Oxygenation of Human Tumors: Evaluation of Tissue Oxygen Distribution in Breast Cancers by Computerized O$_2$ Tension Measurements

P. Vaupel, K. Schlenger, C. Knoop, and M. Höckel

Institute of Physiology and Pathophysiology [P. V., K. S.] and Department of Gynecology and Obstetrics [C. K., M. H.J, University of Mainz, D-6500 Mainz, Germany

ABSTRACT

Direct oxygen partial pressure (pO$_2$) readings in breast cancers, in fibrocystic disease, and in the normal breast have been obtained using a novel technique which allows for the systematic evaluation of the oxygenation status as a function of pathological staging and histological grading. Measurements were performed in awake pre- and postmenopausal patients with well-defined arterial blood gas status.

The measuring procedure encompasses a computerized electrode movement in the tissue which avoids significant compression artifacts and allows routine measurement in human tumors before, during, and after treatment. Using this reliable technique, pO$_2$ measurements in the normal breast and in fibrocystic disease resulted in oxygenation patterns which were characteristic for normal, adequately supplied tissues. The median pO$_2$ values were 65 and 67 mm Hg, respectively, with no pO$_2$ readings below 12.5 mm Hg in the normal breast, and ≤5 mm Hg in fibrocystic disease, respectively. In contrast, in breast cancers the median pO$_2$ value was 30 mm Hg (pooled data for pathological stages T$_1$–T$_4$). To date, 6 of 15 breast cancers exhibited pO$_2$ values between zero and 2.5 mm Hg, i.e., tissue areas with less than half-maximum radiosensitivity. The oxygenation pattern in breast cancers and the occurrence of hypoxia and/or anoxia did not correlate with either the pathological stages and histological grades or with a series of clinically relevant parameters. No significant differences were found between pre- and postmenopausal tumors and between lobular and ductal carcinomas. Tumor-to-tumor variability in the oxygenation pattern was more pronounced than intra-tumor heterogeneity. pO$_2$ variations within a tumor cannot be predicted, e.g., as a function of the measuring site (tumor center versus periphery).

INTRODUCTION

Tumor hypoxia remains an important research topic in clinical and experimental oncology. Although tumor heterogeneity complicates the interpretation of data (1), tissue hypoxia is almost certainly a major factor influencing the clinical response of many tumors to therapy. It is well established that a significant proportion of cells in solid rodent tumors (2–4), in xenografted human tumors (5–7), and in primary or metastatic patient malignancies (8) are hypoxic. Oxygen-deprived clonogenic cells are critical in determining the tumor response to therapy using standard radiotherapy (9) and certain anticancer drugs (10, 11). The role of oxygen in tumor cell proliferation and of hypoxia as a possible causative factor for the development of drug resistance for generation of metastatic variants in solid tumors or as a response modulator during hyperthermia treatment has recently been discussed in detail (12–14). As to whether inherent (intrinsic) properties during radiation therapy or the metabolic micromilieu (including tissue oxygenation) is the dominant factor in treatment outcome is still a subject of controversy (15, 16).

Despite the apparent importance of tumor oxygenation (O$_2$ partial pressure or O$_2$ tension distribution), data on pO$_2$ values in solid tumors are mostly derived from experiments on rodents which do not necessarily reflect the variability of the clinical situation. Due to reliable techniques available now, considerable advances have been made in the past few years in the detection of tumor hypoxia in patients (for a review see Ref. 8). The latter information may be beneficial for designing specifically tailored treatment protocols (i.e., it may be used as a prognostic indicator of whether or not an individual patient would be expected to be a good candidate for a certain treatment), for assessing early tumor response to treatment, and/or for examining potentially useful factors for prediction of long-term tumor response (8).

The objective of this study was to evaluate the oxygenation pattern of primary breast cancers in patients using a novel technique first described by Weiss and Fleckenstein (17) and placing emphasis on a well-defined arterial blood gas status. This technique minimizes tissue compression by the needle electrode and has been shown to represent a valid and reliable method for analysis of the O$_2$ tension distribution in normal tissues (17–20).

In the present study the key questions were as follows: Is this novel technique also applicable to human breast cancers? Do the pO$_2$ data obtained with this method match with earlier results describing low mean O$_2$ tensions in breast cancers together with an anisotropic distribution of the O$_2$ values recorded? This latter question is of great relevance because the earlier investigations were either sporadic or anecdotal (21–24) or used general anesthesia (25) or measurements were performed in selected patients with advanced disease and in a certain depth only (26). Another key issue of this investigation was the comparison of the oxygenation pattern in normal breast tissue, benign lesions (fibrocystic disease), and malignancies.

In this article special emphasis was also given to the evaluation of the oxygenation status as a function of pathological staging and histological grading. In addition, the patient data obtained from these systematic studies should also allow a direct comparison between spontaneous rodent tumors, transplanted animal malignancies, and primary tumors in patients.

MATERIALS AND METHODS

Patients. As part of a prospective study on untreated patients with breast cancer which aims to assess the relevance of pO$_2$ measurements in individual tumors for local control after therapy, we have evaluated intratumor pO$_2$ measurements in 4 pre- and 11 postmenopausal patients (37–81 years old) entering the study. Fifteen women presented with histologically confirmed breast cancer; 5 patients had fibrocystic disease. The cancer patients were referred to the Department of Gynecology and Obstetrics, University of Mainz (Germany) for either surgical or irradiation treatment. None of the tumors had previously been treated with irradiation or chemotherapy. The relevant patient characteristics and tumor data are summarized in Table 1. Pathological staging was performed according to the tumor-nodes-metastasis classification (27). For histological grading the classification suggested by Bloom and Richardson (28) was used. The location and site of each...
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* No. of lymph nodes examined.
mammary tumor were assessed using mammography and clinical examination. The characteristics of patients with fibrocystic disease are given in Table 2.

All patients were fully informed about the experimental nature of the present investigation, gave consent without reservation, and experienced the minimum of discomfort. Complete removal of the tissue containing the electrode tracks by subsequent ablative surgery or inclusion of the electrode tracks into the target volume in case of subsequent radiation therapy were mandatory.

Measurements of Tissue Oxygen Tension Values with Needle Electrodes. For the measurement of tissue oxygen tension (pO2) values, sterile polarographic needle electrodes with stainless steel shafts (of the hypodermic needle type) were used (pO2 histography, model KIMOC-6650; Eppendorf, Hamburg, Germany; see Fig. 1). The probes had a mean shaft diameter of 300 μm. The sharply ground tips of the probes contained a membranized polarographic, recessed microcathode in the form of a gold wire 12 μm in diameter (17). Technical data for the needle electrodes when immersed in 0.9% saline at 37°C and at a polarization potential of −700 mV (toward the silver/AgCl anode placed on the skin of the chest wall next to the measuring site) are: O2 sensitivity before tissue pO2 measurements 1.8 ± 0.15 (SE) and 2.0 ± 0.18 pA/mm Hg pO2 upon recalibration, respectively; response time (T½), <500 ms. As a rule, pO2 studies of individual tumors took less than 10 min.

Calibration was performed in sterile phosphate-buffered saline solution (pH 7.4) immediately before and after pO2 measurements in the tissues. Calibration values were set to the pO2 resulting from equilibrium with air and pure nitrogen (pO2 = 0 mm Hg). The actual calibration values of the probe were calculated from the measured current (which is proportional to the pO2 in the medium), the pO2 in the air (which depends on the actual barometric pressure), the water vapor saturation, and the temperature of the tissue under investigation.

In general, 3 defined radial electrode tracks were evaluated in each tumor. After local anesthesia (50 μl of a 1% mevipacain solution (Scandicain; Astra Chemicals; without addition of a vasoconstrictor agent), a plastic trocar (outer diameter, 0.8 mm) equipped with a hypodermic needle was advanced to an initial depth of approximately 2 mm. The hypodermic needle was then removed and the O2-sensitive probe was placed into the tissue of interest. All electrode tracks could be performed leaving the trocar at one puncture site and guiding the probe was placed into the tissue of interest. The water vapor saturation, the oxygenation pattern of individual tumors. In the case of steep gradients, the automatic electrode progression can be stopped and restarted with smaller step lengths.

The local pO2 was measured 1.4 s after the backward movement. Single local pO2 value measurements were made in less than 40 ms in order to circumvent any significant effect on the recorded local tissue pO2 brought about by the compression of vessels in the vicinity of the needle electrode and the “O2 consumption” of the cathode. Tissue injury due to the electrode movement is rather small with no effect on the pO2 values recorded (18). The accuracy and reproducibility of the pO2 histography technique were tested by comparing two different sets of successive pO2 measurements in normal tissues of patients (19). Direct comparison between the O2-sensitive probes used in this study and Whalen-type microelectrodes with tip diameters ≤15 μm in tumors gave similar results (20).

During the measuring procedure, the single pO2 values were displayed on a monitor screen. At the end of a measurement the O2 probe was automatically removed from the tissue. Using an on-line computing system, pO2 histograms (i.e., pO2 frequency distributions) were obtained with a class width of 2.5 mm Hg. The distribution of the measured pO2 values was characterized by the mean pO2, the median pO2, and the 10 and 90% percentile values. For statistical evaluation of possible differences between groups the Mann-Whitney-U test was used.

As a rule, pO2 measurements in untreated patients were carried out immediately before commencing therapy. All measurements were conducted on conscious women.

Monitoring of Relevant Systemic Parameters. O2 supply (or O2 availability) is the amount of oxygen carried by the blood to a given tissue per unit time. It is the product of the perfusion rate and the arterial O2 concentration, parameters which critically determine tissue oxygenation (besides O2 consumption rate, O2 diffusivity, and diffusion geometry). For this reason basic cardiovascular parameters (e.g., heart rate, arterial blood pressure) and factors determining the arterial O2 concentration, e.g., hemoglobin concentration, hematocrit, arterial oxyhemoglobin saturation (assessed by a pulse oximeter, type N10; Nellcor, Idstein, Germany) were monitored throughout all measuring procedures.

RESULTS

Using the computerized pO2 histography system, pO2 values were recorded in the normal breast, in fibrocystic disease, and in breast cancers of different pathological stages and pathohistological grades. As a rule, the mean (and median) pO2 values were distinctly lower in the malignancies than in the normal tissue or in the breast with fibrocystic disease. The pO2 histograms of tumors were usually shifted to lower O2 tensions whereas in the respective normal tissues and in fibrocystic disease the pO2 distributions were more or less Gaussian. O2 tensions measured in the normal breast of 16 patients (1099 pO2 readings) revealed a median pO2 value of 65 mm Hg (see Fig. 2, top), whereas in 15 cancers of the breast (stages T1-T4; 1068 pO2 readings) the median pO2 was 30 mm Hg (Fig. 2, bottom). Thus far, 6 of 15 breast cancers exhibited pO2 values between zero and 2.5 mm Hg, i.e., tissue areas with less than half-maximum radiosensitivity, whereas in the normal breast pO2 values ≤12.5 mm Hg could not be detected. Since 40% of the tumors investigated contained hypoxic areas and the remaining tumors were normoxic and comparable to normal breast tissue, the pO2 distribution curve is clearly bimodal (see Fig. 2, bottom).
In fibrocystic disease, the pO₂ distribution is similar to that obtained in normal breast tissue with a median pO₂ of 67 mm Hg (362 pO₂ readings in 5 patients). Oxygen tension values below 5 mm Hg were not detected (see Fig. 3).

Pooled pO₂ data for all breast cancers of pathological stages T₁ and T₂ are presented in Fig. 4 (top), whereas the respective pO₂ histogram for malignancies of stages T₃ and T₄ is shown in Fig. 4 (bottom). This compilation provides clear evidence that there are no statistically significant differences between the...
two groups (median pO\textsubscript{2} in T\textsubscript{1}/T\textsubscript{2} tumors, 24 mm Hg; median pO\textsubscript{2} in T\textsubscript{3}/T\textsubscript{4} tumors, 35 mm Hg). This implies that the pathological stages of the breast cancers investigated thus far cannot be the paramount factor determining tumor tissue oxygenation. The median pO\textsubscript{2} is slightly higher and the number of pO\textsubscript{2} readings in the “hypoxic” class (0–2.5 mm Hg) is marginally lower in T\textsubscript{3}/T\textsubscript{4} than in T\textsubscript{1}/T\textsubscript{2} tumors. There is substantial experimental evidence that the occurrence of radiobiological hypoxia does not correlate with the pathological stage and the histological grade. Furthermore, no differences were found between pre- and postmenopausal tumors, between lobular and ductal carcinomas, and between tumors in the upper versus lower quadrants. Correlations between staging or grading and the number of pO\textsubscript{2} readings on zero level, the pO\textsubscript{2} readings from zero to 2.5 mm Hg, the mean or median pO\textsubscript{2}, and the 10 and 90% percentiles could not be detected. Thus far, no correlations have been found between the oxygenation status of the tumors and the extent of necrosis or fibrosis (information based on qualitative evaluation).

There is marked tumor-to-tumor variability, even if tumors of the same stage (T\textsubscript{2}), grade (G2), and histology (ductal carcinomas) are compared (Fig. 5). In the case presented in Fig. 5 (top), all measured pO\textsubscript{2} values are indicative of radiobiological normoxia. In contrast, oxygenation of the breast cancer shown in Fig. 5 (bottom) contains a significant tissue volume (at least approximately 16%) with less than half-maximum radiation sensitivity.

Because of intratumor heterogeneities, a certain number of electrode tracks through the tumor is required to obtain sufficient information on the oxygenation status of an individual tumor. With this technique, 3 electrode tracks with ≥50 pO\textsubscript{2} recordings yielded representative results. Random evaluations of more than 3 electrode tracks in some tumors could not improve the information on the tissue oxygenation, as long as the standard tracks were performed as described. Examples for intratumor heterogeneities are shown in Fig. 6, in which 3 measured pO\textsubscript{2} profiles are shown for 3 different tumors. In all cases the electrode was advanced from superficial tumor layers into central regions. From the measuring diagrams presented there is clear evidence that pO\textsubscript{2} variations can be obtained which cannot be predicted (e.g., as a function of the location of the electrode in the tumor periphery versus the tumor center) and which are independent of all clinical parameters considered in this study.

**DISCUSSION**

Data on hypoxia in human tumors are scarce because of technical limitations. A new concept involving a rapidly and stepwise moving needle oxygen sensor provides a useful technique to advance our knowledge in this research area. Possible artifacts due to compression and/or bleeding caused by the 300-\textmu m O\textsubscript{2} probe seem to be successfully compensated by the rapid...
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Fig. 6. pO2 profiles evaluated in 3 different tumors. Individual profiles were recorded in tracks from the periphery toward the tumor center.

Table 3 Tissue oxygen tensions in breast cancer, in fibrocystic disease, and in the normal breast of patients (n = number of patients)

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<sup>a</sup> Mean.  
<sup>b</sup> Median.

or long-term tumor response and for designing individualized therapeutic regimens.

Oxygen partial pressure distributions for isotransplanted mammary tumors in rodents have been described in detail (2, 29). In general, as a result of a compromised and anisotropic microcirculation, most of these malignancies reveal hypoxic and anoxic tissue areas which are heterogeneously distributed within the tumor mass. In poorly perfused human breast cancer xenografts, hypoxic and anoxic regions were already present at early growth stages and expanded with tumor growth (5, 6). In contrast, s.c. breast cancer xenografts with high perfusion rates have tissue oxygenations comparable to those of most normal organs. This is most probably due to an adequate vascularization of the latter tumors. Only at larger sizes did these tumors “outgrow” their vasculature and hypoxic/anoxic tissue areas develop (6).

Considering data derived from sporadic or anecdotal studies, there is clear indication that the mean (and median) pO2 values in human breast cancers in situ are distinctly lower than in the normal breast (Table 3). This finding reflects the better vascularization in normal breast tissue than in the malignancies (30). Taking all reported data on human breast cancers together (21–26), the number of pO2 readings between zero and 5 mm Hg is 18% (for a review, see Ref. 8). Although this proportion is also 18% in the present study, the median pO2 is 17 mm Hg in the earlier studies (8) and 30 mm Hg in our current investigation. These therapeutically relevant differences are most probably caused by minimizing tissue compression and a minimal “O2 consumption” of the microcathode. There are also pronounced differences between the median pO2 of the normal breast (43 mm Hg in the earlier studies) and the data obtained with the new technique (65 mm Hg). Thus, computerized pO2 histography provides higher pO2 values in breast cancers than those previously reported. Nevertheless, in 40% of the tumors investigated regions with pO2 values ≤2.5 mm Hg and, therefore, areas with less than half-maximum radiosensitivity were found. This portion gives only the minimum fraction since it cannot be excluded that the electrodes passing the tumors in certain directions may have missed hypoxic or anoxic tissue areas.

Substantial tumor-to-tumor pO2 variability was observed in this study. This is in line with the finding that the vascular density and tumor perfusion between patients differed more than between different locations in the same patient [perfusion rates varied by a factor of 15 considering different tumors (30)]. In contrast to the reports of Gatenby et al. (31, 32), who have described a steady drop of the pO2 values from the periphery to the center in 12 metastases of squamous cell carcinomas of the head and neck, and to data published by Fleckenstein et...
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