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# Tissue Oxygen Tension Profiles Close to Brain Arterioles and Venules in the Rat Cerebral Cortex during the Development of Acute Anemia

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Acute anemia (stages 1 and 2) led to decreases in $pO_2$ at the walls of radial venules (lumen diameter 13.1 ± 0.5 μm) and in the tissues at distances of up to 40 μm from the walls, indicating increased extraction of oxygen from the blood by the smallest microvessels. Further decreases in the blood hemoglobin concentration (stage 3) did not produce any significant changes in the nature of tissue $pO_2$ profiles close to the walls of these microvessels. In the intercapillary space, tissue $pO_2$ decreased in proportion to the decrease in the systemic blood hemoglobin concentration, though tissue hypoxia ($p_tO_2 \leq$ 8–10 mmHg) was seen only in tissue in which the microvessels had inadequate (decreased) blood flow responses.

**KEY WORDS:** oxygen tension, $pO_2$ profiles, $pO_2$ gradients, anemia, hypoxia, arterioles, venules, acute normovolemic hemodilution, oxygen microelectrodes.

Hemoglobin is the major transporter of oxygen in the blood and plays a key role in the processes of oxygen transport to the body's tissues. Sharp reductions in hemoglobin concentrations in the circulating blood, i.e., acute anemia, occur in hemorrhage (wounds, trauma, surgical procedures) and in a number of diseases, as well as in acute normovolemic hemodilution procedures performed during the preoperative period prior to transfusing patients with autologous blood. The question of the safe limits of reducing hemoglobin concentrations in these procedures is under extensive discussion in the literature. In the case of healthy subjects, the critical hemoglobin concentration (at which metabolism becomes dependent on the oxygen supply) has been found to lie in the range 3–5 g/dl [16]. In the case of clinical pathology, the boundary of safe hemodilution is significantly higher, at around 9–12 g/dl [27, 30]. The mechanisms supplying oxygen to tissues such as the myocardium and brain in acute normovolemic hemodilution have received little study [12, 13, 23, 47].

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The most suitable measure of tissue oxygen supply is the distribution of oxygen tension ($pO_2$) in the tissue space [25]. In acute anemia, the distribution of tissue $pO_2$ has been found to show a general shift towards lower values, despite the powerful compensatory reaction in terms of brain blood flow [9]. There is no single view in the literature as to the critical hemoglobin concentration (or hematocrit) at which zones of hypoxia appear in brain tissue. The distribution of $pO_2$ in different parts of the microvascular bed of the brain remains poorly studied [1]. Resolution of these questions requires further detailed assessment of the processes of diffusional oxygen transport in the gas exchange spaces of microvessels, i.e., capillaries and the smallest arterioles and venules.

One important characteristic of oxygen transport in anemia is the fact that $pO_2$ in systemic arterial blood is generally increased (due to hyperventilation of the lungs), while that in venous blood is decreased as a result of significant levels of $O_2$ extraction from blood in the capillaries and smallest venules [22, 38, 44]. Thus, the distribution of tissue $pO_2$ in acute anemia is characterized by marked heterogeneity and large drops in $pO_2$ between arteriolar and venular microvessels [1, 37, 45].



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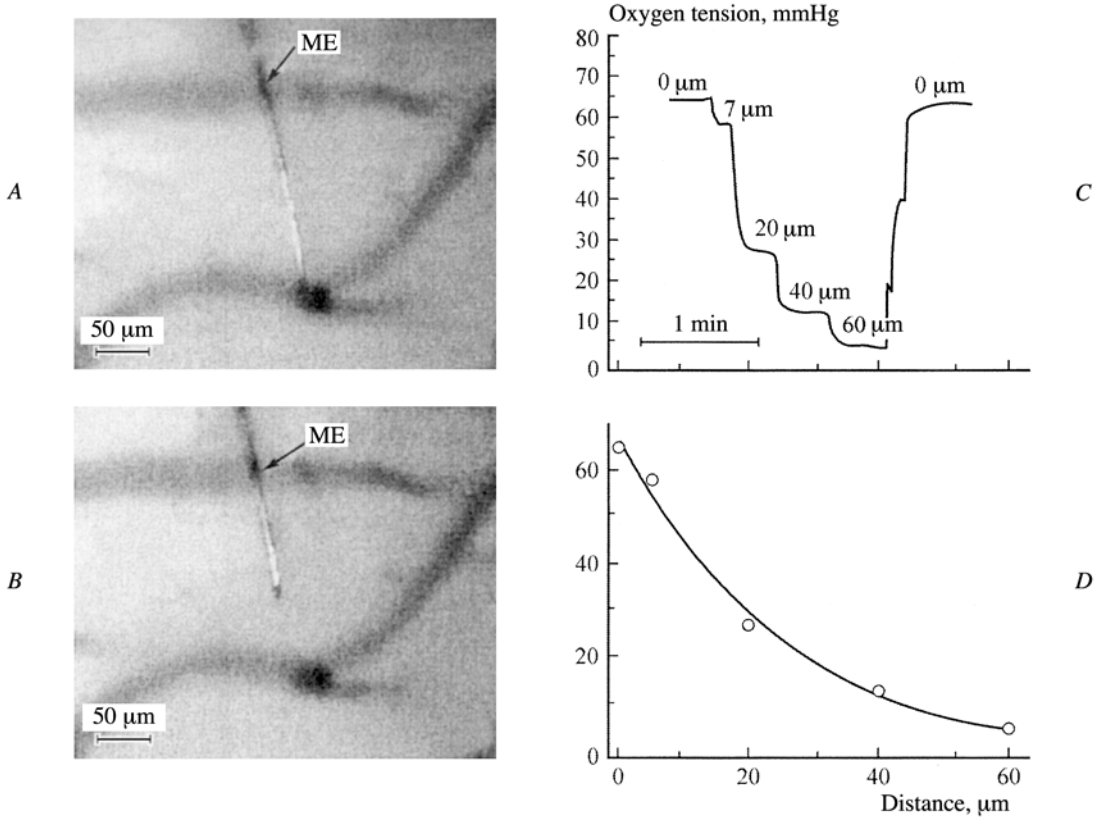


Fig. 1. Recording of tissue $pO_2$ profiles close to the wall of a radial artery with a lumen diameter 17 μm. *A*) Microelectrode (ME) tip at wall of arteriole; *B*) microelectrode tip 40 μm from wall; *C*) recording of $pO_2$ on pen recorder; *D*) tissue $pO_2$ profile at arteriole wall.

The present study included measurements of tissue $pO_2$ profiles by the walls of arterial and venous microvessels in the brain, allowing the contributions of these microvessels to forming the tissue $pO_2$ field to be assessed during the development of acute anemia. Tissue $pO_2$ profiles were obtained in controls ([Hb] = 14.2 ± 0.3 g/dl) and at three levels of normovolemic hemodilution: [Hb] = 10.2 ± 0.2 g/dl (stage 1), 6.9 ± 0.2 g/dl (stage 2), and 3.6 ± 0.2 g/dl (stage 3). In addition, the possible development of tissue hypoxia in these conditions was evaluated by following $p_tO_2$ dynamics in the zone which probably has the lowest $pO_2$ level, i.e., the intercapillary space of the cerebral cortex.

## METHODS

Studies were performed on 14 male Wistar rats weighing 250–310 g anesthetized with ethaminal sodium (surgical dose of 50 mg/kg, anesthetic maintenance dose 10–12 mg/kg/h). Polyethylene catheters (PE-90) were placed in the femoral artery and vein. A tube (internal diameter 1.8 mm) was placed in the trachea to support spontaneous respiration of atmospheric air and to measure the minute volume of respiration (MRV) using gas meters (GS-100). An opening of size 5 × 8 mm was drilled in the right parietal area of the skull and the dura mater was removed at this site. The brain surface was continuously irrigated with solution containing 128 mM NaCl, 4.5 mM KCl, 2.5 mM $CaCl_2$, 1.0 mM $K_2HPO_4$, 1.0 mM $MgSO_4$, 12 mM $NaHCO_3$, and 6 mM glucose. The irrigation solution was equilibrated with atmospheric air and had pH = 7.38 ± 0.05 at 37 ± 1°C. The hemoglobin concentration in systemic blood was decreased by isovolemic hemodilution. A peristaltic pump (Zalimp 304, Poland) was used to exfuse blood from the femoral artery at a rate of about 0.4 ml/min and infuse 5.5% albumin solution into the femoral vein at the same rate.

The blood hemoglobin concentration was measured using the standard hemoglobin cyanide method with a Specol-221 spectrophotometer (Germany). The hematocrit (Hct) was determined using an MTsG-8 microcentrifuge (Russia). Arterial blood gases were measured using an ABL-330 gas analyzer (Radiometer, Denmark). Mean arterial blood pressure (ABP) was monitored using an EMTs-1 instrument (Institute of Physiology, Russian Academy of Sciences, Russia).

Oxygen tension on vessel surfaces and in cerebral cortex tissues was measured using platinum polarigraphic electrodes (tip diameter, including glass insulation, 3–4 μm, recess

TABLE 1. Arterial Blood Parameters in Animals during the Development of Acute Anemia

| Parameter | Hematocrit, % | Hemoglobin, g/dl | pH | $pCO_2$, mmHg |
|---|---|---|---|---|
| Control | 42.5 ± 0.8 ($n$ = 13) | 14.2 ± 0.3 ($n$ = 13) | 7.36 ± 0.01 ($n$ = 12) | 45.2 ± 1.3 ($n$ = 13) |
| Stage 1 | 31.4 ± 0.8 ($n$ = 13) | 10.2 ± 0.2 ($n$ = 13) | 7.38 ± 0.01 ($n$ = 10) | 42.9 ± 1.2 ($n$ = 11) |
| Stage 2 | 20.0 ± 0.6 ($n$ = 13) | 6.9 ± 0.2 ($n$ = 13) | 7.38 ± 0.01 ($n$ = 12) | 40.7 ± 1.5 ($n$ = 13) |
| Stage 3 | 10.2 ± 0.5 ($n$ = 13) | 3.6 ± 0.2 ($n$ = 13) | 7.32 ± 0.03 ($n$ = 11) | 35.2 ± 2.2 ($n$ = 12) |

*Continuation*

| Parameter | $pO_2$, mmHg | BE, mEq/liter | MRV, ml/min/100 g | Arterial BP, mmHg |
|---|---|---|---|---|
| Control | 84.3 ± 3.2 ($n$ = 13) | –0.5 ± 0.6 ($n$ = 12) | 45.2 ± 3.1 ($n$ = 10) | 133.0 ± 3.0 ($n$ = 19) |
| Stage 1 | 89.9 ± 5.3 ($n$ = 11) | –0.2 ± 0.9 ($n$ = 10) | 49.6 ± 4.4 ($n$ = 13) | 95.1 ± 6.7 ($n$ = 27) |
| Stage 2 | 95.0 ± 3.8 ($n$ = 13) | –1.0 ± 0.8 ($n$ = 12) | 57.1 ± 5.2 ($n$ = 12) | 92.0 ± 3.7 ($n$ = 31) |
| Stage 3 | 100.2 ± 4.2 ($n$ = 12) | –6.4 ± 1.7 ($n$ = 11) | 84.8 ± 6.8 ($n$ = 15) | 75.1 ± 3.4 ($n$ = 21) |

7–8 μm) using a standard method, which has been described in detail elsewhere [2, 3, 43]. Microvessels were observed using a LYuMAM K-1 (LOMO, Russia) microscope fitted with contact epiobjectives. The maximum focusing depth of the microscope was 80–100 μm from the brain surface at a total optical system magnification of ×150. Microscope images were recorded using a PIH-756 CCD video camera and a video capture card with a computer and monitor for subsequent analysis. During $pO_2$ measurements, the frontal lens of the objective (diameter about 5000 μm) was placed in immediate contact with the brain surface (without tissue compression), essentially preventing gas exchange between the microareas being studied and the irrigating solution.

Measurements were started at least 15 min after completion of surgical procedures. During this time, the microelectrodes were calibrated and their stability was verified. First, the oxygen current of the electrode in the irrigating solution was measured, after which the electrode tip was placed on the wall of a large arteriole and replaced in the irrigating solution. This procedure was repeated several times until stable electrode readings were obtained in solution and on microvessel walls. Electrode calibration was repeated on numerous occasions during the experiment. Correct recording of tissue $pO_2$ profiles by the walls of radial arterioles or venules requires the effects of diffusion currents of oxygen from other microvessels to be minimized, i.e., there should be no functioning microvessels for at least 70–90 μm along the microelectrode track from the microvessel of interest. It was quite difficult to fulfill this condition in the superficial layers of the cerebral cortex, with their abundant vascularization. Thus, the number of radial microvessels studied was relatively small (7–10 for each stage of hemodilution). We have previously described the methodological characteristics of measurements of tissue $pO_2$ profiles (radial gradients) [4, 6, 17, 36]. $pO_2$ profiles were recorded by withdrawing the microelectrode tip in steps of 10–15 μm from the microvessel wall (Fig. 1).

Gas measures of systemic arterial blood were then determined, along with Hct, [Hb], MRV, and BP, and the experiment then proceeded to the first stage of hemodilution. Exchange perfusion with 5.5% albumin was performed at a rate of ~0.4 ml/min to a blood hemoglobin concentration of ~10 g/dl (Hct = 30%) (stage 1). Repeat measurements of $pO_2$ on the same microvessels were performed at least 5 min after completion of hemodilution. During tissue $pO_2$ profile measurements, microscope images were captured and stored for determination of the distance of the microelectrode from the wall of the vessel being studied. The second stage (stage 2) in decreasing blood [Hb] was to a level of ~7 g/dl (Hct = 20%) and the third (stage 3) was to ~3–4 g/dl (Hct = 10%).

Numerical data were analyzed statistically and plots were constructed using Origin Pro v. 8.0 (OriginLab, USA). All data were presented as mean ± standard error of the mean. Significant differences between means were identified using Student's $t$ test at a significance level of $p < 0.05$.

## RESULTS

Table 1 shows arterial blood values on development of acute anemia in the experimental animals.

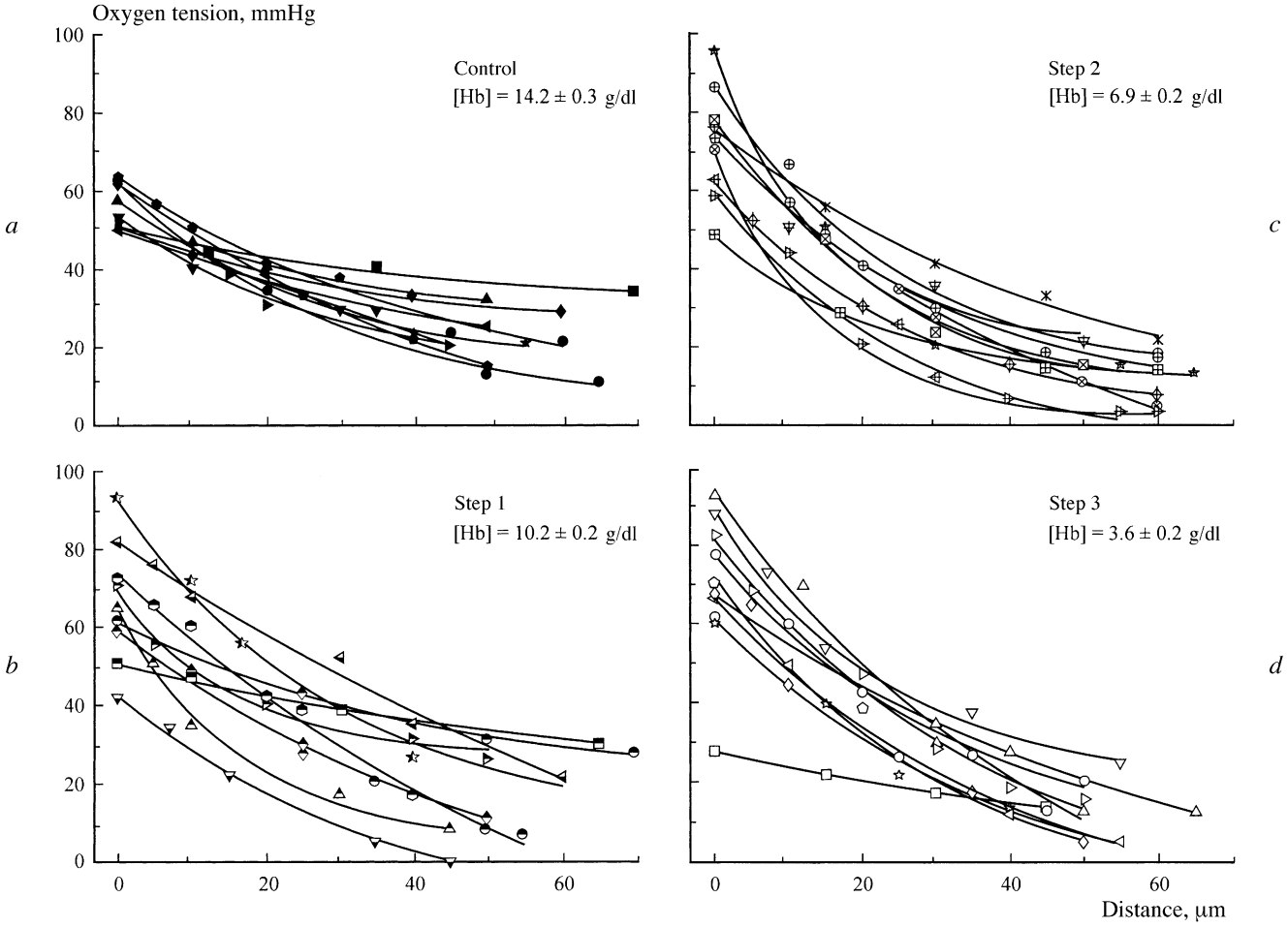


Fig. 2. Tissue $pO_2$ profiles by the walls of radial arterioles (mean lumen diameter 14.7 ± 0.9 μm, $n$ = 11) in the rat cerebral cortex during the development of acute anemia. *a*) Control, [Hb] = 14.2 ± 0.3 g/dl; *b*) stage 1, [Hb] = 10.2 ± 0.2 g/dl; *c*) stage 2, [Hb] = 6.9 ± 0.2 g/dl; *d*) stage 3, [Hb] = 3.6 ± 0.2 g/dl. The abscissas show distance from the microvessel wall, μm; the ordinates show oxygen tension, mmHg.

These result show that the decrease in blood [Hb] was accompanied by significant shifts in blood gas values. Compensatory cardiovascular and respiratory system reactions were accompanied by moderate hypocapnia, significant increases in oxygen tension in the arterial blood system, a nearly two-fold increase in MRV, and a significant reduction in mean arterial blood pressure (stage 3).

Tissue $pO_2$ profiles measured close to the walls of radial arterioles and venules are shown in Fig. 2, *a* and Fig. 3, *a*, respectively. These results show that tissue $pO_2$ 60 μm from arteriole walls was 15–40 mmHg. In the case of venules, tissue $pO_2$ 40 μm from vessel walls was in the range 12–30 mmHg, which was above the hypoxic threshold for brain tissue, measured by many investigators as 8–10 mmHg [14, 20]. It should be noted that the tissue $pO_2$ profiles measured here in control conditions were analogous to those obtained previously for rat [43] and rabbit [3] brain microvessels.

In mild anemia, stage 1, the only measure of systemic arterial blood pressure to decrease significantly from the control level was mean arterial pressure ($p < 0.001$). The corresponding tissue $pO_2$ profiles by the walls of arterioles and venules are shown in Fig. 2, *b* and Fig. 3, *b*, respectively. Radial arterioles showed a characteristic increase in $pO_2$ at the wall, due to the corresponding increase in $pO_2$ in systemic arterial blood and an enhanced rate of brain blood flow due to a reduction in blood viscosity. Tissue 60 μm from the wall showed an insignificant decrease in $pO_2$, on average to ~19 mmHg (from ~21 mmHg in controls). The most marked changes in tissue $pO_2$ at this stage were seen on radial venules – tissue $pO_2$ decreased by an average of 8–10 mmHg on walls and in tissues (Fig. 3, *b*).

The moderate anemia stage, stage 2, was accompanied by systemic compensatory reactions from both the respiratory system (respiratory minute volume increased to 57.1 ± 6.2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ compared with 45.2 ± 3.1 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ in controls) and the cardiovascular system (mean arterial blood pressure decreased to 92.0 ± 3.7 mmHg compared with 133 ± 3 mmHg in controls). At this level of anemia, $pO_2$

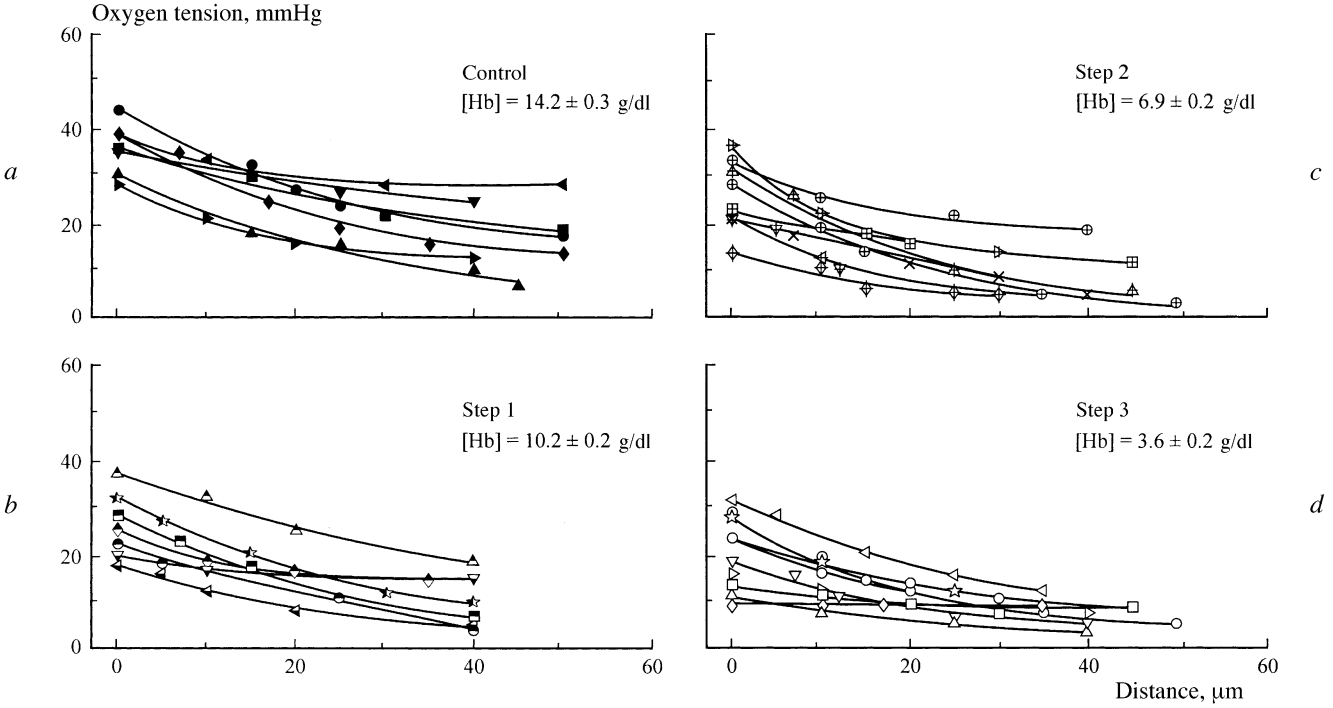


Fig. 3. Tissue $pO_2$ profiles by the walls of radial venules (mean lumen diameter 13.1 ± 0.4 μm, $n$ = 9) in the rat cerebral cortex during the development of acute anemia. For further details see caption to Fig. 2.

on arterial walls increased to a mean of 65–70 mmHg, while $pO_2$ in tissue 60 μm from arteriole walls decreased markedly, to a mean of 10–13 mmHg (Fig. 2, *c*). The nature of the tissue $pO_2$ profile on venules showed virtually no change as compared with stage 1; $pO_2$ on walls increased by a mean of about 25 mmHg, while that at a distance of 30–40 μm from the wall increased by about 8–10 mmHg (Fig. 3, *c*).

In severe anemia, stage 3, the nature of tissue $pO_2$ profiles showed virtually no change as compared with stage 2 (Fig. 2, *d* and Fig. 3, *d*). $pO_2$ on arteriole walls varied over the range 60–95 mmHg, while values at distances of 50–60 μm from walls were in the range 7–30 mmHg (mean about 10–11 mmHg); $pO_2$ on venule walls varied over the range 10–35 mmHg, while $pO_2$ at distances of 30–40 μm from walls varied over the range 8–20 mmHg (mean about 8–10 mmHg).

Figure 4 shows tissue $pO_2$ profiles close to the walls of radial arterioles and venules for control conditions (line 1) and stages 1–3 (lines 2–4, respectively) averaged for all the experimental data. The averaged curve was plotted as $Y = a_1\exp^{-x/t_1} + Y_0$, where coefficients $a_1$, $t_1$, and $Y_0$ were selected automatically by the program (Origin Pro v. 8.0) by sequential iteration to obtain minimal values of $\chi^2$.

The dynamics of tissue $pO_2$ in acute anemia were assessed in a separate series of experiments ($n$ = 9) in which the tip of the oxygen microelectrode was applied to the capillary field at significant distances from large microvessels (Fig. 5). During this experiment, particular attention was paid to maintaining the position of the microelectrode tip in the tissue relative to microvessels, particularly at the second and third stages of hemodilution, during marked respiratory movements of the rat brain surface. In controls, tissue $pO_2$ averaged 29.3 ± 2.8 mmHg, decreasing in mild anemia to 22.4 ± 3.7 mmHg (stage 1), in moderate anemia to 15.9 ± 2.7 mmHg (stage 2), and in severe anemia to 11.5 ± 2.3 mmHg (stage 3, $n$ = 12). It should be emphasized that hypoxic areas in the intercapillary space ($p_tO_2$ < 8–10 mmHg) were detected in occasional cases and only in conditions of impaired or slowed blood flow in the microvessels closest to the microelectrode tip and/or in cases of mild general compensatory cardiovascular and respiratory reactions to acute anemia.

## DISCUSSION

The present experiments yielded measurements of tissue $pO_2$ gradients close to radial arterioles and venules in the rat cerebral cortex during the development of acute anemia. The $p_tO_2$ profiles were characteristic of diffusion flows of oxygen across the walls of these microvessels and allow the contributions of these microvessels to forming the $p_tO_2$ field in acute anemia to be evaluated.

Acute normovolemic hemodilution decreased systemic blood hemoglobin concentration during these experiments

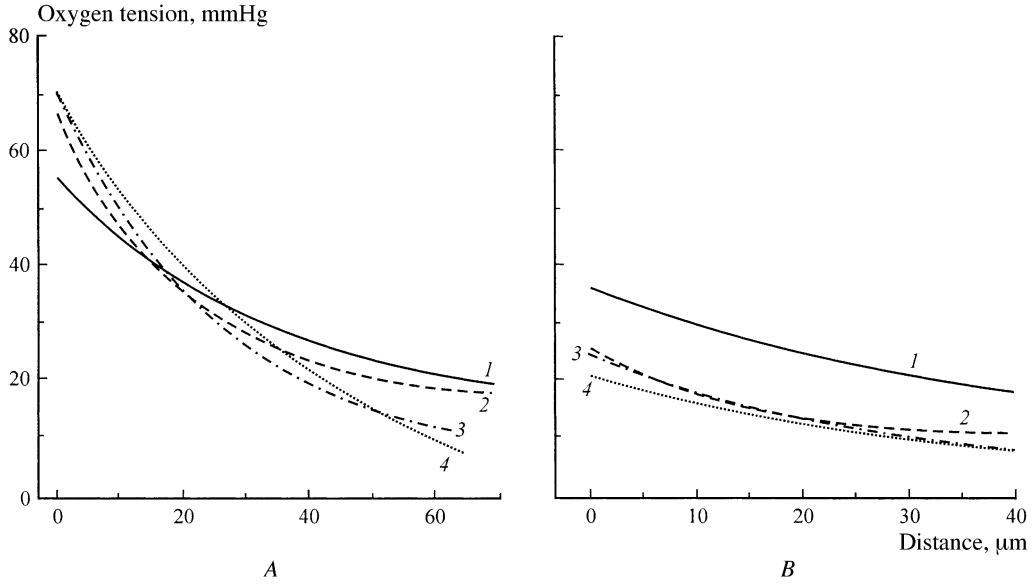


Fig. 4. Averaged tissue $pO_2$ profiles by the walls of radial arterioles (*A*) and radial venules (*B*) in the rat cerebral cortex during the development of acute anemia. *1*) Control, [Hb] = 14.2 ± 0.3 g/dl; *2*) stage 1, [Hb] = 10.2 ± 0.2 g/dl; *3*) stage 2, [Hb] = 6.9 ± 0.2 g/dl; *4*) stage 3, [Hb] = 3.6 ± 0.2 g/dl.

from 14.2 ± 0.3 to 3.6 ± 0.2 g/dl, which was accompanied by an almost four-fold reduction in the blood oxygen level – from 18 to 4.7 ml $O_2 \cdot 100$ ml$^{-1}$. Published data indicate that the anemia-induced increase in brain blood flow is initially determined by blood viscosity (to a hemoglobin in level of 9–10 g/dl) [8, 40] and then to a greater extent by the blood oxygen level [34]. Total oxygen delivery to the brain (the product of brain blood flow and the blood oxygen content) in these conditions may either remain essentially unchanged to quite low [Hb] values, 5 g/dl [42], or decrease at higher blood hemoglobin levels [19, 39]. Thus, oxygen extraction from the blood increases and there is an overall decrease in $p_tO_2$ in the brain. There is extensive literature on brain oxygenation in acute normovolemic hemodilution. Data obtained by some authors indicate that tissue $pO_2$ in the brain is very sensitive to decreases in blood oxygen capacity and decreases even at mild levels of hemodilution [5, 7, 12, 29, 32, 37]. Initially high $pO_2$ levels can show more marked decreases as compared with initially low $pO_2$ levels [7]. Data reported by other groups show that gas exchange conditions in the brain change insignificantly – to [Hb] = 7–9 g/dl [9, 15, 22, 28].

The tissue $pO_2$ field is determined by diffusion flows of oxygen from blood in arterioles, capillaries, and venules [17]. The main contribution to forming this field is made by capillaries and small venules, accounting for more than 80% of the total gas exchange surface area between the blood and tissues [43]. Arterioles, despite their small specific presence in the microcirculatory system [26], are the most powerful sources of oxygen, with high blood $pO_2$ levels and high convective oxygen transport. On development of anemia, the role of arterioles as an oxygen source to tissues increases significantly, as systemic arterial blood $pO_2$ increases (see Table 1) and the rate of brain blood flow increases. $pO_2$ increases on arteriole walls, such that the $pO_2$ gradient between arteriolar blood and tissue increases accordingly (Fig. 2). As a result, the diffusion flow of oxygen from arteriolar blood increases in anemia. As the arteriolar component of the microcirculatory bed gas exchange includes both relatively large arterioles with lumen diameters of 20–50 μm and smaller and correspondingly more numerous arterioles and precapillaries, the total contribution of arterioles to supplying brain tissues in anemia is very significant. It should be noted that arterioles retained their efficiency as an oxygen source in tissues even in conditions of severe anemia (Fig. 2, *d* and Fig. 4). Oxygen tension at the walls of the smallest arterioles and precapillaries, from which blood directly enters capillaries, was about 50–55 mmHg [1], which is close to the corresponding $pO_2$ values for the initial hematocrit in controls [43]. Thus, for the arterial component of the rat cerebral cortex, the increase in the rate of brain blood flow completely compensated for the decreased blood oxygen content (stage 3) and $pO_2$ at the walls of cerebral arterioles was at control levels or even greater. Nonetheless, our data showed that the specific contribution of arterioles to the oxygen supply for tissues decreased on development of anemia, while the contribution of capillaries increased correspondingly.

Our previous results showed that $pO_2$ on capillaries in severe anemia was in the range 20–45 mmHg [1]. At dis-

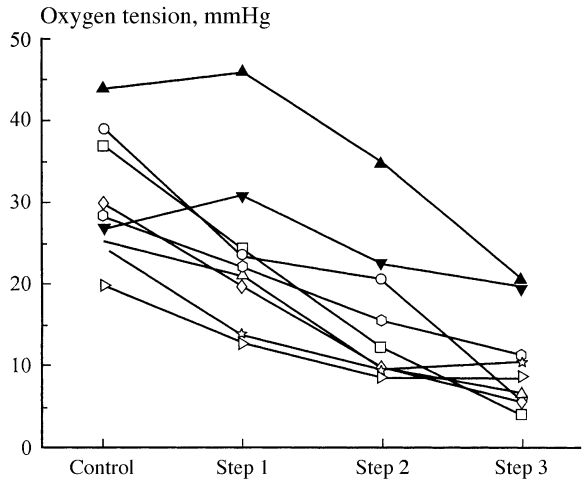


Fig. 5. Dynamics of tissue $pO_2$ in the intercapillary space of the rat cerebral cortex in conditions of decreases in blood hemoglobin from 14.2 ± 0.3 g/dl (control) to 3.6 ± 0.2 g/dl (stage 3). Curve with black symbols show $p_tO_2$ measurements close to precapillaries or very small arterioles.

tances of about 25–30 μm from capillary walls, which is essentially half the distance between capillaries in the cerebral cortex [10, 31], tissue $pO_2$ was 10–20 mmHg (Fig. 5). The intercapillary tissue $pO_2$ gradient was thus about 0.5–0.7 mmHg/μm, which is about twice the value in normal (control) conditions [4, 43]. It follows from Fig. 5 that at most of the points studied, intercapillary $p_tO_2$ decreased proportionally to the reduction in the blood hemoglobin concentration. The curves with black symbols in Fig. 5 show measurement of $p_tO_2$ close to precapillaries or the smallest arterioles. Here, $p_tO_2$ was significantly greater and was close to control values. Thus, even in severe anemia, some proportion of the tissue at the capillary level was in conditions of adequate oxygenation.

Averaged $pO_2$ profiles of radial venules (Fig. 4, *b*) showed that the first stage of hemodilution (mild anemia) led to decreases in $pO_2$ on walls by about 10 mmHg. However, further progression of anemia, to the level of severe anemia, had minor effects on mean $pO_2$ on the walls of radial venules and, accordingly, on tissue $pO_2$ profiles. In all probability, this is evidence for a significant increase in the rate of brain blood flow at the second and third stages of hemodilution. In fact, at the first stage of anemia, adequacy of oxygen supply to the brain was achieved by passive increases in the rate of brain blood flow due to decreases in blood viscosity and increased extraction of oxygen from blood [38]. Brain blood flow increases significantly at hemoglobin concentrations reduced to below 9 g/dl (hematocrit less than 30%) [8, 18, 38]. Published data indicate that circulatory minute volume in rats increases approximately two-fold from control levels in severe anemia, reaching about 52.9 ± 4.3 ml·100 $g^{-1}$·$min^{-1}$ [5]. Overall, the increase in brain blood flow can be by 400–600% [8, 18], which corresponds to redistribution of cardiac output in favor of the brain, myocardium, liver, and kidneys [11, 33]. Blood flow in capillaries in the cerebral cortex also show sharp increases, reaching 1500–2000 μm/sec, which is 3–4 times greater than in controls [15]. Compensatory reactions in blood flow rate are directed to minimizing the longitudinal $pO_2$ gradient at the smallest gas-exchange microvessels and thus to maintaining the maximal $pO_2$ in the blood within microvessels. Venules, along with arterioles and capillaries, are involved in supplying blood to the tissues surrounding them, and tissue $pO_2$ 30–40 μm from venule walls decreases to 9–11 mmHg, i.e., to the level of the hypoxic threshold for brain tissue, which is 8–10 mmHg, only at the stage of severe anemia (stage 3), [14, 20, 21, 34, 35].

Our data indicate that overall, the critical threshold of acute anemia (presence of tissue hypoxia) occurs when the hemoglobin concentration decreases to 3–4 g/dl. Nonetheless, this threshold is reached in some parts of the brain at higher [Hb] levels, i.e., 6–7 g/dl (Figs. 2, 3). This is seen only around microvessels with weak blood flow reactions to the anemic stimulus. Whether this occurs because of natural heterogeneity in blood flow in microvessels or for some instrument-related reason (effects of the experiment) cannot be said with confidence.

The results obtained here on the smallest gas-exchanging microvessels are in good agreement with data from numerous clinical and experimental studies assessing the critical threshold of acute normovolemic hemodilution. It follows from these studies that although the first signs of cerebral hypoxia can be apparent at [Hb] = 6–7 g/dl [12, 13], impairments to oxidative metabolism occur only at [Hb] = = 3–4 g/dl [8, 13]. It is interesting to note that in conditions of experimental anemia of 5–6 g/dl, cognitive functions in healthy volunteers were virtually unimpaired [46]. Our studies present the first evidence of radial tissue $pO_2$ gradients close to the walls of cerebral cortical arterioles or venules in rats on development of acute anemia ([Hb] ~ 3–4 g/dl). Overall, an oxygenation level above the hypoxic threshold (~8–10 mmHg) is maintained in brain tissue. This occurs as a result of significant inputs from compensatory mechanisms on the parts of the cardiovascular and respiratory systems. Hypoxic patches arise in these conditions primarily because of insufficient (weakened) blood flow reactions in local microvessels. These conclusions are based on direct measurements of $pO_2$ at the smallest microvessels and in cerebral cortical tissue in rats in conditions of direct visual observation of the microcirculatory fields being studied.

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