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Oxygen in Wound Healing and Infection

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Abstract. It is a fundamental clinical observation that wounds do not heal in tissue that does not bleed, and they almost always heal in tissue that bleeds extensively. Continuous supply of oxygen to the tissue through microcirculation is vital for the healing process and for resistance to infection. Evaluation of tissue perfusion and oxygenation is important in all types of wound patients. Monitoring systems should measure the hemodynamic situation and the ability of the cardiovascular system to deliver an adequate volume of oxygen to meet the metabolic demands of the peripheral tissue. Oxygen therapy is important in relation to both healing and resistance to infections. External factors have been shown to significantly decrease the peripheral oxygen supply, and supplementary perioperative oxygen to reduce the surgical wound infection rate by one- half in patients undergoing colorectal resection. Hyperbaric oxygen therapy may be beneficial in situations where the nutritive flow and oxygen supply to the healing tissue are compromised by local injury, and particularly if anaerobic infection is present. However, the definitive proof for the effect and indications of this therapy in wound healing still has to be established. It can be concluded that adequate delivery of oxygen to the wound tissue is vital for optimal healing and resistance to infection. Assessment of perfusion and oxygenation is essential for the wound patient, as well as the treating personnel. The indication for hyperbaric oxygen treatment still needs to be defined. During wound healing the continuity and function of the damaged tissue are re-established. This is only possible through a restoration of the microcirculation and thereby the nutrition to the tissue. The main component of the nutrition is oxygen, which is critically important for healing a wound by production of granulation tissue and for ensuring resistance against infection. This has been shown experimentally, but recently a short period of supplementary oxygen has been shown to decrease wound complications in clinical practice as well.

The wound healing process involves numerous functions, many of which are dependent on the presence of oxygen. Collagen production and development, which influences the strength of the wound, is directly correlated with the partial oxygen pressure Po_2 of the tissue (P_tO_2) [1–3]. Synthesis of collagen, cross-linking, and the resulting wound strength is reliable of the normal function of specific enzymes [1–5]. The function of these enzymes is directly related to the amount of oxygen present—e.g., hydrolyzation of proline and lysine by hydroxylase enzymes [6]. These enzymes have a Km (concentration of substrate resulting in a half-maximal rate of enzyme activity) of oxygen from 20 to 100 mmHg [7, 8], and the production of collagen has been found proportional to P_tO_2 up to 120 mmHg [3, 5]. The limit for production of collagen seems to be a P_tO_2 of 20 mmHg.

The production of epithelial tissue depends primarily on the degree of hydration and oxygen. Although a moist wound environment increases the rate of epithelialization by a factor of 2 to 3 [9, 10], the optimal growth of epidermal cells is found at an oxygen concentration of 10% to 50% [11–13]. Hyperbaric oxygen treatment increases the proliferation of the fibroblasts and the differentiation and epidermopoesis of the keratinocytes, but not the proliferation of keratinocytes [14].

The production of lactate in combination with oxygen is also important in healing. Lactate in combination with growth factors stimulates the proliferation of fibroblasts and regeneration of new vessels (angiogenesis). However, a sufficient P_tO_2 is also necessary for these processes.

Angiogenesis is critical important in wound healing, and hypoxia has been identified as an important trigger for transcription of angiogenetic factors [15]. The cell response to hypoxia has been extensively studied in the last decade. Hypoxia introduces a cellular stress reaction and initiates a complex genetic cascade. Hypoxia-inducible factor 1 (HIF-1) has been identified as a transcription factor that is induced by hypoxia [16].

In the presence of normal oxygen tensions HIF-1 transceptional activity is ubiquuinated and degraded [17]. HIF-1 seems to upregulate genes involved in glucose metabolism and angiogenesis under hypoxia, and in a model of myocardial and cerebral ischemia the factor seems to protect cells from damage. The exact molecular mechanisms of how hypoxia is sensed by the cells are still unknown.

Oxygen and Tissue Perfusion

Delayed or arrested healing and development of infection result from decreased perfusion and, consequently, oxygenation of the tissues. This is most clearly demonstrated in the well-perfused tissue anal region, where the healing normally is good in spite of massive contamination. P_tO_2 is based on the following factors: (1) delivery of oxygen from the lungs to the tissue (i.e., oxygenation of arterial blood, circulation); (2) transport of oxygen from blood to tissue (i.e., oxygen partial pressure in blood, the diffusion distance); and (3) oxygen consumption in tissue [18]. At present, P_tO_2 measurements are the best way to observe the oxygen status of the tissue.

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Oxygen delivery is normally more dependent on oxygen bound to hemoglobin in the erythrocytes than on the arterial partial pressure of oxygen (Po_2). This is particularly true for muscle tissue, which has small intercapillary distances and a high consumption of oxygen [19]. In subcutaneous tissue, however, the intercapillary distances are higher and the consumption of oxygen is relatively low. Trauma of this tissue is followed by injured microcirculation and contraction of the vessels. Increased diffusion distances then develop, and the Po_2 becomes the major means of oxygen transport. Slowly healing tissues as subcutis, tendon, fascia, and bone then become dependent on Po_2 in blood and tissue and, to a lesser degree, on the concentration of hemoglobin in blood [20]. Anemia with hematocrit values of 15–20 will, in cases of normal heart function and normal tissue perfusion, be of minor importance for the Po_2 in the wound area and consequently will not affect the healing. In the subcutaneous tissue there is constant oxygen consumption, which means that in tissues with a sufficient peripheral tissue perfusion the Po_2 in tissue and blood correlate. A significant rise in Pto_2 after increased F_io_2 therefore indicates normal tissue perfusion [21].

Measurement of P_to_2 can be accomplished by introducing a small oxygen sensor in the tissue. Subcutaneous tissue is the first tissue to suffer from oxygen deprivation and the last to be normalized, for which reasons this tissue level is the optimal place for monitoring general tissue perfusion [22]. Clinically, measurement of the blood saturation (pulse oximetry) is used routinely. This method, however, reflects primarily the oxygen conditions in the blood, and it only has value in situations where all factors that influence P_to_2 are functioning optimally.

To normalize this value to non-surgical level after major surgical procedures, the patients must be given supplementary oxygen [23]. The need for supplementation may result from impaired tissue perfusion. In any case, in these situations a normal oxygen saturation (pulse oximetry) value will not correlate with the P_to_2 and cannot be used to evaluate the level of oxygen in the tissue.

In hyperbaric oxygenation pure oxygen at a pressure of 3 atm raises the diffusion distance of oxygen in the tissue by a factor of 3 to 4 in the arterial end of the capillary and by a factor of 2 in the venous end [24]. Although hyperbaric oxygen treatment has shown little effect on the healing of normal uncomplicated wounds, there have been suggestions that it is effective in complicated ischemic wounds in arteriosclerotic or diabetic patients. A final proof of such an effect is, however, still needed; for this, randomized trials have to be initiated.

Oxygen and Influencing Factors

Internal as well as external factors influence the P_to_2. In subcutaneous tissue the tissue perfusion is extremely dependent on hemodynamic conditions, cooling, pain, fear, smoking, and medical compounds. Many of these factors are encountered during surgery. The early arterial hypoxemia related to anesthesia occurs in the early postoperative hours, and the late hypoxemia related to a decrease in lung capacity is based primarily on reduced function of the diaphragm 2 to 3 days postoperatively [25]. Early hypoxemia and reduced tissue perfusion enhance the risk of wound complications. The influence of late hypoxemia, however, is not well understood.

In surgical patients smoking is known to increase the risk of necrosis of the wound edge, diminish the cosmetic result, and increase the risk of wound infection in a variety of surgical ambulatory and in-patient surgical procedures. It has been associated with the risk of anastomotic leakage after bowel surgery and an increased recurrence rate after hernia surgery [17, 26, 27]. These damaging effects on the healing process are provided by different mechanisms. Nicotine is quickly absorbed and starts a release of catecholamines, resulting in peripheral vascular constriction followed by decrease in perfusion rate of 42%. Furthermore the CO in the cigarette smoke will reduce the oxygen content of the blood. Smoking one cigarette has been shown to decrease the tissue perfusion by more than 30% in more than 45 minutes in specific areas of the body [28]. In such areas the production of collagen is 1.8 times higher in non-smokers than in smokers (more than 20 cigarettes per day) [29]. However, recent studies have raised a number of questions about the role of nicotine in smoking-related diseases. In a recently published study, a nicotine patch did not result in wound healing defects [30]. This and other findings concerning nicotine might change the initial interpretation; that tissue hypoxia is secondary to the vasoconstrictive effect of nicotine to a question of whether nicotine alone or other factors can cause local tissue hypoxia [17].

Oxygen and Postoperative Infection

The most frequent complication found in surgical wounds is still infection. Bacteria in wounds are normally destroyed by intracellular oxidative mechanisms inside the leukocyte, and molecular oxygen is necessary for production of oxygen radicals, especially bactericidal superoxide. The oxygen concentration in the breathing air directly correlates with the size of the necrosis generated by injection of bacteria [31]. The critical level for this seems to be below 30 to 40 mmHg. In a human study of colorectal patients, a direct correlation between subcutaneous Po_2 and the resulting postoperative wound infection rate has been shown [21]. If a rise of oxygen concentration in the breathing air did not result in an increased subcutaneous Po_2, 45% of the patients developed a postoperative infection. If, however, the tissue perfusion was sufficient to cause an increase of Po_2 in subcutaneous tissue to 90 mmHg or more, no patient developed wound infection. Beside decreased production of oxygen radicals, hypoxia causes premature activation of the leukocytes leading to a decrease in their effect on bacteria. Production of interleukin (IL)-2 and IL-8 is also decreased if hypoxia is present.

In one third of all wound infections the bacteria found are sensitive to the antibiotic provided during the treatment course [32]. Decreased perfusion may be the reason for this. Experimental studies have shown that antibiotics and oxygen are additive [33–35], and antibiotics are less effective in hypoxic wounds [36, 37]. Whereas antibiotic delivery started more than 3 hours after the tissue trauma and bacterial contamination have no effect on the wound infection rate, oxygen has been shown to have an antibacterial effect after 6 hours [2]. The exact time period of effect for oxygen delivery is still not known. Using the SENIC score system it was found that 40% of infections occurred in the 55% of patients classified as having uncontaminated wounds [38]. Infection in clean wounds traditionally has been rationalized as due to unrecognized contamination. In fact, reduced perfusion may be the reason for the decreased resistance for even small degrees of bacterial contamination [21].

Smoking also results in a higher incidence of postoperative wound infections. This effect has even been described for minor, clean wounds [30]. A significant difference in infection rate (12% in smokers compared to 2% in never-smokers; $p < 0.05$) was found. Preoperative abstinence from smoking has been found to reduce postoperative wound infections significantly [39]. The exact timing

or abstinence has, however, been discussed. In the minor clean wound study 4 weeks abstinence was found to reduce the wound infection rate to the level of never-smokers [30].

Oxygen and Clinical Practice

Oxygen has for a long time been used in clinical practice to enhance wound healing. Locally, oxygen has been applied to the wound surface to increase regeneration of epithelium. The effect of this treatment has not yet been fully established. Systemic administration of oxygen through the lung and the cardiovascular system, however, is known to improve wound healing and decrease the risk of infection [3, 5, 19, 31]. Supplementary oxygen in the inspired air for the first 2 postoperative days has reduced the postoperative wound infection rate after colorectal surgery [21]. Recently it has been shown that these patients benefit from as little as preoperative and 2 hours postoperative oxygen supplementation administered by mask [40]. An inspired oxygen concentration of 80% decreased the wound infection rate by one half (11.2% against 5.2%; $p = 0.01$) compared to an oxygen concentration of 30%. Oxygen administration during and 2 hours after surgery is accomplished in the operation room and the recovery room. This is an easy, cost-effective, and useful way to decrease the infection rate in colorectal patients. Furthermore this treatment has beneficial side effects. Supplementary oxygen treatment should from the author's point of view be a standard procedure for the treatment of all colorectal patients. Future studies may clarify the optimal time period for oxygen administration, and which types of surgery have beneficial effect of supplementary oxygen.

Local hypoxia and bacterial contamination primarily are primarily dependent on surgical technique; oxygenation of the patient is essentially dependent on the expertise of the anesthesiologist. Optimal collaboration betweenthe surgeon and the anesthesiologist is therefore of vital importance. This collaboration is especially important for the delivery of oxygen treatment during surgery, in the recovery room, and throughout the first postoperative day. From the development of a standardized description of the treatment plan and a realistic quality assurance program for the patient during the preoperative, intraoperative, and postoperative periods the collaboration can be improved [41]. Oxygen treatment and monitoring of oxygen tension and saturation could be performed as described in Table 1. These procedures and measurements can be performed during operation, but they should be continued in the recovery room and in the surgical wards for the first, and perhaps the second, postoperative day.

Problems with delayed healing and infection of wounds are in most cases related to oxygen delivery to the wound tissue. However, it must be emphasized that in clinical daily life not all types of problem wounds will be oxygen related. For example, in pure venous leg ulcers the pathophysiology is not fully understood, but the etiology seems to derive from the upright position of humans and the resulting increased pressure in the venous vessels of the leg. In diabetic foot lesions the main problem is the risk of infection, which can be seen even in almost normal perfusion of the foot. The problem probably is based on a reduced ability of the leukocytes to kill bacteria in the diabetic patients. In some cases of problem wounds in association with immunological defects, the tissue is not ischemic and lack of oxygen is not the main problem. A careful clinical evaluation and assessment of tissue perfusion and oxygenation in the wound and surrounding areas are therefore essential parts of the treatment of all problem wounds. In clinical practice problem wounds often are found in the lower extremity; if there is no pulse in the foot arteries, tissue perfusion can be evaluated by measurement of toe-pressure, ankle-arm index (Doppler system), or transcutaneous oxygen.

Table 1. Proposal for monitoring and treatment in major and minor surgery of patients with organ dysfunction and symptoms.

Monitoring
Direct measurements of the subcutaneous oxygen tension in an artificial wound and the upper arm
Continuous measurement in the first 2 postoperative days
(Is the best method but not routine today)
Measurement of the oxygen saturation in blood (pulse oximetry)
Continuous measurement in the first 3 postoperative days
(Routine in many countries)
Treatment
Using a mask (e.g., Hudson mask)
Oxygen 80% and nitrogen 20% during surgery and the following 2 hours
Double tube nasal oxygen-delivery system. (Single nasal oxygen catheter has not been shown effective—personal observations)
Starts after treatment with oxygen mask in case of low oxygen values in tissue and low values of blood saturation

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See "Note added in proof"

Conclusions

Oxygen is vital for the healing of wounds and avoidance of infection postoperatively. Supplementary systemic oxygen has been shown to decrease the infection rate after colorectal surgery. Indications for local and hyperbaric oxygen treatment of problem wounds still need to be proven in future research.

Résumé. Une observation fondamentale en clinique est qu'en absence de saignement, les tissus ne cicatrisent pas et son corollaire, les tissus cicatrisent presque toujours lorsqu'ils saignent abondamment. L'apport d'oxygène en continu dans la microcirculation est essentiel dans le processus de cicatrisation et dans la résistance à l'infection. L'évaluation de la perfusion et de l'oxygénation tissulaires est importante chez tous les patients en voie de cicatrisation. Il faut des systèmes de monitorage pour mesurer la situation hémodynamique et la capacité du système cardiovasculaire à délivrer un volume adéquat d'oxygène afin de couvrir les besoins métaboliques des tissus périphériques. On a démontré le rôle important de l'oxygénothérapie dans la cicatrisation et la résistance aux infections. Certains facteurs externes sont connus pour diminuer de façon significative l'apport vers la périphérie de l'oxygène et on sait que l'apport d'oxygène supplémentaire en périopératoire réduit par deux le taux d'infection des plaies opératoires chez les patients opérés d'une résection colorectale. L'oxygénothérapie hyperbare peut être utile dans des situations où l'apport nutritif et d'oxygène aux tissus est compromis par les lésions locales et particulièrement si une infection à anaérobie est présente. Cependant, la preuve définitive de l'effet et les indications de cette thérapie restent à trouver. On peut conclure que l'apport d'une quantité adéquate d'oxygène au niveau de la plaie est vitale pour une cicatrisation optimale et la résistance aux infections. L'évaluation de la perfusion et de l'oxygénation est essentielle aussi bien pour le patient dans la période de cicatrisation que pour le personnel qui le traite. L'indication de l'oxygénothérapie hyperbare reste à définir.

Resumen. Una observación clínica fundamental es que las heridas no cicatrizan en tejidos que no sangran y que casi siempre cicatrizan en tejidos que sangran abundantemente. La provisión continua de oxígeno a los tejidos a través de la microcirculación es vital para el proceso de cicatrización, así como en la resistencia a la infección. La evaluación de la perfusión y la oxigenación tisulares es importante en todo tipo de heridas. Los sistemas de monitoría deben determinar la situación hemodinámica y la habilidad del sistema cardiovascular para proveer un adecuado volumen de oxígeno para atender las demandas metabólicas del tejido periférico. La

oxígenoterapia ha demostrado ser importante tanto en lo relativo a cicatrización como a la resistencia a infecciones. Se ha demostrado que factores externos disminuyen significativamente a la mitad, el riesgo de infección en pacientes sometidos a resección colo-rectal. La oxígenoterapia hiperbárica puede resultar beneficiosa en situaciones en las cuales el flujo nutricional y la provisión de oxígeno a los tejidos en vía de cicatrización estén comprometidos por lesiones locales y, particularmente, en presencia de infección anaeróbica. Sin embargo, aún no se ha comprobado en forma definitiva el efecto y las indicaciones de esta modalidad terapéutica en el proceso de la cicatrización de heridas. Se puede concluir que la provisión de oxígeno a los tejidos lesionados es vital para una óptima cicatrización y para la resistencia a la infección. La debida determinación del estado de perfusión y de oxigenación es algo esencial en el manejo del paciente con heridas y debe ser conocida por el personal a cargo de su tratamiento. Todavía está por definirse la indicación de la oxígenoterapia hiperbárica.

Note added in proof

Since this manuscript has been proofread a study focusing on the use of perioperative hyperoxia has been published (Pryor KO, Fahey TJ, Lien CA, Goldstein PA (2004) ″Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population″ JAMA 291:79–87). It does not support the routime use of high FIO2 in patients undergoing abdominal surgery to reduce surgical site infections. This study is not in all aspects directly comparable to earlier studies in this area, but the results of this study emphasize the need for further investigations, before the precise indications of the use of supplementary oxygen, as described in Table 1, are known.

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