Pulmonary Circulation and Respiration in Hypoxic and Circulatory Hypoxias

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A key role in the development of abnormal types of breathing such as apneusis and gasping is played by hypoxia of the brain. Apneusis arises at a relatively early stage of brain hypoxia and is sometimes viewed as a variant of the normal respiratory rhythm with protracted inspiration; this type of breathing is subject to humoral and reflexive influences. Gasping (sharp, energetic inspirations with more or less prolonged pauses in between) supervenes with further progress of the brain hypoxia and is unresponsive to external influences [2,10,14]. Progressive hypoxia has been shown to cause decreases in both the amplitude and frequency of impulses in the phrenic nerve [12].

The objectives of this study were to compare the impact of hypoxic hypoxia on pulmonary circulation and respiration with that of circulatory hypoxia and to examine the hemodynamic changes in the presence of which pathological types of breathing emerge.

MATERIALS AND METHODS

In acute tests (hypoxic or circulatory hypoxia) on 40 cats of both sexes weighing 2-4 kg, linear and volume blood flow rates in the pulmonary artery and vein of the lower lobe, blood pressure (B.P.) in the pulmonary and femoral arteries, and respiratory excursions of the chest were studied under Nembutal anesthesia (40-50 mg/kg intraperitoneally) using an ultrasonic technique to measure blood flow rates [6], micromanometers to measure blood pressure [7], and tensometric sensors for measuring respiratory excursions. In some cats, the balance between the right and left ventricular outputs was also estimated with an analog computer as the ratio of the mean blood flow rate in the pulmonary cone to that in the ascending aorta. After ultrasonic sensors were placed on the appropriate vessels of artificially ventilated cats, the chest was sutured in layers, and the animals were transferred to natural respiration.

Hypoxic hypoxia (15 cats) was induced by causing the animals to inhale, via valves, a gaseous mixture consisting of 3% to 5% O_2 in nitrogen. These mixtures were used because, as found in our previous study [9], mixtures with higher oxygen concentrations (7-10% O_2) did not usually disrupt the respiratory rhythm.

Circulatory hypoxia (17 cats) was produced by bloodletting from the femoral artery in an amount equal to 20-50% of the circulating blood volume (CBV); 5 to 30 min later (depending on the condition of the animal), the CBV was restored by slow intravenous reinfusion of heparinized

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autologous blood. In the remaining 8 cats, bled as described above, the microcirculation in the lungs was studied using a biomicroscopic procedure [5]. To this end, a capillary perfusion index (CPI) was calculated as the total length of blood-perfused alveolar capillaries per 10,000 μ^2 of lung area.

It should be noted that while the pulmonary circulation and microcirculation in hypoxic hypoxia have been investigated in detail, the existing knowledge of how they function following blood loss is inadequate.

RESULTS

In cats with hypoxic hypoxia, only insignificant alterations in cardiac output (an increase or decrease by 10-15%) were observed (Fig. 1, *a*), usually without any disturbance of the balance between the right and left ventricular outputs if the respiration and cardiac activity remained normal. After respiratory arrest, however, there occurred a redistribution of the blood to the greater circulation (Fig. 1, *b*). The systemic B.P. rose by 10-20 mm Hg at first and later fell to a level slightly below baseline. A large rise (1.5 to 2-fold) of B.P. in the pulmonary artery and increased resistance of the pulmonary vascular bed were noted, as were increases by 10-15% of the blood flow in the pulmonary lobar artery and vein (Fig. 1, *c*). The respiratory changes varied from one animal to another.

In four cats that had been inhaling the hypoxic mixture for a prolonged period (>30 min), the respiratory rhythm remained normal, although both the amplitude and frequency of respiratory movements were increased and periodic deep inspirations were noted (see Fig. 1). In the remaining 11 cats of this group, a sudden respiratory arrest occurred after 3 to 20 min of hypoxia in the presence of hemodynamic changes usual for this condition; exposure to the hypoxic mixture was then discontinued and artificial ventilation was instituted. This proved ineffective in five cats - cardiac arrest ensued. In two other cats, breathing of the gasping type was observed after the artificial ventilation, followed by complete respiratory arrest. In the remaining four cats, artificial ventilation led to normalization of the respiratory rhythm.

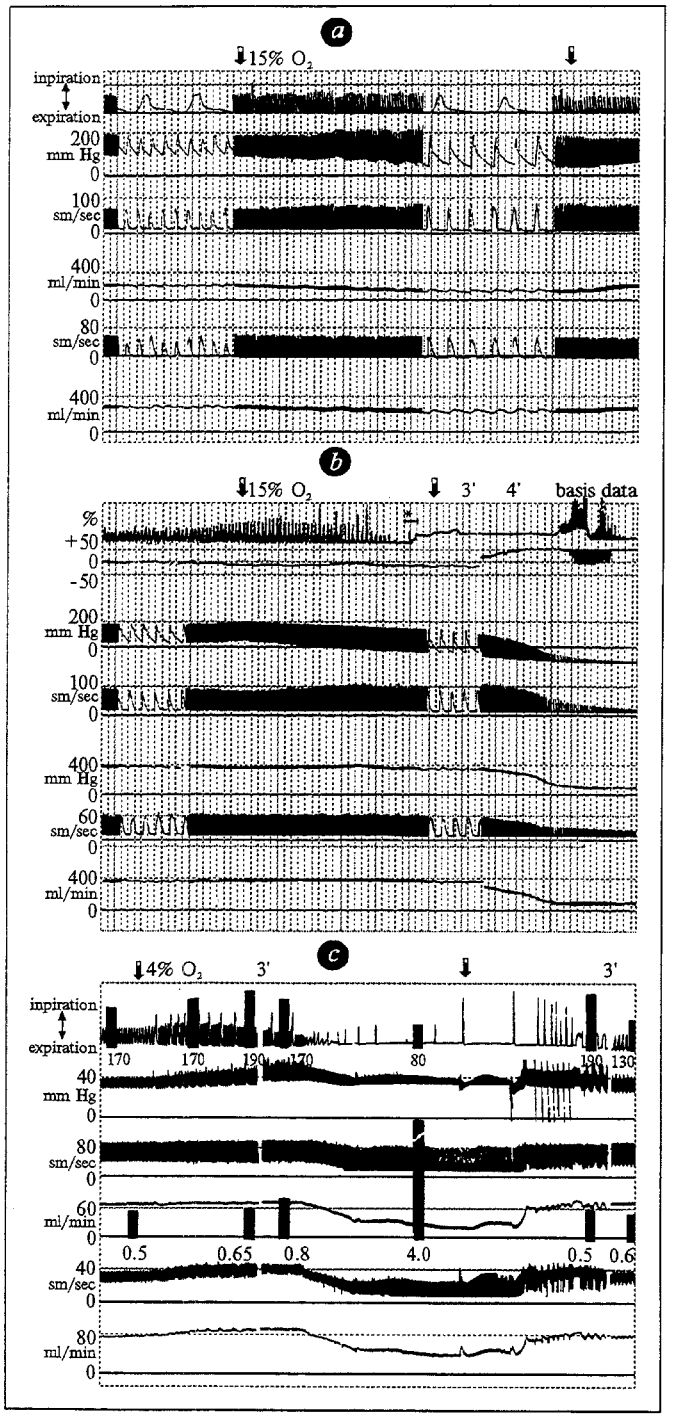

Fig. 1. Effects of hypoxic hypoxia on pulmonary and systemic circulation and respiration. From top down: *a*) B.P. in femoral artery; linear blood flow rate in ascending aorta; volume blood flow rate in ascending aorta; linear blood flow rate in pulmonary cone; and volume blood flow rate in pulmonary cone. *b*) respiration; balance between right and left ventricular outputs in relative units (upward course of curve signifies an increase of blood flow in ascending aorta over that in pulmonary cone); B.P. in femoral artery; linear blood flow rate in ascending aorta; volume blood flow rate in ascending aorta; linear blood flow rate in pulmonary cone; and volume blood flow rate in pulmonary cone. *c*) respiration; B.P. in pulmonary artery; linear blood flow rate in lower-lobe pulmonary artery; volume blood flow rate in lower-lobe pulmonary artery; linear blood flow rate in lower-lobe pulmonary vein; and volume blood flow rate in lower-lobe pulmonary vein. In *c*, upper bars indicate B.P. in the femoral artery while the lower bars indicate resistance of the pulmonary vascular bed. Here and in Figs. 2 and 3 the thin line under each curve designates zero level. Arrows mark the beginning and end of inhalation of the hypoxic mixture. Time scale: 1 and 10 sec.

Thus, nearly half (7 out of 15) of the animals died as a result of hypoxic hypoxia.

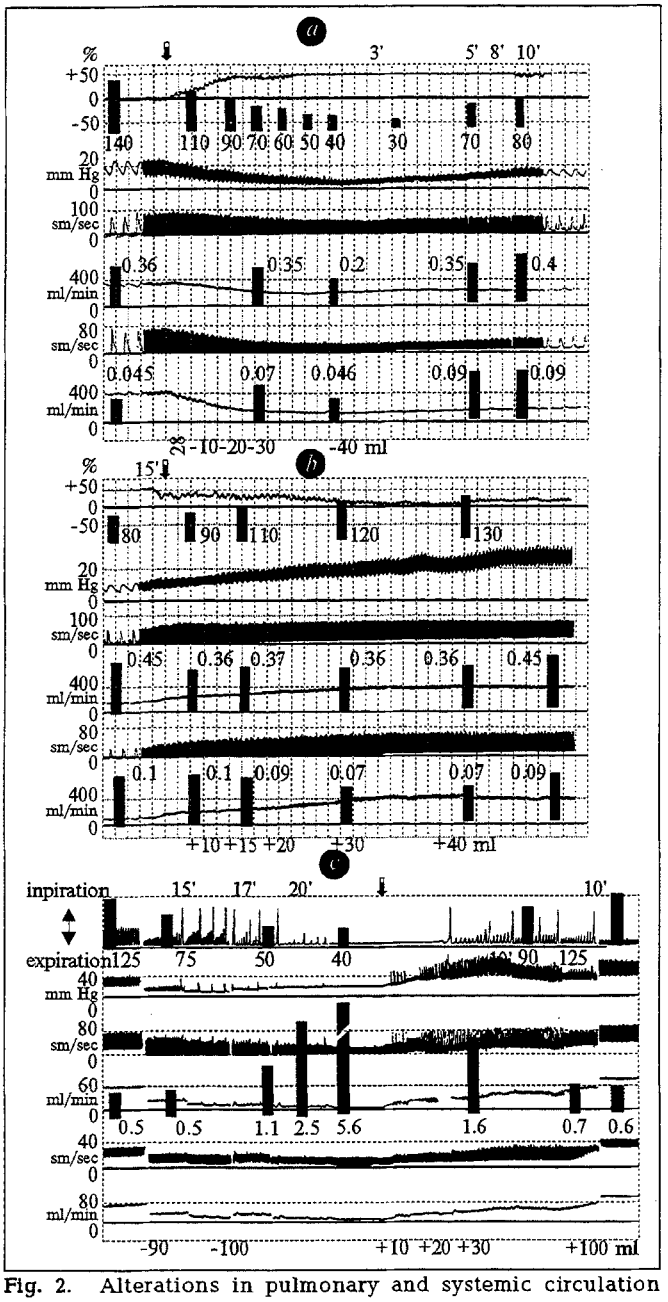

Fig. 2. Alterations in pulmonary and systemic circulation following acute blood loss (*a*) and reinfusion of autologous blood (*b*). From top down: *a* and *b*) balance between right and left ventricular outputs; B.P. in pulmonary artery; linear blood flow rate in ascending aorta; volume blood flow rate in ascending aorta; linear blood flow rate in pulmonary cone; volume blood flow rate in pulmonary cone. *c*) respiration; B.P. in pulmonary artery; linear blood flow rate in lower–lobe pulmonary artery; volume blood flow rate in lower–lobe pulmonary artery; linear blood flow rate in lower–lobe pulmonary vein; and volume blood flow rate in lower–lobe pulmonary vein. The upper bars in this figure indicate B.P. in the femoral artery and total peripheral resistance, while the lower bars indicate resistance of the pulmonary vascular bed. Arrows mark the beginning of blood loss and of blood reinfusion. Figures with the minus sign signify blood loss in ml and those with the plus sign, reinfused blood in ml.

Cats with circulatory hypoxia caused by acute blood loss showed a fall in the systemic B.P. to 40-50 mm Hg together with a decreased cardiac output. The right ventricular output was reduced to a greater extent than the left, i.e. the balance between the two outputs was upset, with a redistribution of the reduced CBV to the greater circulation (Fig. 2, *a*) so as to maintain blood supply to such vital organs as the heart, brain, and respiratory musculature [3, 8]. This was reflected in an altered pulmonary circulation: the pulmonary B.P. fell considerably and blood flow in the pulmonary artery and vein was, on average, only 16% of its baseline value (5%-27%) (Fig. 2, *a*). In some cats the pulmonary vascular resistance did not change significantly (Fig. 3, *a*), whereas in others it increased considerably and the respiratory rhythm was disrupted (Fig. 3, *a*).

In 8 of the 17 bled cats, there occurred partial restitution of all hemodynamic parameters (compensated blood loss [3, 4]). Some animals exhibited increased blood flow in the lobar pulmonary vein without any changes in the blood inflow along the lobar pulmonary artery (Fig. 3, *a*), which can be taken as an indirect indication of augmented blood flow in the bronchial arteries, since two-thirds of the venous drainage from the bronchial arterial system occurs via the pulmonary veins [11]. Cats in which a tendency for recovery was observed were bled again. The occurrence of pathological breathing after acute blood loss depends not so much on the total amount of blood lost as on the resultant hemodynamic changes, in particular a fall in the systemic B.P. (to 30-40 mm Hg) and, apparently, a sharp (3- to 10-fold) rise in the pulmonary vascular resistance. The time course of these changes varied from one animal to another.

In cats with circulatory hypoxia, the development of pathological breathing (apneusis, gasping) proceeded in a more consistent and gradual manner than in those with hypoxic hypoxia. During bloodletting, the respiratory rate increased and periodic deep inspirations appeared. Then, when the B.P. had fallen to 30-50 mm Hg, the breathing became less frequent and more shallow. Apneusis and gasping were exhibited by 9 of the 17 cats; in one cat respiratory arrest ensued (Figs 2. *c* and 3).

Very shortly after the start of reinfusion (when 20-40 ml of autologous blood were introduced to cats that had lost 80-100 ml), an increase in cardiac output with restoration of the balance between the right and left ventricular outputs was observed (Fig. 2, *b*), as were rises in the systemic and arterial B.P. and restitution of the normal respira-

tory rhythm. In addition, resistance of the pulmonary vascular bed decreased to its baseline level (Figs. 2, *c* and 3, *c*). The pathological type of breathing persisted for a longer time in only two cats. In five cats, cardiac arrest occurred even though the CBV had been restored. In one cat, respiratory and then cardiac arrest occurred at the beginning of blood reinfusion, when the hemodynamic parameters had already returned to normal. It should be noted that some cats developed a cardiac abnormality (extrasystoles) during the reinfusion procedure. In this group, about a third (6 out of 17) of the animals died.

We have shown previously [1] that the capillary perfusion index (CPI) increases in hypoxic hypoxia as PaO_2 falls and B.P. in the pulmonary artery rises. These alterations, reflecting those in the size of the bed of functional gas-exchanging capillaries, should be regarded as an important adaptive response of the pulmonary circulation to hypoxic hypoxia. For cats with circulatory hypoxia, however, opposite results were obtained: as the systemic and pulmonary B.P. was falling, so was the CPI, which was close to zero when the pulmonary B.P. was very low (Table 1). This finding is in accord with the reported drop in this index with a fall in the pulmonary B.P. observed in other animal models of hypoxia [13,15]. Reinfusion of blood led to a progressive rise of this index, but it always remained somewhat below its baseline value. It is of interest that in cats infused with physiological saline instead of blood, the pattern of variation in the CPI was similar to that in animals reinfused with blood, even although the number of formed elements in the pulmonary capillaries was of course smaller.

Like other authors [3,4], we noted both a compensated and a decompensated type of blood loss. The compensation in a bled animal is, however, very fragile and can be easily abolished through additional interventions. Thus, partial compensation involving rises in the systemic and arterial B.P. and normalization of the respiratory pattern was shown by some cats that had lost as much as 45% (70-90 ml) of the CBV (Fig. 3, *a*), but this compensation was completely reversed following an additional slight blood loss (5-10 ml): the systemic B.P. then fell to 30-40 mm Hg, the pulmonary B.P. also decreased, and the respiratory rhythm was again disrupted so that reinfusion of blood was required in order to return the various parameters to normal (Fig. 3, *b*). In some cats, falls in the systemic and pulmonary B.P., a rise in the pulmonary vascular resistance, and respiratory rhythm abnormalities followed by respiratory

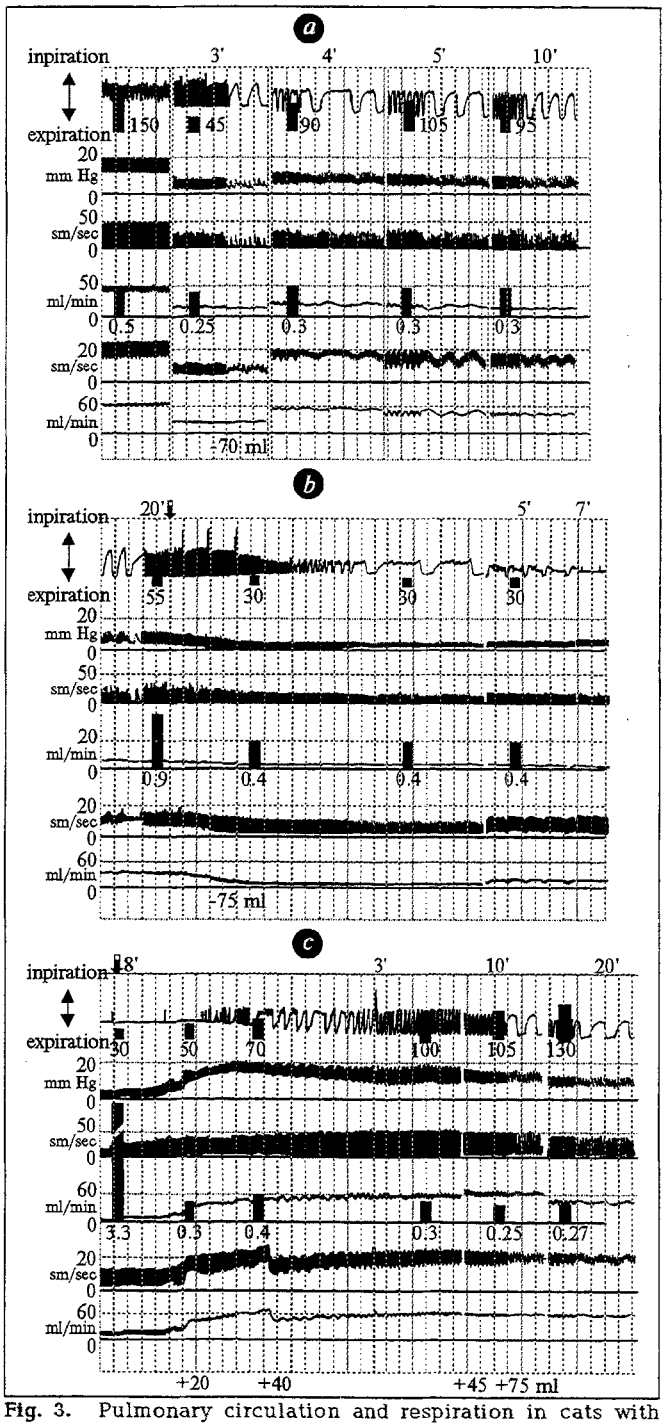

Fig. 3. Pulmonary circulation and respiration in cats with acute blood loss. From top down: *a*, *b*, and *c*) respiration; B.P. in the pulmonary artery; linear blood flow rate in lower-lobe pulmonary artery; volume blood flow rate in lower-lobe pulmonary artery; linear blood flow rate in lower-lobe pulmonary vein; and volume blood flow rate in lower-lobe pulmonary vein. The upper bars indicate B.P. in the femoral artery and the lower bars, resistance of the pulmonary vascular bed. Top figures in *a*, *b*, and *c*, time in minutes after the start of blood loss or of blood reinfusion. *b* and *c* are continuations of *a* and show the time course of variations in the parameters concerned during a typical test. *a*) at 10 min after the loss of 70 ml blood, partial compensation occurs. *b*) at 20 min a further loss of 5 ml blood abolishes the compensation. *c*) recovery only occurs after blood reinfusion.

TABLE 1. Values of the Pulmonary Capillary Perfusion Index in Cats after Acute Blood Loss (80±10 ml)

Time after blood loss, min	Blood pressure in femoral artery, mm Hg	Blood pressure in pulmonary artery, mm Hg	Capillary perfusion index, μ^{-1}
0	150±15	19±3	440±12
5	100±10	10±4	400±12
15	70±10	10±3	210±10
30	40±10	3–5	0–50

arrest were observed even after the loss of much less blood (20% of the CBV), and the reinfusion of blood was of no avail - the animals died.

This study has shown that the time course and nature of respiratory abnormalities in hypoxic hypoxia differ from those in circulatory hypoxia. In an earlier study, we found that an initial increase of the blood supply to the brain in hypoxic hypoxia is succeeded by its reduction under the influence of hypocapnia developing as a consequence of hyperventilation. This is attended by a sharp fall in PO_2 in brain tissues [8], which aggravates the impact of the severe hypoxic hypoxia on brain structures, including the respiratory center, and causes a sudden respiratory arrest. In the case of acute blood loss, PO_2 in brain tissues decreases in a more gradual manner than in other organs, remaining above zero even after cardiac arrest [8]. This observation may explain why respiratory abnormalities arise less frequently in circulatory than in hypoxic hypoxia and develop gradually, by passing through the "transitional" stages of apneusis and gasping.

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