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Topical Dissolved Oxygen Penetrates Skin: Model and Method

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Background. **It has been commonly perceived that skin receives its oxygen supply from the internal circulation. However, recent investigations have shown that a significant amount of oxygen may enter skin from the external overlying surface. A method has been developed for measuring the transcutaneous penetration of human skin by oxygen as described herein. This method was used to determine both the depth and magnitude of penetration of skin by topically applied oxygen.**

Material and Methods. **An apparatus consisting of human skin samples interposed between a topical oxygen source and a fluid filled chamber that registered changes in dissolved oxygen. Viable human skin samples of variable thicknesses with and without epidermis were used to evaluate the depth and magnitude of oxygen penetration from either topical dissolved oxygen (TDO) or topical gaseous oxygen (TGO) devices.**

Results and Conclusion. **This model effectively demonstrates transcutaneous penetration of topically applied oxygen. Topically applied dissolved oxygen penetrates through >700 μm of human skin. Topically applied oxygen penetrates better though dermis than epidermis, and TDO devices deliver oxygen more effectively than TGO devices.**

Key Words: **topical oxygen; dissolved oxygen; transcutaneous; wound healing; hypoxia.**

INTRODUCTION

Chronic wounds are those that "fail to progress through a normal, orderly, and timely sequence of repair [1]." Several key processes in wound healing are dependent upon an adequate supply of oxygen. Chronic wounds are often in need of an adequate supply due to poor perfusion, which causes a decreased oxygen tension. Oxygen is necessary for multiple wound healing processing including bacterial killing by leukocytes, synthesis, and hydroxylation of collagen, proliferation of fibroblasts, promotion of wound resurfacing by keratinocytes, oxidative pathways for ATP formation, and nitric oxide dependent signaling pathways [2,3].

There is an association between tissue oxygenation and wound healing in the clinical setting. For example, nonhypoxic wounds with O_2 levels greater than 30 mmHg typically have little or no accumulated necrotic debris, develop normal granulation tissue, and close uneventfully [4]. In contrast, wounds with less than 30 mmHg are termed hypoxic and, depending on O_2 levels, follow predictable courses. Wounds with 13–30 mmHg of O_2 usually have accumulated necrotic deposits over the wound bed, form little or no granulation tissue, and are stalled or very slow to heal. Wounds with less than 13 mmHg of O_2 tension have insufficient oxygen to support even static metabolic activities and become gangrenous.

The goal of an oxygen therapy for wound care is to transfer sufficient oxygen to interstitial tissues to maintain a concentration near the 40 mmHg found in healthy, well perfused tissues. Therapies such as surgical revascularization and hyperbaric oxygen therapy have demonstrated that improved perfusion and oxygenation of the wound accelerates healing. These procedures are expensive and often unavailable to many patients. This report is on a new method for measuring the capacity of topically applied oxygen delivery devices to penetrate through human skin samples. Topical dissolved oxygen (TDO) and topical gaseous oxygen (TGO) devices were analyzed using this *in vitro* model. We hypothesized that topical oxygen devices can effectively deliver oxygen into and through viable human skin and that TDO may be more effective than TGO in doing so.

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MATERIALS AND METHODS

Model and Apparatus for Transcutaneous Oxygen Transfer

The objective was to determine the rate at which oxygen was transferred from oxygen delivering devices to physiologic saline through test substrates. This was done by using saline (0.9% NaCl) equilibrated to 21% saturation/159 mmHg partial pressure oxygen content of atmospheric air at 37°C in an apparatus designed for measuring dissolved oxygen (Fig. 1). The apparatus consisted of an 11 mL chamber for the containment of fluid (saline) in a closed system with a 2 cm × 2 cm window onto which human skin samples of varying thicknesses were adhered. The apparatus described in Fig. 1 was filled with saline equilibrated with atmospheric oxygen at 159 mmHg and maintained at 37°C. To determine baseline transfer kinetics for oxygen delivery, a support polypropylene mesh was adhered across the sample window and used as control recordings. The topical oxygen devices were placed on the mesh and recordings were made, to assay the effects of 100% gaseous oxygen, the entire apparatus was placed into a Captair airtight glovebox (Terra Universal, Fullerton, CA), and medical grade 100% oxygen was applied at a continuous flow rate of 5 L/min.

Measurements were taken with a Diamond General Chemical microsensor (Ann Arbor, MI) instrument for the amperometric measurement of dissolved oxygen. A silicone disk was placed around a chemical microsensor, Clark style dissolved oxygen probe. The Clark probe was inserted into fluid chamber and held in place with flexible clear NexCare 3M (St. Paul, MN, USA) medical tape. The final assembly was set in a water bath at 37°C. Measurements were recorded after 5 min intervals for 90 min.

Oxygen Delivery Devices

Two topical dressings were tested, a hydrophilic closed-cell oxygen foam [5], and an alginate-catalyst dressing treated with a 0.3% hydrogen peroxide (Fisher Scientific, Pittsburg PA.) solution [6]. One hundred percent gaseous oxygen was used in some of the testing for comparative purposes. The foam dressing was a polyacrylate polymer specifically modified to enhance flexibility, elasticity, and moisture absorbency. The polyacrylate matrix was initially a semi-solid gel and was transformed to a closed-cell, oxygen rich foam by a proprietary treatment. The alginate-catalyst dressing consisted of the hydrophilic alginate Kaltostat (ConvaTec, Skillman, NJ.) containing ~60–80 $\mu g/cm^2$ of the inorganic catalyst manganese dioxide (Sigma-Aldrich, St. Louis, MO). An aqueous substrate of 0.3% H_2O_2 was added to the dressing and was subsequently decomposed to produce high levels of oxygen and water.

Human Donor Skin Samples

Viable human organ donor skin samples were obtained through Community Tissue Services in Portland, Oregon and designated for research purposes. Donors were Caucasian men and women whose ages were not revealed for privacy purposes. Three skin sample thicknesses were tested. Two dermal thicknesses, intermediate (0.012–0.018 in. or 304–457μm) and thick (0.018–0.030 in. or 457–762 μm) harvested at the time of organ donation were tested. An intermediate (0.012 in. or 304 μm) split-thickness sample consisting of epidermis and dermis was also tested. It was hypothesized that skin samples with epidermis would present a greater barrier to oxygen penetration than would dermis only samples of equivalent thickness. All samples were excised from the back or thigh using a dermatome. The samples were stored in the cell culture media RPMI-1640 (Invitrogen, Carlsbad, CA.) and refrigerated at 4°C until use. No samples were used after 2 wk in storage. Skin samples were fixed over the window of the test apparatus using veterinary skin adhesive. The saline was equilibrated to atmospheric levels of oxygen, 159 mmHg, using an aerator and room air at 37°C. Topical dressing devices were placed atop the skin samples and recordings of dissolved oxygen were made for 90 min. Only intermediate dermis was tested using 100% gaseous oxygen, in which case the entire apparatus was placed inside an airtight glove box with continuous 5 L/min flow of 100% oxygen gas.

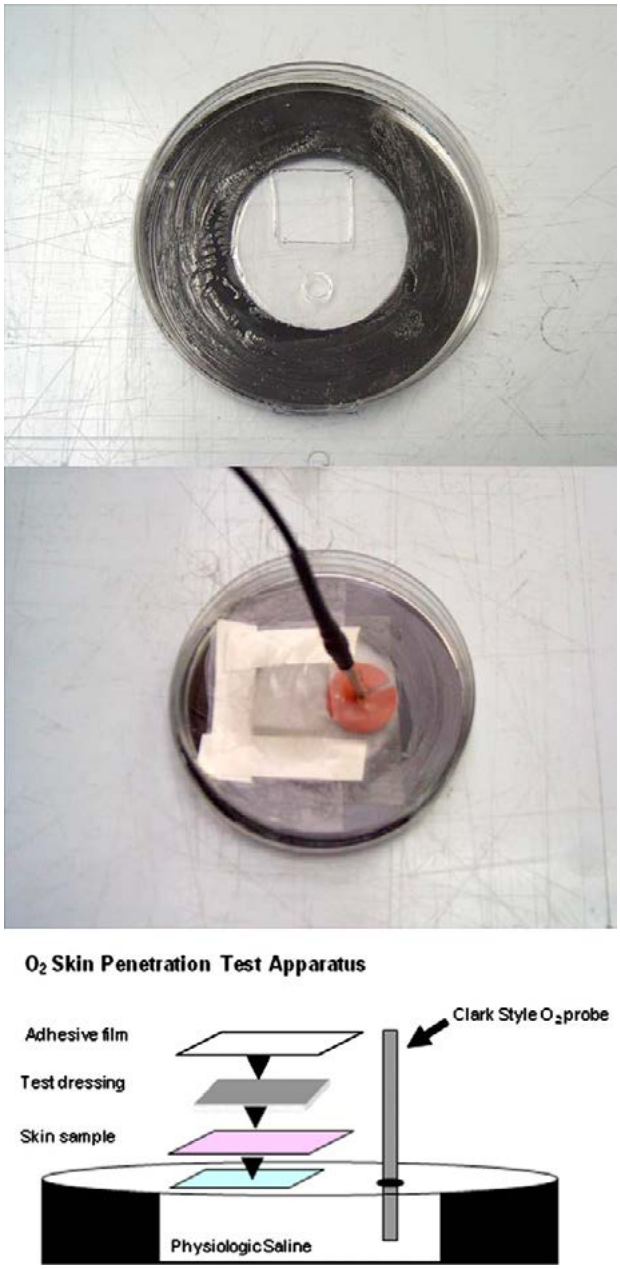


FIG. 1. Photographs and diagram of apparatus for measuring delivery of dissolved oxygen. Constructed from silicone sheeting and polystyrene dish. An 11 mL volume fluid chamber (7 mm depth × 46 mm diameter) within dish filled with saline. A 2 cm × 2 cm sample window over fluid chamber. Oxygen transfer test material (i.e., skin sample) is adhered over window. Oxygen release into a fluid medium was measured using the Diamond General Chemical micro-sensor (Clark Style Electrode).

Calculation of Oxygen Volume

Partial pressure measurements of oxygen were converted to mg/L of oxygen in saline within the apparatus. The value was based on the

solubility of oxygen at 37°C and 1.54 S/m conductivity of a 0.9% saline solution [7, 8], whereas a partial pressure of 159 mmHg is equal to 6.31 mg/L oxygen solubility.

Statistical Analysis

Results are expressed as means ± standard deviation. Student's *t*-test was used to assess the statistical significance between two means. Differences were considered significant when $P < 0.05$.

RESULTS

Baseline Production of Dissolved Oxygen by TDO and TGO Devices

Initial experiments were performed to determine the transfer kinetics of oxygen from the delivery device to saline without introducing the variable of interposed human skin in the system. As shown in Fig. 2, dissolved oxygen (dO_2) measurements begin to rise immediately with each device. The TDO devices showed an initial high rate of oxygen transfer, which was significantly greater than TGO device at 30 min (P value < 0.005 closed cell foam and P value < 0.05 alginate catalyst), and also at 60 min (P value < 0.005 closed cell foam and P value < 0.01 alginate catalyst) shown in Table 1. The maximum change in oxygen partial pressure reached 231 mmHg for the closed-cell oxygen foam, 152 mmHg for the alginate catalyst dressing, and 109 mmHg for gaseous oxygen. There was a significant difference in peak oxygen level achieved at 90 min comparing a TDO with TGO ($P < 0.05$, closed cell foam).

Transfer of dO_2 Through Human Skin by TDO and TGO Devices

These experiments examine the ability of the TDO and TGO devices to deliver oxygen through interposed viable human skin in the apparatus. As seen in Fig. 3, each device effectively transferred oxygen through intermediate thickness (0.012–0.018 in. or 304–457 μm) dermis samples. TDO devices were significantly more effective in transferring oxygen across viable human dermis than TGO device at 30 min (P value < 0.005 for closed cell foam and P value < 0.01 alginate catalyst), and at 60 min (P value < 0.05 for closed cell foam), as seen in Table 1. There was also a significant difference in peak oxygen level reached at 90 min by a TDO device compared with the TGO device (P value < 0.05, closed cell foam).

Transfer of dO_2 Through Variable Thickness Human Skin Samples by TDO

Next, the diffusion of oxygen from devices through thick dermis (0.018–0.030 inch or 457–762 μm) was measured. Both TDO devices were able to cause an elevation in the transfer of oxygen, but there was no significant difference in rate between the two TDO devices. As shown in Fig. 4, the closed-cell foam dressing achieved a change in partial pressure of 148 mm Hg for the closed-cell foam and 111 mm Hg for the alginate-catalyst. The level of partial pressure due to oxygen delivery in the thick dermis was comparable

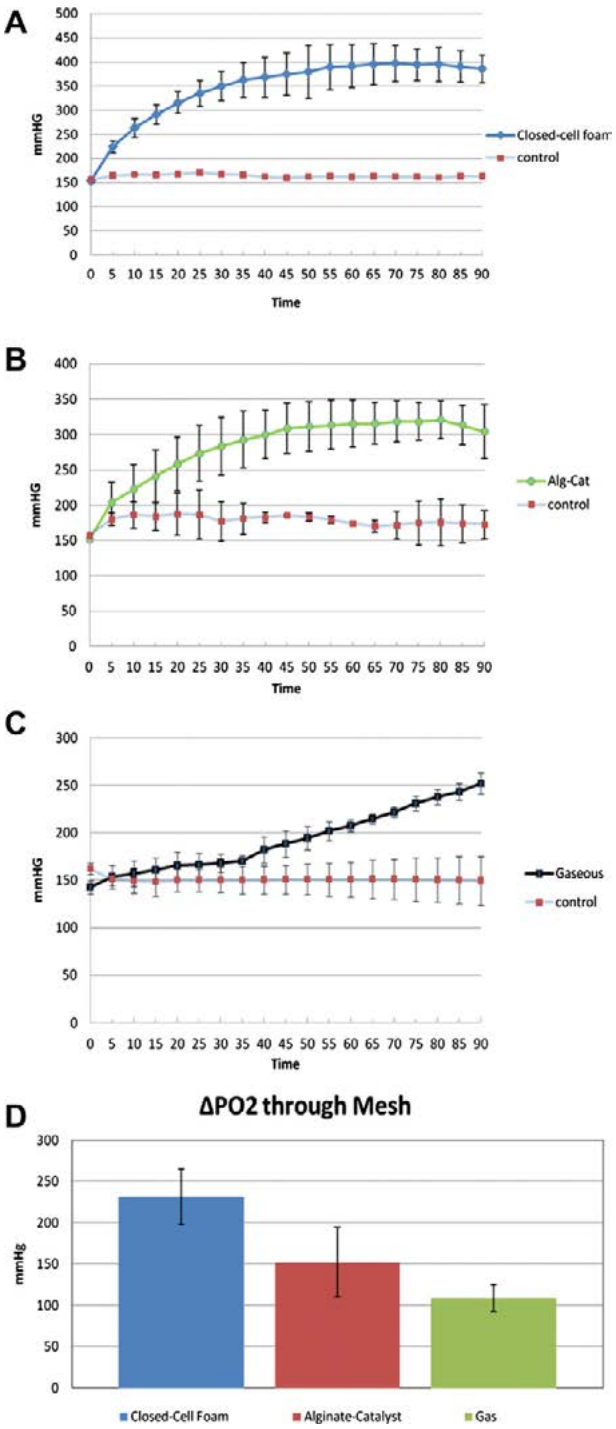
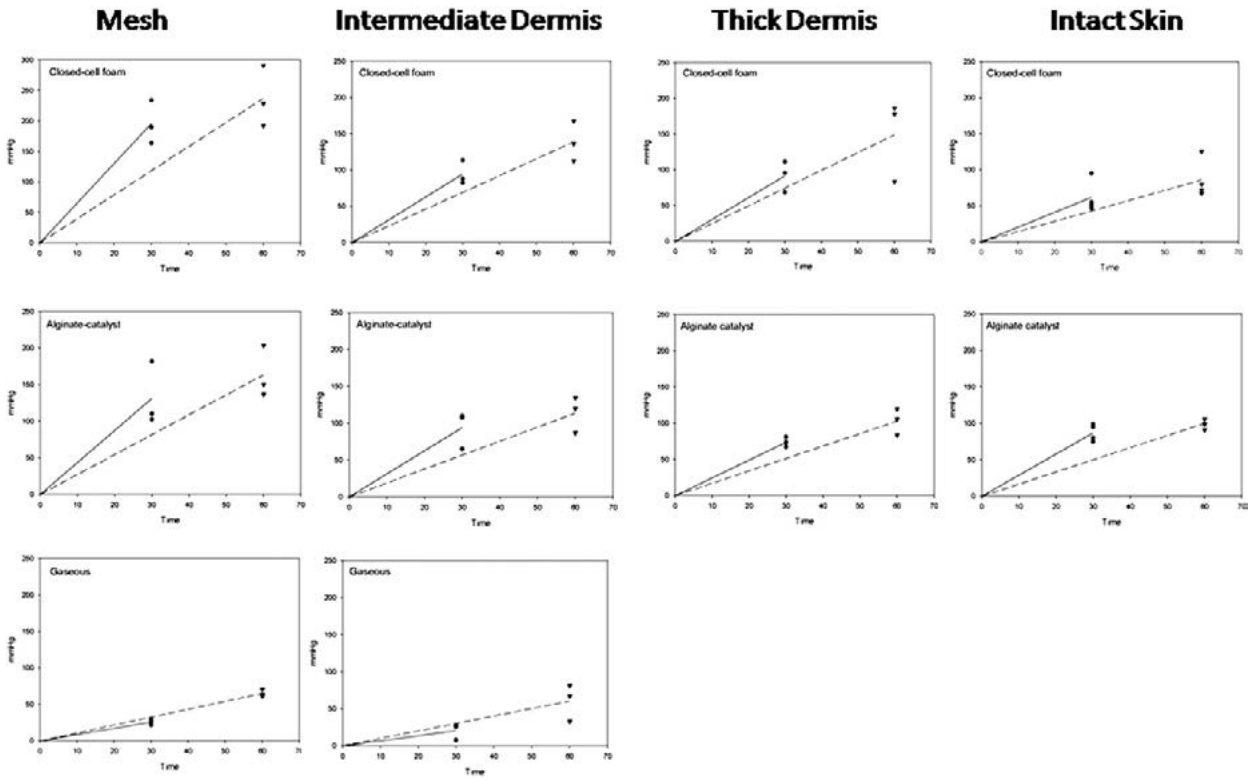


FIG. 2. Transfer of dissolved oxygen for control recording into saline at 37°C; $n = 3$ oxygen delivery devices; $n = 2$ control. (A) Foam dressing; (B) alginate-catalyst dressing; (C) 100% gaseous oxygen; (D) change in partial pressure at 90 min from T = 0. Closed cell foam greater than gaseous ($P < 0.05$).

TABLE 1

Rate of Change in Oxygen Partial Pressure Per Min at 30 Min:60 Min (mmHg/Min)

	Skin sample			
Topical oxygen device	Control	Intermediate dermis 304-457 μm	Thick dermis 457-762 μm	Epidermis 304 μm
Closed-cell foam	6.5*:4.0*	3.2*:2.3*	3.1:2.5	2.1:1.4
Alginate catalyst	4.4*:2.7*	3.1*:1.9	2.5:1.7	2.9:1.7
Gaseous	1.1:0.9	1.0:0.7	na	na



Rate is expressed as change in mm Hg per min, in which starting partial pressure was subtracted from partial pressure at each time point. Values are means of multiple measurements. Both closed-cell foam and alginate catalyst dressings showed significantly ($P < 0.05$) faster rates than gaseous oxygen in controls at 30 and 60 min. Only closed-cell foam showed significantly faster rates through intermediate dermis at 30 and 60 min relative to gaseous oxgyen. The alginate catalyst was significantly faster through intermediate dermis at 30 min relative to gaseous (na = not applicable).

*Denotes a significance ($p > 0.05$) relative to gaseous sample.

to that attained in the intermediate dermis, with no significant difference between the two TDO devices.

Transfer of dO_2 Through Human Skin Sample With and Without Epidermis by TDO

The efficiency of oxygen delivery in skin samples with or without dermis was also investigated. An intermediate (0.012 in. or 304 μm) split thickness skin sample containing the entire epidermis and part of the dermis was used in this investigation. We hypothesized the epidermis would present a greater barrier to oxygen penetration than dermis alone. This was contrasted to a dermis only sample of equivalent thickness. However, no significant difference in rate of oxygen penetration was observed when TDO devices were applied to epidermal *versus* non-epidermal skin samples. Figure 5 shows that the maximum change in oxygen partial pressure achieved by closed-cell foam dressing was 96 mmHg and the alginate-catalyst dressing reached 102 mmHg in this skin sample with no significance between the two devices.

Table 1 shows a comparison of the rate of oxygen partial pressure change between the different TDO and TGO devices. Both TDO devices demonstrate a faster rate of oxygen penetration then does the TGO device. Rate of oxygen transfer through equal thickness

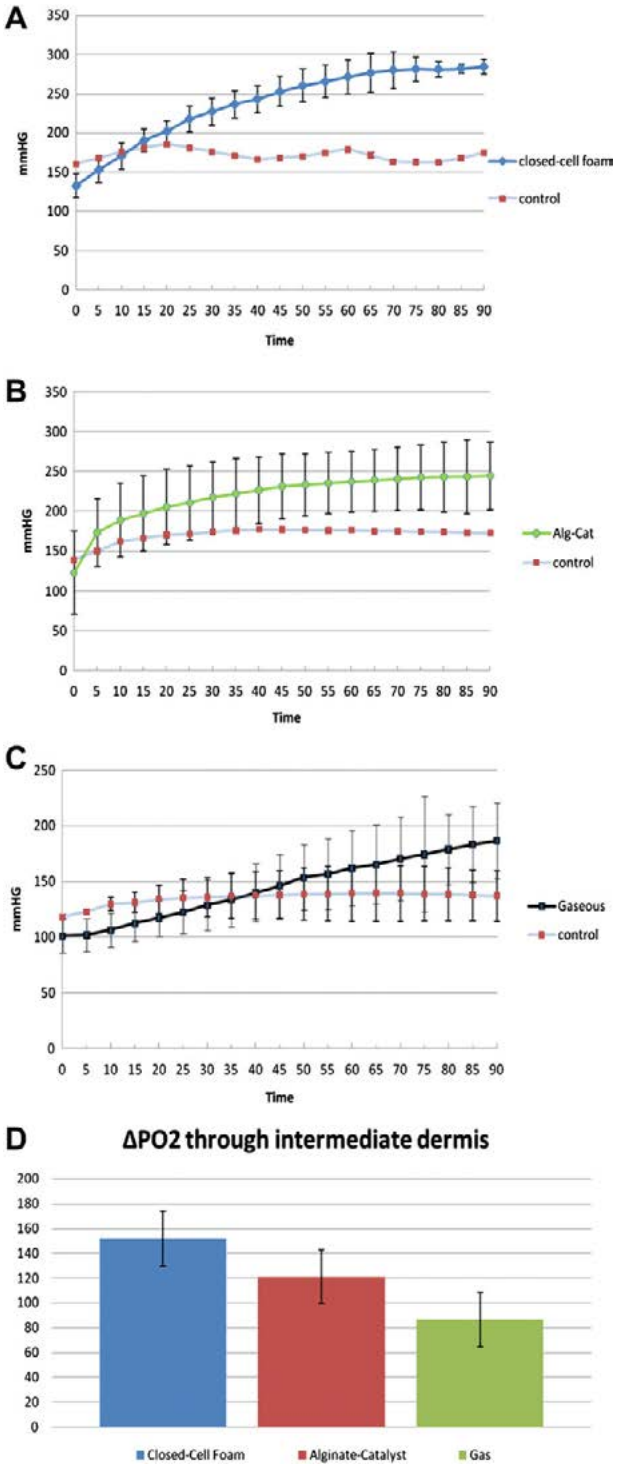


FIG. 3. Transfer of dissolved oxygen through intermediate dermis (304–457 μm) into saline at 37°C; $n = 3$ oxygen delivery devices; $n = 2$ control. (A) Foam dressing; (B) alginate-catalyst dressing; (C) 100% gaseous oxygen; (D) change in partial pressure at 90 min. from T = 0. Closed cell foam greater than gaseous ($P < 0.05$).

samples of skin with or without epidermis was different but not significant. Also, alginate-catalyst TDO was more effective through intact skin than closed-cell foam TDO though the difference was not significant.

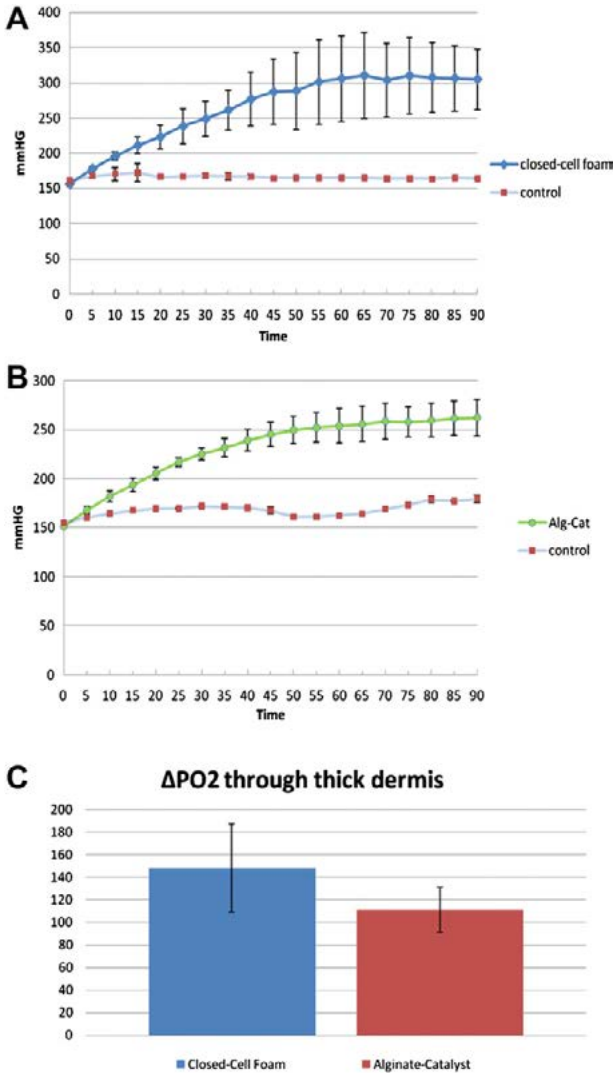


FIG. 4. Transfer of dissolved oxygen through thick dermis (457–762 μm) into saline at 37°C; $n = 3$ oxygen delivery devices; $n = 2$ control. (A) Foam dressing; (B) alginate-catalyst dressing; (C) change in partial pressure at 90 min from T = 0.

Table 2 represents the volume of oxygen delivered during the initial 30 min of measurement derived from the Figs. 2–5. Initially, there is a maximal oxygen driving gradient that lessens as the saline reservoir accumulates oxygen. Therefore, the rate of oxygen transfer gradually trends toward a plateau. If the reservoir were living skin, oxygen would be continually extracted and the maximal oxygen driving gradient would likely be preserved.

DISCUSSION

Topical Oxygenation Background

Distribution of oxygen through human dermal tissue is dependent upon oxygen partial pressure gradients and the solubility of oxygen in the tissue. These factors

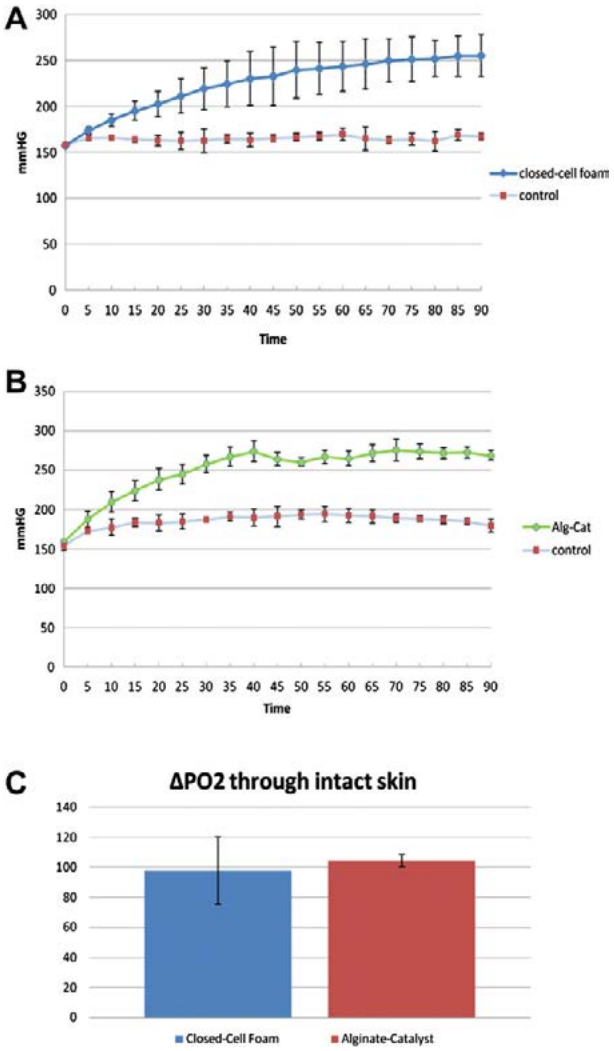


FIG. 5. Transfer of dissolved oxygen through intact skin, epidermis, and dermis (304 μm), into saline at 37°C; $n = 4$ oxygen delivery devices; $n = 3$ control. (A) Foam dressing; (B) alginate-catalyst dressing; (C) change in partial pressure at 90 min from T = 0.

determine whether the tissue layers can be supplied by external atmospheric or internal vascular sources of oxygen. This allocation of oxygen involves internal transport by cutaneous circulation *via* dermal papillae and externally by transcutaneous diffusion of atmospheric oxygen. The first evidence of cutaneous respiration occurred when Gerlach (1851) secured a varnished horse bladder to his skin and then measured a decrease in oxygen content and increase in carbon dioxide after 24 h. In terms of the respiratory needs of the individual, the contribution by skin is negligible, providing only ~2% of total respiration needs [9]. However, in several lower vertebrates, cutaneous respiration has been shown to contribute significantly to physiologic needs [10]. Cutaneous respiration in a prenatal marsupial mammal is the primary site of respiration [11]. In humans, cutaneous respiration is seen in preterm infants of <31 wk, where oxygen and carbon dioxide exchange

TABLE 2

Rate of Oxygen Delivered Through Skin During Initial 30 min (μL/Min)

	Skin sample			
Topical oxygen device	Control	Intermediate dermis 304-457 μm	Thick dermis 457-762 μm	Epidermis 304 μm
Closed-cell foam	2.1*	1.0*	0.97	0.63
Alginate catalyst	1.4*	0.97	0.77	0.9
Gaseous	0.27	0.2	na	na

Amount is expressed as the μL of oxygen per min. Values are means of multiple measurements. Both closed-cell foam and alginate catalyst dressings showed significantly ($P < 0.05$) larger volumes than gaseous oxygen through control at 30 min. Only closed-cell foam showed significantly greater volumes through intermediate dermis at 30 min relative to gaseous oxgyen (na = not applicable).

*Denotes a significance (P > 0.05) relative to gaseous sample.

was 5 to 6 times higher than an adult, and may provide up to 20% of physiologic need [12].

Measurements of Topical Oxygenation

The degree to which cutaneous respiration can contribute to dermal metabolic needs is dependent upon the depth to which topical oxygen penetrates into human skin. Penney *et al.* (1968) took sheets of isolated human stratum corneum and measured the diffusion of oxygen from a chamber of water equilibrated with air to a chamber that contained water deoxygenated by nitrogen [13]. It was shown that oxygen diffused through the stratum corneum, raising the oxygen partial pressure of the de-oxygenated water. The thickness of the stratum corneum was estimated to average 12 μm. Gruber *et al.* (1970) used full-thickness skin samples to demonstrate that gaseous oxygen can penetrate into live dermis taken from the abdomen [14]. Exposing samples to 100% gaseous oxygen at a pressure of 3 atms, oxygen could penetrate to 300–340 μm passing through the epidermis into the dermis. Although, measurements at deeper dermis layers, 1.8–2.2 mm, showed no change in oxygen. Also, oxygen administered at 1 atm was unable to penetrate even at the more superficial layers. Using an oxygen flux optode, a more advanced technique for measuring cutaneous oxygen, Stucker [15] showed that atmospheric oxygen supplies the outer 250–400 μm of human skin *in vivo*.

Our data has confirmed and extended these existing observations. Viable human skin samples demonstrated oxygen penetration by both the TDO dressings and TGO. In most cases, TDO devices deliver oxygen into skin faster and to greater depth than do TGO devices. Our model has demonstrated oxygen penetration into viable skin by TDO devices to beyond 700 μm,

a depth previously not reported in the literature. In addition, our model is the first to compare viable human skin samples with and without epidermis. It has been felt that the epidermis, including the stratum corneum, provided a significant barrier to transcutaneous oxygenation. Our initial data show that the epidermis is not prohibitive of transcutaneous oxygenation.

The average adult has 2 square meters (20,000 cm^2) of skin that weighs approximately 4000 g. This gives a single square centimeter of skin a mass of 0.2 g (4000 g/20000 cm^2). It has been reported that skin consumes 5 mL/min of oxygen from circulating blood supply [16] (5 mL/min/4000 g equals 1.25 μL/min per g of oxygen consumption). In our model, we used skin tissue samples of 4 square centimeters (0.8 g). This area of tissue would consume generally 1 μL/min of oxygen. According to Table 2, the TDO devices have a potential delivery capacity of 40–60 μL within the initial 30 min as shown in control recording. When measured through intact skin the TDO devices deliver 20–27 μL of oxygen. This mode of topical oxygen delivery could therefore meet nearly all of the physiologic oxygen requirements of skin.

Topical Oxygenation *via* Dissolved Oxygen or Gaseous Oxygen Sources

For oxygen to become biologically available, it must leave the gaseous phase and enter the liquid phase so that it can diffuse into a cell. Gaseous oxygen must overcome several barriers and partial resistances to enter the liquid phase, including the resistance within the gas film to the phase boundary, penetration of the phase boundary itself, and transfer from the phase boundary to the liquid. A dissolved oxygen source does not have these limitations. It was therefore hypothesized that a dissolved oxygen source would be more effective than a gaseous oxygen source for providing transcutaneous oxygenation. Movement of oxygen within the tissue is governed by Graham's law of diffusion stating that gases move independently and at different rates from areas of high pressure to low pressure. Once in the tissue extracellular matrix, the diffusion of oxygen occurs at a rate dictated by diffusion coefficient, which for human dermis has been estimated at $1.8–3.1 \times 10^{-5}$ cm^2/s [17]. If one begins with a higher oxygen concentration from the source, there will be greater tissue penetration. Our data confirm that topically applied dissolved oxygen penetrates the human skin at a faster rate and to a greater depth than does topically applied gaseous oxygen. This may be clinically relevant, as oxygen therapy may be achieved to a greater tissue depth and in a shorter time with TDO devices. The transport of oxygen to tissue is faster when the oxygen is dissolved in fluid. The fact that removal of the lipid rich stratum corneum increases the diffusion of oxygen through the skin suggests the importance of oxygen dissolved in a solution [18]. The removal of the stratum corneum can also increase transcutaneous oxygenation of hemoglobin due to the removal of the corneal lipid rich layer and an increased surface water content of the skin, which allows applied dissolved oxygen to directly enter the skin [19]. Therefore, as expected, in our results, the topical dressings that deliver oxygen dissolved in a fluid phase (TDO) were more capable of oxygen delivery than 100% gaseous oxygen (TGO). Not only is the final partial pressure of oxygen delivered by TDO devices greater than that from TGO after 90 min, but the rate of transfer is faster as well.

There are several ways oxygen may penetrate through skin, which has porous and nonporous regions. Oxygen is a small molecule and can easily pass through skin pores, which span the full thickness of skin layers. Eccrine sweat glands vary in number throughout the body (up to 350/cm^2 in the palmer skin), and each gland has a pore 15–20 μm in size [20]. Alternatively, oxygen may cross the nonporous portion of the skin, possibly *via* transmembrane proteins such aquaporin, whose tetrameric structures create oxygen permeable channels that allow passage of oxygen [21]. An earlier study contrasting oxygen passage across sheets of viable and nonviable epidermis showed similar rates, suggesting that the major route of oxygen transmission is mediated by physiochemical structure rather than active cellular function [22].

Other topical oxygen delivery modalities have been developed. A supersaturated oxygen emulsions (SOS) containing perfluorocarbon which, due to its high affinity and carrying capacity, is capable of incorporating high levels of oxygen has been shown to improve wound healing in animal model [23,24]. Recent reports have shown topically applied gaseous oxygen can increase pO2 of superficial wound tissue and has shown promise clinically [25,26]. Epithelial healing is improved by a transdermal sustained delivery treatment with bubbled gaseous oxygen [27].

This study reports on the transcutaneous delivery of oxygen using an *in vitro* viable human skin penetration model. It has now been shown that the oxygen penetration through >700 μm of live human dermis can be achieved with both gaseous and topical dissolved oxygen delivery devices. Our use of dermis only skin samples offers similarity to a partial thickness wound, which lacks epidermis (such as partial thickness burn or excoriation). The ability to deliver topical oxygen to partial thickness wounds may allow the clinician to support the metabolically active wounded tissue, which may be compromised by ischemia. We have demonstrated that TDO devices can provide the necessary

oxygen supply to ensure skin survival, even in the absence of tissue perfusion. This measurement platform offers a reliable tool for the evaluation of topical oxygen delivery to simulated wound environments.

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