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# Oxygen Diffusivity in Tumor Tissue (DS-Carcinosarcoma) under Temperature Conditions within the Range of 20–40° C

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*Summary.* The $O_2$ diffusion constants D and K of tumor tissue (DS-Carcinosarcoma in the rat kidney) were determined at temperatures of 20, 30, 37, and 40° C. The following mean values were obtained for the conditions of 37° C: $D = 1.75 \cdot 10^{-5}$ cm²/s and $K = 1.9 \cdot 10^{-5}$ $mlO_2/cm \cdot min \cdot atm$. Within the range of 20–40° C, temperature variations in tumor tissue cause changes in the $O_2$ diffusion coefficient D of 2.0–2.5%/° C and in the Krogh $O_2$ diffusion constant K of 0.5–1.5%/° C. The measured $O_2$ diffusion constants for tumor tissue correspond to values of normal tissue with similar water content. This indicates that the insufficient $O_2$ supply in DS-Carcinosarcoma is due not to unfavorable $O_2$ diffusivity of the tumor tissue but rather to a decreased convective $O_2$ transport and to insufficient capillarization. An analysis of $O_2$ diffusion in DS-Carcinosarcoma tissue using the determined $O_2$ diffusion constants lead to the result that, under the conditions of arterial normoxia and normocapnia, critical $O_2$ supply conditions are to be expected when the intercapillary distance exceeds approximately 120 µm.

*Key words:* Tumor tissue – $O_2$ diffusion – $O_2$ diffusion coefficient D – Krogh's diffusion constant K – Critical $O_2$ supply.

## INTRODUCTION

The solution of problems concerning tumor metabolism, tumor growth, the formation of tumor necrosis, and the radiotherapy of tumors [1,9,15,23,26,31–33,36–38] requires a thorough knowledge of $O_2$ supply in tumor tissue. Since direct measurements of tissue $O_2$ tension in tumors can normally be made only in animal experiments [3,4,38], the question concerning $O_2$ tension distribution in tumor tissue must, in most cases, be answered with the aid of mathematical analyses of $O_2$ diffusion [31,32,36–38]. An important prerequisite for such investigations is the knowledge of the $O_2$ diffusion constants in tumor tissue. Because these values were not known until now, earlier studies had to employ the appropriate constants for water or estimated values. The aim of this study was to directly determine the $O_2$ diffusion coefficient D and the Krogh $O_2$ diffusion constant K of tumor tissue (DS-Carcinosarcoma) and their temperature dependence within the range of 20–40° C. It was also designed to clarify the question whether the $O_2$ diffusivity in tumor tissue is, in fact, significantly lower than in normal tissues as to be expected from the results of Rieger [26].

## MATERIAL AND METHODS

The $O_2$ diffusion constants *D* and K of tumor tissue (DS-Carcinosarcoma) were determined using a modified experimental device for investigating $O_2$ diffusion in biological media described by Thews [11,13,35]. The principle of this method is the determination of $O_2$ diffusion through a tissue layer at known $O_2$ tension gradients. The experimental arrangement consists of three interconnected chambers. The first chamber (gas perfusion chamber) is an open system which can be perfused with various gas mixtures of known $O_2$ tension. This chamber borders a second chamber (diffusion chamber) in which the tissue to be investigated can be placed. The exact dimensions of the cylindrical chamber are: $\phi = 5$ mm, $d = 0.5$ mm. The third chamber (measurement chamber) is a glass container whose flat sides can be placed perpendicular to the light beam of a photometer (Eppendorf photometer, 436 nm). This measurement chamber is filled with a diluted hemoglobin solution which serves as indicator for the $O_2$ concentration and tension present therein. A stirring system, driven from outside the chamber, permits a continuous mixing of the indicator solution. The 3 chambers are separated from one another by a gaspermeable synthetic membrane (Teflon, 12 µm). Temperatures inside the chambers can be maintained with an exactness of ± 0.1° C.

After filling the diffusion chamber with material to be investigated, the gas perfusion chamber and the measurement chamber

are perfused with $N_2$ and $N_2$-equilibrated hemoglobin solution ($S_{O_2}$ = 0%), respectively. As soon as the entire experimental system including the test material is free of $O_2$ – as evidenced by the absorption of the indicator solution – the measurement chamber is closed. Under these conditions, there is diffusion only through the test material which is between the gas perfusion chamber and the measurement chamber. The $O_2$ diffusion within the experimental system is then effected by a rapid change of $O_2$ tension in the gas perfusion chamber from 0 to approximately 760 mm Hg and is measured by the change in the absorption of the indicator solution. The appropriate values for the $O_2$ concentration and the $O_2$ tension in the measurement chamber can be obtained from the registered absorption values of the indicator. The changes of both parameters during the diffusion experiments serve as the basis for determining the $O_2$ diffusion constants $D$ and K of the tumor tissue under investigation [35].

In order to determine the $O_2$ concentration and the $O_2$ tension in the measurement chamber from the directly measured indicator solution absorption, the hemoglobin concentration and the $O_2$ dissociation curve of the indicator must be known. The indicator solution was produced by diluting fresh human blood with aqua dest. and phosphate buffer. The hemoglobin content of the blood was determined photometrically by means of the cyanhemiglobin method. The dilution was 1:1000 (0.1 ml blood, 0.5 ml phosphate buffer, 94.9 ml aqua bidest.). The pH of the indicator solution could be adjusted to 8.0 at 20° C by means of the $Na_2HPO_4$ – $KH_2PO_4$ buffer; the mean hemoglobin content was $16.3 \cdot 10^{-3}$ g per 100 ml. The $O_2$ dissociation curve of the hemoglobin solution is known for the conditions of 20, 30, and 37° C [12]. The course of the $O_2$ dissociation curve at 40° C was determined with the help of the temperature coefficient:

$$\Delta \log P_{O_2} = 0.024 \cdot \Delta T \quad (1)$$

calculated from the measurements at hand. This practice seemed appropriate since the $O_2$ dissociation curves of the indicator, as determined for various temperature conditions by means of the above equation, correspond closely with the directly measured curves. The temperature coefficient for the course of the $O_2$ dissociation curve of the highly diluted hemoglobin solution corresponds to that of normal blood.

The presence of hemoglobin in the test material and the $O_2$ consumption of the cells should lead to an apparent increase of "tissue $O_2$ solubility" under these conditions and thus to an error in the measurement. In order to eliminate both of these factors, the tumor tissue was cleared of blood by means of a perfusion with Haemaccel® and tissue respiration was stopped by adding KCN to the perfusion solution. As a result of lacuna-like and cystiform blood vessels present in the tumors, it cannot be fully excluded that minute quantities of blood remained in some of the investigated tissue slices. The determination of the $O_2$ diffusion constant K would not be influenced. On the other hand the determination of the $O_2$ diffusion coefficient $D$ must, under these conditions, lead to values lower than the true constant.

The influence of the $O_2$ diffusion resistance of the two Teflon membranes on the results could be eliminated through comparative measurements made after filling the diffusion chamber with water, whose exact $O_2$ diffusion constants are known [11,17].

The investigations were conducted on DS-Carcinosarcoma from rat kidney. The tumor tissue was produced by injecting DS-Carcinosarcoma ascites cells into normal kidney parenchyma [16,27,38]. In the course of 8 – 10 days, the infiltrating and destructively growing tumor completely replaced the normal kidney parenchyma. The tissue-isolated growing tumors were removed on the 9 – 11th day after implantation before tissue necrosis had set in. Immediately prior to removal, the tumor circulation system was perfused with Haemaccel® during anaesthesia (Nembutal®, 30 mg/kg b.w., i.p.). Macroscopically visible tissue necrosis was not found in any of the kidney tumors investigated. The tumor tissue was divided into various test portions and passed into liquid nitrogen in preparation for the $O_2$ diffusion measurements. The frozen tissue slices (d = 0.5 mm) could then be precisely positioned in the diffusion chamber. Tissue not immediately examined was stored in small closed airtight glass containers at −30 to −40° C. Tissue water content was determined by freeze drying.

## RESULTS

A total of 73 investigations of $O_2$ diffusion in DS-Carcinosarcoma tissue were conducted at temperatures of 20, 30, 37, and 40° C. The mean weight of the tumors studied was 5.9 g and the mean water content was 82.1 g% (g/100 g wet weight). The mean values for the $O_2$ diffusion coefficient $D$ and for the Krogh's $O_2$ diffusion constant K of the tumor tissue are summarized in Table 1. The values for the $O_2$ solubility coefficient $\alpha$ were calculated from the results using the following equation:

$$\alpha = \frac{K}{D} \quad (2)$$

The temperature dependence of the $O_2$ diffusion constants of DS-Carcinosarcoma tissue is presented in Figures 1 and 2. The directly determined mean

Table 1. $O_2$ diffusion constants $D$ and K and $O_2$ solubility coefficients $\alpha$ for tumor tissue (DS-Carcinosarcoma) at temperatures of 20, 30, 37 and 40° C. Values presented are mean values ± S.E.M.

| Temp. (° C) | $n$ | $O_2$ diffusion coefficient $D$ ($10^{-5}$ cm$^2 \cdot$ s$^{-1}$) | $n$ | Krogh's diffusion constant K | | $O_2$ solubility coefficient $\alpha$ | |
|---|---|---|---|---|---|---|---|
| | | | | ($10^{-5}$ ml $O_2 \cdot$ cm$^{-1} \cdot$ min$^{-1} \cdot$ atm$^{-1}$) | ($10^{-10}$ µmol $\cdot$ cm$^{-1} \cdot$ s$^{-1} \cdot$ Pa$^{-1}$) | ($10^{-2}$ ml $O_2 \cdot$ ml$^{-1} \cdot$ atm$^{-1}$) | ($10^{-9}$ µmol $\cdot$ l$^{-1} \cdot$ Pa$^{-1}$) |
| 20 | 10 | 1.25 ± 0.05 | 19 | 1.70 ± 0.07 | 1.25 | 2.24 | 9.87 |
| 30 | 21 | 1.55 ± 0.06 | 18 | 1.75 ± 0.05 | 1.29 | 1.93 | 8.50 |
| 37 | 22 | 1.75 ± 0.04 | 20 | 1.90 ± 0.08 | 1.40 | 1.79 | 7.89 |
| 40 | 20 | 1.90 ± 0.07 | 16 | 2.00 ± 0.10 | 1.47 | 1.75 | 7.71 |

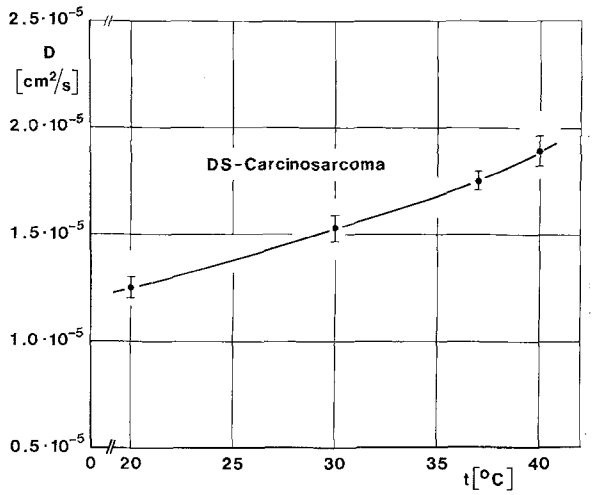


Fig. 1. Temperature dependence of $O_2$ diffusion coefficient $D$ of tumor tissue (DS-Carcinosarcoma) within the range 20–40° C. Abscissa: temperature; ordinate: $O_2$ diffusion coefficient $D$

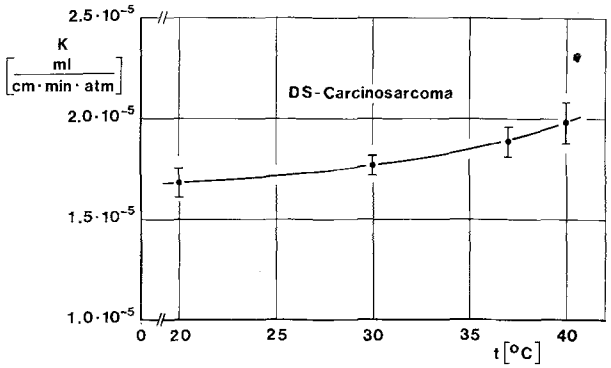


Fig. 2. Temperature dependence of Krogh's diffusion constant K of tumor tissue (DS-Carcinosarcoma) within the range 20–40° C. Abscissa: temperature; ordinate: Krogh's $O_2$ diffusion constant K

values, and not the rounded off values, serve as the basis for the graphical demonstration of the influence of temperature on the $O_2$ diffusion constants as well as for the calculations of the $O_2$ solubility coefficient $\alpha$. In the temperature range of 20–40° C the diffusion coefficient $D$ increases 2.0–2.5% per 1° C increase. The corresponding changes in Krogh's diffusion constant K are 0.5–1.5% per 1° C change. For the temperature coefficient $Q_{10}$, these constants have values of 1.2–1.25 and 1.05–1.2, respectively.

## DISCUSSION

Results of direct measurements of the $O_2$ diffusion constants $D$ and K for tumor tissue had not be available until the present study. Rieger [26], using data from Vaupel et al. [38,39], calculated very low values for the $O_2$ diffusion coefficient $D$ of DS-Carcinosarcoma tissue, namely $0.8 \cdot 10^{-6} - 1.6 \cdot 10^{-6}$ cm²/s. These values measure approximately one tenth of the values directly determined here. The investigations of Thomlinson and Gray [37] and Tannock [31,32] on the $O_2$ diffusion in tumor tissue employed for the $O_2$ diffusion coefficient $D$ either the value for water or a value lying between that of water and muscle tissue. Both of these constants are larger than the $O_2$ diffusion coefficient $D$ measured at 37° C.

The $O_2$ diffusion constants of DS-Carcinosarcoma tissue as determined at temperatures of 37 and 40° C are somewhat lower than the values which we presented in a preliminary communication [14]. The reason for this lies in the fact that the number of investigations has been increased and that the results of measurements conducted on nonhomogeneous tissue slices possibly containing necrosis were eliminated. Additionally, the evaluation of the constants was improved by considering the influence of the perfusion solution in the tumor vessels on the tissue $O_2$ diffusion.

The determined values for the $O_2$ diffusion coefficient $D$ and for the Krogh $O_2$ diffusion constant K of tumor tissue at 37° C fit well into the series of comparable data obtained for different tissues, for blood and for water (Table 2). When water content is similar, there is no essential difference between the $O_2$ diffusion constants of normal tissues on the one hand and the corresponding constants of DS-Carcinosarcoma tissue on the other hand. The demonstrated insufficiency of the $O_2$ supply of DS-Carcinosarcoma of the rat kidney [38] cannot thus be attributed to extremely low $O_2$ diffusion constants of tumor tissue. It is rather the result of both insufficient convective $O_2$ transport to the tumor cells and an enlargement of the area to be supplied by the individual capillaries during tumor growth [32,38].

When one takes into account the water content of the tumors studied, a mean $O_2$ diffusion coefficient $D$ of approximately $1.5 \cdot 10^{-5}$ cm²/s at 37° C can be expected according to Vaupel [39]. The results of the direct measurements are larger but lie within the range of deviation of this data. The close correspondence of the $O_2$ diffusion coefficient $D$ determined in tumor tissue with the appropriate constants of normal tissues with comparable water content is an important indication that the tissue slices under investigation were completely, or almost completely cleared of blood. Were blood present in the tissue probes, the measurements would have led to considerably lower values.

The temperature dependence of the $O_2$ diffusion constants of DS-Carcinosarcoma tissue corresponds closely to findings for water, for muscle tissue and for

Table 2. $O_2$ diffusion coefficient $D$, Krogh's $O_2$ diffusion constant K and water content for different tissues, blood and water at 37° C. To convert the values not determined at 37° C, the following temperature coefficients were used: 2.5% · (° C)$^{-1}$ for $D$ and 1.0% · (° C)$^{-1}$ for K (11, 21)

| Material | $O_2$ diffusion coefficient $D \cdot 10^5$ (cm$^2$/s) | Krogh's diffusion constant K · $10^5$ (ml $O_2$/cm · min · atm) | Water content (g%) | References |
|---|---|---|---|---|
| Water | 3.2 | – | 100 | [17] |
| Water | 3.3 | 4.7 | 100 | [11] |
| Bovine serum | 1.86 | – | 92–94[b] | [42] |
| Bovine serum | 2.4 | – | 92–94[b] | [20] |
| Bovine serum | 2.54 | – | 92–94[b] | [7] |
| Human plasma | 1.82 | – | 94.5[a] | [29] |
| Human plasma | 2.18 | – | 94.5[a] | [8] |
| Human blood | (1.24) | – | 80[a] | [29] |
| Human blood | (1.62) | – | 80[a] | [8] |
| Human erythrocyte | (0.8) | 1.3 | 68[a] | [13] |
| Rat lung | 2.3 | 2.5 | 77–85[b] | [11] |
| Cat cerebral cortex | (1.54) | 1.29 | 80[b] | [6] |
| Mouse- and rat cerebrum (gray matter) | 1.7 | 2.3 | 80[b] | [35] |
| Rabbit cerebrum (gray matter) | 1.9 | – | 80[b] | [10] |
| Rat heart muscle | 1.5 | 1.9 | 76–82[b] | [13] |
| Frog skeletal muscle | – | 1.6 | 79–82[b] | [21] |
| Rat skeletal muscle | – | 2.23 | 76[b] | [18] |
| Rat diaphragm | – | 1.3 | 76[b] | [41] |
| Guinea pig liver | 1.0–1.2 | – | 70–75[b] | [10] |
| Rabbit kidney cortex | 1.0 | – | 74–80[b] | [10] |
| Frog connective tissue | – | 1.36 | – | [21] |
| Human aorta (intima) | 0.85 | – | – | [19] |
| Human aorta (media) | 1.0 | – | – | [19] |
| DS-Carcinosarcoma in rat kidney | 1.75 | 1.9 | 82 | This study |

Values not directly measured are given in parenthesis. Values for the water content are taken from (5[a], 28[b])

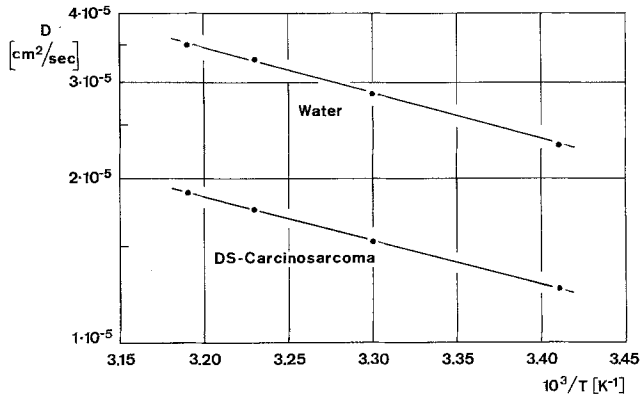


Fig. 3. Effect of temperature on $O_2$ diffusion coefficient $D$ of tumor tissue (DS-Carcinosarcoma) in log coordinates. Abscissa: reciprocal absolute temperature; ordinate: $O_2$ diffusion coefficient $D$

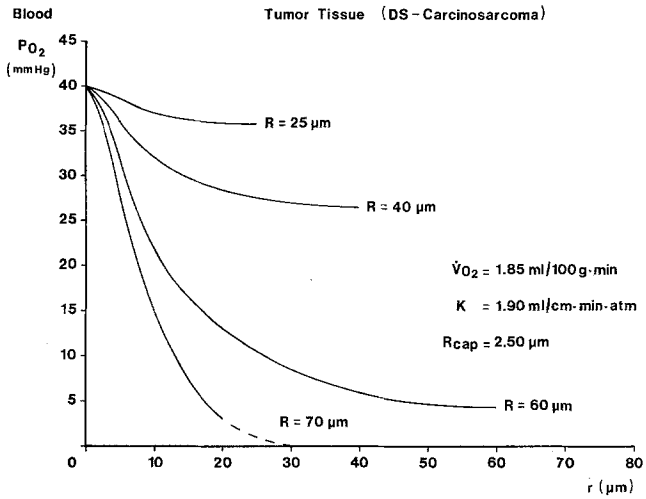


Fig. 4. Radial $O_2$ tension profiles at the venous end of the Krogh tissue cylinder in DS-Carcinosarcoma for the conditions of a cylinder radius of 25, 40, 60, and 70 µm. Abscissa: distance $r$ from venous end of tumor capillary; ordinate: $O_2$ tension

pulmonary tissue [7, 11, 17, 21]. One obtains a constant value for $D_0$ of $1.2 \cdot 10^{-2}$ cm$^2$/s by inserting the determined values for $D$ into the Arrhenius equation for the temperature dependence of the diffusion coefficients of nonelectrolytes:

$$D = D_0 \cdot e^{-E/RT} \tag{3}$$

Herein is: $D$ diffusion coefficient (cm$^2$/s), $D_0$ constant independent of temperature (cm$^2$/s), $E$ activating energy (kcal/mol), $R$ gas constant (erg/grd mol), $T$ absolute temperature (K).

Using a logarithmic coordinate system, the influence of temperature on the $O_2$ diffusion coefficient $D$ for tumor tissue must be represented as a straight line (Fig. 3). The activating energy $E$ for the $O_2$ diffusion in DS-Carcinosarcoma tissue was found to be 4.0 kcal/mol according to the equation:

$$E = 4.56 \cdot 10^{-3} \cdot T_1 \cdot T_2/(T_1 - T_2) \cdot \log(k_1/k_2) \text{ (kcal/mol)} \tag{4}$$

$k_1$ and $k_2$ represent the values for the $O_2$-diffusion coefficient $D$ determined at the temperatures $T_1$ and $T_2$.

The corresponding value for the $O_2$ diffusion in water is 3.85 kcal/mol [11].

Employing the determined $O_2$ diffusion constant K of tumor tissue together with the $O_2$ consumption rate of 1.85 ml $O_2$/100 g · min as determined on DS-Carcinosarcoma ascites cells under unlimited $O_2$ supply conditions [2], an $O_2$ diffusion analysis at 37° C led to $O_2$ tension profiles at the venous end of the capillary supply area as presented in Figure 4. As a

model for the supply area of a single capillary, the Krogh tissue cylinder [22, 34] was employed. For the calculations, intercapillary distances as measured in comparable tumors of DS-Carcinosarcoma with weight of approximately 6 g [38, 40] were used. Since the intercapillary distances of these tumors varied between approximately 40 and 130 μm, the calculations were carried out for the conditions of tissue cylinders with radii of 25, 40, 60, and 70 μm. A value of 40 mm Hg for the $O_2$ tension at the wall of the venous end of the tumor capillary was assumed. The mean $O_2$ tension of the venous tumor blood (DS-Carcinosarcoma in the rat kidney) under arterial normoxia and normocapnia is 41.5 mm Hg [38]. Axial $O_2$ diffusion in the tissue cylinder parallel to the capillary was not considered since the results presented here would not be essentially modified [34]. The convective $O_2$ flux in the extracellular space [24] was likewise not taken into account as the investigations of Swabb et al. [30] have shown that $O_2$ diffusion transport far outweighs conductive $O_2$ transport inside tumor tissue.

As seen in Figure 4, critical $O_2$ supply conditions in the tissue of DS-Carcinosarcoma are to be expected when the distance between neighbouring capillaries exceeds 120–130 μm and the radius of the tissue cylinder correspondingly increases above 65–70 μm. Although the Krogh tissue cylinder model only approximately describes the actual conditions in the tumor tissue, this result corresponds closely with the fact that necrosis could not be detected in tumors (DS-Carcinosarcoma) where the intercapillary distances did not exceed 130 μm. In older tumors presenting necrosis, the largest intercapillary distances attained values far in excess of this critical $O_2$ diffusion distance [38, 40]. The determined value for the tissue cylinder radius by which critical $O_2$ supply conditions are to be expected is comparable to results of Tannock [32] and Vaupel [38]. The calculated $O_2$ tensions correspond closely with values directly measured in DS-Carcinosarcoma tissue [38]. The results of the $O_2$ diffusion analysis serve, therefore, as additional evidence that the determined $O_2$ diffusion constants do in fact accurately reflect the $O_2$ diffusivity of DS-Carcinosarcoma tissue.

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