In-vivo singlet oxygen dosimetry of clinical 5-aminolevulinic acid photodynamic therapy

Hans-Joachim Laubach,* Sung K. Chang,‡ Seonkyung Lee,‡ Imran Rizvi,* David Zurakowski,‡ and Tayyaba Hasan‡

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Abstract. Photodynamic therapy (PDT) is a viable treatment option for a wide range of applications, including oncology, dermatology, and ophthalmology. Singlet oxygen is believed to play a key role in the efficacy of PDT, and on-line monitoring of singlet oxygen during PDT could provide a method to establish and customize the treatment dose clinically. This work is the first report of monitoring singlet oxygen luminescence in vivo in human subjects during PDT, demonstrating the correlation of singlet oxygen levels during PDT with the post-PDT photobiological response.

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(most pronounced). Median of the four readings is reported to minimize any potential interobserver variability. The photobiological response to the $I_{long}$ treatment sites were more pronounced and more clinically significant compared to $I_{short}$ treatment sites. Consistent with Ref. 9, edema and erythema response peaked at 15 min and 24 h following PDT, respectively. Subsequent analysis was performed using the maximal photobiological skin response: acute edema at 15-min post-PDT and erythema at follow-up 24-h post-PDT. PS-induced $^{1}O_2$ signal was defined by change in $^{1}O_2$ luminescence between pre-ALA (time of minimum PpIX concentration) and pre-PDT (time of maximum PpIX concentration) time points.

Several researchers have shown that the degree of erythema and edema following ALA-PDT is predictive of clinical outcome in various dermatologic conditions. To evaluate the relationship between $^{1}O_2$ signal and photobiological skin responses (edema and erythema), we applied repeated-measures linear mixed model analysis. Using this model, the $^{1}O_2$ luminescence signal significantly correlated with acute edema in $I_{long}$ sites ($P=0.01$) and 24-h follow-up erythema for $I_{long}$ and $I_{short}$ combined ($P=0.028$) (Table 1). Equality of slopes for $I_{short}$ and $I_{long}$ sites was assessed with an F-test to decide whether a common slope parameter.

**Table 1** Effect of $^{1}O_2$ signal on photobiological responses based on a linear mixed model regression analysis of the data. Slope of the linear correlation between $^{1}O_2$ signal and photobiological response in either $I_{short}$ sites, $I_{long}$ sites, or the combined data are reported. Edema is measured at post-PDT; erythema is measured at follow-up. The slope test shows the comparison of slopes estimated from $I_{short}$ sites and $I_{long}$ sites using an F-test. ST is statistically significant. CI=confidence interval.

<table>
<thead>
<tr>
<th>$^{1}O_2$ signal</th>
<th>Edema*</th>
<th></th>
<th>Erythema*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope test†</td>
<td>0.009 (ST)</td>
<td>0.527</td>
<td></td>
</tr>
<tr>
<td>$I_{short}$ sites only</td>
<td>$-0.002$ ($-0.015$, $0.011$)</td>
<td>$0.747$</td>
<td></td>
</tr>
<tr>
<td>$I_{long}$ sites only</td>
<td>$0.035$ ($0.011$, $0.059$)</td>
<td>$0.010$ (ST)</td>
<td></td>
</tr>
<tr>
<td>Combined sites</td>
<td>$0.017$ ($0.002$, $0.031$)</td>
<td>$0.028$ (ST)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1 Representative images of treatment sites with 1 h ($I_{short}$) or 3 h ($I_{long}$) of ALA application time. The phototoxic reaction in $I_{long}$ sites (edema immediately after PDT and erythema 24 h afterward) is more intense than in $I_{short}$ sites.

Fig. 2 Scatter plots illustrating the relationship between $^{1}O_2$ luminescence signal versus (a) acute edema rating and (b) erythema rating 24 h after PDT. Regression-based fits to the $I_{short}$, $I_{long}$, and combined data are shown by the red dashed line, the blue dotted line, and the solid green line, respectively. (Color online only.)
could be modeled to describe this correlation. The relationship between erythema and \( \text{O}_2 \) signal showed no significant difference in slopes between \( I_{\text{short}} \) and \( I_{\text{long}} \) sites (\( P=0.527 \)). As a result, correlation between follow-up erythema and \( \text{O}_2 \) signal was investigated with a common slope fitted to the combined dataset for the \( I_{\text{short}} \) and \( I_{\text{long}} \) sites (Fig. 2). The interpretation is that the percent change in \( \text{O}_2 \) signal from baseline is positively correlated for both sites in a similar way, and thus can be described using a common slope.

On the other hand, the correlation between acute edema and \( \text{O}_2 \) signal was modeled separately for \( I_{\text{short}} \) and \( I_{\text{long}} \) sites because they had unequal slopes (\( P=0.009 \)) (Fig. 2). In fact, greater edema was significantly correlated with greater percent change from baseline in \( \text{O}_2 \) signal but only for the \( I_{\text{long}} \) sites (\( P=0.01 \)), not \( I_{\text{short}} \) sites (\( P=0.747 \)) (Table 1). Interestingly, only \( I_{\text{long}} \) sites showed a significant correlation between \( \text{O}_2 \) signal and acute edema (Fig. 2). It is possible that the minor acute edema at the \( I_{\text{short}} \) sites (median score of 0.25 out of 10) may not have been clearly discernable by the blinded investigators in a 2-D photograph, and thus may not have correlated significantly with the quantitative \( \text{O}_2 \) signal.

Unexpectedly, a decrease in \( \text{O}_2 \) signal after the incubation period was observed in some treatment sites. This might be related to modification of skin optical properties by ALA and its carrier. A carrier-only control treatment site could potentially provide additional information when incorporated in future studies.

This is the first study showing the feasibility of monitoring PS-generated \( \text{O}_2 \) signal in vivo in human subjects. \( \text{O}_2 \) signal measured immediately prior to PDT light irradiation correlated significantly with the photobiological response to ALA-PDT in normal skin. As a result, monitoring \( \text{O}_2 \) production in the skin is predictive of the clinical ALA-PDT outcome and is a helpful tool for customizing the clinical ALA-PDT treatment.

Acknowledgments
This work was supported by NIH SBIR Phase II grant R44 CA096243 and in part by NIH grant P01 CA84203. We also thank Oleg Akilov, Mehran Puoris'haag, Fernandez Sakamoto, and Kana Watanabe for evaluating the phototoxic response from the clinical photographs.

References