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Clinical Paper

Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa

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Abstract. The aim of this study was to evaluate the effect of hyperbaric oxygen therapy (HBOT) on vascular function and tissue oxygenation in irradiated facial skin and gingival mucosa. Twenty-two patients, aged 51–90 years, were randomly allocated to a treatment or control group. All had a history of radiotherapy (50–70 Gy) to the orofacial region 2–20 years previously. Skin and mucosal perfusion were recorded with laser Doppler flowmetry (LDF). Tissue oxygenation was recorded by transcutaneous oximetry ($TcPO_2$). Measurements were taken before HBOT and 3 and 6 months after a mean of 28 HBOT sessions (partial pressure of oxygen of 240 kPa for 90 min). For control subjects, measurements were taken on two occasions 6 months apart. After HBOT, blood flow in mucosa and skin after heat provocation increased significantly ($P < 0.05$). $TcPO_2$ increased significantly in the irradiated cheek ($P < 0.05$), but not at reference points outside the field of radiation. There were no differences between the 3- and 6-month follow-ups. In the control group, no significant changes in LDF or $TcPO_2$ were observed. It is concluded that oxygenation and vascular capacity in irradiated facial skin and gingival mucosa are increased by HBOT. The effects persist for at least 6 months.

Keywords: angiogenesis; blood flow; laser Doppler flowmetry; microcirculation; radiotherapy; transcutaneous oximetry.

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Radiotherapy is an established treatment modality in the management of head and neck cancer, either used alone or as an adjunct to surgery and/or chemotherapy. Despite advances in dose planning, some healthy tissue will still be included in the field of radiation and sustain injury. During the intensive phase of radiotherapy, tissue injury is evident clinically as mucositis and dermatitis, caused by a depletion of proliferating cells and by inflammatory responses[1]. These acute side effects eventually resolve during the post-irradiation period.

The acute vascular effects include hyperemia and increased vascular permeability, with perivascular fibrin leakage. Over time, the vessels continue to deteriorate, with obliterative endarteritis, thrombosis, and reduced neovascularization, eventually leading to hypovascularity, hypoxia, and fibrosis of the tissue[2]. These effects may remain subclinical for many years, but lead to atrophy, contracture, and potentially debilitating necrosis of soft tissue and bone.

Hyperbaric oxygen therapy (HBOT) is used to induce angiogenesis and increase oxygen tension to improve wound healing in irradiated tissue. Breathing oxygen at an

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increased pressure allows more oxygen to be dissolved in blood plasma. This is thought to induce a steep oxygen gradient between hypoxic, irradiated tissue and surrounding normal tissue, thereby stimulating angiogenesis mediated by macrophages[3]. Recent studies have provided further insight into the mechanisms underlying the effect of HBOT on irradiated tissue: HBOT increases levels of growth factors, such as vascular endothelial growth factor (VEGF)[4], and stimulates vasculogenic stem cell mobilization from the bone marrow in response to oxidative stress[5].

The use of HBOT has been supported by animal studies[2], tissue oxygen studies[6], and randomized clinical trials in various tissues[7–9]. However, the level of evidence is still considered relatively poor[10], and conflicting clinical results are reported in the literature[11]. Furthermore, Rudolph et al. reported normal oxygen tension levels in irradiated skin long after radiotherapy[12]. This contradicts the concept of irradiated tissue as a chronic hypoxic wound; hence there has been less focus on research into the effects of radiation on vascular tissue[13].

Thus there is a need for further investigation of the role of microcirculation and the effect of HBOT on late radiation-induced tissue injury. Doll et al. applied laser Doppler flowmetry to assess cutaneous microvascular tissue after radiation[14]. This method is now available for clinical application and has been evaluated for use in gingival mucosa[15]. Furthermore, provocation testing using oxygen breathing can be used for transcutaneous oxygen measurements[16] and may yield further insight into microvascular function in irradiated tissue. To the best of our knowledge, there are no previously published reports of functional assessment of the effect of HBOT on microcirculation in irradiated tissue.

The aim of the present study was to test the null hypothesis of no effect of HBOT on vascular function and oxygen tension in irradiated facial skin and gingival mucosa.

Materials and methods

Ethics

Participation in the study was based on the written informed consent of each subject. The study protocol was approved by the regional committee for medical research ethics and the privacy ombudsman for research. The study was conducted in accordance with the Declaration of Helsinki.

Subjects

The subjects comprised 22 patients, 15 men and seven women, age range 51–90 years. Patients formerly treated for head and neck cancer and referred to the Hyperbaric Medical Unit at Haukeland University Hospital, Bergen, Norway, were consecutively recruited and allocated to a treatment group ($n = 14$) or a control group ($n = 8$). Group assignment was made after enrolment using a predetermined randomized allocation sequence. The inclusion criterion was a history of radiotherapy $\geq$50 Gy to an area including the oral cavity. Exclusion criteria were unwillingness to receive HBOT, previous treatment with HBOT, active malignant disease or other medical conditions precluding HBOT, and inability to attend the follow-up regimen. Fifty-four patients were invited to participate, giving a participation rate of 41%. Patients were not asked to give any reason for non-participation. The patient characteristics, radiation dose, and time elapsing since radiotherapy are summarized in Table 1. Indications for HBOT were clinical osteoradionecrosis, xerostomia, or as a prophylactic measure before tooth extraction or other surgical procedures. Radiotherapy had been given by fractionated three-dimensional conformal radiotherapy with multiple fields. Dose-fractionation was 2 Gy per day, 5 days per week. The individual dose plans were evaluated to identify the areas of maximal irradiation.

Table 1. Patient characteristics.

Male/female	HBO group ($n = 14$)		Controls ($n = 8$)	
	9/5		6/2	
	Mean	Range	Mean	Range
Age, years	65	51–90	60	53–73
Blood pressure, mmHg				
Systolic	133	104–150	128	108–154
Diastolic	74	63–91	76	61–93
Radiation dose, Gy	66	50–70	65	50–70
Time since radiation, years	6	2–20	4	2–6

HBO, hyperbaric oxygen.

Hyperbaric oxygen therapy (HBOT)

Patients received HBO treatment once daily, 5 days a week, for an average of 28 days. The patients were compressed with oxygen in a monoplace hyperbaric chamber to a pressure of 240 kPa within 10–15 min. Oxygen was breathed at this pressure for 90 min, in three cycles of 30 min, with breathing of compressed air from an oronasal mask for 5 min between cycles. They were decompressed to atmospheric pressure in 7–10 min.

Laser Doppler flowmetry (LDF)

LDF is based on the frequency shift of backscattered laser light from moving objects, to assess the flow of blood cells in superficial vessels[17]. The magnitude of the shift and the intensity of the backscattering are processed, yielding information on perfusion, calculated as the average speed multiplied by the concentration of blood cells in the tissue layers beneath the probe. The instruments were calibrated using a latex suspension, in accordance with the manufacturer's instructions.

Transcutaneous oximetry ($TcPO_2$)

The principle underlying this method of measurement is that temperature-induced vasodilation increases oxygen availability to levels greater than the metabolic demand of local tissue. Oxygen then diffuses from skin capillaries through dermis and epidermis to the sensor. An electrochemical reaction between diffused O_2 molecules and a cathode in the $TcPO_2$ sensor produces an electrical current proportional to the amount of consumed oxygen.

Gingival and skin perfusion measurements

Gingival perfusion was recorded on the buccal gingiva within the field of maximum radiation dose, using a custom-made, tooth-supported acrylic splint. A custom-designed gingival thermostatic multiprobe (Perimed AB, Järfälla, Sweden) was secured by a probe holder fixed to the acrylic splint. Measurements were preferably taken at an edentulous gingival site. In dentate sites, the probe was placed at least 5 mm away from the gingival sulcus or dental papilla, in order to avoid

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areas possibly affected by gingival inflammation. Skin perfusion was recorded on the cheek, within the field of maximum radiation dose and within a limited area that could be reproduced using anatomical landmarks.

Thermostatic probes (Probe 457; Perimed AB, Järfälla, Sweden) were fixed to the skin using double-sided adhesive tape. The probes were connected to PF 5010 laser Doppler perfusion monitoring units and PF 5020 temperature units. The data were recorded in arbitrary perfusion units (PU) and analyzed using PeriSoft software (Perimed AB). Basal flow was recorded for 10 min to allow for stabilization. The probes were then heated and kept at 44 °C on skin and 42 °C on gingiva, followed by 10 min registration. The averages of the last 3 min of each session were recorded.

$TCPO_2$ measurements

$TcPO_2$ measurements were taken using Radiometer TINA TCM30 monitors (Radiometer Medical A/S, Copenhagen, Denmark) and recorded and analyzed using PeriSoft software (Perimed AB). Membranes were replaced in accordance with the manufacturer's instructions and the probes were calibrated to room air and preheated to 44 °C. After allowing 10 min of basal laser Doppler registration, the oxygen tension probes were fixed using standard adhesive fixation rings on the forehead, the second left intercostal space, and on the cheek immediately distal to the laser Doppler probe. In order to achieve stable values, basal registration was carried out for 20 min. The subjects were then given 100% oxygen by mask (15 l/min) and registration continued for 10 min. These methods are described in detail in a previous paper by the same authors[15].

In the treatment group, measurements were taken before the start of HBOT and on two subsequent occasions, 3 and 6 months after treatment. In the control group, the subjects agreed to wait for at least 6 months for the HBOT and measurements were taken on two separate occasions 6 months apart. All measurements were taken by the same investigator, in a temperature-controlled room without visual or auditory distractions. The subjects were allowed to acclimatize for 15 min prior to measurement. Blood pressure, heart rate, and oxygen saturation were monitored using a semiautomatic sphygmomanometer and pulse oximeter (Philips M3046A, Philips Healthcare).

Statistics

The data were entered and analyzed using IBM SPSS Statistics version 19.0 software (IBM Corp., Armonk, NY, USA). The randomized allocation sequence was made by using the random number generator function in SPSS based on an estimated enrolment of 50 patients. Paired differences were analyzed by Wilcoxon signed-rank test. The level of statistical significance was set at $P < 0.05$.

Results

There were no significant differences between the groups with respect to current use of tobacco, blood pressure, cardiovascular health, diabetes, or other microvascular diseases. No major therapeutic complications were observed.

Gingival mucosa

LDF disclosed no significant differences in basal blood flow before and after treatment. The percentage changes from basal value as well as maximal flow after heat provocation increased significantly after HBO ($P < 0.05$). This effect persisted at the 3- and 6-month follow-ups (Fig. 1). In the control group, no significant differences were observed (Table 2).

Skin

Basal temperature blood flow, percentage changes from basal value, and maximal flow after heat provocation was all significantly increased after HBO ($P < 0.05$). The effect was more pronounced for maximal than for basal flow. No significant differences were observed between the two follow-up measurements (Table 2, Fig. 2).

Before treatment, $TcPO_2$ in the irradiated cheek was significantly lower than at the reference points in the forehead and the second intercostal space. After HBO, $TcPO_2$ was significantly increased in the cheek, both by breathing air and by oxygen provocation ($P < 0.05$), but not in the forehead or the second intercostal space. Cheek $TcPO_2$ remained lower than in the second intercostal space, but did not differ from forehead $TcPO_2$ after HBO. The elevated tissue oxygen levels were stable at follow-up (Table 2).

In the control group, there were no significant changes in LDF or $TcPO_2$ measurements at any site throughout the observation period.

Discussion

Irradiated tissue often becomes necrotic as a result of surgical trauma[18]. The normal tissue response to a wound is hyperemia caused by vasodilation, which increases the supply of oxygen and nutrients to the wound, in order to induce healing[19]. Hence the ability of the tissues to increase perfusion on demand is an important prerequisite for predictable healing.

An important finding in this study was the significant increase in maximal blood flow measured after HBOT by heating the laser Doppler probes. This occurred both in gingival mucosa and skin and may indicate a vascular bed with improved healing capacity[20].

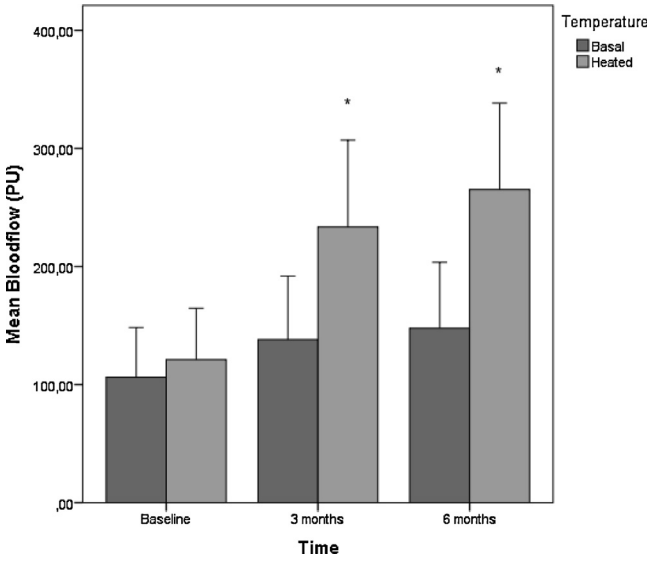

Fig. 1. Changes in gingival blood flow after HBO. *Significantly increased compared to baseline ($P < 0.05$). Error bars represent ±2 SE.

Table 2. Measurements of blood flow by LDF and oxygenation by $TcPO_2$ (mean ± SD).

		HBO group			Controls	
		Baseline	3 months	6 months	Baseline	6 months
Blood flow (PU)						
Gingiva						
	Basal	106 ± 79	138 ± 100	148 ± 104	128 ± 112	122 ± 97
	Heated[b]	121 ± 82	233 ± 137[a]	265 ± 137[a]	148 ± 129	146 ± 104
	PC (%)	19 ± 16	91 ± 99[a]	119 ± 131[a]	16 ± 42	25 ± 47
Cheek						
	Basal	54 ± 41	91 ± 107[a]	106 ± 131[a]	67 ± 54	68 ± 50
	Heated[b]	104 ± 64	275 ± 237[a]	306 ± 237[a]	142 ± 67	143 ± 79
	PC (%)	149 ± 188	322 ± 317[a]	271 ± 271[a]	175 ± 182	135 ± 69
$TcPO_2$ (kPa)						
Forehead						
	Basal	5.3 ± 2.1	5.3 ± 1.5	5.5 ± 1.4	5.5 ± 1.6	5.8 ± 1.4
	Oxygen[c]	18.7 ± 9.5	18.1 ± 5.0	18.3 ± 5.1	17.0 ± 7.4	15.1 ± 5.3
Cheek						
	Basal	3.9 ± 1.8	5.7 ± 2.1[a]	5.7 ± 1.0[a]	4.2 ± 1.2	3.9 ± 1.5
	Oxygen[c]	14.0 ± 5.8	20.1 ± 8.5[a]	19.8 ± 6.5[a]	14.0 ± 5.0	12.7 ± 4.6
Intercostal						
	Basal	7.2 ± 1.8	7.3 ± 2.0	7.9 ± 1.3	8.6 ± 2.4	8.3 ± 1.9
	Oxygen[c]	19.5 ± 7.0	20.9 ± 7.0	20.9 ± 5.8	15.5 ± 4.4	19.4 ± 6.0

LDF, laser Doppler flowmetry; $TcPO_2$, transcutaneous oximetry; SD, standard deviation; PU, arbitrary perfusion units; PC, percent change from basal after heating.
[a] Significantly increased compared to baseline ($P < 0.05$).
[b] Heated: gingiva heated to 42 °C and skin to 44 °C.
[c] Oxygen: oxygen inhalation.

In gingival mucosa, there were no significant differences in pre- and post-treatment basal temperature blood flow. This is in contrast to the report by Granström and Fagerberg-Mohlin in which laser Doppler measurements in mucosa doubled in the HBO-treated group compared to an untreated group[21]. However, the groups were not matched with respect to age and health; the patients in the conservatively treated group were generally older and in poorer health. Nevertheless, baseline values of blood flow were similar in the two groups. All patients in the cited study had established osteoradionecrosis. By contrast, in the present study, most subjects had no signs of necrosis at baseline and measurements were taken on clinically normal gingival mucosa; hence the measurements may have been taken in tissues less severely affected by radiation.

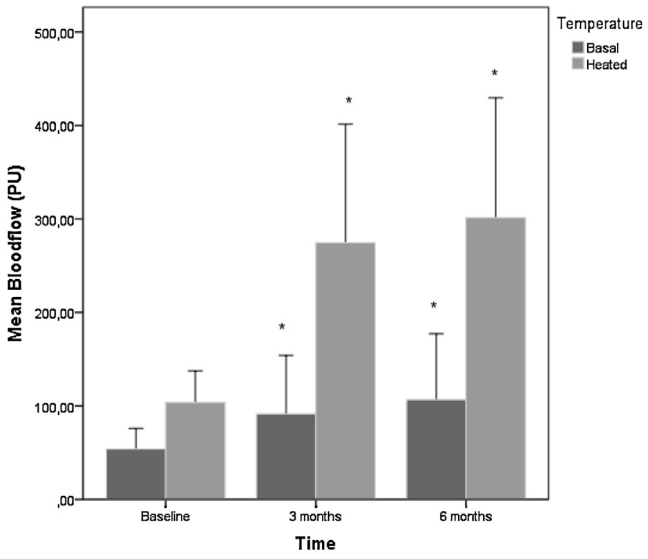

Fig. 2. Changes in irradiated cheek skin blood flow after HBO. *Significantly increased compared to baseline ($P < 0.05$). Error bars represent ±2 SE.

The finding of normal basal blood flow before treatment but poor vasodilation capacity, may indicate injury to irradiated tissue at subclinical levels: under conditions of low physiological strain, homeostasis may be normal, but when demand is increased, impairment of homeostatic function may become clinically evident as a non-healing wound.

In contrast to gingival mucosa, basal blood flow in skin increased after HBOT. This may be due to more severe vascular effects in skin than in mucosa and might indicate a greater tendency in mucosa to vasodilation of non-obliterated vessels, in order to compensate for the reduced vascular density. This compensatory effect has been shown in a histomorphometric study of human buccal mucosa by Handschel et al.[22]. An increased lumen in deeply located vessels in the connective tissue 6–12 months after 60 Gy irradiation was reported, along with a decreased number of capillaries in the sub-epithelial and connective tissue layers. A pronounced effect on basal skin blood flow was also reported by Granström and Fagerberg-Mohlin with continuous improvement from study start to 90 days post-treatment[21]. Patients in this series received

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up to 60 HBO treatments using a previously determined protocol.

Oxygen tension measurements in the HBOT setting have been taken transmucosally[6] and transcutaneously[21,23]. In the study by Thorn et al.[6], gingival transmucosal oxygen tension levels were shown to increase after 30 HBO sessions, from a mean of 50% to a mean of 86% of non-irradiated controls. Beehner and Marx[23] compared oxygen tension on the central radiation port on cheek skin to a reference point on the left second intercostal space during a course of HBOT and reported an increase from 30% of the reference value, reaching a plateau at 82% of the reference value after 20–30 HBO sessions. This increase was shown to persist for several years. An oxygen tension level of 80–85% of non-irradiated tissue was thought to represent the maximal effect attainable by HBOT. This finding that maximal angiogenic potential is reached after 30 HBO treatments could not be confirmed by Granström and Fagerberg-Mohlin who reported a steady increase in $TcPO_2$ for the 90 days of the study, in accordance with the same authors' findings on laser Doppler blood flow. A change in standard routines, increasing the number of HBO treatments from 30 to 40, has been recommended for patients with chronic radiation injury outside the orofacial region where primary healing is intended[24]. This is claimed to yield favourable results, but remains scientifically unproven.

Normal $TcPO_2$ levels in the forehead, cheek, and left second intercostal space skin have previously been reported by the present authors[15]. This study showed significantly lower oxygen tension in forehead and cheek skin compared to the left second intercostal space in normal skin, supporting earlier findings[25]. Using reference points outside the facial region, as in the report by Beehner and Marx[23], may therefore lead to underestimation of the effect of HBOT.

In the present study, transcutaneous oxygen tension was significantly increased in irradiated cheek skin after HBOT, confirming previous findings. However the $TcPO_2$ values achieved after HBOT reached the level of published normal values of $TcPO_2$ in non-irradiated cheek skin[15]. This may be due to the fact that baseline levels of $TcPO_2$ were not as low as those reported in earlier studies[6,23]. In contrast to the present study, the subjects of these earlier studies comprised only patients with osteoradionecrosis, indicating severe tissue injury. The inter-individual variation in radiosensitivity of normal tissue is well known[26]. Therefore although all patients in the present study had a history of substantial irradiation, the tissue effects may have been less severe. Furthermore the first measurements after HBOT were made 3 months after therapy. This allows inclusion of possible continuous effects after completion of therapy. The timing of optimal vascularization after HBOT warrants further investigation: this may be of clinical importance in the timing of surgical interventions after preoperative HBO.

Baseline values of $TcPO_2$ in irradiated skin were significantly lower than at the reference point in the forehead. Rudolph et al. presented data on normal tissue oxygenation even decades after irradiation[12]. The present results support those of earlier studies showing persistently reduced oxygen tension in irradiated skin[2].

There were no differences in perfusion and tissue oxygenation at 3 and 6 months after HBOT. This indicates that the effects of HBOT are long-lasting or even permanent, as concluded by earlier studies[23]. In accordance with the same report, there were no changes in $TcPO_2$ before and after HBO at the reference points outside the field of radiation. This may indicate that hypoxia is essential for the angiogenic effect of HBOT.

The reported improvement in vascular capacity and oxygen tension may be due to neoangiogenesis[2], but also improved endothelial function. The response of blood flow to continuous heating is recognized as being biphasic. An early peak is mediated by C-fibre nociceptors triggering vasodilation, followed by a late phase of nitric oxide-dependent vasodilation[27]. An impaired nitric oxide-mediated vasodilation has been shown in irradiated blood vessels associated with a lack of expression of endothelial nitric oxide synthase[28]. This could therefore partly explain the reduced reactivity to heat provocation seen after radiotherapy.

Delanian and Lefaix have proposed that the factors maintaining tissue injury after radiation are dysregulation of the release of growth factors, e.g. transforming growth factor beta 1 (TGFβ1), and continuous attack of reactive oxygen species (ROS)[13]. HBO has been shown to enhance oxidative stress resistance in endothelium[29] and this may be an important mechanism in the repair of vascular function. Concentrations of ROS and nitric oxide species (NOS) are elevated during the transient hyperoxia in HBO. These serve as signal molecules for growth factors, cytokines, and hormones, and have been shown to play an important role in neoangiogenesis and wound healing[30]. The observed effects by HBOT in the present study are therefore most likely a combination of increased vascular density and improved function. However, further investigation is needed to fully understand the role of HBOT in irradiated tissue and wound healing.

Within the limitations of this study it is concluded that the vascular capacity in irradiated facial skin and gingival mucosa and tissue oxygenation in irradiated facial skin is increased by HBOT. The vascular effects persist for at least 6 months.

Funding

University of Bergen.

Competing interests

None declared.

Ethical approval

The study protocol was approved by the Regional Committee for Medical Research Ethics in Western Norway (REK Vest), reference 218.05, and the Privacy Ombudsman for Research at the Norwegian Social Science Data Services (NSD).

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