

How Oxygen Works in Wound Healing

This is a summary overview of the current scientific and clinical literature regarding the mechanisms and efficacy of oxygen in wound healing. Detailed information with references follows the front page. Information regarding what Continuous Diffusion of Oxygen (CDO) is, how it differs from other oxygen technologies and supporting clinical evidence can be found in the EO₂ guidance document “How CDO Works”.¹ CDO is essentially moist wound therapy plus oxygen: pure humidified oxygen is continuously added into an oxygen diffusion dressing.



1. Increases Cell Metabolism and Energy

Oxygen boosts vitality to support increased demand during healing - oxygen is required for intracellular processes like biosynthesis, movement, and transport need energy to be functional, as well as for cell survival



2. Faster Wound Closure (up to 4.6x)

Increasing oxygen levels results in faster cell proliferation, reepithelialization and collagen formation – wounds heal up to 4.6x faster than moist wound therapy alone



3. Rapid Pain Relief (as fast as several hours)

Increasing oxygen levels relieves hypoxic pain resulting in significant pain reduction – some patients report complete pain relief within several hours



4. Greater Wound Perfusion & Angiogenesis

Oxygen levels directly affect the rate and quality of new blood vessel growth in the wound bed - the creation of new blood vessels, angiogenesis, is essential to the growth and survival of repair tissue



5. Naturally Antibacterial

Increased oxygen levels aid the natural capacity to fight infection - oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), used by phagocytes such as neutrophils and macrophages in bactericidal activity and the removal of necrotic cellular debris



6. Better Strength & Appearance

Oxygen levels directly affect the rate and quality of collagen formation – oxygen is required for proper fiber formation and cross-linking to form organized collagen, resulting in better strength and appearance



7. Promotes Growth Factor Signaling Transduction

Oxygen kicks off a signaling cascade - ROS are essential for the signaling processes of growth factors and processes such as leukocyte recruitment, cell motility, angiogenesis and extracellular matrix formation



1. Increases Cell Metabolism and Energy

Oxygen is required for intracellular processes like biosynthesis, movement, and transport need energy to be functional, as well as for cell survival²

- Oxygen dependent enzymes include:
 - Adenosine triphosphate (ATP) for chemical energy, which fuels most active cellular processes such as during wound healing.³ Increased energy demand of the healing tissue leads to a hypermetabolic state wherein additional energy is generated from oxidative metabolism increasing the oxygen demand of the healing tissue.^{4,5,6,7} ATP thus generated powers tissue repair
 - NADPH (nicotinamide adenine dinucleotide phosphate) oxygenase for respiratory burst (reactive oxygen species release), the activity of which is critically required to produce the redox signals required for wound healing^{8,9,10}
- Aerobic glycolysis, β -oxidation of fatty acids, and the citric acid cycle are tightly attached to the energy acquisition by oxidative phosphorylation and are therefore oxygen dependent¹¹
- If oxygen levels are too low (<20 mmHg pO₂), cells convert to anaerobic metabolism and go into survival mode in which wound healing activities such as mitosis (cell division, and therefore reepithelialization) and collagen production are impaired^{12,13,14}
- Prolonged exposure to extremely low oxygen levels, if not alleviated by oxygen, can result in cell death and tissue necrosis due to the inability of the cells to repair the spontaneous decay of cell components (DNA, RNA, proteins) and inability to maintain calcium pumps which require ATP to function^{15,16}



2. Faster Wound Closure (up to 4.6x faster than moist wound therapy)

Increasing oxygen levels results in faster cell proliferation, reepithelialization and collagen formation

- The continuous, topical addition of pure oxygen (CDO therapy) over diabetic wounds has been shown to increase the rate of wound closure, by as much as 460% relative to moist wound therapy^{17,18,19,59}
- Adding oxygen improves closure in wounds that are larger, more chronic and weight-bearing,^{17,18} as well as those that are deeper²⁰
- CDO therapy has been shown to achieve full wound healing in a variety of wounds that were resistant to other advanced therapy treatments^{17,18,19,20,21,22,28,29}
- Fibroblast proliferation and protein production have been reported to be optimal at 160 mmHg, i.e. at pO₂ levels 2-fold to 3-fold higher than those found in healthy tissues²³, indicating that supplemental oxygen increases the rate of wound repair
- Endothelial progenitor cells (EPCs) are essential in wound healing, but their circulating and wound level numbers are decreased in diabetes. Elevated oxygen levels (hyperoxia) reverse the diabetic defect in EPC mobilization²⁴
- EPC mobilization into circulation is triggered by hyperoxia through induction of nitric oxide (NO) with resulting enhancement in ischemic limb perfusion and wound healing^{25,26,27}



3. Rapid Pain Relief (as fast as complete pain relief within hours)

Increasing oxygen levels relieves hypoxic pain resulting in significant pain reduction –patients have been reported to experience complete pain relief within several hours

- The addition of a continuous flow of pure oxygen over a variety of wound types has been shown to significantly decrease pain in short time frames – over half of the 20 patients experienced at least a 75% reduction within 4 days²⁸



How Oxygen Works in Wound Healing

- With a patient serving as her own control, CDO had reduced pain from 8 to 2 and she had ceased pain medication. She removed CDO for a few days and the pain increased to 10. Upon reapplying CDO, pain quickly reduced to 2 again.²⁹
- In a study of 10 patients with venous ulcers, CDO therapy was reported to significantly ($P < .009$) reduce pain in a six-week period. The corresponding mean reduction in wound size was 58.9%.³⁰
- Several case series reviews report significant pain reduction in very painful wounds.^{31,32}



4. Greater Wound Perfusion & Angiogenesis

The creation of new blood vessels, angiogenesis, is essential to the growth and survival of repair tissue. Oxygen levels directly affect the rate and quality of new blood vessel growth

- Sufficient oxygen levels are required for correct collagen synthesis (posttranslational hydroxylation)³³, without which the new capillary tubes assemble poorly and remain fragile^{34,35,36}
- Supplemental oxygen accelerates blood vessel growth³⁷
- Moderate hyperoxia increases the appearance of new blood vessels in wounds³⁸
- The rate of angiogenesis is directly proportional to oxygen levels in injured tissues and rates of collagen deposition increase proportionally with oxygen levels to more than 250 mmHg³⁵
- Conversely, hypoxic wounds deposit collagen poorly and become infected easily^{39,40}



5. Naturally Antibacterial

Oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), used by phagocytes such as neutrophils and macrophages in bactericidal activity and the removal of necrotic cellular debris

- NADPH oxidase, also known as leukocyte oxidase, supports macrophage survival (delay of apoptosis)⁴¹ and enables dead cell cleansing by phagocytosis⁴²
- NADPH oxidase in wound phagocytes, such as neutrophils and macrophages, produces superoxides (O_2^- and H_2O_2) for bactericidal activities⁴³ – in fact, ~98% of oxygen consumed by these cells is used to produce ROS during phagocytosis⁴⁴
- Leukocyte activity (production of ROS and hence oxidative killing) is directly proportional to local oxygen concentration^{45,46}
- Optimal ROS production is seen at oxygen levels of greater than 300 mmHg¹⁹, levels which can only be achieved with supplemental oxygen⁴⁷
- At the wound site, ROS are generated by almost all wound-related cells⁵¹
- The efficacy of supplemental oxygen has been shown to be similar to antibiotic administration and has additive effects when used together^{48,49}



6. Increases Collagen Synthesis and Tensile Strength

Oxygen is essential to make and properly organize collagen, which is the primary component of skin, accounting for 70-80% (dry weight – without water) and acts as the structural scaffold of skin. Organized collagen is bundled into fibers (like strands in rope), which are interwoven and can be stretched in multiple directions without tearing (the collagen fibers are woven similar to fabric)

- Oxygen is required for the hydroxylation of proline and lysine in procollagen⁵⁰
- Several posttranslational steps in collagen synthesis are oxygen dependent. The enzymes prolyl hydroxylase, lysyl hydroxylase and lysyl oxidase all require oxygen^{51,52,53}
 - Formation of cross-linked triple-helices via the oxygen-dependent enzyme prolyl

How Oxygen Works in Wound Healing

- hydroxylase and excreted as collagen fibers
 - Collagen fibers are arranged into linear fibrils via cross-linking by lysyl hydroxylase
 - Linear fibrils are cross-linked by lysyl oxidase - a necessary step to achieve the necessary tensile strength for healed wounds
- Higher oxygen concentrations increase the amount of collagen deposition⁴⁰ and tensile strength^{54,55,56}
- The rate limiting step is the rate of prolyl hydroxylation^{52,53}
- The oxygen level required for optimal prolyl hydroxylase activity is at oxygen levels approaching 250 mmHg, exceeding those present in normal wounds^{57,58}
- It has been shown that increasing oxygen above normal physiologic levels enhances collagen synthesis and tensile strength in both animal and human subjects^{54,55,56} and can increase the level of collagen organization⁵⁹
- Correction of vasoconstriction and hypoxia can result in a 10-fold increase in collagen deposition in wound repair^{40,55,60,61}



7. Promotes Growth Factor Signaling Transduction

Reactive oxygen species (ROS) are essential for the signaling processes of growth factors and processes such as leukocyte recruitment, cell motility, angiogenesis and extracellular matrix formation

- Signal transduction of growth factors happens through ROS⁶²
- ROS such as hydrogen peroxide (H₂O₂) increase vascular endothelial growth factor (VEGF) production in macrophages and keratinocytes^{63,64}
- VEGF is a major long-term angiogenic stimulus at the wound site
 - oxygen treatment induces VEGF mRNA levels in endothelial cells and macrophages^{65,66,67}
 - oxygen treatment increases VEGF121/165 protein expression in wounds⁶⁸ and facilitates the release of VEGF165 from cell-associated stores⁶⁹
- Platelet-derived growth factor (PDGF) requires ROS in its role to regulate cell growth and division⁷⁰, and PDGF plays a significant role in blood vessel formation (angiogenesis)⁵¹
- ROS has effects on other processes such as cytokine action, cell motility and extracellular matrix formation⁸
- Conversely, tissue hypoxia will limit redox signaling and disable the function of several growth factors (e.g., PDGF, VEGF, keratinocyte growth factor, insulin-like growth factor, transforming growth factor- α) and numerous molecular mechanisms (e.g., leukocyte recruitment, cell motility, integrin function), which rely on redox signaling^{10,71,72}

NOTES:

- Some sections of the above text with citations are directly extracted from the referenced literature without quotations
- Recommended summary articles on oxygen in wound care include articles by Sen², Tandara and Mustoe¹¹, Gordillo and Sen⁵¹ and Schreml et al⁷³

REFERENCES

- ¹ EO2 White Paper: How CDO Works. p/n 690023 (current revision)
- ² Sen CK. Wound Healing Essentials: Let There Be Oxygen. *Wound Rep Reg* 2009; 17: 1–18.
- ³ Ichioka S, Ando T, Shibata M, Sekiya N, Nakatsuka T. Oxygen consumption of keloids and hypertrophic scars. *Ann Plast Surg* 2008; 60: 194–197.
- ⁴ Gupta A, Raghurib R. Energy metabolism in the granulation tissue of diabetic rats during cutaneous wound healing. *Mol Cell Biochem* 2005; 270: 71–77.
- ⁵ Hohn DC, Ponce B, Burton RW, Hunt TK. Antimicrobial systems of the surgical wound. I. A comparison of oxidative metabolism and microbicidal capacity of phagocytes from wounds and from peripheral blood. *Am J Surg* 1977; 133: 597–600.
- ⁶ Matsuda T, Clark N, Hariyani GD, Bryant RS, Hanumadass ML, Kagan RJ. The effect of burn wound size on resting energy expenditure. *J Trauma* 1987; 27: 115–118.
- ⁷ Im MJ, Hoopes JE. Energy metabolism in healing skin wounds. *J Surg Res* 1970; 10: 459–464.
- ⁸ Sen CK. The general case for redox control of wound repair. *Wound Repair Regen* 2003; 11: 431–438.
- ⁹ Roy S, Khanna S, Nallu K, Hunt TK, Sen CK. Dermal wound healing is subject to redox control. *Mol Ther* 2006; 13: 211–220.
- ¹⁰ Sen CK, Roy S. Redox signals in wound healing. *Biochim Biophys Acta* 2008; 1780: 1348–1361.
- ¹¹ Tandara AA, Mustoe TA. Oxygen in Wound Healing – More Than a Nutrient. *World J Surg* 2004; 28: 294–300.
- ¹² LaVan FB, Hunt TK. Oxygen and wound healing. *Clin Plast Surg* 1990; 17: 463–472.
- ¹³ Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation. *Ann Plast Surg* 2003; 51: 210–218.
- ¹⁴ Hunt TK. Basic principles of wound healing. *J Trauma* 1990; 30: S122–S128.
- ¹⁵ Milton SL, Prentice HM. Beyond anoxia: The physiology of metabolic downregulation and recovery in the anoxia-tolerant turtle. *Comparative Biochemistry and Physiology, Part A* 2007; 147: 277–290.
- ¹⁶ Stys PK, Ransom BR, Waxman SG, Davis PK. Role of extracellular calcium in anoxic injury of mammalian central white matter. *Proc Natl Acad Sci* 1990; 87: 4212–4216.
- ¹⁷ Niederauer MQ, Michalek JE, Armstrong DG. A Prospective, Randomized, Double-Blind Multicenter Study Comparing Continuous Diffusion of Oxygen Therapy to Sham Therapy in the Treatment of Diabetic Foot Ulcers. *J Diabetes Science Tech*. 2017, Special Issue, 1-9. DOI: 10.1186/1745-0198-9-1
- ¹⁸ Niederauer MQ, Michalek JE, Liu Q, Papas, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *J Wound Care* 27(9):s30-s45 2018.
- ¹⁹ Lavery LA, Niederauer MQ, Papas KK, Armstrong DG. Does Debridement Improve Clinical Outcomes in People with DFU Ulcers Treated with CDO? *Wounds* 31(10):246-251 2019. Epub 2019 July 31
- ²⁰ Yu J, Lu S, McLaren A, Perry JA, Cross KM. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. *Wound Rep Regen*. 2016;24(6):1066-1072.
- ²¹ Urrea-Botero G. Can continuous diffusion of oxygen heal chronic toe ulcers? *Podiatry Today*. 2015;28(10).
- ²² Couture M. Does continuous diffusion of oxygen have potential in chronic diabetic foot ulcers? *Podiatry Today*. 2015;28(12).
- ²³ Pandit AS, Faldman DS. Effect of oxygen treatment and dressing oxygen permeability on wound healing. *Wound Repair Regen* 1994; 2: 130-137.
- ²⁴ Gallagher KA, Liu ZJ, Xiao M, Chen H, Goldstein LJ, Buerk DG, Nedeau A, Thom SR, Velazquez OC. Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha. *J Clin Invest* 2007; 117: 1249–1259.
- ²⁵ Goldstein LJ, Gallagher KA, Bauer SM, Bauer RJ, Baireddy V, Liu ZJ, Buerk DG, Thom SR, Velazquez OC. Endothelial progenitor cell release into circulation is triggered by hyperoxia-induced increases in bone marrow nitric oxide. *Stem Cells* 2006; 24: 2309–2318.
- ²⁶ Gallagher KA, Goldstein LJ, Thom SR, Velazquez OC. Hyperbaric oxygen and bone marrow-derived endothelial progenitor cells in diabetic wound healing. *Vascular* 2006; 14: 328–337.
- ²⁷ Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. *Am J Physiol Heart Circ Physiol* 2006; 290: H1378–H1386.
- ²⁸ Bowen J, Ingersoll MS, Carlson R. Effect of CDO on Pain in Treatment of Chronic Wounds. *Wound Central* 2(4):186-195 2018.
- ²⁹ Brannick B, Engelthaler M, Jadzak J, Wu S. A closer look at continuous diffusion of oxygen therapy for a chronic, painful venous leg ulcer. *Podiatry Today*. 2014;27(11).
- ³⁰ Mani R. Topical oxygen therapy for chronic wounds: a report on the potential of Inotec, a new device for delivering oxygen to chronic wounds. *J Wound Technol*. 2010;9:1-4.
- ³¹ Lowell DL, Nicklas B, Weeily W, Johnson F, Lyons MC. Transdermal continuous oxygen therapy as an adjunct for treatment of recalcitrant and painful wounds. *Foot Ankle Online J*. 2009;2(9):4.
- ³² Hirsh F, Berlin SJ, Holtz A. Transdermal oxygen delivery to wounds: a report of 6 cases. *Adv Skin Wound Care*. 2008;22:20-24.
- ³³ Mussini E, Hutton JJ, Jr. Udenfriend S. Collagen proline hydroxylase in wound healing, granuloma formation, scurvy, and growth. *Science* 1967; 157: 927–929.
- ³⁴ Berthod F, Germain L, Tremblay N, Auger FA. Extracellular matrix deposition by fibroblasts is necessary to promote capillary-like tube formation in vitro. *J Cell Physiol* 2006; 207: 491–498.
- ³⁵ Hopf HW, Gibson JJ, Angeles AP, Constant JS, Feng JJ, Rollins MD, Zamirul Hussain M, Hunt TK. Hyperoxia and angiogenesis. *Wound Repair Regen* 2005; 13: 558–564.
- ³⁶ Hunt TK, Aslam RS, Beckert S, Wagner S, Ghani QP, Hussain MZ, Roy S, Sen CK. Aerobically derived lactate stimulates revascularization and tissue repair via redox mechanisms. *Antioxid Redox Signal* 2007; 9: 1115–1124.
- ³⁷ Knighton D, Silver I, Hunt T. Regulation of wound healing and angiogenesis—effect of oxygen gradients and inspired oxygen concentrations. *Surgery* 1981; 90: 262–270.
- ³⁸ Sheikh AY, Rollins MD, Hopf HW, Hunt TK. Hyperoxia improves microvascular perfusion in a murine wound model. *Wound Repair Regen* 2005; 13: 303–308.
- ³⁹ Hunt TK, Zederfeldt B, Goldstick TK. Oxygen and healing. *Am J Surg* 1969; 118: 521–525.

How Oxygen Works in Wound Healing

- ⁴⁰ Jonsson K, Jensen J, Goodson W, Scheuenstuhl H, West J, Hopf H, Hunt T. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. *Ann Surg* 1991; 214: 605–613.
- ⁴¹ Wang Y, Zeigler MM, Lam GK, Hunter MG, Eubank TD, Khramtsov VV, Tridandapani S, Sen CK, Marsh CB. The role of the NADPH oxidase complex, p38 MAPK, and Akt in regulating human monocyte/macrophage survival. *Am J Respir Cell Mol Biol* 2007; 36: 68–77.
- ⁴² Brown JR, Goldblatt D, Buddle J, Morton L, Thrasher AJ. Diminished production of anti-inflammatory mediators during neutrophil apoptosis and macrophage phagocytosis in chronic granulomatous disease (CGD). *J Leukoc Biol* 2003; 73: 591–599.
- ⁴³ Babior BM. Oxygen-dependent microbial killing by phagocytes (first of two parts). *N Engl J Med* 1978; 298: 659–668.
- ⁴⁴ Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, Chang M, Le AX, Hopf HW, Hunt TK. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* 1997; 132: 991–996.
- ⁴⁵ Rabkin JM, Hunt TK. Infection and oxygen. In Davis JC, Hunt TK, editors, *Problem Wounds: The Role of Oxygen*, New York, Elsevier, 1988: 1–16.
- ⁴⁶ Cianci P. Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy? *Wound Repair Regen* 2004;12(1):2-10.
- ⁴⁷ Wattel F, Mathieu D. Oxygen and wound healing. *Bull Acad Natl Med* 2005; 189: 853–864.
- ⁴⁸ Knighton D, Halliday B, Hunt T. Oxygen as an antibiotic: the effect of inspired oxygen on infection. *Arch Surg* 1984; 119: 199–204.
- ⁴⁹ Knighton D, Halliday B, Hunt T. Oxygen as an antibiotic. *Arch Surg* 1986; 121: 191–195.
- ⁵⁰ Hunt TK, Zederfeldt B, Goldstick TK. Oxygen and healing. *Am J Surg* 1969; 118: 521–525.
- ⁵¹ Gordillo GM, Sen CK. Revisiting the Essential Role of Oxygen in Wound Healing. *Amer J Surg* 2003; 186: 259–263.
- ⁵² Prockop D, Kivirikko K, Tuderman L, Guzman N. The biosynthesis of collagen and its disorders (part 1). *N Engl J Med* 1979; 301: 13–23.
- ⁵³ Prockop D, Kivirikko K, Tuderman L, Guzman N. The biosynthesis of collagen and its disorder (part 2). *N Engl J Med* 1979; 301: 77–85.
- ⁵⁴ Niinikoski J. Effect of oxygen supply on wound healing and formation of experimental granulation tissue. *Acta Physiol Scand* 1970; 78: 1–72.
- ⁵⁵ Hunt T, Pai M. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. *Surg Gynecol Obstet* 1972; 135: 561–567.
- ⁵⁶ Stephens F, Hunt T. Effect of changes in inspired oxygen and carbon dioxide tensions on wound tensile strength. *Ann Surg* 1971; 173: 515.
- ⁵⁷ Hutton J, Tappel A, Udenfried S. Cofactor and substrate requirements of collagen proline hydroxylase. *Arch Biochem Biophys* 1967; 118: 231–240.
- ⁵⁸ Myllyla R, Tuderman L, Kivirikko K. Mechanism of the prolyl hydroxylase reaction. 2. Kinetic analysis of the reaction sequence. *Eur J Biochem* 1977; 80: 349–357.
- ⁵⁹ Asmis R, Qiao M, Zhao Q. Low-Flow Oxygenation of Full-Excisional Skin Wounds on Diabetic Mice Improves Wound Healing by Accelerating Wound Closure and Reepithelialization. *Int Wound J* 2010 ; 7: 349-357.
- ⁶⁰ Hopf H, Hunt T, West J, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* 1997; 132: 997–1004.
- ⁶¹ Hartmann M, Jonsson K, Zederfeldt B. Effect of tissue perfusion and oxygenation on accumulation of collagen in healing wounds. Randomized study in patients after major abdominal operations. *Eur J Surg* 1992; 158: 521–526.
- ⁶² Sundaresan M, Yu ZX, Ferrans VJ, et al. Regulation of reactive oxygen species generation in fibroblasts by Rac1. *Biochem J* 1996; 318: 379–382.
- ⁶³ Sen CK, Khanna S, Babior BM, et al. Oxidant-induced vascular endothelial growth factor expression in human keratinocytes and cutaneous wound healing. *J Biol Chem* 2002; 277: 33284–33290.
- ⁶⁴ Cho M, Hunt TK, Hussain MZ. Hydrogen peroxide stimulates macrophage vascular endothelial growth factor release. *Am J Physiol Heart Circ Physiol* 2001; 280: H2357–H2363.
- ⁶⁵ Maniscalco WM, Watkins RH, Finkelstein JN, Campbell MH. Vascular endothelial growth factor mRNA increases in alveolar epithelial cells during recovery from oxygen injury. *Am J Respir Cell Mol Biol* 1995; 13: 377–386.
- ⁶⁶ Deaton P, McKellar C, Culbreth R, et al. Hyperoxia stimulates interleukin-8 release from alveolar macrophages and U937 cells: attenuation by dexamethasone. *Am J Physiol* 1994; 267: L187–192.
- ⁶⁷ Darrington R, Godden D, Park M, et al. The effect of hyperoxia on expression of cytokine mRNA in endothelial cells. *Biochem Soc Trans* 1997; 25: 2925.
- ⁶⁸ Sheikh A, Gibson J, Rollins M, et al. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg* 2000;153:1293–1297.
- ⁶⁹ Shenberger JS, Zhang L, Powell RJ, Barchowsky A. Hyperoxia enhances VEGF release from A549 cells via post-transcriptional processes. *Free Radic Biol Med* 2007; 43: 844–852.
- ⁷⁰ Sundaresan M, Yu ZX, Ferrans VJ, et al. Requirement for generation of H₂O₂ for platelet-derived growth factor signal transduction. *Science* 1995; 270: 296–9.
- ⁷¹ Roy S, Khanna S, Sen CK. Redox regulation of the VEGF signaling path and tissue vascularization: hydrogen peroxide, the common link between physical exercise and cutaneous wound healing. *Free Radic Biol Med* 2008; 44: 180–192.
- ⁷² Roy S, Khanna S, Rink C, Biswas S, Sen CK. Characterization of the acute temporal changes in excisional murine cutaneous wound inflammation by screening of the wound-edge transcriptome. *Physiol Genomics* 2008; 34: 162–184.
- ⁷³ Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. *Brit J Derm* 2010; 163: 257-268.