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Imaging tumor hypoxia: Blood-borne delivery of imaging agents is fundamentally different in hypoxia subtypes

Peter Vaupel* and Arnulf Mayer
Department of Radiooncology and Radiotherapy
University Medical Center, 55131 Mainz, Germany
**vaupel@uni-mainz.de*

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Dedicated to the memory of Professor Britton Chance on the occasion of his 100th birthday (July 24th, 2013), and remembering many exciting discussions on the oxygenation of breast cancer, on tumor hypoxia in general and imaging of the oxygenation status of malignant tumors.

Hypoxic tissue subvolumes are a hallmark feature of solid malignant tumors, relevant for cancer therapy and patient outcome because they increase both the intrinsic aggressiveness of tumor cells and their resistance to several commonly used anticancer strategies. Pathogenetic mechanisms leading to hypoxia are diverse, may coexist within the same tumor and are commonly grouped according to the duration of their effects. Chronic hypoxia is mainly caused by diffusion limitations resulting from enlarged intercapillary distances and adverse diffusion geometries and — to a lesser extent — by hypoxemia, compromised perfusion or long-lasting microregional flow stops. Conversely, acute hypoxia preferentially results from transient disruptions in perfusion. While each of these features of the tumor microenvironment can contribute to a critical reduction of oxygen availability, the delivery of imaging agents (as well as nutrients and anticancer agents) may be compromised or remain unaffected. Thus, a critical appraisal of the effects of the various mechanisms leading to hypoxia with regard to the blood-borne delivery of imaging agents is necessary to judge their ability to correctly represent the hypoxic phenotype of solid malignancies.

Keywords: Delivery of imaging agents; tumor hypoxia; hypoxia subtypes; chronic hypoxia; acute hypoxia.

1. Introduction

Hypoxic subvolumes which show complex spatial and temporal heterogeneities can be detected in approximately 50–60% of all human tumors.[1–3] Tumor hypoxia is known to trigger (mal-)adaptive processes, increased tumor aggressiveness and

resistance to O_2-dependent therapies (e.g., standard radiotherapy, some forms of chemotherapy, photodynamic therapy, immunotherapy and hormonal therapy), all together leading to a poor patient outcome.[4–6] Since hypoxia is an independent and negative prognostic factor, assessment of oxygen deficiencies in tumors in the clinical setting by noninvasive imaging techniques may be helpful to identify patients with poor prognosis that could benefit from increasing the radiotherapy dose homogeneously to the gross tumor volume or to escalate the radiation dose selectively to the hypoxic region(s), a technique phrased "dose painting". New highly conformal and accurate radiation

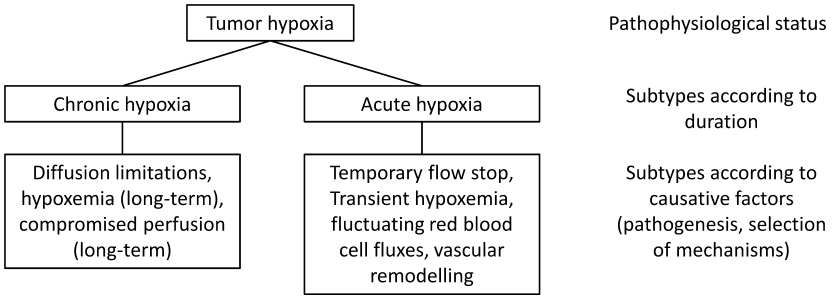

Fig. 1. Classification of tumor hypoxia according to duration (traditional classification), and systematization based on pathogenetic (causative) mechanisms.

Table 1. Causes and time frames of chronic and acute hypoxia (selection of mechanisms, modified[17]).

A. Chronic hypoxia	
Synonyms used	Continuous h., diffusion-limited h., sustained h., long-term h.
Causes (pathogenesis)	1. Diffusion-limited hypoxia – enlarged diffusion distances – adverse diffusion geometries (concurrent versus countercurrent tumor microvessels, Krogh- versus Hill-type diffusion geometry) – extreme longitudinal intravascular oxygen gradients – shunt perfusion 2. Hypoxemic hypoxia – tumor-associated anemia – therapy-induced anemia – small liver tumors (primary and metastatic) supplied by portal vein – HbCO-formation in heavy smokers 3. Compromised perfusion of microvessels – disturbed Starling forces due to high interstitial fluid pressure (transmural coupling) – solid-phase stress by nonfluid components (compression)
Time frame	hours → weeks (under experimental conditions)
B. Acute hypoxia	
Synonyms used	Transient h., short-term h., perfusion-limited h., cyclic h., fluctuating h., intermittent h.
Causes (pathogenesis)	1. Temporary flow stop in microvessels – due to cell aggregates and/or fibrin clots – ischemic hypoxia due to vascular remodeling 2. Transient hypoxemia – temporal plasma flow in microvessels – fluctuating red blood cell fluxes
Time frame	Minutes → hour (not well defined; spontaneous hypoxia cycles show spatial and temporal irregularities)

technology, such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) make these methods feasible.[7]

In order to detect and quantify tumor hypoxia and to assess its topological distribution within a tumor as well as changes in extent (severity) and location upon radiotherapy, the contenders for human application are repeated, sequential PET measurements using ^{18}FMISO, ^{18}FAZA, ^{18}FEF5 and ^{64}CuATMS.[7–11] For detection, all techniques mentioned require injection of the respective exogenous marker (imaging agent). In this paper, the problem of fundamental differences in the blood-borne delivery of these substances in hypoxia subtypes (chronic and acute hypoxia, and subtypes thereof) will be outlined.

2. Tumor Hypoxia

As already mentioned, most locally advanced tumors contain hypoxic subvolumes, which are heterogeneously distributed both within and between tumors. In cancers of the uterine cervix, the extent of hypoxia and its intratumor location is independent of clinical size, grade, stage, histology, lymph node status and various patient demographics. Hypoxia has unequivocally been shown to act as an independent, negative prognostic factor for overall survival

Table 2. Subtypes of chronic hypoxia according to causative mechanisms and associated blood-borne transport capacities.

Causes	Diffusion limitations	Hypoxemia	Interstitial hypertension or solid stress
Blood flow	maintained	maintained	reduced/abolished[a]
Nutrient supply (e.g., glucose, glutamine)	maintained	maintained	reduced/abolished[a]
Blood-borne delivery of anticancer agents	maintained	maintained	reduced/abolished[a]
Blood-borne delivery of imaging agents	**maintained**	**maintained**	**reduced/abolished**[a]

[a]pressure-dependent.

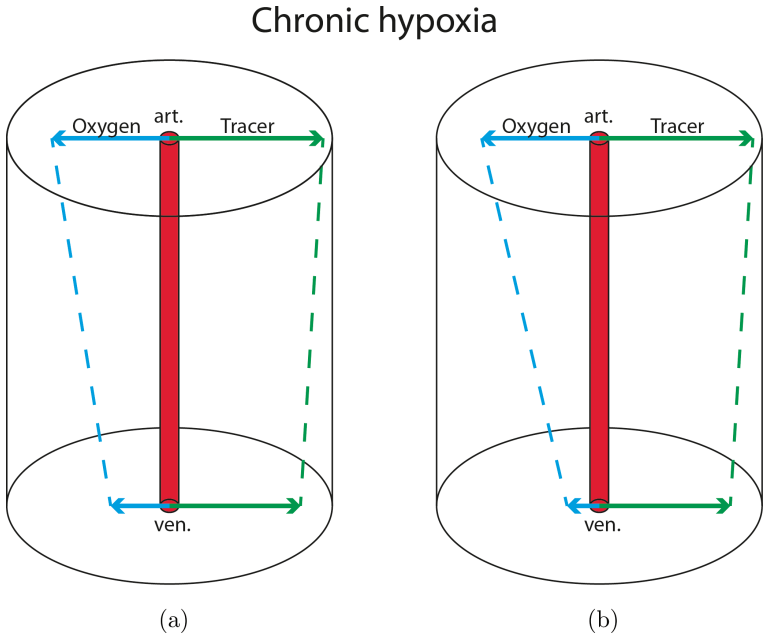

Fig. 2. Chronic hypoxia. Schematic representation of the radial diffusion distances for oxygen (blue) and hypoxia tracer (green) within a tissue cylinder surrounding a straight tumor capillary running from the arterial (art.) to the venous end (ven.) (a) Normoxemic conditions combined with enlarged diffusion distances leading to diffusion limited chronic tumor hypoxia. (b) Effect of anemia (combined with enlarged diffusion distances) on the oxygen and tracer diffusion distances in chronic hypoxia. The broken lines represent the critical diffusion distances for both substances.

Table 3. Subtypes of acute hypoxia according to causative mechanisms and associated blood-borne transport capacities.

Causes	Flow stop	Transient plasma flow
Perfusion	abolished	maintained
Nutrient supply	abolished	maintained
Blood-borne delivery of anticancer agents	abolished	maintained
Blood-borne delivery of imaging agents	**abolished**	**maintained**

(cervix cancer) or for local control (head and neck cancer).[1–5] Based on underlying pathogenetic (causative) mechanisms and their duration, two major types have been identified: chronic and acute hypoxia (see Fig. 1). This traditional classification is based on empirical observation and generally does not take into account the multiple pathogenetic processes involved: chronic hypoxia is mainly caused by diffusion limitations,[12] whereas acute hypoxia has been thought to preferentially result from temporary flow stops.[13,14] In each of these hypoxia types, oxygen supply is critically reduced, but perfusion-dependent delivery of diagnostic (imaging) and therapeutic agents, availability of nutrients and removal of waste products and repair competence can vary substantially or may be completely unaffected.[15] Thus, detailed differentiation of tumor hypoxia may impact on our understanding of tumor biology and may aid in the development of novel treatment strategies (e.g., modulation of fractionation schedules), in tumor targeting and in tumor detection by imaging, and thus is of utmost clinical relevance far beyond any academic discussion.[16]

2.1. *Chronic hypoxia and its subtypes*

Chronic hypoxia seems to be the dominating type of hypoxia with pronounced heterogeneities between individual tumors of the same entity and between tumor types.[17]

The various causes and the estimated time frame of chronic hypoxia are listed in Table 1. By definition, a reduced or abolished oxygen supply is inherent in each of these pathogenetic mechanisms, leading to chronic hypoxia. Perfusion-dependent nutrient supply, delivery of anticancer agents (e.g., chemotherapeutic drugs, antibodies or immune cells) or diagnostic agents for tumor imaging can be impaired or abolished or may not be affected, depending on the underlying causative mechanism (see Table 2).[18] A schematic representation of the

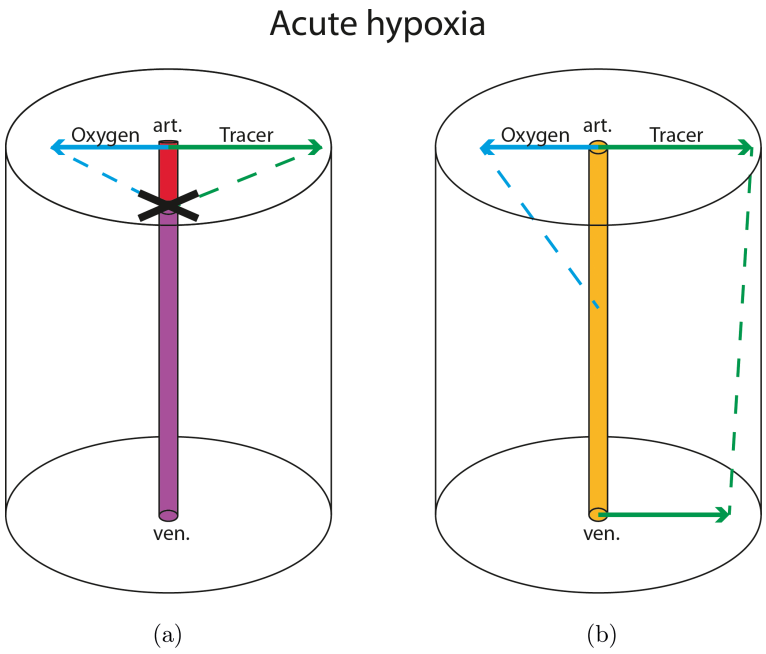

Fig. 3. Acute hypoxia. Schematic representation of the radial diffusion distances for oxygen (blue) and hypoxia tracer (green) within a tissue cylinder surrounding a straight tumor capillary running from the arterial (art.) to the venous end (ven.). (a) Temporary vascular obstruction near the arterial end of the capillary (black cross). Desaturated, nonflowing blood is present distal to the point of vascular occlusion (purple). (b) Effect of transient sole plasma flow (yellow) on the oxygen and tracer diffusion distances in acute hypoxia. The broken lines represent the critical diffusion distances for both substances.

radial diffusion distances for oxygen and hypoxia tracers drops within a tumor cell cylinder around a straight microvessel is exemplarily shown for two types of chronic hypoxia in Fig. 2.

2.2. *Acute hypoxia and its subtypes*

With regard to the pathophysiology, acute hypoxia can be divided into two further subgroups: ischemic and hypoxemic, the latter being characterized by plasma flow only (see Table 1). In fluctuating or intermittent hypoxia, caused by spontaneous fluctuations of red blood cell fluxes, hypoxia levels during the temporary drop of intravascular hematocrit are often not reached.[19] In these cases, effects preferentially triggered by the formation of reactive oxygen species have to be considered. Ischemic hypoxia is preferentially caused by transient flow stops or critically reduced perfusion rates due to physical obstructions, such as aggregates of tumor cells or blood cells and/or fibrin plugs within the vessel lumen. In analogy with Table 2, relevant delivery conditions for blood-borne agents are listed for the subtypes of acute hypoxia in Table 3.[18] Examples for two types of acute hypoxia (temporary vascular occlusion and transient plasma flow only) are shown in Fig. 3.

3. Conclusions

Blood-borne delivery of imaging agents seem to be different for different subtypes of chronic ("static") and acute ("dynamic") hypoxia. Thus, a distinction between and quantification of these subtypes may be mandatory. Furthermore, this detailed differentiation of tumor subtypes may impact on our understanding of tumor biology and may aid in the development of novel treatment strategies and thus is of great clinical relevance. Eventually, classification of hypoxia subtypes may also result in a better understanding of mismatches between blood flow and hypoxia in tumor imaging.

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References

1. P. Vaupel, A. Mayer, M. Höckel, "Tumor hypoxia and malignant progression," *Methods Enzymol.* **381**, 335–354 (2004).
2. P. Vaupel, M. Höckel, A. Mayer, "Detection and characterization of tumor hypoxia using pO_2 histography," *Antioxid. Redox. Signal.* **9**, 1221–1235 (2007).
3. P. Vaupel, A. Mayer, "Hypoxia in cancer: Significance and impact on clinical outcome," *Cancer Metastasis Rev.* **26**, 225–239 (2007).
4. M. Höckel, C. Knoop, K. Schlenger, B. Vorndran, E. Baussmann, M. Mitze, P. G. Knapstein, P. Vaupel, "Intratumoral pO_2 predicts survival in advanced cancer of the uterine cervix," *Radiother. Oncol.* **26**, 45–50 (1993).
5. M. Höckel, K. Schlenger, B. Aral, M. Mitze, U. Schäffer, P. Vaupel, "Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix," *Cancer Res.* **56**, 4509–4515 (1996).
6. A. Mayer, P. Vaupel, "Hypoxia, lactate accumulation, and acidosis: Siblings or accomplices driving tumor progression and resistance to therapy?" *Adv. Exp. Med. Biol.* **789**, 203–209 (2013).
7. M. R. Horsman, L. S. Mortensen, J. B. Petersen, M. Busk, J. Overgaard, "Imaging hypoxia to improve radiotherapy outcome," *Nat. Rev. Clin. Oncol.* **9**, 674–687 (2012).
8. A. R. Padhani, K. A. Krohn, J. S. Lewis, M. Alber, "Imaging oxygenation of human tumours," *Eur. Radiol.* **17**, 861–872 (2007).
9. S. T. Astner, K. Shi, P. Vaupel, M. Molls, "Imaging of tumor physiology: Impacts on clinical radiation oncology," *Exp. Oncol.* **32**, 149–152 (2010).
10. F. C. Gaertner, M. Souvatzoglou, G. Brix, A. J. Beer, "Imaging of hypoxia using PET and MRI," *Curr. Pharm. Biotechnol.* **13**, 552–570 (2012).
11. J. L. Tatum, G. J. Kelloff, R. J. Gillies, J. M. Arbeit, J. M. Brown, K. S. Chao, J. D. Chapman, W. C. Eckelman, A. W. Fyles, A. J. Giaccia, R. P. Hill, C. J. Koch, M. C. Krishna, K. A. Krohn, J. S. Lewis, R. P. Mason, G. Melillo, A. R. Padhani, G. Powis, J. G. Rajendran, R. Reba, S. P. Robinson, G. L. Semenza, H. M. Swartz, P. Vaupel, D. Yang, B. Croft, J. Hoffman, G. Liu, H. Stone, D. Sullivan,

"Hypoxia: Importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy," *Int. J. Radiat. Biol.* **82**, 699–757 (2006).
12. R. H. Thomlinson, L. H. Gray, "The histological structure of some human lung cancers and the possible implications for radiotherapy," *Br. J. Cancer* **9**, 539–549 (1955).
13. J. M. Brown, "Evidence for acutely hypoxic cells in mouse tumours, and a possible mechanism of reoxygenation," *Br. J. Radiol.* **52**, 650–656 (1979).
14. D. J. Chaplin, R. E. Durand, P. L. Olive, "Acute hypoxia in tumors: Implications for modifiers of radiation effects," *Int. J. Radiat. Oncol. Biol. Phys.* **12**, 1279–1282 (1986).
15. C. Bayer, K. Shi, S. T. Astner, C. A. Maftei, P. Vaupel, "Acute versus chronic hypoxia: Why a simplified classification is simply not enough," *Int. J. Radiat. Oncol. Biol. Phys.* **80**, 965–968 (2011).
16. C. Bayer, P. Vaupel, "Acute versus chronic hypoxia in tumors: Controversial data concerning time frames and biological consequences," *Strahlenther. Onkol.* **188**, 616–627 (2012).
17. C. A. Maftei, C. Bayer, K. Shi, S. T. Astner, P. Vaupel, "Quantitative assessment of hypoxia subtypes in microcirculatory supply units of malignant tumors using (immuno-)fluorescence techniques," *Strahlenther. Onkol.* **187**, 260–266 (2011).
18. P. Vaupel, A. Mayer, "Hypoxia in tumors: Pathogenesis- related classification, characterization of hypoxia- subtypes, and associated biological and clinical implications," *Adv. Exp. Med. Biol.*, in press (2014).
19. S. Matsumoto, H. Yasui, J. B. Mitchell, M. C. Krishna, "Imaging cycling tumor hypoxia," *Cancer Res.* **70**, 10019–10023 (2010).