen synthesis, neutrophil degranulation and bacterial killing are dependent on the presence of tissue oxygen in partial pressures greater than 30–40 mmHg.[1,2] Tissue hypoxia has been demonstrated in wounds that fail to heal promptly; such wounds are collectively called ‘problem wounds’.[3] Measurement of tissue oxygenation is a component of the comprehensive evaluation of problem wounds. Invasive electrodes were first pioneered by Clark and then miniaturised by Silver.[4,5] Hunt first described measurement of tissue oxygenation in humans over 40 years ago.[6] Non-invasive transcutaneous oximetry (TCOM) probes were developed almost a decade later.[7] Since Hunt’s original work, there has been considerable evolution of the process, using invasive and non-invasive techniques, summarised in a recent review.[8]

TCOM is the process of measuring oxygen tension (partial pressure) on the skin surface, and was originally used in neonatology.[9] TCOM *estimates* tissue oxygenation by measuring the diffusion of extracellular oxygen into a heated sensor on the skin. TCOM is the only non-invasive measure of tissue oxygenation currently available and avoids the risks of invasive measurement such as tissue disruption around the wound, infection and exacerbation of non-healing lesions.

Sheffield and Workman reported the use of invasive electrodes to confirm hypoxia in chronic wounds and demonstrated improvement in tissue oxygenation when breathing hyperbaric oxygen (HBO).[10,11] TCOM may assist the rational selection of patients who may benefit from hyperbaric oxygen therapy (HBOT) thus allowing more selective application of limited hyperbaric resources.[12] This assumes that TCOM accurately reflects wound tissue oxygenation and that improvement in tissue oxygenation

Table 1
Abbreviations and definitions

Abbreviation	Meaning	Further explanation
TCOM	Transcutaneous oxygen measurement	
P_aO_2	Arterial oxygen partial pressure	Oxygen partial pressure measured in arterial blood
$P_{tc}O_2$	Transcutaneous oxygen partial pressure	Oxygen partial pressure measured by transcutaneous oximetry
P_wO_2	Wound oxygen partial pressure	Oxygen partial pressure measured in the wound
P_IO_2	Inspired oxygen partial pressure	Oxygen partial pressure in the inspired gas
HBOT	Hyperbaric oxygen therapy	Delivery of oxygen under pressure as a therapeutic modality
ATA	Atmospheres absolute	The pressure relative to a vacuum
RPI	Regional perfusion index	The ratio of $P_{tc}O_2$ in the region of interest, (e.g., near a problem wound; peri-wound) relative to a reference 'normal' $P_{tc}O_2$ (e.g., in the chest). This is expressed mathematically as RPI = $P_{tc}O_2$ peri-wound/$P_{tc}O_2$ chest.
BPI	Bilateral perfusion index	The ratio of $P_{tc}O_2$ in the region of interest in one limb relative to the reference opposite limb $P_{tc}O_2$

will accelerate healing in hypoxic wounds. This paper will critically examine the evidence underpinning these assumptions. Table 1 summarises the abbreviations and definitions that are used in this review.

The aims of this paper are to:

- define the normal ranges for tissue oxygen partial pressures
- review studies where TCOM has been used to define tissue hypoxia
- correlate $P_{tc}O_2$ with clinical outcomes
- review the role of TCOM in the assessment of problem wounds for HBOT
- develop an assessment algorithm based on available evidence from the literature.

We will also identify unanswered questions in order to facilitate further research.

Methods

We intended to capture all clinical trials and case series involving TCOM in the setting of problem wounds and HBOT from 1982 to 2006. Electronic searching used the MeSH terms: blood gas monitoring; transcutaneous; wound healing; peripheral vascular disease; diabetes; and hyperbaric oxygenation. We searched Central (the Cochrane database of controlled clinical trials), Medline (PubMed), DORCTIHM, CINAHL and EMBASE.

We also hand-searched books covering the combination of problem wounds and hyperbaric oxygen therapy, as well as proceedings and workshops from the Undersea and Hyperbaric Medicine Society, the European Underwater and Baromedical Society, the South Pacific Underwater Medicine Society and international congresses on hyperbaric medicine. Finally a search was undertaken of references identified in papers located by the initial search.

RESULTS OF THE SEARCH

Our initial search identified 178 papers of interest. Of these, we rejected 33 review papers with no new data and 47 that did not present relevant data. A further seven could not be located. The remaining 91 papers contributed to this review.

Results

The TCOM procedure, its limitations and issues affecting accuracy have been described in detail elsewhere.[13,14] Figure 1 provides a schematic summary of the process and Figure 2 demonstrates sensors applied around a problem wound.

It is important to note that TCOM *does not* measure the wound oxygen tension (P_wO_2) but rather the oxygen tension in the skin *surrounding* the wound (i.e., peri-wound $P_{tc}O_2$). This is a potential limitation of the procedure as wound oxygenation is likely to be lower than the $P_{tc}O_2$ adjacent to the wound. We have been unable to identify a head-to-head comparison of transcutaneous oximetry with invasive oximetry, either for raw data tissue oxygen measurements, or in relation to clinical outcomes. It is not clear whether or not such a comparison would improve our understanding of wound oxygenation because the process of inserting invasive oximetry electrodes may actually adversely affect the modality it seeks to measure (P_wO_2), by inducing tissue oedema or haemorrhage.[6] Some centres recommend using a reference reading on the chest, and calculation of a regional perfusion index (RPI). A number of authors quote a bilateral perfusion index (BPI) comparing the affected limb with its contralateral partner.[15–19] Most of the clinical outcome studies evaluating the role of TCOM in patients treated with HBO have focused on the peri-wound $P_{tc}O_2$, and have not used either of these indices.[20–4]

Figure 1
Schematic diagram of the polarographic electrode on the skin with oxygen diffusing through a semipermeable membrane to the electrolyte solution

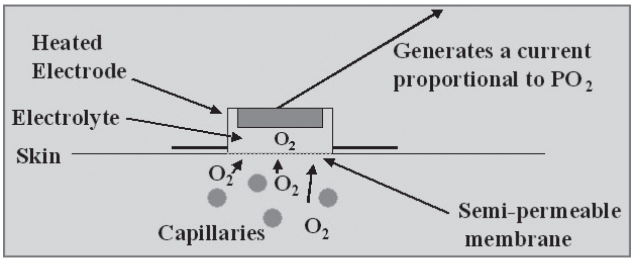
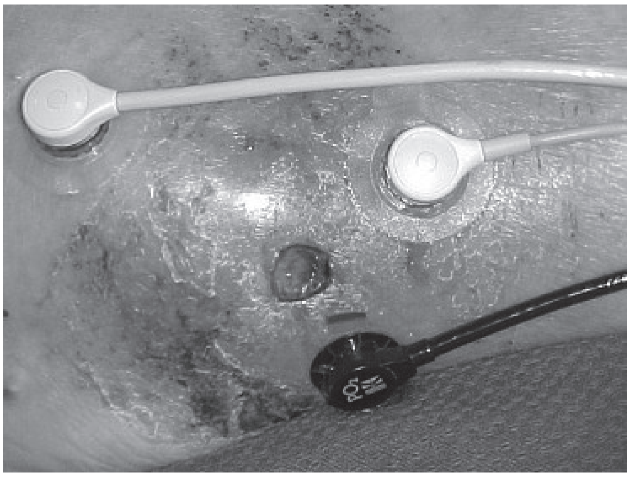


Figure 2
Transcutaneous oximetry electrodes situated adjacent to a problem wound



DEFINING NORMAL TISSUE OXYGENATION USING TCOM

Several studies have attempted to define normal ranges for the lower limb in healthy subjects (Table 2). It has been reported that chest readings are not significantly different from leg oxygenation and that females had significantly higher $P_{tc}O_2$ in their legs than males.[25] This group also demonstrated changes in limb tissue oxygenation as limb position changed. Significant increases in foot (+18.3%) and leg (+27.2%) $P_{tc}O_2$ were observed when the leg was placed in a dependent position and similar falls noted when the legs were elevated. It has been reported that $P_{tc}O_2$ falls with age; however, these findings were not confirmed by other studies.[26–8] $P_{tc}O_2$ values tend to be consistent over time, varying on average around 10% in healthy individuals.[29] In individuals free of vascular disease, lower limb $P_{tc}O_2$ is not affected by exercise; however, in individuals with peripheral vascular disease (PVD), there is a significant fall in $P_{tc}O_2$ during and after exercise.[30,31]

DEFINING HYPOXIA AND VALIDATING TCOM IN RELATION TO CLINICAL OUTCOMES

Early studies using TCOM demonstrated that chronic indolent soft-tissue wounds were severely hypoxic, with wound PO_2 levels (P_wO_2) ranging from 5 to 20 mmHg.[10,11] $P_{tc}O_2$ values adjacent to indolent problem wounds were < 20 mmHg compared with control values of 30–50 mmHg.[10]

We identified 56 studies involving 4,751 patients that attempted to correlate TCOM with clinical outcomes (Table 3). Twelve studies involved HBO, and will be covered later in

Table 2
Normal $P_{tc}O_2$ readings in healthy individuals

Lead author, reference, year	Study population (n)	Average age (years)	Reference $P_{tc}O_2$ site	$P_{tc}O_2$ mmHg (± SD or range)	Comments
Dowd et al[27] 1983[1]	(205)	Unknown	Lower leg – M Lower leg – F	70 72	Male/female difference not statistically significant. No significant trend $P_{tc}O_2$ vs age.
Dowd et al[28] 1983[2]	'Normal' volunteers (161)	45	Foot Leg Chest (n = 91)	67 ± 11 70 ± 9 69 ± 11	No significant difference chest vs leg or foot.
Hauser et al[26] 1983	Healthy, asymptomatic subjects (12)	Unknown	Foot	65 ± 3	Chest and limb $P_{tc}O_2$ fell with increasing age.
Dooley et al[25] 1997	Healthy (72)	34.2	Foot Lower leg – M Lower leg – F Chest	63.0 to 67.4 48.8 to 56.0 59.3 to 64.8 63.4 to 68.5	Foot and leg values increased in dependent position (+18.3% and +27.2%) and decreased in elevated position (-18.1% and -28.2%). Male/female readings significantly different

Table 3
Publications reporting clinical outcomes that have been correlated with $P_{tc}O_2$ measurements or indices derived from TCOM (*involved hyperbaric oxygen)

Outcome measure/Year	First author	Patient numbers	Ref
Predicted healing			
1982	Franzeck	35	58
1983	Dowd	62	27
1984	Cina	100	59
1987	Hauser	113	60
1988	Oishi	80	61
1988	Wyss	162	62
1991	Wattel*	59	21
1991	Pecoraro	46	63
1992	Campagnoli*	28	48
1992	Pinzur	38	64
1994	Conlon	24	65
1995	Yablon	11	66
1996	Bunt	147	67
1996	Bouachour*	36	19
1996	Claeys	86	68
1996	Dooley*	60	49
1996	Padberg	204	39
1996	Smith*	26	56
1999	Kalani	50	69
2001	Grolman*	36	22
2002	Strauss*	190	24
2002	Fife*	1,144	23
2003	Abidia*	16	43
2003	DeGraaff	96	91
Success of procedure			
1986	Rhodes	60	70
1988	Lalka	62	71
1989, 1990	Ameli	105	32, 33
1991	Stein	127	34
1993	Mathieu*	15	54
1997	Hanna	29	72
2005	Poredos	56	73
Predicted severity of symptoms/disease			
1984	Hauser [1]	25	15
1984	Hauser [2]	46	16
1984	Hauser [3]	24	74
1984	Byrne	138	30
1984	Wyss	188	36
1988	Kram	32	75
1988	Lalka	62	71
1988	Moosa	22	76
1989, 1990	Ameli	105	32, 33
1991	Stein	127	34
1992	Reiber	80	77
1994	Ubbink	130	78
1995	Ballard	55	79
Predicted amputation +/- level			
1982	Burgess	37	80
1982	White	25	40
1984	Wyss	188	36
1984	Katsamouris	37	81
1985	Harward	101	82
1987	Dowd	101	83
1988	Bongard	26	84
1990	Wattel*	20	20
1992	Reiber	80	77
1992	Chambon	33	85
2005	Zgonis*	35	57
Predicted successful vascular reconstruction			
1988	Kram	32	75
1992	Scheffler	64	86
1997	Ray	41	87
2002	Stalc	57	88
2003	Wagner	34	89
2005	Caselli	43	90

the review. Study methodologies were diverse, and outcomes could be classified into five major categories:

1 prediction of healing
2 success of surgical procedure
3 predicted severity of symptoms or disease
4 predicted level of amputation
5 predicted success of vascular reconstruction.

Fifteen studies (1,137 patients) demonstrated that TCOM provided better overall predictive capability than Doppler studies measuring ankle-brachial index (ABI) and segmental pressures, or laser fluximetry across one or more of the five outcome measures (Table 4). Three studies suggested TCOM showed similar ability and one reported laser Doppler fluximetry to have better predictive capability than TCOM.[32–5]

Other indirect methods of measuring tissue oxygenation have not reliably predicted the fate of a problem wound. Arterial calcific medial sclerosis in diabetics may artificially elevate ankle blood pressures, making Doppler studies in these patients unreliable.[36] This may be one reason why TCOM has proven superior to ABI measurement in diabetics. However, over half of the authors in Table 4 studied non-diabetics or mixed populations. TCOM has also been used to evaluate the impact of local pressure or stretching on the skin. Falls in $P_{tc}O_2$ levels were observed in patients with tetraplegia with and without pressure ulcers.[37]

Table 4
Studies where TCOM has demonstrated outcome prediction superior to Doppler studies of ankle-brachial index and segmental pressures, or laser fluximetry

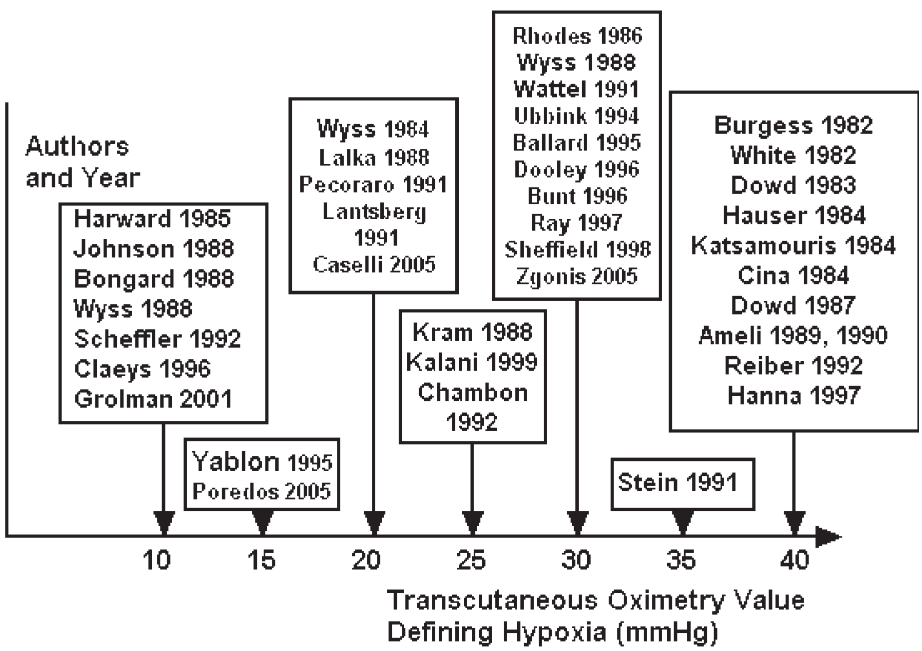
Outcome measure			
Year	**First author**	**Patient numbers**	**Reference**
Predicted healing			
1988	Wyss	162	62
1994	Conlon	24	65
1995	Ballard	55	79
1996	Padberg	204	39
1999	Kalani	50	69
Success of procedure			
1988	Lalka	62	71
1997	Hanna	29	72
1997	Ray	41	87
Predicted severity of symptoms/disease			
1984	Hauser [1]	25	15
1984	Hauser [2]	46	16
1994	Ubbink	130	78
Predicted amputation +/- level			
1982	White	25	40
1984	Wyss	188	36
Predicted successful vascular reconstruction			
1988	Kram	32	75
1992	Scheffler	64	86

In an experimental model, Melis demonstrated significant falls in $P_{tc}O_2$ when skin was undermined and stretched in plastic surgical procedures.[38]

Based on these data, there have been attempts to define a 'cut off' (sic) value where TCOM predicts success or otherwise of a procedure (such as amputation), or predicts healing. Sheffield wrote (1998) "*No single value can be specified 'normal' O_2 tension for all tissue. Rather there exists a series of gradients.*"[14] $P_{tc}O_2$ values will depend on the patient population, the technique used and site of measurement, the position of the limb and the therapeutic intervention. Study design is also important. Some authors attempted to define a $P_{tc}O_2$ value below which all patients failed the treatment regimen, whereas others attempted to define a value above which all patients have successful outcomes. Usually there was a 'grey zone' between the values determined for success or failure. This provides one explanation for the considerable variability of $P_{tc}O_2$ values defining hypoxia (Figure 3).

Calculations of sensitivity and specificity have been used to provide guidance regarding the usefulness of measuring $P_{tc}O_2$ in the above studies; however, there is considerable diversity in study design. The majority do not test the intervention of HBOT, hence the sensitivity and specificity data are not helpful to the hyperbaric clinician. In addition, these calculations provide little comfort to the patient who is in the 'statistical grey zone', where neither success nor failure is guaranteed. Padberg's group attempted to account for this variability by producing a graph of probability of healing versus $P_{tc}O_2$.[39] Their method of presenting their results provides the clinician with meaningful data to present to the patient. For a given $P_{tc}O_2$ value, there is a quotable

Figure 3
Defining hypoxia using transcutaneous oximetry



percentage chance of healing. They also showed that diabetes mellitus and renal failure increased the $P_{tc}O_2$ value required for successful healing.[39]

The clinical endpoints of the studies cited varied greatly. In Table 3, 24 studies investigated TCOM for the ability to predict healing in patients with pre-existing problem wounds, 13 studies investigated prediction of procedural or vascular reconstruction success, and 11 studies examined TCOM as a predictor of amputation level. A further 13 studies assessed the ability of TCOM to predict severity of symptoms or disease. In addition, the inclusion criteria varied across these studies, making direct comparison problematic. Some studied only diabetic patients, others peripheral vascular disease without diabetes or mixed populations.

Given the differences in methodologies and outcome measurements used in the available literature, it is not surprising that there is a broad spread of hypoxic TCOM values up to 40 mmHg. For healing to occur, 50 mmHg may be a more appropriate value.[40] This at least provides the clinician with some guidance when assessing new patients. Any treatment algorithm must allow for this 'grey zone' in definitions; it is reasonable to define wound hypoxia as $P_wO_2 \leq 40$ mmHg, with allowances up to ≤ 50 mmHg for patients with other factors such as diabetes and renal failure.[36,39]

THE ROLE OF TCOM IN THE ASSESSMENT OF PROBLEM WOUNDS FOR TREATMENT WITH HBOT

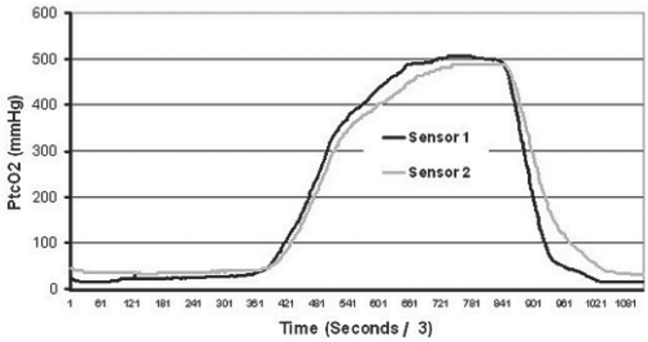
Transcutaneous oximetry has been used to predict success of a treatment intervention in Tables 3 and 4 under two broad models, based on the timing of TCOM relative to the intervention:

- TCOM *before* the treatment intervention, to measure the level of oxygenation in the patient's target tissue, and assess if this is sufficient to allow success of the treatment (e.g., amputation at a particular level, or healing of an ulcer with conservative management);
- TCOM *after* the treatment intervention to assess if the intervention caused sufficient increase in $P_{tc}O_2$ to result in successful healing.

Both models may have potential for assessing the role of TCOM in the treatment of problem wounds with HBOT.

HBOT has demonstrated some success as a treatment for refractory problem wounds and radiation-injured tissue.[41–5] As a therapeutic intervention, HBOT is unique in that P_IO_2 is increased during delivery of oxygen under pressure and its effect on $P_{tc}O_2$ can be measured (Figure 4). When evaluating the role of TCOM in this context, it would be expected that the treatment intervention (HBOT) would acutely increase P_wO_2 (Figure 4), and as healing progresses, lead to progressive improvements in surrounding tissue oxygenation. Peri-wound $P_{tc}O_2$ increases with increased P_IO_2, and this increase is amplified when breathing oxygen at pressures of greater than one atmosphere.[20,21,23,46–9]

Figure 4
Real-time measurement of $P_{tc}O_2$ (peri-wound) in a patient breathing air, then HBO at 2.4 ATA



Site of measurement	Peak values of $P_{tc}O_2$ (mmHg) breathing: Room air	100% O_2	HBO 2.4 ATA
Chest	58	286	725
Sensor 1	33	40	507
Sensor 2	18	54	488

There is a close correlation between arterial oxygen partial pressure (P_aO_2) and $P_{tc}O_2$ in the hyperbaric environment.[25] In some patients, physiological $P_{tc}O_2$ levels are only achievable in the hyperbaric environment (Figure 4), and the elevation of P_wO_2 from baseline is far greater than the proportionate increase in P_IO_2.[21] The patient in Figure 4 had failed to increase $P_{tc}O_2$ breathing 100% oxygen at 1 ATA, but a brisk increase occurred in HBO.

In one series, baseline $P_{tc}O_2$ levels adjacent to the hypoxic wounds when breathing air were less than 15 mmHg, and these increased over the course of multiple HBO exposures to above 30 mmHg.[10] This effect has also been observed for oedematous wounds, and was associated with healing.[49] Delayed tissue injury from radiation therapy is another example of a specific type of problem wound. In patients who had received head and neck irradiation for cancer, tissue around the oral cavity was hypoxic and the hypoxia was restored to 80% of normal values over a course of 15–30 HBO treatments.[41,50–2] The HBO-induced angiogenic response in irradiated tissue was well documented, and the authors showed that increases in $P_{tc}O_2$ were correlated with clinical success (tooth socket, bone and mucosal healing) that was sustained for up to 3 years.[41,50–2]

In diabetic patients, improvements in $P_{tc}O_2$ on the dorsum of the foot were reported at the completion of HBOT, compared with controls.[42] Similar findings were reported by another study in a recent abstract.[53] In the first study, even though there were fewer major amputations in the HBOT group compared with controls, the authors did not specifically relate the TCOM values to outcome.[42]

Thus HBOT leads to an acute change in the ambient tissue environment, with subsequent angiogenesis leading to

Table 5. Studies using TCOM as outcome predictor in subjects receiving HBOT (PVD – peripheral vascular

Author	Year	Number of subjects	Study description	Threshhold $P_{tc}O_2$ value	Outcomes
Mathieu et al[18]	1990	33 patients, post-traumatic upper and lower limb ischaemia 16 with and 17 without arterial injury	Use of TCOM in air, 100% oxygen and HBO 2.5 ATA to predict need for amputation. Used bilateral perfusion index (BPI)	No value determined at air, 100% O_2, or HBO Recommended HBO if BPI > 0.2 and < 0.4; no outcome data to support this	No amputation: $P_{tc}O_2$ HBO = 425 ± 292 mmHg Amputated: $P_{tc}O_2$ HBO = 114 ± 148 mmHg Air and 100% O_2 values not significant BPI < 0.4 sensitivity 100%, specificity 94% BPI < 0.2 gives 100% predictive value for amputation
Wattel et al[20]	1990	20 patients mixed PVD (9 cases) or diabetes (11 cases)	Use of TCOM in air, 100% oxygen and HBO 2.5 ATA to predict healing in patients receiving HBOT	No value determined for air or 100% O_2, $P_{tc}O_2$ < 50 mmHg in HBO – all worsened $P_{tc}O_2$ > 100 mmHg in HBO – all healed	Data not tabulated to enable sensitivity and specificity Healed $P_{tc}O_2$ in HBO = 635 ± 388 mmHg Not healed $P_{tc}O_2$ in HBO = 45 ± 20 mmHg (P = 0.003) Rise of $P_{tc}O_2$ in HBO significant 100% O_2 values not significant
Wattel et al[21]	1991	59 diabetic patients	Use of $P_{tc}O_2$ to predict healing in patients receiving HBOT, used absolute values and ratios relative to reference sensor on chest	Only values in HBO useful $P_{tc}O_2$ > 450 mmHg in HBO 2.5ATA included all successes	Success = HBO $P_{tc}O_2$ = 786 ± 258 mmHg Failure = HBO $P_{tc}O_2$ = 323 ± 214 mmHg; P < 0.005 Ratios in HBO also significantly different No sensitivity/specificity data
Campagnoli et al[48]	1992	28 patients, lower limb ulcers mixed aetiology (24 diabetic)	Use of $P_{tc}O_2$ to predict healing in patients receiving HBOT, used absolute values	$P_{tc}O_2$ > 400 mmHg	Minimal statistical analysis performed If $P_{tc}O_2$ > 400 mmHg achieved in HBO – all healed
Mathieu et al[54]	1993	15 patients, post-pedicle musculocutaneous flap transplantation referred for HBOT	Predictive value $P_{tc}O_2$ in HBO for healing. Measured absolute values and flap perfusion index relative to chest 3hr post-op	$P_{tc}O_2$ > 70 mmHg in HBO 2.5ATA	$P_{tc}O_2$ > 70 mmHg in HBO predicted flap success $P_{tc}O_2$ <= 35 mmHg in HBO predicted flap failure No values predictive in air or 100% O_2 HBO values: failure = 12 ± 12 mmHg; success 378 ± 385 mmHg (P < 0.01) **7/15 total success**
Bouachour et al[19]	1996	36 patients with crush injuries (RCT)	Measured BPI as a secondary outcome of treating crush injuries with HBO	Not assessed	HBO group more likely to achieve complete healing and less likely to receive extra surgery. BPI breathing air, measured in HBOT group improved progressively from 0.4 to 0.8. No significant change in placebo group
Dooley et al[49]	1996	60 patients, oedematous non-healing leg wounds	Measured $P_{tc}O_2$ and predicted healing following HBO treatment	No threshold value determined	Pre-treatment $P_{tc}O_2$ correlated with degree of oedema, did not predict healing. HBO significantly reduced oedema. 20 patients lost to follow up
Faglia et al[42]	1996	68 diabetic patients (RCT)	Assessed risk of major amputation with and without HBO. Measured change in $P_{tc}O_2$	Not assessed	HBO group significantly less likely to receive major amputation. (Absolute Risk Reduction 26%) $P_{tc}O_2$ breathing air improved significantly in treatment group, from 5.0 ± 5.4 to 14.0 ± 11.8 mmHg, P = 0.0002

disease, HBO – hyperbaric oxygen, TCOM – transcutaneous oximetry, RCT – randomised controlled trial)

Author	Year	Number of subjects	Study description	Threshhold $P_{tc}O_2$ value	Outcomes
Smith et al[56]	1996	26 patients (16 diabetic)	Used $P_{tc}O_2$ to predict response of wounds to 40 HBO treatments using wound scores. Measured $P_{tc}O_2$ breathing air, 100% O_2 and in HBO at 2.4 ATA	P_wO_2 > 800 mmHg in HBO	Responders had higher wound PO_2 on 100% O_2 (284 vs 132 mmHg), and in HBO (1047 vs 509 mmHg) P_wO_2 > 800 mmHg linked to HBO response Overall response rate 9/26
Lindstrom et al[55]	1998	20 patients with tibial shaft fractures requiring an intramedullary nail (RCT)	Five days HBO at 2.5 ATA; improvement on $P_{tc}O_2$ or blood flow compared with air breathing	Measured flow in tibialis posterior artery and $P_{tc}O_2$ at three days after surgery	Tibialis posterior artery flow improved significantly in the HBO group but there was no significant difference in $P_{tc}O_2$ at three days after surgery Measurements not correlated with clinical outcomes
Grolman et al[22]	2001	36 patients, critical limb ischaemia and non-healing ulcers, (24 diabetic, 9 renal failure)	Used $P_{tc}O_2$ to predict which patients benefit from HBO. Used increase in $P_{tc}O_2$ >10 mmHg breathing 100% oxygen vs air at 1 ATA as indicator of potential response	Rise in $P_{tc}O_2$ > 10 mmHg breathing 100% oxygen	Absolute value of TCOM not predictive Breathing surface oxygen, if rise in $P_{tc}O_2$ > 10 mmHg, 19/27 healed, vs 1/9 if $P_{tc}O_2$ <= 10 mmHg HBO $P_{tc}O_2$ not assessed
Lin et al[53]	2001	29 diabetic patients (RCT)	HBO 30 treatments compared with standard care for improved healing of diabetic foot wounds, or improved indicators of vascular state	Not assessed	$P_{tc}O_2$ increased over 30 HBO treatments 36 ± 21 to 56 ± 21 mmHg; P < 0.01 Laser Doppler flow improved significantly No significant improvement in ankle-brachial index
Fife et al[23]	2002	1,144 diabetic patients with lower extremity ulcers	Determined if pre-treatment air $P_{tc}O_2$, or in-chamber $P_{tc}O_2$ predictive of healing	$P_{tc}O_2$ in ambient air not predictive of outcome in HBO $P_{tc}O_2$ > 200 mmHg predictive of success	In-chamber $P_{tc}O_2$ > 200 mmHg best discriminator (74% reliable) $P_{tc}O_2$ < 15 mmHg air at 1ATA and in-chamber $P_{tc}O_2$ < 400 mmHg; negative outcome 75.8% reliable, 73.3% positive predictive value
Strauss et al[24]	2002	190 patients, foot and ankle wounds (no demographic data)	Determined $P_{tc}O_2$ values in HBO that correlate with healing wound	$P_{tc}O_2$ < 100 mmHg in HBO = less chance of response $P_{tc}O_2$ < 50 mmHg in HBO, all had amputations	$P_{tc}O_2$ > 200 mmHg in HBO associated with wound healing Sensitivity 0.8, Specificity 0.44, positive predictive value 0.88, negative predictive value 0.3, accuracy 74% Healing rate 88% if $P_{tc}O_2$ > 100 mmHg
Abidia et al[43]	2003	16 diabetic patients RCT	Assessed role of HBOT in ischaemic diabetic lower limb ulcers	Not assessed	No difference in $P_{tc}O_2$ between pre and post treatment in either group; no difference between groups; 2 withdrew; 5/8 healed in HBO group, 1/8 healed placebo
Zgonis et al[57]	2005	35 patients, 40 feet	Use of pre-operative $P_{tc}O_2$ to predict healing in patients receiving partial foot amputations then 20 HBO treatments	$P_{tc}O_2$ > 29 mmHg successful outcome	$P_{tc}O_2$ > 29 mmHg pre-operative = successful outcome Difficult to determine if HBO influenced outcome

sustained increases in $P_{tc}O_2$ levels, demonstrable with TCOM. Therefore, in patients receiving HBOT, the pre-treatment $P_{tc}O_2$ breathing air might not correlate with outcome, because the treatment itself has potential to change the measurement. When assessing the role of TCOM as an outcome predictor in patients receiving HBOT, it would, therefore, be most appropriate to undertake TCOM during exposure to HBO and after the course of HBOT, as per the second model above. This is an important issue when interpreting outcome data for the HBOT studies that follow.

HYPERBARIC OXYGEN AS A TREATMENT FOR PROBLEM WOUNDS – CORRELATING TCOM WITH CLINICAL OUTCOMES

Based on the above evidence, the rationale for the use of HBOT for problem wounds is:

- problem wounds are often hypoxic
- elevated P_IO_2 (during HBOT) has been shown to acutely correct the hypoxia around problem wounds
- HBOT has been associated with healing in problem wounds
- HBOT has been associated with sustained improvement in $P_{tc}O_2$.

Given these premises, is there evidence that HBO increases $P_{tc}O_2$ in problem wounds that is linked to improved outcomes? If the evidence exists, how might it best be applied in clinical guidelines?

Table 5 summarises the 16 studies (12 in Table 3) identified that have investigated the role of TCOM in the assessment of problem wounds receiving HBOT.[18–24,42,43,48,49,53–7] Early studies investigated if TCOM values in air, 100% oxygen and HBO, measured before treatment, were predictive of healing when HBOT was used for post-traumatic ischaemia, PVD wounds, diabetic wounds and pedicle flaps.[18,20,21,54] Pre-treatment $P_{tc}O_2$ values breathing air could not be correlated with improvements of limb oedema or wound condition that were associated with HBOT.[49]

These studies generally concluded that only $P_{tc}O_2$ measured in HBO was useful and the $P_{tc}O_2$ values measured breathing air or 100% oxygen at 1 ATA were not useful in predicting outcome. This is logical because HBO was the therapeutic intervention, and patients responding to treatment should be able to demonstrate some effect on $P_{tc}O_2$ in HBO if hypoxia is relevant in their problem wound. When the above authors attempted to define a threshold $P_{tc}O_2$ value breathing HBO, each of the studies produced a different result. A threshold value was determined for poor outcome in HBOT when $P_{tc}O_2 < 50$ mmHg.[20] Threshold values for positive outcome ranged between $P_{tc}O_2 > 70$ mmHg in pedicle flaps and > 450 mmHg in HBOT for diabetic wounds.[21,54] A similar threshold of $P_{tc}O_2 > 400$ mmHg was reported for mostly diabetic patients.[48] Two studies related their outcomes in traumatic ischaemia and crush injuries to the TCOM BPI.[18,19] A BPI < 0.2 predicted universally poor outcomes.[18] Individuals sustaining an amputation had lower $P_{tc}O_2$ values than those whose limbs were saved.[18] If patients were going to respond to HBOT, then a progressive improvement in BPI occurred during the course of treatment.[19] Other studies in diabetic patients have not linked improvements in $P_{tc}O_2$ values after HBOT with outcomes such as healing or risk of amputation.[42,53] In another study of only 16 diabetic patients there was no significant difference in $P_{tc}O_2$ values post-treatment compared with before HBOT.[43] Five days' HBOT in patients with tibial shaft fractures resulted in improved tibialis posterior artery blood flow; however, $P_{tc}O_2$ did not change.[55] The clinical significance of these findings in traumatic injuries is unclear.[55]

In a mixed population of patients receiving 40 HBO treatments for problem wounds, $P_{tc}O_2$ was measured breathing air, oxygen and HBO at 2.4 ATA prior to treatment.[56] They found that 8 out of 9 'responders' had $P_{tc}O_2$ > 800 mmHg in HBO, whereas only 1 out of 6 patients with $P_{tc}O_2 < 800$ mmHg were 'responders'. Despite demonstrating that 'responders' had higher values breathing 100% oxygen and HBO, a threshold value was not suggested. A further weakness of this study was the use of wound scores rather than wound healing to define response.

In 36 patients with critical limb ischaemia and non-healing ulcers, of whom 18 had failed revascularization and 24 were diabetic, the absolute $P_{tc}O_2$ values in 100% oxygen were not predictive of outcome but a rise in $P_{tc}O_2 > 10$ mmHg was positively associated with healing.[22]

Pre-operative $P_{tc}O_2$ as a predictor of healing was evaluated in patients receiving partial foot amputations followed by 20 HBO treatments.[57] A $P_{tc}O_2 > 29$ mmHg was predictive of healing. From the data presented, it was not possible to determine if HBOT influenced the outcome.

In 144 patients with problem foot wounds treated with HBO, 126 (88%) remained healed at one year if $P_{tc}O_2$ had measured > 200 mmHg during HBOT, compared with 17 out of 29 patients (59%) whose $P_{tc}O_2$ in the hyperbaric chamber was < 100 mmHg.[24] An 'intermediate responder' group with $P_{tc}O_2$ values of 100–200 mmHg in HBO also had healing rates of 88%. In their discussion, Strauss et al stated that using $P_{tc}O_2 > 200$ mmHg in HBO to define 'responders' had low specificity and negative predictive value. This is not surprising when the 'intermediate responders' had the same healing rate as the 'responders'. Their discussion was somewhat confusing when they stated that their protocol was modified to define 'intermediate responders' as $P_{tc}O_2$ values of 50–200 mmHg in HBO. From the data presented it is not possible to determine how they arrived at their decision. An overall healing rate of 83% is an exceptional result. Unfortunately, although data were collected prospectively on 159 of the 190 patients in the series, the study presented only very limited patient demographic data and statistical analysis, and the numbers of HBO treatments were not recorded, making assessment of this case series difficult.

In the largest series to date of the role of TCOM in predicting outcomes for patients receiving HBOT, 1,144 consecutive diabetic patients with lower-limb problem wounds were retrospectively studied in a multicentre 10-year review.[23] The aim was to assess if TCOM breathing air, oxygen and HBO correlated with patient outcomes. Whether absolute value of $P_{tc}O_2$ breathing oxygen at ambient pressure or the percentage increase in $P_{tc}O_2$ correlated with outcome was also assessed. Success with HBOT was defined as complete epithelialisation or partly healed (complete granulation); failure was defined as partial granulation only or requiring amputation. Sixty-eight patients had no outcome data available and nine died, leaving 1,067 for analysis. Of these, 756 had full follow-up information. TCOM was conducted at ambient pressure breathing air for 629 patients, oxygen for 499 patients, and HBO for 221 patients.[23]

At two weeks post-HBOT, 117 out of 118 patients defined as 'healed' after HBOT remained healed. At four-week follow up, 390 out of 446 patients defined as 'partial healing' after HBOT were classified as healed. Overall, 68.4% of all wounds were fully healed at follow up. The mean number of HBO treatments for success was 34. The HBOT regime was interrupted in 15.9% and these patients had significantly worse outcomes. Worse outcomes were noted with increasing grades of wound severity. No difference in outcome was noted in patients treated with HBO at 2.0 ATA versus 2.4 ATA.[23]

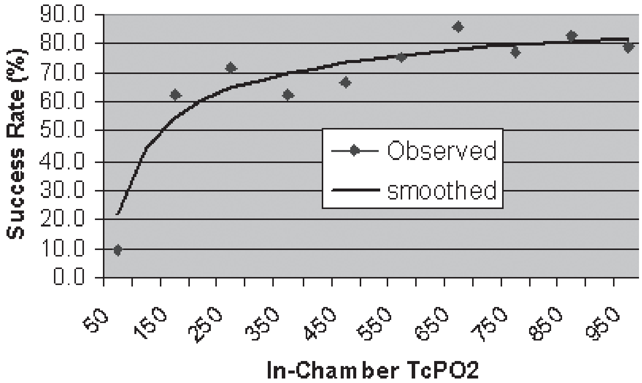
This study reported treatment failure as their outcome measure.[23] They found that $P_{tc}O_2$ values breathing air at ambient pressure had almost no predictive value for benefit from HBOT, apart from confirming that the wounds were hypoxic. Breathing 100% oxygen at ambient pressure, the absolute $P_{tc}O_2$ value was more reliable than the increase with oxygen challenge; however, the best reliability achieved was 69.9%. If $P_{tc}O_2$ < 35 mmHg breathing 100% oxygen, the failure rate with HBOT was 41%. In-chamber $P_{tc}O_2$ < 200 mmHg breathing HBO was the best single discriminator for failure with HBOT. Using this threshold value, the test had a reliability of 74% (positive predictive value for failure to heal 58.3%, sensitivity 23.3%, specificity 93.8%, false negatives 23.5%). For in-chamber $P_{tc}O_2$ < 100 mmHg, the likelihood of failure was 90%. A graph of HBOT success versus in-chamber $P_{tc}O_2$ re-calculated from Fife's data is shown in Figure 5 (Otto G, personal communication, June 2006). A slightly higher degree of discrimination is achieved by combining the $P_{tc}O_2$ measurements breathing air at ambient pressure with $P_{tc}O_2$ measurements breathing HBO.[23]

Summary of HBO data – conclusions and recommendations

There are limitations to all of the studies reviewed. However, it is still possible to formulate available evidence from TCOM research to guide our clinical decisions in treating problem wounds with HBOT:

- TCOM produces a valid estimate of wound oxygenation, and the available literature suggests that $P_{tc}O_2$ values less than 40 mmHg provide evidence that a wound is hypoxic. A higher value of $P_{tc}O_2$ < 50 mmHg may be appropriate to define hypoxia in diabetics and patients with renal failure.
- TCOM breathing air is unable to predict benefit of subsequent HBOT.
- TCOM breathing 100% oxygen has some predictive value. If $P_{tc}O_2$ < 35 mmHg, then the failure rate is 41%, with an overall accuracy of 69%.
- If in-chamber $P_{tc}O_2$ < 100 mmHg, then the failure rate with HBOT is between 41 and 90%. In-chamber $P_{tc}O_2$ < 50 mmHg is predictive of HBOT failure.
- In-chamber $P_{tc}O_2$ measured breathing HBO is the best single predictor of response to HBOT. $P_{tc}O_2$ > 200 mmHg is a useful predictor of success (74% to 88% reliable). Earlier small studies suggest that in-chamber $P_{tc}O_2$ values should be greater than 400–450 mmHg to guarantee success.

Figure 5
Percentage of successful outcome related to $P_{tc}O_2$ breathing HBO for healing of problem wounds. Line of best fit calculated using least squares exponential regression model. Data from Fife et al, Table 7[23] (TcPO2 = transcutaneous oxygen pressure (mmHg))

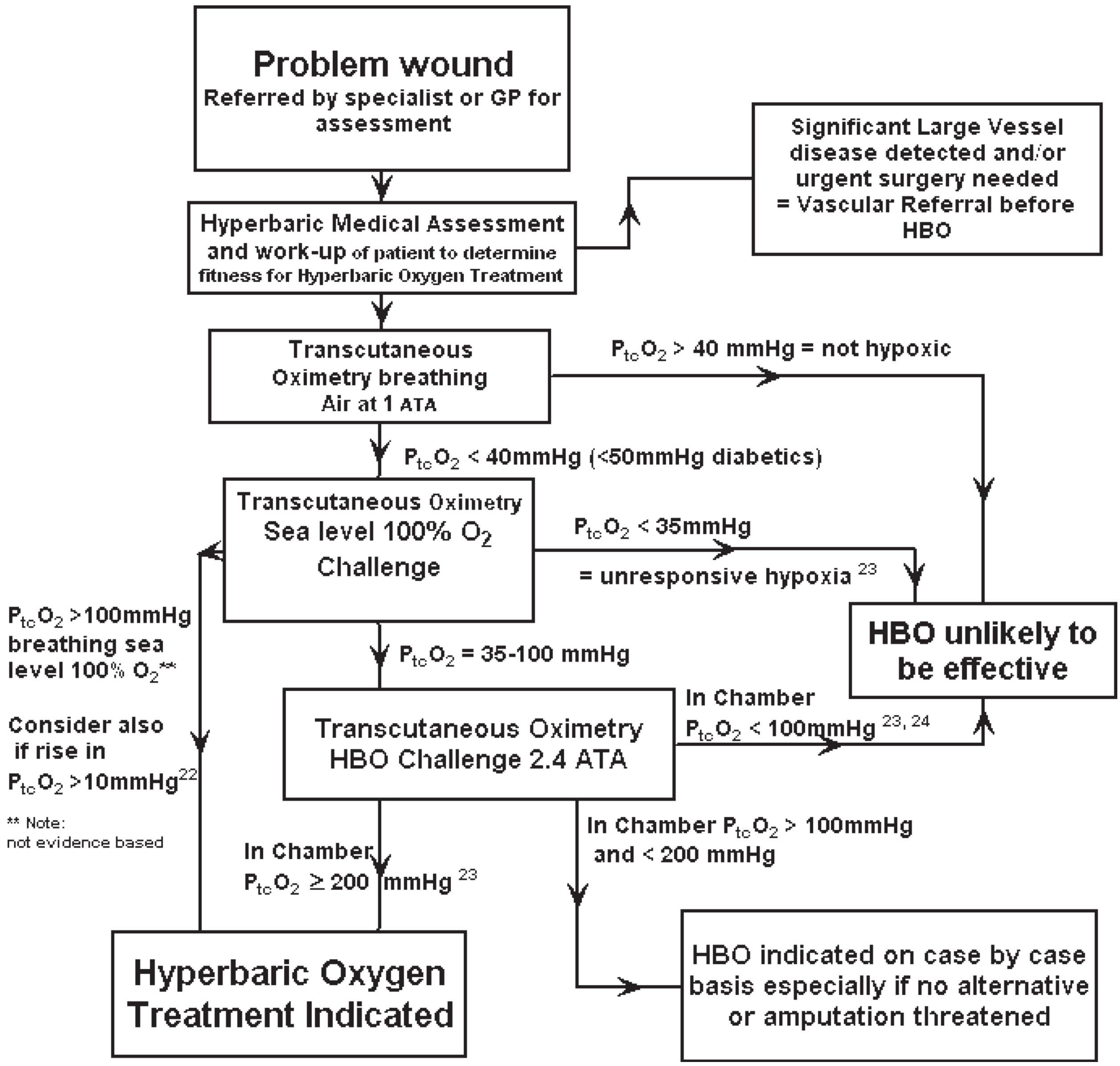


%success = 100 – 5.73 x (TCOM)$^{-0.5046}$

Figure 6 presents a decision flowchart using TCOM to guide clinicians when determining suitability of patients for HBOT. Patients with significant arterial disease should first receive a vascular surgical opinion before commencing HBOT. In assessing suitability for HBOT, the initial step is to confirm that the wound is hypoxic breathing air. Fife et al recommended "*patients with normal values of $TcPO_2$ in air should not be selected for hyperbaric oxygen therapy unless there are mitigating circumstances…*"[23]

Some hyperbaric facilities do not have the capability to undertake in-chamber TCOM, hence it is reasonable to perform an oxygen challenge breathing 100% oxygen at ambient pressure. Data from Strauss et al's 'intermediate responders' suggests that if $P_{tc}O_2$ >100 mmHg breathing HBO, then there is an 88% chance of healing.[24] By inference, if $P_{tc}O_2$ >100 mmHg can be reached breathing 100% oxygen at ambient pressure, then it should be higher breathing HBO. However, until a threshold value breathing 100% oxygen at

Figure 6
Problem wound algorithm, incorporating use of TCOM in selection process (with references)



ambient pressure is determined that suggests benefit from HBOT, uncertainty will exist.

There is a need to validate 100% oxygen, ambient-pressure TCOM threshold values in a larger prospective study to determine if it is useful in predicting response to HBOT. In the interim, we have selected threshold values breathing 100% oxygen at ambient pressure of 35 mmHg for 'non responders' and 100 mmHg to define 'responders'.[23,24] Grolman's group suggested that a rise in $P_{tc}O_2$ > 10 mmHg breathing 100% oxygen at ambient pressure had better predictive value for HBOT success (70%) than the actual $P_{tc}O_2$ value.[22]

When evaluating TCOM in the hyperbaric environment, current studies suggest a high chance of success with HBOT if $P_{tc}O_2$ > 200 mmHg. If the $P_{tc}O_2$ < 100 mmHg, then patients are unlikely to respond to HBOT. Where $P_{tc}O_2$ = 100–200 mmHg, then HBOT should be recommended on a case-by-case basis, especially if there is no viable alternative treatment.

Unanswered questions requiring further research

The above conclusions and recommendations have been drawn from research that has significant limitations. Most of the studies were retrospective, non-randomised and with small numbers. Even the RCTs had small numbers and did not clearly link TCOM with clinical outcomes. A larger, prospective multicentre trial is required to further clarify the role of TCOM in assessment of problem wounds treated with HBOT. In this larger study, TCOM values (in air, 100% oxygen at ambient pressure, and HBO) measured before and after HBOT, need to be carefully correlated with clinically significant outcomes. A number of basic validation studies are also required, for example:

- studies to correlate invasive P_wO_2 with $P_{tc}O_2$ values
- studies to link the measurement of $P_{tc}O_2$ breathing air, 100% oxygen and HBO, in health and disease, to determine the degree of correlation between values
- studies to validate the use of 100% oxygen at ambient pressure to predict HBO response
- studies of post-HBOT $P_{tc}O_2$ values to evaluate their correlation with clinically meaningful outcomes.

Sheffield stated in 1998 "*At this writing, $P_{tc}O_2$ is as much an art as a science*."[14] Since his review we have advanced some way towards defining the role of TCOM in the assessment of problem wounds for treatment with HBOT. There remains considerable work to be done before TCOM is firmly established with a foundation of evidence expected of modern medical procedures.

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