Impact of Hemoglobin Levels on Tumor Oxygenation: the Higher, the Better?

Peter Vaupel[1], Arnulf Mayer[1], Michael Höckel[2]

Background and Purpose: Tumor hypoxia has been linked to tumor progression, the development of treatment resistance, and thus poor prognosis. Since anemia is a major factor causing tumor hypoxia, the association between blood hemoglobin concentration (cHb) and tumor oxygenation status has been examined.
Patients and Methods: Published data on the relationship between pretreatment cHb values and tumor oxygenation (in terms of median pO_2 values, hypoxic fractions) have been summarized. Pretreatment O_2 tension measurements were performed in histologically proven experimental tumors, human breast cancers, squamous cell carcinomas of the head and neck, and cancers of the uterine cervix and of the vulva. In order to allow for a comparison between solid tumors and normal tissues, pO_2 measurements were also performed in healthy tissue in anemic and nonanemic patients. cHb was determined at the time of the pO_2 measurements.
Results: Based on current information from experimental and clinical studies there is increasing evidence that anemia is associated with a detrimental tumor oxygenation status. Increasing cHb values are correlated with significantly higher pO_2 values and lower hypoxic fractions. Maximum tumor oxygenation in squamous cell carcinomas is observed at normal (gender-specific) cHb values (approximately 14 g/dl in women and approximately 15 g/dl in men). Above this "optimal" Hb range, the oxygenation status tends to worsen again. In anemic patients, tumor oxygenation is compromised due to a decreased O_2 transport capacity of the blood. At the upper edge of the Hb scale, a substantial increase in the blood's viscous resistance to flow in "chaotic" tumor microvessels is thought to be mainly responsible for the observed restriction of O_2 supply.
Conclusion: Review of relevant clinical data suggests that a maximum oxygenation status in solid tumors is to be expected in the range 12 g/dl < cHb < 14 g/dl for women and 13 g/dl < cHb < 15 g/dl for men. Considering the "optimal" cHb range with regard to tumor oxygenation, the concept of "the higher, the better" is therefore no longer valid. This finding has potentially far-reaching implications in the clinical setting (e.g., inappropriate erythropoietin treatment of nonanemic tumor patients).

Key Words: Hemoglobin concentration · Anemia · Hematocrit · Tumor oxygenation · Tumor hypoxia · Squamous cell carcinomas · Breast cancers

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Einfluss des Hämoglobingehalts auf die Tumoroxygenierung: je höher, desto besser?

Hintergrund und Ziel: Hypoxie trägt ursächlich zur Tumorprogression, Therapieresistenz und damit zur schlechteren Prognose von Tumorpatienten bei. Ein wesentlicher pathogenetischer Faktor für das Auftreten einer Tumorhypoxie ist die Anämie. Aus diesem Grund wurde die Abhängigkeit der Tumoroxygenierung von der Hämoglobinkonzentration (cHb) untersucht.
Patienten und Methodik: Publizierte Daten zum Zusammenhang zwischen prätherapeutischen cHb-Werten und der Tumoroxygenierung (charakterisiert durch mediane pO_2-Werte, hypoxische Fraktionen) wurden kritisch analysiert. Untersucht wurden Experimentaltumoren, Mammakarzinome, Kopf-Hals-Tumoren und Plattenepithelkarzinome der Zervix und der Vulva. Darüber hinaus wurde zum Vergleich auch der Oxygenierungsstatus von Normalgeweben bei anämischen und nichtanämischen Patienten erfasst. Die Messung der Hb-Konzentration erfolgte zeitnah mit der pO_2-Messung.
Ergebnisse: Experimentelle und klinische Studien zeigen eindeutig, dass niedrige cHb-Werte in der Regel mit einer schlechten Tumoroxygenierung einhergehen. Die Zunahme des Hb-Gehalts führt zu einer signifikanten Verbesserung der Tumoroxygenierung. Die höchsten medianen pO_2-Werte bzw. niedrigsten hypoxischen Fraktionen in Plattenepithelkarzinomen findet man im Bereich der (geschlechtsspezifischen) Normalwerte (ca. 14 g/dl bei Frauen und etwa 15 g/dl bei Männern). Bei Überschreiten dieses „optimalen" Bereichs nimmt die O_2-Versorgung des Tumorgewebes wieder ab. Bei anämischen Patienten verschlechtert sich aufgrund der eingeschränkten O_2-Transportkapazität der Oxygenierungsstatus der Tumoren. Bei relativ hohen Hb-Konzentrationen tritt ebenfalls eine zunehmende Verschlechterung der O_2-Versorgung auf, die im Wesentlichen auf eine Perfusionsstörung infolge eines stark gestiegenen viskösen Strömungswiderstands des Bluts im „chaotischen" Gefäßbett der Tumoren zurückzuführen ist.

[1] Institute of Physiology and Pathophysiology, University of Mainz, Germany,
[2] Department of Obstetrics and Gynecology, University of Leipzig, Germany.

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Schlussfolgerung: Klinische Daten lassen den Schluss zu, dass eine maximale Tumoroxygenierung bei Frauen zwischen 12 und 14 g/dl und bei Männern zwischen 13 und 15 g/dl zu erwarten ist. Aufgrund dieses Befunds ist das Konzept „je höher, desto besser" nicht länger vertretbar. Darüber hinaus ergibt sich eine Reihe klinisch relevanter Konsequenzen (z.B. unangemessene Erythropoietintherapie bei nichtanämischen Tumorpatienten).

Schlüsselwörter: Hämoglobingehalt · Anämie · Hämatokritwert · Tumoroxygenierung · Tumorhypoxie · Plattenepithelkarzinome · Mammakarzinome

Introduction

Tissue hypoxia is a powerful and independent adverse prognostic factor in solid malignancies. One major factor causing tumor hypoxia is a decreased O_2 transport capacity of the blood resulting from tumor-associated and/or therapy-induced anemia, which is a frequent complication seen in cancer patients (e.g., [6, 45]).

In this review, current information compiled from experimental and clinical studies is presented which illustrates the relationship between tumor oxygenation and hemoglobin levels (cHb). Additionally, the relevance of anemia and tumor hypoxia as negative prognostic factors is briefly outlined.

Tumor Hypoxia and Anemia as Adverse Prognostic Factors

An adverse *prognostic impact of tumor hypoxia* in various tumor entities – including cancers of the uterine cervix, head and neck, and soft tissue sarcomas – has been repeatedly demonstrated (for reviews see [19, 47, 90]). In cervical carcinomas, this impact on prognosis was found to be independent of treatment modality, being evident even in cases treated with surgery alone [31]. This finding speaks strongly in favor of a hypoxia-induced enhancement of aggressiveness resulting in malignant progression.

The role of hypoxia as a tumor promoter is indisputable [68]. Even so, the possibility that the aforementioned causality may be reversed also deserves consideration. If this were the case, then the inherently most malignant tumors would necessarily also be the most hypoxic [13, 58]. On closer inspection, these two possibilities may not necessarily contradict each other, but may rather even be complementary. If hypoxia does indeed promote the malignant phenotype, then the most (inherently) malignant tumor cells would in turn be capable of generating a hypoxic environment. A combination of both scenarios would mean that hypoxia is the cause of increased aggressiveness since it promotes tumor progression, while at the same time being a consequence of aggressive malignant growth that leads to defective ("chaotic") vascular morphology and function together with other alterations in the nonmalignant part of the tumor, thereby creating an environment which is adjusted to the pathophysiological demands of the tumor.

Multivariate analyses have shown that hypoxia is a powerful prognostic factor in locally advanced cancers of the uterine cervix [21, 30–34, 40, 75], in squamous cell carcinomas of the head and neck [9, 53–56, 69] and in soft-tissue sarcomas [8, 52]. This parameter, being independent of other prognostic factors which can be pretherapeutically assessed, such as clinical tumor size or stage, may therefore become clinically useful [61].

The *prognostic significance of anemia* in patients with solid tumors has been documented in a series of clinical studies (for reviews see [10, 11, 16, 26, 27, 57, 59, 84]). Some of these investigations suggest that Hb levels during and at the end of radiation therapy are of prognostic significance with respect to tumor recurrence and survival. Hb levels were significant prognostic factors even after adjustment for other prognostic parameters such as tumor stage and histology [24, 76].

The mechanism(s) by which treatment efficacy and survival are compromised by anemia is (are) not fully understood, but may include an intensification of tumor hypoxia, a more general compromise of the patients' well-being [15, 44], poorer transport kinetics of small cytotoxic drugs (i.e., drug delivery) in oligocythemic states [29, 65, 66, 95], or remodeling of tumor microvessels [83]. Whether Hb levels at the start of therapy (or at presentation, e.g., [14, 22, 25, 28, 46, 62]), at the nadir during therapy (e.g., [26, 81]), at the peak during therapy (e.g., [41]), or at the end of (radio)therapy (e.g., [81, 94]) are of prognostic value in terms of better disease-free and overall survival is still being assessed in ongoing studies.

Relationship between Hemoglobin Level and Tumor Oxygenation: Animal Studies

The results of several preclinical studies using *experimental tumors* unequivocally showed tumor hypoxia in anemic rodents to be more pronounced than in nonanemic animals. Furthermore, there is clear evidence that correction of anemia can lead to an improvement in tumor oxygenation.

The first report describing the direct measurement of the oxygenation status in anemic versus nonanemic animals was communicated by Lavey & McBride [43]. In this study (summarized later by Lavey [42]), a strong correlation between hematocrit (Hct) and oxygenation within FSa murine fibrosarcomas was presented. In a subsequent study by Terris & Minchinton [78], a progressive drop of Hct values from 42% to 23% was associated with a decrease from 20 mmHg to 10 mmHg for mean pO_2 values in murine squamous cell carcinomas.

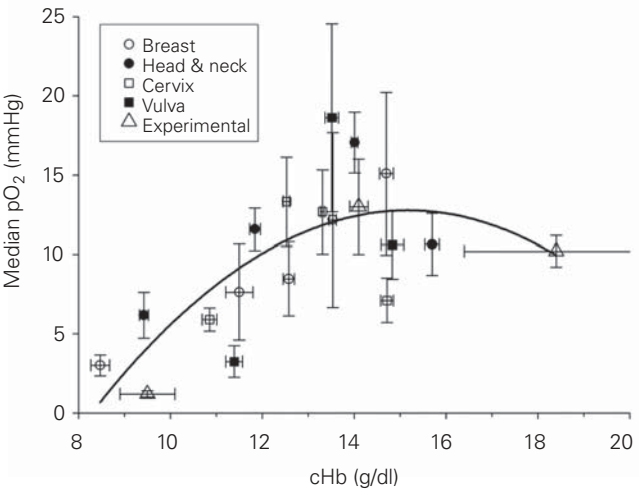

Figure 1. Association between Hb levels (cHb) and median pO_2 values in experimental rat sarcomas [37, 38], squamous cell carcinomas of the head and neck [5], of cervical and vulvar cancers [93], and cancers of the breast [91]. Values are means ± SEM. The line indicates the quadratic regression (2p = 0.002).

Abbildung 1. Abhängigkeit der medianen pO_2-Werte in Experimentaltumoren (Ratte [37, 38]), in lokal fortgeschrittenen Kopf-Hals-Tumoren [5], in Karzinomen der Cervix uteri und der Vulva [93] sowie in Mammakarzinomen [91] vom Hämoglobingehalt (cHb). Angegeben sind Mittelwerte ± SEM. Die Kurvenanpassung erfolgte durch quadratische Regression (2p = 0,002).

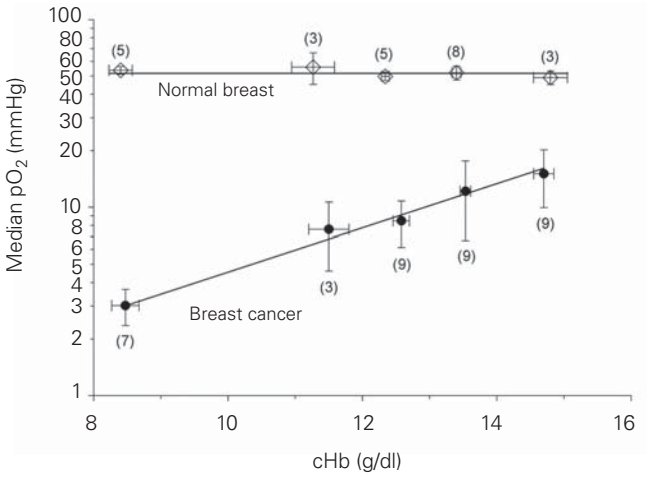

Figure 2. Median pO_2 values in breast cancers (lower line) and within the normal breast tissue (upper line) as a function of pretreatment hemoglobin concentration (cHb). Values are means ± SEM; number of patients investigated in brackets (adapted from Vaupel et al. [91]).

Abbildung 2. Mediane pO_2-Werte in Mammakarzinomen (untere Kurve) und in normalem Brustgewebe (obere Gerade) in Abhängigkeit von der prätherapeutischen Hämoglobinkonzentration (cHb). Angegeben sind Mittelwerte ± SEM; Zahl der untersuchten Tumoren bzw. Patientinnen in Klammern (nach Vaupel et al. [91]).

Kelleher et al. [36–39] investigated the oxygenation status in a tumor-associated or chemotherapy-induced anemia model of the rat using O_2 microsensors. In these studies, decreases in the Hb concentrations of approximately 30% were induced. This moderate anemia resulted in a worsening of tumor oxygenation as reflected in a pronounced decrease in the median O_2 partial pressure (median pO_2 value) from 13 mmHg to approximately 1 mmHg (see Figure 1) and a significant increase in the size of the hypoxic fraction (HF) of pO_2 values ≤ 2.5 mmHg (HF 2.5) from 21% to 76%. Worsening of the oxygenation status was also observed at Hb levels > 16 g/dl.

Kelleher et al. [36] also investigated the effect of erythropoietin (rhEPO) and transfusions of fresh donor blood on tumor oxygenation in the preclinical setting. Both the administration of rhEPO over 14 days or an acute transfusion with red blood cells increased Hb levels in anemic rats. This rise was associated with a significant improvement of the tumor oxygenation status in small tumors (< 1.4 ml), although a full recovery of the oxygenation to levels found in nonanemic animals could not be achieved.

In tumor-bearing mice, correction of anemia with darbepoietin, a long-acting analog of EPO, also improved tumor oxygenation as demonstrated using the exogenous hypoxia marker EF5 [51] or pimonidazole [66].

The question of whether a correction of anemia is associated with an increased sensitivity to radiation and O_2-dependent chemotherapy was investigated in rodent models by Thews et al. [79, 80], Silver & Piver [67], Stüben et al. [71–73], Pinel et al. [60], Shannon et al. [66], and Ning et al. [51]. All studies found that anemia correction (most probably via improving tumor oxygenation) can play a pivotal role in increasing the therapeutic efficacy of irradiation and O_2-dependent chemotherapy. A study designed to examine the impact of anemia on the antitumor efficacy of O_2-dependent photodynamic therapy (PDT) in a murine tumor model also showed that anemia can negatively influence the therapeutic effectiveness. Correspondingly, anemia correction could restore the antitumor effects of PDT [23].

Hypoxia is also common in *spontaneous canine tumors*. In a recently published study, the mean corpuscular volume (MCV) showed a negative correlation with the hypoxic fractions ≤ 2.5 mmHg, ≤ 5 mmHg, and ≤ 10 mmHg [1]. Furthermore, the packed cell volume (= Hct) negatively correlated with the hypoxic subvolume of the tumors investigated.

Relationship between Hemoglobin Level and Tumor Oxygenation: Clinical Observations

Breast Cancer

In the clinical setting, a direct correlation has been found between Hb levels and median intratumor pO_2 values in breast cancer patients [87, 91]. Median pO_2 values correlated positively over an Hb range from 8.5 to 14.7 g/dl with a fivefold increase (3–15 mmHg) in the median pO_2 (see Figure 2). By contrast, the pO_2 values in normal breast tissue were substan-

tially higher (52 mmHg), remaining constant irrespective of the Hb level. This phenomenon indicates a physiological compensation in anemic patients most probably related to an increase in perfusion in normal tissues [92].

Cancer of the Uterine Cervix

Dunst & Molls [18] described a linear relationship between Hb levels and tumor oxygenation when Hb concentrations were below the normal physiological range. In 67 cervical cancers, the median pO_2 was significantly lower in anemic patients as compared to nonanemic women. In a subsequent publication [17], no significant correlation between pretreatment Hb levels and pretreatment oxygenation parameters was found. These authors did, however, discover a significant correlation between the tumor oxygenation status at approximately 20 Gy and the corresponding Hb levels at that time during treatment. The hypoxic fraction (pO_2 < 5 mmHg) strongly correlated with the Hb level, and a trend was observed for the median pO_2.

Analyzing data from 51 patients with primary cervical carcinoma, Knocke et al. [40] were unable to confirm a correlation between initial (pretreatment) Hb levels (range: 8.4–17.0 g/dl) and median pO_2 values or hypoxic fractions ≤ 2.5 mmHg and ≤ 5 mmHg.

In another study involving 80 patients, there was again no correlation between oxygenation and the pretreatment Hb levels [21]. Data reported thereafter by Fyles et al. [20] relating Hb levels to the oxygenation status in cervix cancers showed a more complex relationship. Evaluating data from 91 patients, these authors reported that seven of eight patients

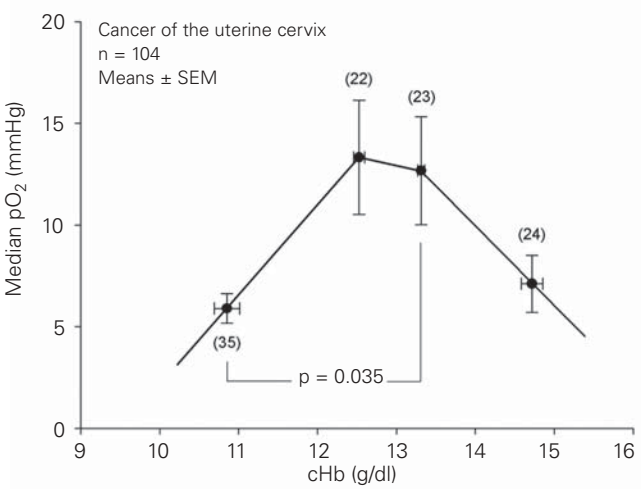

Figure 3. Correlation between pretreatment hemoglobin concentration (cHb) and median pO_2 values in cancers of the uterine cervix. Values are means ± SEM; numbers of tumors investigated are given in brackets (adapted from Vaupel et al. [93]).

Abbildung 3. Mediane pO_2-Werte in lokal fortgeschrittenen Zervixkarzinomen in Abhängigkeit vom prätherapeutischen Hämoglobingehalt (cHb). Angegeben sind Mittelwerte ± SEM; Zahl der untersuchten Karzinome in Klammern (nach Vaupel et al. [93]).

(≈ 87%) with Hb levels ≤ 10 g/dl had hypoxic tumors, whereas only 33 of 69 patients (≈ 48%) with Hb levels between 10 and 14 g/dl presented with hypoxic tumors (HF 5 > 50%). Ten of 14 patients (≈ 71%) with Hb concentrations > 14 g/dl presented with hypoxic tumors, suggesting that there is an "optimal" Hb range for the oxygenation status of cervix cancers with a worsening below and above this "optimal" range. When the delivery of oxygen to solid tumors as a function of Hb levels is modeled [20, 35] and the systemic effects of anemia are taken into account, then this relationship can in fact be predicted. The investigators attributed the poor oxygenation status of cervical cancers at higher Hb levels to the effect of carbon monoxide (CO) binding on O_2 release from red blood cells in smokers. They concluded that the increased blood viscosity at high Hb concentrations was not associated with hypoxia [20]. Given this association between Hb levels and tumor hypoxia (defined as HF 5 > 50%), it is, however, surprising that there is only a modest relationship between Hb levels and oxygenation status when HF 5 values are presented as a function of the initial Hb concentrations.

The reduction in O_2 delivery at low Hb levels may be higher in patients with sickle trait and intratumoral sickling, which can dramatically increase resistance to flow and further limit the effect of anemia per se on tumor oxygenation [49].

Analysis of the oxygenation status in cervix cancers as a function of pretreatment Hb levels (cHb) was performed by dividing patients into three groups based on "high" (above median cHb; median cHb of age-matched healthy women = 13.95 g/dl [48]), "intermediate" cHb values (12 g/dl < cHb < 13.95 g/dl; two subgroups), and anemic patients (cHb < 12 g/dl [82]). Using this classification, a correlation between Hb levels and median pO_2 values as shown in Figure 3 was obtained [93]. In anemic patients, the median pO_2 was 6 mmHg (cHb = 10.8 ± 0.2 g/dl). In tumors of anemic women, all median pO_2 values were < 16 mmHg. At a mean Hb level of 13.0 ± 0.1 g/dl, the median pO_2 significantly increased to 14.5 mmHg and declined thereafter to 6 mmHg in the group with the highest Hb values (cHb = 14.9 ± 0.2 g/dl). Although the O_2 transport capacity of the blood must have been increased, in the latter group, no median pO_2 values > 20 mmHg were noted. The oxygenation status tended to worsen between the "intermediate" and the "high" cHb concentrations as shown in Figure 3. From this finding it can be concluded, that an optimal Hb level with regard to the oxygenation status of cancers of the uterine cervix has to be assumed at cHb values of between 12 and 14 g/dl. In this group, median pO_2 values ranged from 1 to 44 mmHg. These data suggest that an optimal Hct or cHb range exists with regard to the median pO_2. The rise in the median pO_2 is based on an increase in the transport capacity of the blood with increases in cHb at values up to approximately 14 g/dl. At higher cHb values, this effect is counteracted by a substantial increase in the viscous resistance to flow (i.e., a deterioration of the blood's rheological properties) caused by a pronounced increase in blood viscosity which is further aggravated by a

high vascular permeability (leaky blood vessel walls) which obligatorily leads to a hemoconcentration (9–15% of the plasma flow extravasate during tumor passage [86]).

The restricted O_2 supply at higher cHb values is thus primarily caused by hyperviscosity in tortuous, elongated, dilated and functionally abnormal tumor microvessels, which counteracts and finally may overweigh the higher O_2 transport capacity which might have been expected in this range. This decline in the oxygenation status at high cHb or Hct values is not tumor-specific. In healthy individuals, the maximum O_2 availability is obtained at the physiological Hct and cHb. Above Hct values of 40–45%, the systemic O_2 transport capacity substantially declines [96].

Treatment of anemia can improve the oxygenation status of cervical cancers. In a case report, transfusion of red blood cells was followed by a rise in the median pO_2 and a drastic fall in the hypoxic fractions (HF 2.5 and HF 5 [85]). Clinical trials are consistent with this result [74]. However, higher Hb concentrations after blood transfusion resulted in a substantially improved tumor oxygenation in only 50% of the patients. In this study, an increase of the initial Hb level from < 9.0 g/dl to > 11.5 g/dl after transfusion led to higher 50th percentiles, but unchanged 10th percentiles, suggesting that transfusion would not reduce tumor hypoxia extensively, although this may have been due to pO_2 readings being obtained from necrotic tissue. In a review by Fyles et al. [20], the authors conclude that red blood cell transfusion or erythropoietin treatment ameliorate the oxygenation status in cervix cancers in only a proportion of anemic patients.

Cancer of the Vulva

Using the same cHb grouping as described above, a correlation between Hb levels and median pO_2 values in vulvar cancer as shown in Figure 4 was obtained [93]. In principle, the pattern found in vulvar cancer was similar to that observed in cervical carcinomas. In anemic patients, the median pO_2 in carcinomas of the vulva was 3 mmHg (cHb = 11.3 ± 0.5 g/dl). In this group, all median pO_2 values were < 9 mmHg. At a mean Hb level of 13.5 ± 0.5 g/dl (representing the "normal" range of cHb), the median pO_2 was significantly higher (19 mmHg) and declined at higher cHb values (14.8 ± 0.7 g/dl) to a median pO_2 of 11 mmHg. In this latter group, no median pO_2 values > 17 mmHg were seen. From these data, Vaupel et al. [93] concluded that an optimal Hb level with regard to the oxygenation status should be expected at cHb values between 12 and 14 g/dl. Over this cHb range, the median pO_2 values were between 2 and 58 mmHg.

Analysis of the data published by Stone et al. [70] show that node-negative patients had higher pretreatment Hb levels (13.9 g/dl) than patients with nodal spread (12.0 g/dl). The higher Hb levels (13.9 g/dl) correlated with a median pO_2 of 12 mmHg and an HF 5 of 16.5%, whereas the lower Hb concentration was associated with a median pO_2 of 5 mmHg and an HF 5 of 52.5%.

Head-and-Neck Cancer

A series of studies on head-and-neck cancer patients could not substantiate a correlation between Hb levels (or Hct) and the oxygenation status [2, 14, 55, 64, 77].

By contrast, other investigations clearly suggest that Hb concentrations can impact tumor oxygenation. A significant linear correlation was described for the oxygenation of primary tumors (not for metastases) and Hb levels regarding the median pO_2 and the hypoxic fraction ≤ 5 mmHg [3, 50]. Similarly, Stadler et al. [69] reported a linear correlation between Hb levels and hypoxic fractions (HF 2.5 and HF 5) or hypoxic subvolume. Brizel et al. [7] also found a (weak) association between higher Hb levels and higher median pO_2 values ($p = 0.04$). For patients with cHb < 13 g/dl, only 12% of the cancers investigated had a median pO_2 > 10 mmHg. When cHb at presentation was > 13 g/dl, 42% of the tumors exhibited pO_2 values > 10 mmHg.

In another study by Rudat et al. [63] patients with anemia (cHb ≤ 11 g/dl) showed a statistically significant larger fraction of pO_2 values ≤ 2.5 mmHg (HF 2.5 = 33.9%) compared to patients with mild anemia or normal Hb concentration (HF 2.5 = 22.6%). In a further study [12], the percentage of values ≤ 10 mmHg was 34% in tumors of nonanemic patients compared with 47% in anemic patients, and 69% in the most anemic patients (cHb < 11.5 g/dl). Using linear correlation analysis, a tendency was found for higher median tumor pO_2 values to be associated with greater Hb concentrations.

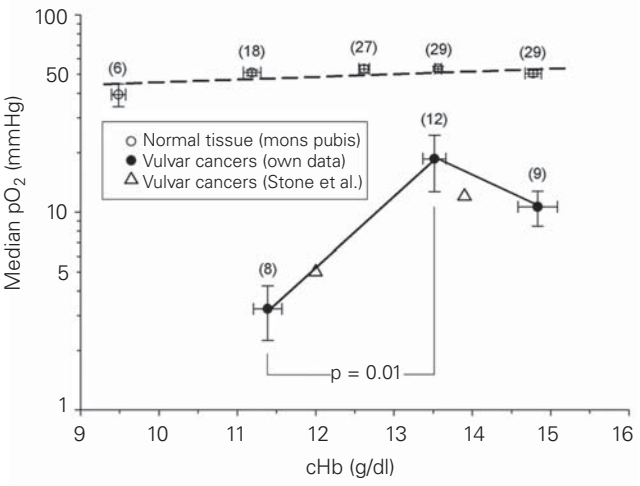

Figure 4. Median pO_2 values in primary and recurrent cancers of the vulva (lower curve) and within the normal subcutis (mons pubis, broken line) as a function of pretreatment hemoglobin concentration (cHb). Values are means ± SEM; number of patients investigated in brackets (modified from Vaupel et al. [93], and complemented by data of Stone et al. [70]).

Abbildung 4. Einfluss des prätherapeutischen Hämoglobingehalts (cHb) auf die medianen pO_2-Werte in Primär- und Rezidivtumoren der Vulva (untere Kurve) sowie in der Subkutis des Mons pubis (gestrichelte Gerade). Angegeben sind Mittelwerte ± SEM aus eigenen Untersuchungen [93] sowie Mittelwerte von Stone et al. [70]. Zahl der untersuchten Tumoren bzw. Patientinnen in Klammern.

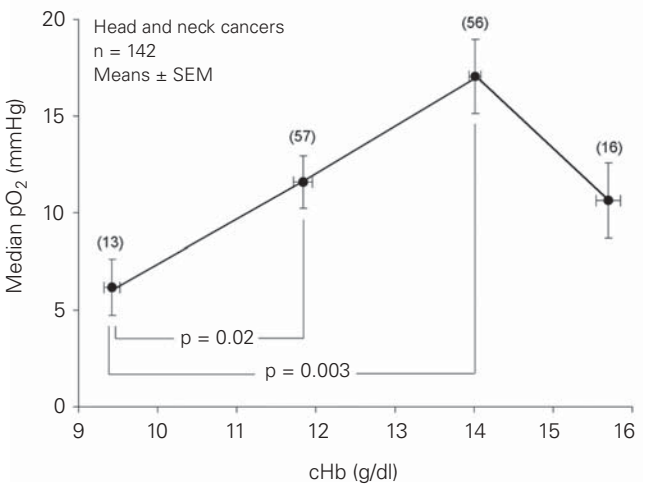

Figure 5. Correlation between pretreatment hemoglobin concentration (cHb) and median pO_2 values in cancers of the head and neck. Values are means ± SEM; numbers of tumors investigated are given in brackets (adapted from Becker et al. [5]).

Abbildung 5. Mediane pO_2-Werte in Kopf-Hals-Tumoren in Abhängigkeit vom prätherapeutischen Hämoglobingehalt (cHb). Angegeben sind Mittelwerte ± SEM; Zahl der untersuchten Tumoren in Klammern (nach Becker et al. [5]).

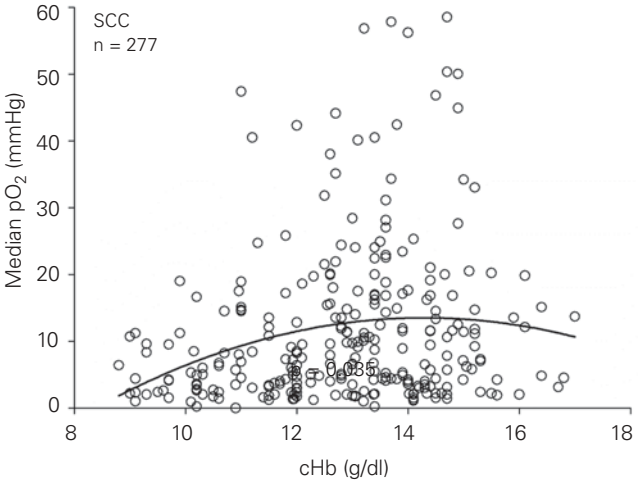

Figure 6. Relationship between pretreatment hemoglobin levels (cHb) and the median pO_2 in 277 patients with squamous cell carcinomas (SCC) of the head and neck [5], of the uterine cervix and of the vulva [93]. The line indicates the quadratic regression (2p = 0.001).

Abbildung 6. Einfluss der prätherapeutischen Hämoglobinkonzentration (cHb) auf die medianen pO_2-Werte von 277 Patienten mit Plattenepithelkarzinomen (SCC). Berücksichtigt wurden die Daten von Kopf-Hals-Tumoren [5] sowie von Karzinomen der Zervix und der Vulva [93]. Die Kurvenanpassung erfolgte durch quadratische Regression (2p = 0,001).

Data published by Becker et al. [4, 5] corroborate with our observations on cancers of the uterine cervix [93]. The former study suggested a "decrease of tumor pO_2 not only at low Hb levels but also at the upper end of the Hb scale", although only a limited number of patients with squamous cell carcinomas of the head and neck showing "high" cHb levels could be assessed. A reevaluation of the original data of Becker et al. [5], in which the data were plotted following classification of the cHb values into defined ranges, indicates that a maximum tumor oxygenation is achieved at cHb values of between 13 and 14 g/dl. This cHb range represents an optimum in terms of the opposing effects of increasing the blood's oxygen-carrying capacity and rising viscous resistance to flow. A trend toward lower median oxygen partial pressures at Hb concentrations > 15 g/dl is evident (Figure 5, [88, 89]).

An international multicenter study on 356 head-and-neck cancers confirmed this nonlinear relationship between Hb concentrations and tumor oxygenation in agreement with previous reports on cervical and vulvar cancers [53]. In this latter study values of HF 2.5 and HF 5 were, however, not significantly associated with Hb concentrations.

In order to interpret this observation of a maximum tumor oxygenation in the "normal" Hb range with lower pO_2 values above and below the physiological range, median pO_2 values measured can be correlated with a calculated O_2 transport index: O_2 transport capacity/viscous resistance to flow (with O_2 transport capacity = cHb [g/dl] × Hüfner's number; Hüfner's number = 1.39 ml O_2/g Hb). This index clearly indicates that an optimal cHb range (or Hct range) exists with regard to the median pO_2 [93].

In human cancers of the head and neck, casuistic observations also support the notion that treatment of anemia might improve tumor oxygenation as shown by pO_2 measurements prior to and after transfusion in selected patients. Upon transfusion the median pO_2 increased and the fraction of hypoxic readings decreased [18].

Conclusion

Evidence has accumulated showing that up to 50–60% of locally advanced solid tumors may exhibit hypoxic and/or anoxic tissue areas. Tumor-associated or therapy-induced anemia are major pathogenetic factors that can contribute to the development of hypoxia (anemic hypoxia). Whereas in normal tissue this type of hypoxia can (primarily) be compensated by an increase in local blood flow rate, locally advanced tumors (or at least larger tumor areas) cannot adequately counteract the restriction of O_2 supply and thus the development of hypoxia, i.e., anemic hypoxia in tumors is a frequent complication in cancer patients. Whereas in some studies no correlation is seen between Hb level and tumor oxygenation status, there is increasing evidence that low Hb levels are indeed associated with a poor tumor oxygenation, and that increasing Hb concentrations are correlated with higher pO_2 values and lower hypoxic tissue fractions. This has been shown for the preclinical (experimental) and clinical setting. Clinical observations on cancers of the head and neck, of the uterine cervix and of the vulva

are indicative of a nonlinear relationship between Hb level and tumor pO_2 values (Figure 6): maximum tumor oxygenation is observed between 13 and 15 g/dl with a worsening tumor oxygenation in anemia and at Hb levels above the median Hb concentrations of healthy, adult persons, providing gender-specific differences and age-related variations are taken into account. The model fit of the quadratic regression was highly significant with $2p = 0.001$. Included in this nonmonotonous relationship were 277 squamous cell carcinomas of the head and neck [5], of the uterine cervix and of the vulva [93].

Addendum

To allow a better comparison of the data published, the following conversions for Hb levels (cHb) and hematocrit values (Hct) were used:

- 1 g/dl = 0.6206 mmol Hb/l [for cHb],
- Hct (%) = 3 × cHb (g/dl) [for conversion from Hct to cHb].

Unfortunately, in several reports erroneous units for Hb levels (mg/dl instead of g/dl) and a misleading sample declaration (*serum* Hb levels instead of *blood* Hb levels) have been used.

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Address for Correspondence
Univ.-Prof. Dr. Peter Vaupel, MA
Institute of Physiology and Pathophysiology
University of Mainz
Duesbergweg 6
55099 Mainz
Germany
Phone (+49/6131) 3925-929, Fax -774
e-mail: vaupel@uni-mainz.de