Oxygenation Gain Factor: A Novel Parameter Characterizing the Association between Hemoglobin Level and the Oxygenation Status of Breast Cancers

Peter Vaupel, Arnulf Mayer, Susanne Briest, and Michael Höckel

Institute of Physiology and Pathophysiology, University of Mainz, Mainz, and Department of Obstetrics and Gynecology, University of Leipzig, Leipzig, Germany

Abstract

Tumor hypoxia has been linked to acquired treatment resistance, tumor progression, and poor prognosis. Because anemia is a major causative factor for the development of hypoxia, the association between blood hemoglobin concentration (cHb) and breast cancer oxygenation was examined in this study. In addition, a novel parameter characterizing the relationship between oxygenation status and rising cHb is introduced: the oxygenation gain factor (OGF). In breast cancer patients, median cHb over the range 8.5–14.7 g/dl correlated positively with the median pO2 (3–15 mm Hg), yielding an average OGF of 2 mm Hg/dl/g. In contrast, in normal tissues (normal breast, subcutis, and skeletal muscle) the median pO2 values were substantially higher (52 mm Hg, 51 mm Hg, and 37 mm Hg, respectively) and remained constant irrespective of the hemoglobin level over the range from 10 to 16 g/dl (OGF = 0 in grade I anemia and nonanemic patients). Moderately lower median pO2 values in subcutis and skeletal muscle were only observed in grade II anemia (8 g/dl < cHb ≤10 g/dl), although this would appear to be of no biological relevance. Conversely, in breast cancers, even mild anemia (grade I anemia) is a major causative factor for the development of hypoxia or anoxia.

Introduction

The introduction of the computerized pO2-histogram system (Eppendorf, Hamburg, Germany) for reliable measurements of tissue oxygen (O2) tensions (pO2) in the clinical setting allowed for the first time the systematic study of the oxygenation status in accessible, locally advanced tumors (1, 2). Over the last decade, assessment of tumor oxygen profiles determined with this O2 microsensor technique repeatedly demonstrated that the presence of tissue hypoxia (i.e., tissue areas with critically reduced oxygen levels) or even anoxia (no measurable O2 levels) are characteristic pathophysiological properties of solid tumors (3–5). In addition, hypoxia proved to be an independent, strong prognostic parameter in these malignancies (3–6). Irrespective of the mode of treatment, patients with hypoxic tumors had a significantly poorer outcome than those with better oxygenated lesions of the same clinical size and stage. More important than its potential impact on the present treatment options are new insights into the fundamental role of tumor hypoxia in tumor propagation, malignant progression, acquired treatment resistance, and poor long-term prognosis (3, 4, 7).

Hypoxia is predominantly caused by structural and functional abnormalities of the newly formed tumor microvessels arising from neovascularization, by a compromised microcirculation, by enlarged diffusion distances, and by tumor-associated and/or therapy-induced anemia (3). The role of anemia in the development of tumor hypoxia as a consequence of a reduced O2-carrying capacity of the blood has been demonstrated in an experimental tumor model (8, 9). These experimental data have provided strong evidence of a relationship between decreased Hb levels and a poor oxygenation status in solid tumors.

Using data from an ongoing prospective study examining the oxygenation status in breast cancers, this investigation is intended to evaluate a possible relationship between Hb levels and pretreatment tumor oxygenation in conscious patients. This is to our knowledge the first study relating blood Hb levels (anemia of grades I and II included, National Cancer Institute system) to the oxygenation status of breast cancers. Results obtained may have important implications for studies identifying inter alia the power of prognostic factors, the requirement of RBC transfusions, and/or the benefit of erythropoietin treatment of anemic patients.

Materials and Methods

The evaluation of intratumoral pO2 distributions in locally advanced breast cancers was conducted at the Department of Obstetrics and Gynecology, University of Leipzig from January 1999 through December 2002. The study design was approved by the Local Human Ethics Committee, and all of the enrolled patients gave informed written consent. Pretreatment pO2 measurements were performed on 37 conscious patients with breast cancer using the pO2 histogram system after a standard procedure, which has been described in detail previously (1, 7, 10). All of the pO2 measurements were performed under ultrasound guidance of the O2 sensor. For the description of the oxygenation status of the breast cancers, the median pO2 and the fraction of pO2 readings ≤2.5 mm Hg and ≤5 mm Hg were stated. In all of the patients, cHb was determined by standard procedures in venous blood samples before pO2 measurements.

Results are expressed as means ± SE. Differences between groups were assessed by the Wilcoxon test. The significance level was set at α = 5% for all of the comparisons.

Results and Discussion

Patient and Tumor Characteristics. The age range of the enrolled patients was 42–90 years (median, 65 years). Twelve of the women were premenopausal, and 25 were postmenopausal. Largest tumor diameter ranged from 1.0 to 5.2 cm (median, 2.5 cm). All of the tumors were invasive and were classified according to the Tumor-Node-Metastasis staging system (Union Internationale Contra Cancer, 1997). pT-stages were pT1c (n = 10), pT2 (n = 19), pT3 (n = 5), and pT4b (n = 3). According to histopathologic classification, 28 cancers were ductal, 7 lobular, 1 was intracystic, and 1 apocrine. Histological grades were G1 (n = 5), G2 (n = 20), and G3 (n = 12). Nodal status was N0 (n = 10), N1 (n = 23), N2 (n = 1), and NX (n = 3). M stage was M0 (n = 8), M1 (n = 2), and MX (n = 27).

Approximately 63% of the breast cancers investigated exhibited hypoxic tissue areas (pO2 ≤2.5 mm Hg), which were heterogeneous distributed within the tumor masses. The median pO2 was 6 mm Hg. The fraction of pO2 values ≤2.5 mm Hg was 25%, and 58.5% of the pO2 values were ≤5 mm Hg. When tumors of different...
sizes were compared, there was no evidence of a correlation between the median pO₂ and the maximum tumor diameter. This implies that the oxygenation in breast cancers and the occurrence of hypoxia and/or anoxia do not correlate with the clinical and pathological stages. In addition, the oxygenation pattern does not correlate with tumor location within the breast, N stage, histological type, and grade, nor with a series of other clinically relevant parameters (e.g., hormone receptor status, parity, and menopausal status).

Pretreatment median cHb measured in our patient cohort was 13.0 g/dl (range, 8.0–15.3 g/dl). Larger tumors or higher stages tended to correlate with lower cHb values (12.95 g/dl in patients with tumors ≥2.5 cm diameter versus 12.05 g/dl in patients with cancers ≤2.5 cm). At presentation, 27% of our breast cancer patients were anemic. This value is in line with data published earlier (e.g., 28.7%; Ref. 11).

Association between Hb Levels and Breast Cancer Oxygenation. In patients with normal Hb levels (cHb ≥12 g/dl) the median pO₂ was significantly higher than in anemic patients (P = 0.015). Additionally, analysis of the oxygenation status as a function of baseline cHb was performed by dividing the patients into five groups based on “high” (above median cHb; median cHb of age-matched healthy women = 14.0 g/dl; Ref. 12), “intermediate” cHb values (13.0 g/dl < cHb ≤14.0 g/dl), “lower-normal” cHb values (12.0 g/dl ≤ cHb ≤ 13.0 g/dl), mild anemia (grade I, 10.0 g/dl < cHb < 12.0 g/dl), and moderate anemia (grade II, 8.0 g/dl < cHb ≤ 10.0 g/dl).

On the basis of this separation, a correlation between Hb levels and median pO₂ values as shown in Fig. 1 was obtained. In moderately anemic patients all of the median pO₂ values were <6 mm Hg. At a mean Hb level of 8.5 ± 0.2 g/dl, the median pO₂ was 3 mm Hg. With increasing cHb values the median pO₂ exponentially increased (log pO₂ = 0.114 cHb - 0.472; r² = 0.985) reaching a maximum

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* Unpublished observations.
In conclusion, this study clearly shows that the oxygenation status of primary breast cancers critically depends on the whole blood Hb level (cHb), with median cHb (over the range 8.5–14.7 g/dL) correlating with exponentially greater median pO2 values (3–15 mm Hg) yielding an average OGF of 2 mm Hg/dL. In contrast, in normal tissues (subcutis and skeletal muscle) the median pO2 values are substantially higher (51 mm Hg and 37 mm Hg, respectively) and are relatively constant over hemoglobin levels from 10 to 16 g/dL (grade II anemia and nonanemic patients). Only in moderate anemia (grade II anemia, 8 g/dL < cHb ≤ 10 g/dL) were relatively small decreases in the median pO2 values observed (−9% in skeletal muscle and −23% in the subcutis), which is most probably without any biological relevance.

Acknowledgments

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References


Table 1: OGF in solid tumors and in normal tissues as a function of whole blood hemoglobin levels (cHb)

<table>
<thead>
<tr>
<th>Tumors</th>
<th>OGF (mmHg·dL/g)</th>
<th>cHb range (g/dL)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancers</td>
<td>1.5</td>
<td>8.5–11.9</td>
<td>This study</td>
</tr>
<tr>
<td>Head and neck cancers</td>
<td>3.1</td>
<td>12.0–14.7</td>
<td>This study</td>
</tr>
<tr>
<td>Cervix cancers</td>
<td>2.4</td>
<td>9.4–14.0 (13)</td>
<td></td>
</tr>
<tr>
<td>Vulvar cancers</td>
<td>3.5</td>
<td>10.0–13.0 (18)</td>
<td></td>
</tr>
<tr>
<td>Normal tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal breast</td>
<td>0</td>
<td>8.4–14.8</td>
<td>This study</td>
</tr>
<tr>
<td>Subcutis</td>
<td>4.6</td>
<td>9.3–11.9</td>
<td>This study</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>0</td>
<td>8.5–10.2</td>
<td>(19)</td>
</tr>
</tbody>
</table>

OGF values from Refs. 13, 18, and 19 were calculated from published cHb and pO2 data.

*OGF describes the rise in the median pO2 (mmHg) per 1 g/dL increment in cHb on the basis of comparisons between patients with different Hb levels (OGF = ΔpO2/ΔcHb).

OGF values in tissues with high median pO2 values (e.g., in normal breast and in the subcutis) are of minor biological importance because these tissues are already adequately supplied.

ΔpO2 measurements performed in patients with renal anemia treated with erythropoietin.

Negative OGF describes a decrease in tissue pO2 with increasing cHb.

In locally advanced solid tumors these two adaptive (compensatory) mechanisms may not work because flow regulation is limited, if not impossible, and O2 extraction ratios are already high at physiological Hb levels (17).

a M. Höckel and P. Vaupel, unpublished observations.


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