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# Indomethacin Restricts Cerebral Blood Flow during Pressure Ventilation of Newborn Pigs

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**ABSTRACT. Unanesthetized newborn pigs were studied to evaluate the immediate (10 min) and delayed (45 min) effects of increased ventilation pressure coupled with cyclooxygenase inhibition. Cardiac output and cerebral blood flow were measured at a low (5 cm $H_2O$) and high (30 cm $H_2O$) mean airway pressure ($\overline{Paw}$) before and 45 min after 5 mg/kg of indomethacin. In a second group, these parameters were also measured 10 min after indomethacin was given during ventilation at a $\overline{Paw}$ of 30 cm $H_2O$. Before treatment with indomethacin, increasing $\overline{Paw}$ decreased cardiac output without affecting cerebral blood flow. Baseline ($\overline{Paw}$ = 5 cm $H_2O$) cerebral blood flow decreased 40% 45 min after indomethacin treatment. Adding the stress of a ventilation-induced drop in cardiac output did not further depress cerebral blood flow. When indomethacin was administered during high $\overline{Paw}$, cerebral blood flow decreased markedly within 10 min. Cerebral oxygen consumption was maintained by increasing oxygen extraction. Therefore, indomethacin decreases cerebral blood flow at a high $\overline{Paw}$. The fall in cerebral blood flow decreases brain oxygen delivery. However, cerebral oxygen consumption is maintained by an increase in oxygen extraction (*Pediatr Res* 24: 59–62, 1988)**

**Abbreviations**

**$\overline{Paw}$, mean airway pressure**
**$CMRO_2$, cerebral metabolic rate of oxygen**
**CSF, cerebrospinal fluid**

Positive pressure ventilation can adversely affect the cardiovascular system of newborns. Increasing ventilation pressure depresses cardiac output but maintains blood flow to the brain, heart, and adrenals (1). Maintenance of blood flow to the brain during ventilation with high airway pressure may involve vasodilator prostanoid production (2), possibly in response to an increased sagittal sinus pressure. We designed this series of experiments to delineate further the role that cerebral prostanoid production plays during mechanical ventilation. In addition, we examined the cerebral oxygen consumption during pressure ventilation, specifically to test the hypothesis that the brain can maintain oxygen consumption during periods of compromised cerebral blood flow by increasing oxygen extraction.

## MATERIALS AND METHODS

*Animal preparation.* Seventeen newborn pigs (0.8–2.2 kg) had vascular catheters placed under general anesthesia (halothane, $N_2O$, and oxygen) on the first or second day of life. A polyurethane catheter was placed in the descending aorta (via an umbilical artery) for blood sampling, measurement of arterial blood pressure, and administration of drugs. A second catheter was placed in the left ventricle via the right carotid artery. We have confirmed previously that ligation of this vessel does not alter cerebral blood flow or its distribution under a variety of conditions. (1, 3). The catheters then were tunneled subcutaneously to the flank and placed in a cloth pouch. After surgery the piglets were given benzathene penicillin, gentamicin, and colloidal iron and were placed in cages warmed by overhead lamps. They were provided with a continual supply of pig milk substitute and water. Experimentation was performed on the third postoperative day with the unanesthetized animals resting comfortably in a cloth sling.

*Protocol for group 1 (n = 9).* The piglet was intubated with a 3.0 mm (id) straight, uncuffed endotracheal tube and a 5.0 fr feeding tube was passed into the stomach. Piglets were given 10–15 ml of pig milk substitute during long wait periods. The animals then were placed into the cloth slings and the arterial catheter connected to a pressure transducer and a recorder (Beckman R511A). Animals were ventilated with a time-cycled, pressure-limited Baby Bird infant respirator. The proximal airway port was connected through a pressure transducer to the recorder. The animals were allowed a period of 10–20 min to adjust to the experimental conditions. A 10-min period of minimal ventilation ($\overline{Paw}$ = 5 cm water, inspiratory time 0.5 s, respiratory rate = 20 bpm) followed. At the end of this period arterial blood gases and pH were measured and 15 $\mu$m radionuclide microspheres were injected into the left ventricle for determination of cardiac output and its distribution. $\overline{Paw}$ then was increased to 30 cm water by increasing both peak inspiratory and end expiratory pressures, and a second 10-min period was allowed for the animals to stabilize. Arterial blood gases and pH were determined and a second microsphere injection was made. The ventilator was returned to the minimal settings and indomethacin trihydrate (5 mg/kg intravenous) was given. This dose was chosen as previous study has shown that 5 mg/kg will cross the blood brain barrier in sufficient quantity to render cortical levels of prostanoids nondetectable (4). The animals then were gavage fed and ventilated at a $\overline{Paw}$ = 5 cm $H_2O$ for 45 min. At this time the above protocol was repeated at mean airway pressures of 5 and 30 cm water.

*Protocol for group 2 (n = 8).* On the day of study the animals were intubated and a feeding tube was inserted. The sagittal sinus was cannulated by first anesthetizing the scalp with lidocaine and then making a 2-cm incision to expose the midline of the skull. The sagittal sinus was cannulated with a 20-gauge Teflon catheter, which was connected through a pressure transducer to the recorder. The animals then were placed in a cloth sling and allowed to become accustomed to the study environment. The following data were collected at a $\overline{Paw}$ of 5 and 30 cm water: arterial blood gases and pH, arterial and sagittal sinus oxygen saturation, Hb concentration, and cardiac output and its distri-

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bution using radionuclide microspheres. With the $\overline{Paw}$ still increased, indomethacin trihydrate (5 mg/kg intravenous) was given. Ten minutes later, similar data were collected. Then, the $\overline{Paw}$ was decreased to 5 cm water. Forty-five min later the data collections at $\overline{Paw}$ of 5, 30, and 30 cm water were repeated. We repeated the increase in $\overline{Paw}$ postindomethacin to test whether the cerebral blood flow response to an increase in airway pressure had been altered by eliminating cerebral prostanoids.

*Blood chemistry determinations and cerebral $O_2$ consumption.* Arterial pH, $PO_2$ and $PCO_2$ were determined using an Instrumentation Laboratories blood gas analyzer. An American Optical Reflection Oxymeter (corrected to newborn pig blood) was used to determine percent saturation of the Hb in arterial and sagittal blood. Blood Hb was determined using a Reichert Hemoglobinometer. Venous $PO_2$ was determined from the venous $O_2$ saturation using the oxygen dissociation curve. The capacity of the Hb was assumed to be 1.39 ml $O_2$/g of Hb. Blood oxygen content then was calculated as $CO_2$ = (g Hb/100 ml × 1.39 ml $O_2$/g Hb × percent saturation of Hb with $O_2$) + dissolved $O_2$ (ml $O_2$/100 ml blood). The arterial venous oxygen content difference ($CAO_2 - CVO_2$) is the arithmetic difference of these two values. The $CAO_2 - CVO_2$ difference also represents oxygen extraction. $CMRO_2$ was calculated as (arterial $CO_2$ − venous $CO_2$) × cerebral blood flow ÷ 100. Cerebral vascular resistance was calculated as (mean arterial blood pressure − mean sagittal sinus pressure) ÷ cerebral blood flow.

*Microsphere determination of cardiac output and cerebral blood flow.* Approximately 300,000–500,000, 15 μm radioactive microspheres ($^{46}Sc$, $^{95}Nb$, $^{103}Ru$, $^{113}Sn$, $^{57}Co$) were counted in a gamma counter before injection into the left ventricle. Withdrawal of reference blood through a dorsal aortic catheter began 15 s before microsphere injection and continued for 2 min after the injection. After the experiment, the animal was killed and the brain removed and cut into regions. Determination of radioactivity was done by differential spectroscopy. Cardiac output was calculated as cardiac output = (reference withdrawal rate) × (counts injected) × (counts in reference withdrawal)$^{-1}$. Cerebral and regional blood flow at the time that the microspheres were injected was calculated by using the formula: $Q = C \times R \times CR^{-1}$, where Q = blood flow in ml/min × 100 g, C = counts/100 g tissue, R = rate of withdrawal of reference blood sample in ml/min, and CR = total counts in reference arterial blood sample.

*Statistical analysis.* All values are presented as mean ± SEM. Comparisons were made using a one-way analysis of variance with replications and a Scheffé's post hoc test. $P < 0.05$ was required for significance.

## RESULTS

Table 1 summarizes our results from the first group of animals. When $\overline{Paw}$ was increased from 5 cm to 30 cm $H_2O$, cardiac output dropped from 388 ± 34 to 169 ± 20 ml/kg·min while cerebral blood flow was maintained. Indomethacin decreased baseline cerebral blood flow by 40% to 52 ± 7 ml/min·100 g. After indomethacin a drop in cardiac output similar to that seen in untreated piglets was seen when $\overline{Paw}$ was increased. Sixty-five min after indomethacin cerebral blood flow was 62 ± 8 ml/min·100 g during a second ventilation-induced drop in cardiac output. Arterial blood gases and pH as well as blood pressure were stable throughout the study period. Blood Hb was 8.0 ± 1 g at the start of the study and 8.0 ± 0.7 g at end.

Table 2 and Figures 1 and 2 summarize the data from the second group of animals. When $\overline{Paw}$ was increased from 5 cm to 30 cm $H_2O$, cardiac output dropped from 337 ± 22 to 142 ± 15 ml/kg·min. Cerebral blood flow (Fig. 1) was unchanged during increased $\overline{Paw}$ (80 ± 6 at 5 cm $H_2O$ $\overline{Paw}$ *versus* 79 ± 9 ml/min · 100 g at 30 cm $H_2O$). $CMRO_2$ and sagittal sinus $PO_2$ also were unchanged. Sagittal sinus pressure increased significantly from 4.8 ± 0.5 to 15.4 ± 1.4 mm Hg when $\overline{Paw}$ was increased. Cerebral vascular resistance (Fig. 2) decreased significantly from 0.81 ± 0.07 to 0.53 ± 0.03 mm Hg·100 g·min/ml when $\overline{Paw}$ was increased. When indomethacin was administered at a $\overline{Paw}$ of 30 cm $H_2O$, cardiac output remained reduced, and cerebral blood flow fell to 37 ± 4 ml/min·100 g. Cerebral oxygen consumption remained constant. The stable $CMRO_2$ was accomplished by an increase in oxygen extraction ($CAO_2 - CVO_2$) which is seen also in the significant drop in sagittal sinus $PO_2$ (from 32 ± 2.2 to 23 ± 1.6 mm Hg). Sagittal sinus pressure remained elevated. Cerebral vascular resistance increased to 1.53 ± 0.14 mm Hg·100 g·min/ml. Forty-five min after indomethacin administration during minimal ventilation ($\overline{Paw}$ = 5 cm $H_2O$), cardiac output had returned to normal while cerebral blood flow and sagittal sinus $PO_2$ remained decreased. $CMRO_2$ was unchanged. Cerebral vascular resistance was increased compared to normal ventilation before indomethacin. Increasing $\overline{Paw}$ to 30 cm $H_2O$ 55 min after indomethacin increased sagittal sinus pressure and depressed cardiac output whereas cerebral blood flow and venous $PO_2$ were not depressed further. Although $CMRO_2$ tended to decline, the decline was not statistically significant. Cerebral vascular resistance continued to be higher than preindomethacin values. Arterial blood pressure, blood gases, and pH also were unchanged. Hb remained at 7.5 ± 0.5 g throughout the study.

Table 1. *$\overline{Paw}$, cardiac output (CO), cerebral blood flow (CBF), arterial blood pressure (BP) and arterial blood gases/pH for group 1 (n = 9) (mean ± SEM)*

| Time (min) | 10 | 20 | 25 | 70 | 90 |
|---|---|---|---|---|---|
| $\overline{Paw}$ (cm $H_2O$) | 5 | 30 | | 5 | 30 |
| | | | INDO | | |
| CO (ml/kg·min) | 388 ± 34 | 169 ± 20* | | 310 ± 35 | 130 ± 30* |
| CBF (ml/min·100 g) | 86 ± 7 | 86 ± 11 | | 52 ± 7* | 62 ± 8* |
| BP (mm Hg) | 72 ± 18 | 70 ± 14 | | 69 ± 12 | 68 ± 14 |
| Arterial | | | | | |
| pH | 7.38 ± 0.03 | 7.39 ± 0.02 | | 7.38 ± 0.03 | 7.40 ± 0.03 |
| $PCO_2$ (mm Hg) | 33.2 ± 2.02 | 31.4 ± 1.61 | | 31.6 ± 1.92 | 30.9 ± 1.66 |
| $PO_2$ (mm Hg) | 78.6 ± 4.84 | 81.9 ± 4.34 | | 85.8 ± 4.18 | 85.3 ± 4.28 |

* Statistically significant change from initial value.

At the time when cerebral blood flow was decreased, regional brain blood flow was decreased uniformly. There was no regional redistribution of blood flow. For example, at the period when overall cerebral blood flow fell (high $\overline{Paw}$ 10 min after indomethacin) from 80 ± 6 to 37 ± 4 ml/min·100 g brain stem blood flow fell from 65 ± 6 to 39 ± 4 ml/min·100 g, and cerebellar blood flow fell from 63 ± 5 to 38 ± 4 ml/ min·100 g.

## DISCUSSION

Indomethacin administration in a dose sufficient to inhibit cerebral prostanoid production reduces cerebral blood flow significantly. When the stress of high ventilation pressure is added to indomethacin administration, cerebral perfusion is compromised further. Cerebral oxygen consumption is maintained during these periods of decreased cerebral blood flow by increasing oxygen extraction.

$CMRO_2$ is dependent on oxygen delivery (oxygen delivery is the product of cerebral blood flow and arterial oxygen content) and oxygen extraction ($CAO_2 - CVO_2$). Increasing blood flow in response to a decrease in arterial oxygen content appears to be the dominant mechanism used by the brain to maintain a steady $CMRO_2$ (5). Decreasing arterial oxygen content results in an increase in cerebral blood flow, thus a steady rate of oxygen delivery in fetal, newborn, and adult sheep (6). With steady oxygen delivery, increased oxygen extraction is not required to

Table 2. *P̄āw̄, cardiac output (CO), $CMRO_2$, oxygen extraction ($CAO_2$-$CVO_2$), sagittal sinus $PO_2$ ($SSPO_2$), sagittal sinus pressure (SSP), arterial blood pressure (BP), and arterial blood gases/pH for group 2 (n = 8) (Mean ± SEM)*

| Time (min) | 10 | 20 | 25 | 35 | 70 | 80 | 90 |
|---|---|---|---|---|---|---|---|
| P̄āw̄ (cm $H_2O$) | 5 | 30 | INDO | 30 | 5 | 30 | 30 |
| CO (ml/kg·min) | 337 ± 22 | 142 ± 15* | | 183 ± 37* | 310 ± 30 | 129 ± 12* | 90 ± 4* |
| $CMRO_2$ ($mlO_2$/100 g·min) | 2.28 ± 0.29 | 2.40 ± 0.37 | | 2.02 ± 0.23 | 2.41 ± 0.38 | 2.00 ± 0.22 | 2.47 ± 0.30 |
| $CAO_2$-$CVO_2$ (ml $O_2$/100 ml) | 3.3 ± 0.4 | 3.6 ± 0.5 | | 6.1 ± 0.4* | 5.0 ± 0.4* | 5.0 ± 0.6* | 4.7 ± 0.5* |
| $SSPO_2$ (mm Hg) | 32 ± 2.2 | 30 ± 1.3 | | 23 ± 1.6* | 26 ± 0.8* | 26 ± 0.9* | 27 ± 1.0* |
| SSP (mm Hg) | 4.8 ± 0.5 | 15.4 ± 1.4* | | 15.0 ± 0.9* | 4.1 ± 0.8 | 15.3 ± 1.3* | 15.7 ± 0.9* |
| BP (mm Hg) | 64 ± 12 | 62 ± 14 | | 66 ± 10 | 70 ± 15 | 62 ± 18 | 60 ± 14 |
| Arterial | | | | | | | |
| pH | 7.39 ± 0.03 | 7.38 ± 0.03 | | 7.34 ± 0.03 | 7.39 ± 0.03 | 7.4 ± 0.04 | 7.37 ± 0.02 |
| $PCO_2$ (mm Hg) | 33.0 ± 1.41 | 33.4 ± 0.78 | | 31.5 ± 4.11 | 32.5 ± 1.59 | 30.0 ± 1.04 | 30.8 ± 1.40 |
| $PO_2$ (mm Hg) | 87.6 ± 2.25 | 83.6 ± 3.56 | | 86.3 ± 4.78 | 85.2 ± 2.89 | 87.5 ± 4.44 | 90.1 ± 2.58 |

* Statistically significant change from initial value.

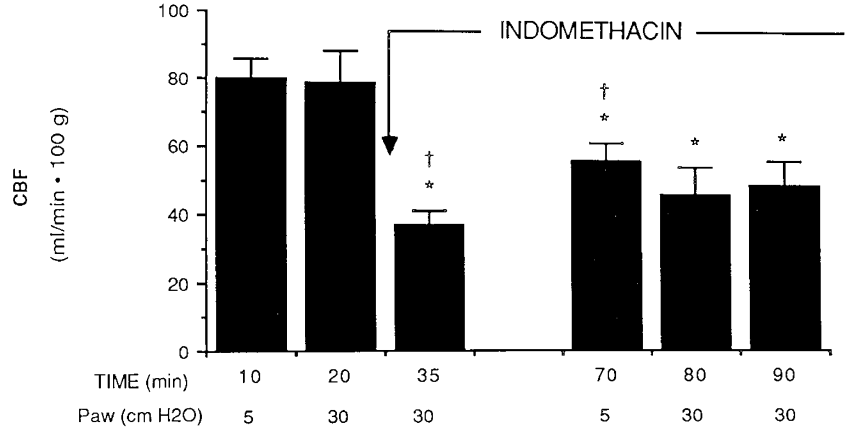


Fig. 1. Cerebral blood flow (*CBF*) values for group 2 (mean ± SEM). * denotes statistical difference from initial value; † denotes statistical difference from the immediately previous value.

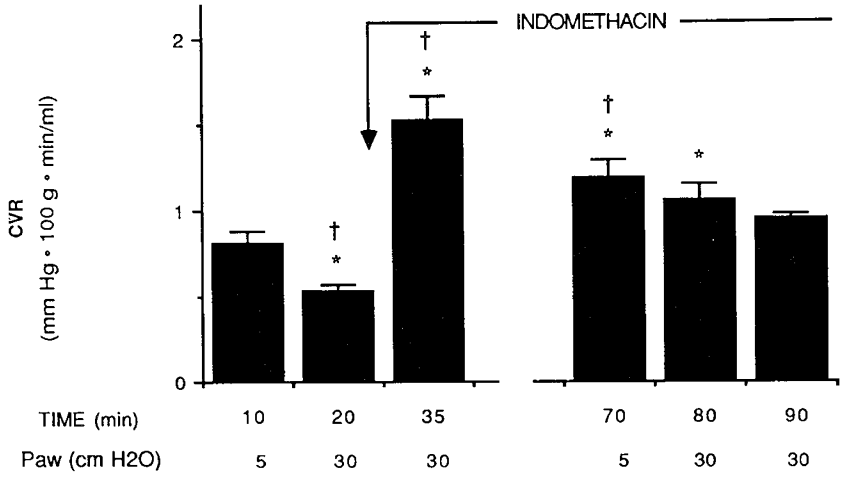


Fig. 2. Cerebral vascular resistance (*CVR*) values for group 2 (mean ± SEM). * denotes statistical difference from the initial value; † denotes statistical difference from the immediately previous value.

maintain $CMRO_2$. It is believed generally that the newborn brain will increase oxygen extraction in response to a decrease in oxygen delivery (7), but studies testing this hypothesis have provided conflicting results. Gardiner (8) has shown that in the calf a fall in oxygen delivery (during hypoxic hypoxia) is associated with a fall in $CMRO_2$ whereas others (9, 10) have shown that restricting cerebral blood flow (and therefore oxygen delivery) in the lamb results in an increase in oxygen extraction and a stable metabolic rate. The present study supports the concept that the brain of newborn pigs can increase oxygen extraction when oxygen delivery is compromised by a decrease in cerebral blood flow.

When prostanoid synthesis was intact, cerebral vascular resistance fell in response to an increase in airway pressure. Inhibition of prostanoid production while airway pressure was high led to a sharp increase in vascular resistance and a significant drop in

cerebral blood flow. This suggests that dilator prostanoid synthesis was involved in maintaining cerebral blood flow during increased $\overline{Paw}$. This may further suggest that prostanoids are important in maintaining cerebral autoregulation. Subsequently, cerebral vascular resistance declined 35–55 min after indomethacin. This drop in resistance occurred during a period of increased airway pressure, but it is unclear what role alternating ventilation pressures had in changing vascular resistance. During the same time period (35–55 minutes postindomethacin) oxygen extraction remained above baseline values whereas sagittal sinus $PO_2$ remained below control values. It seems reasonable to speculate that the decline in cerebral vascular resistance seen 70, 80, and 90 min after indomethacin may have been in response to tissue hypoxia. It is likely that the decreased tissue $PO_2$, reflected by a low venous $PO_2$, can produce vasodilation inasmuch as tissue hypoxia causes vasodilation via a mechanism independent of prostanoids (11). This difference in cerebral blood flow response to an increased $\overline{Paw}$ appears temporally related to indomethacin administration. We speculate that the immediate drop in cerebral blood flow is due to an abrupt inhibition of vasodilator prostanoids (unopposed pressors). The response of the cerebral circulation 55–65 min after indomethacin must involve other systems that may act to blunt the ventilation effect.

Previously we have shown that increasing $\overline{Paw}$ significantly decreases cardiac output beginning at a $\overline{Paw}$ of 15 cm $H_2O$ (1). In the present experiments, we used a higher $\overline{Paw}$ (30 cm $H_2O$) to depress cardiac output. During preliminary studies used to design these experiments, we observed that awake animals require higher ventilation pressures to depress cardiac output. We speculate that this difference is due to the effect of anesthesia on the medullary cardiovascular center and possibly arterial baroreceptors.

Indomethacin decreases cerebral blood flow in both laboratory (3) and clinical studies (12). Indomethacin inhibits prostanoid production via cyclooxygenase inhibition, and we have shown that indomethacin given in a dose of 5 mg/kg crosses the blood brain barrier in sufficient quantity to inhibit cortical CSF production of prostanoids (4). This is associated with a 20–30% reduction in regional brain blood flow (3). A smaller dose (0.2 mg/kg) of indomethacin produces a modest but significant decrease in cerebral blood flow during hemorrhagic hypotension (13). In contrast, baseline cerebral blood flow in the present study was decreased by 30 to 40% 45 min after indomethacin. The differences in cerebral blood flow depression seen postindomethacin during the present study *versus* our previous work may be attributable to the use of continuous positive airway pressure. Similarly, clinical studies (12, 14–16) have shown that cerebral blood flow velocity is decreased by 20–40% after the administration of the initial dose of 0.2 mg/kg of indomethacin.

During the perinatal period the cardiovascular system is influenced significantly by prostanoids (17), with control of cerebral hemodynamics apparently influenced by locally produced vasoactive prostanoids. Cortical CSF of newborn pigs has measurable amounts of prostanoids that significantly increase with asphyxia (3), hemorrhage (18), positive pressure ventilation (2), application of norepinephrine (19), acetylcholine (20), and histamine (21). Prostanoid production in response to such a range of stimuli underscores the importance of prostanoids in maintaining cerebral perfusion during stress situations. Therefore, the interruption of prostanoid production in the newborn may have a significant impact on the animal's ability to respond to stress.

Pressure ventilation of human newborns is recognized as a risk factor for intracranial bleeding (22). The high association between pressure ventilation and neonatal intracranial hemorrhage may be secondary to the stress that increasing intrathoracic pressure has on cerebral hemodynamics. Increasing airway pressure increases sagittal sinus pressure. Increasing cerebral venous pressure could disrupt the fragile capillary structure of the germinal matrix. An increase in venous pressure coupled with a constant arterial pressure, however, requires the cerebral circulation to vasodilate to maintain blood flow. This vasodilation is in part mediated by prostanoids (2) and could conceivably act to extend a cerebral bleed. Restricting vasodilation during positive pressure ventilation by the administration of indomethacin may be a factor in minimizing neonatal intracranial hemorrhage (23).

In summary, mechanical pressure ventilation adversely affects both cardiac output and cerebral hemodynamics and the addition of indomethacin in sufficient quantity to block cerebral prostanoid production further decreases cerebral blood flow at high ventilation pressures. Constant cerebral oxygen consumption is maintained by increasing oxygen extraction and decreasing venous oxygen content, thus maintaining a steady oxygen metabolic rate.

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