Hypoxic hypometabolism in the anesthetized turtle, Trachemys scripta

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Hicks, James W., and Tobias Wang. Hypoxic hypometabolism in the anesthetized turtle, Trachemys scripta. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R18–R23, 1999.—A hypometabolic response during acute exposure to hypoxia has been measured in both endothermic and ectothermic vertebrates. In the turtle, we determined the metabolic response to normocapnic hypoxia and hypercapnic hypoxia. In addition, we tested the hypothesis that hypoxic hypometabolism was a regulated response that did not depend on O₂ availability. Metabolic, cardiovascular, and blood gas measurements were collected in anesthetized turtles under two conditions: during normocapnic hypoxia [fractional inspired O₂ FIO₂ = 0.1 and 0.05] and during hypercapnic hypoxia [FIP₅₀₂ = 0.1 and 0.05 plus fractional inspired CO₂ (FICO₂) = 0.05]. During normoxia, rate of O₂ consumption (VO₂) was 0.82 ml·min⁻¹·kg⁻¹ and was reduced by nearly 30% at the lowest FIO₂. Normocapnic hypoxia of FIO₂ = 0.1 had no significant effect on VO₂. The addition of 5% CO₂ to the inspired air did not enhance the effects of hypoxia. Injections of 2,4-dinitrophenol increased VO₂ during hypercapnic hypoxia in some animals to levels greater than those measured during normoxia. We conclude that hypoxia produces a hypometabolic state in anesthetized turtles, and the pharmacological stimulation of VO₂ counters the effects of hypoxia on metabolism. The hypoxic hypometabolism in turtles most likely represents a regulated response and does not reflect limited O₂ availability at the cellular level. Finally, we hypothesize that hypoxemia induced by the right-to-left cardiac shunt often associated with diving may trigger the development of a hypometabolic state and therefore contribute to the prolongation of aerobic dive times.

hypoxia; reptile; metabolism; 2,4-dinitrophenol; cardiac shunts; diving

ALL VERTEBRATES exhibit cardiovascular and ventilatory responses to acute hypoxia that, together, help maintain an adequate oxygen supply to the metabolizing tissue. As an alternative strategy, some animals enter a hypometabolic state that reduces the actual rate of ATP turnover and lessens the demand on the cardiorespiratory systems during conditions of limited oxygen availability (16). The hypometabolic state is a regulated response that involves changes in membrane permeability, reductions in active membrane transport, and downregulation of various synthetic pathways, such as protein synthesis (2, 16, 24, 25). Oxygen shortage is suggested as the causative factor that induces the hypometabolic state (20, 31), and recently some of the cellular transduction pathways for this response have been described (16, 17, 25).

In ectothermic vertebrates, several studies document downregulation of cellular metabolism in response to anoxia; turtles, for example, reduce heat production by 85% during anoxic submergence (18, 26). Similar results are reported for amphibians (38). However, although the reduction in metabolism as a response to anoxia is well established for a variety of ectotherm vertebrates (18, 26, 38), the effects of milder oxygen lack (i.e., hypoxia) have received less attention. It therefore remains to be investigated whether ectothermic vertebrates exhibit metabolic depression during hypoxia.

Many reptiles and amphibians experience internal hypoxia caused by intermittent breathing patterns and the presence of large right-to-left (R-L) cardiac shunts (4, 22, 33, 35, 40). During diving and periods of apnea, the development of the R-L shunt can occur rapidly and reduces arterial oxygen levels, in some cases, to values approaching mixed venous oxygen levels (4, 40). In addition, the R-L shunt recirculates metabolically produced CO₂ to the systemic arterial blood as venous admixture, consequently increasing arterial Pco₂ (Paco₂) and reducing arterial pH (39). Is it possible, therefore, that the development of a R-L shunt and the subsequent changes in arterial blood gases and pH can trigger a hypometabolic state?

The present study was designed to determine if hypoxemia or a combination of hypoxemia and hypercapnia, in the range normally experienced by turtles during diving, reduces aerobic metabolism. We chose to study the red-eared slider (Trachemys scripta) because this species normally exhibits long-lasting breath holds that are associated with the development of large R-L shunts and reduced blood oxygen levels (4, 36, 40, 41).

MATERIALS AND METHODS

Experimental animals. This study was performed on freshwater red-eared turtles, Trachemys scripta Gray (body mass, 1.1–1.3 kg; mean = 1.26 kg; n = 5) obtained from Lemberger (Oshkosh, WI) and air-freighted to Odense University. All animals were housed (4–6 wk before study) in a large (0.8 × 1.2 m) fiberglass tank containing fresh water and free access to dry platforms allowing for behavioral thermoregulation. Animals were fed on trout pellets several times a week, but food was withheld for at least 3 days before experimentation.

Animal preparation. On the day of experimentation, turtles were anesthetized with an intramuscular injection of pentobarbital sodium (Nembutal; 30 mg/kg). Animals were placed in the supine position, tracheostomized, and mechanically ventilated with humidified room air (2–3 breaths/min) at a tidal volume of 25–30 ml/kg (Harvard ventilator, model HI 665). Occlusive PE-50 polyethylene catheters were inserted...
into the left carotid artery and the jugular vein. These saline-filled catheters were advanced toward the heart ∼2–4 cm. These catheters were used for blood sampling, and the venous catheter also acted as an infusion port for 2,4-dinitrophenol (DNP). To access the central vascular blood vessels, a 2–3 cm portion of the plastron was removed with a bone saw. The pectoral muscles were gently loosened from the excised piece, and bleeding from small superficial vessels, a 2-

Table 1. Blood gas composition of arterial and venous blood from anesthetized and artificially ventilated Trachemys scripta at various levels of inspired O2 and CO2 tensions

<table>
<thead>
<tr>
<th></th>
<th>0.21 FIO2</th>
<th>0.10 FIO2</th>
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<th>0.05 FIO2</th>
<th>DNP</th>
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<tr>
<td>Arterial</td>
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<td>PO2, mmHg</td>
<td>91.2 ± 4.4</td>
<td>54.2 ± 2.6*</td>
<td>25.1 ± 0.8*</td>
<td>92.9 ± 5.8</td>
<td>50.8 ± 1.5*</td>
<td>21.4 ± 1.8*</td>
<td>35.5 ± 4.4</td>
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<tr>
<td>cO2, mmol/l</td>
<td>3.68 ± 0.26</td>
<td>3.25 ± 0.27</td>
<td>1.88 ± 0.21*</td>
<td>3.30 ± 0.27*</td>
<td>2.12 ± 0.10*</td>
<td>0.83 ± 0.10*</td>
<td>1.33 ± 0.19*</td>
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<td>[Hb], mmol/l</td>
<td>3.72 ± 0.30</td>
<td>3.65 ± 0.31</td>
<td>3.61 ± 0.33</td>
<td>3.65 ± 0.38</td>
<td>3.02 ± 0.37</td>
<td>3.39 ± 0.38</td>
<td>2.54 ± 0.37</td>
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<tr>
<td>HbO2 saturation, %</td>
<td>96 ± 3</td>
<td>89 ± 5</td>
<td>52 ± 6*</td>
<td>89 ± 7</td>
<td>73 ± 9</td>
<td>24 ± 3*</td>
<td>59 ± 12</td>
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<td>pH</td>
<td>7.84 ± 0.03</td>
<td>7.84 ± 0.03</td>
<td>7.83 ± 0.04</td>
<td>7.47 ± 0.04*</td>
<td>7.43 ± 0.03*</td>
<td>7.40 ± 0.04*</td>
<td>7.21 ± 0.06</td>
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<td>[HCO3]−, mmol/l</td>
<td>31.3 ± 1.6</td>
<td>29.6 ± 1.3</td>
<td>29.0 ± 1.2</td>
<td>31.5 ± 1.2</td>
<td>32.8 ± 1.3</td>
<td>31.2 ± 1.3</td>
<td>26.4 ± 0.9</td>
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<tr>
<td>PCO2, mmHg</td>
<td>15.7 ± 1.3</td>
<td>14.6 ± 1.1</td>
<td>14.7 ± 0.7</td>
<td>17.0 ± 3.4*</td>
<td>14.6 ± 2.1*</td>
<td>42.7 ± 3.5*</td>
<td>58.2 ± 7.6</td>
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Venous

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<th></th>
<th>0.21 FIO2</th>
<th>0.10 FIO2</th>
<th>0.05 FIO2</th>
<th>0.21 FIO2</th>
<th>0.10 FIO2</th>
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<th>0.21 FIO2</th>
<th>0.10 FIO2</th>
<th>0.05 FIO2</th>
<th>DNP</th>
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<tr>
<td>PO2, mmHg</td>
<td>52.4 ± 3.5</td>
<td>41.0 ± 4.0*</td>
<td>18.8 ± 1.3*</td>
<td>51.8 ± 4.8</td>
<td>30.9 ± 4.1*</td>
<td>12.5 ± 1.3*</td>
<td>16.0 ± 0.9†</td>
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<td>cO2, mmol/l</td>
<td>3.25 ± 0.26</td>
<td>2.66 ± 0.34*</td>
<td>1.26 ± 0.25*</td>
<td>2.55 ± 0.25*</td>
<td>1.46 ± 0.10*</td>
<td>0.41 ± 0.09*</td>
<td>0.49 ± 0.12*</td>
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<tr>
<td>[Hb], mmol/l</td>
<td>3.66 ± 0.26</td>
<td>3.55 ± 0.31</td>
<td>3.65 ± 0.31</td>
<td>3.69 ± 0.30</td>
<td>3.30 ± 0.39</td>
<td>3.36 ± 0.38</td>
<td>2.53 ± 0.34†</td>
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<tr>
<td>HbO2 saturation, %</td>
<td>77 ± 4.6</td>
<td>75 ± 4.6</td>
<td>74 ± 4.6</td>
<td>69 ± 7*</td>
<td>47 ± 8*</td>
<td>12 ± 3*</td>
<td>22 ± 8*</td>
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<tr>
<td>pH</td>
<td>7.79 ± 0.04</td>
<td>7.79 ± 0.04</td>
<td>7.76 ± 0.04</td>
<td>7.50 ± 0.04*</td>
<td>7.42 ± 0.04*</td>
<td>7.42 ± 0.05*</td>
<td>7.19 ± 0.05*</td>
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<tr>
<td>[HCO3]−, mmol/l</td>
<td>32.2 ± 2.0</td>
<td>30.6 ± 1.7</td>
<td>29.8 ± 0.9</td>
<td>32.1 ± 1.4</td>
<td>33.4 ± 1.1</td>
<td>31.8 ± 1.5</td>
<td>29.4 ± 0.7†</td>
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<tr>
<td>PCO2, mmHg</td>
<td>18.3 ± 2.4</td>
<td>17.2 ± 1.5</td>
<td>17.1 ± 3.6</td>
<td>14.3 ± 3.6*</td>
<td>43.4 ± 3.5*</td>
<td>42.6 ± 4.6*</td>
<td>65.7 ± 6.7†</td>
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Values are means ± SE; n = 5 animals. FIO2, O2 fraction of inspired gas; FICO2, CO2 fraction of inspired gas; DNP, 2,4-dinitrophenol; PO2, oxygen partial pressure; cO2, oxygen content; [Hb], hemoglobin concentration; HbO2 saturation, hemoglobin-oxygen saturation; [HCO3], bicarbonate concentration; PCO2, carbon dioxide partial pressure. *Significant difference from control condition (0.21 FIO2, 0.00 FICO2); †significant difference from preceding condition (0.10 FIO2, 0.05 FICO2).
Fig. 1. Rate of O$_2$ consumption (V$_{O2}$) of Trachemys scripta, as a function of fractional inspired O$_2$ (FIO$_2$). Reduction in V$_{O2}$ at FIO$_2$ = 0.05 was reversed on reexposing animals to FIO$_2$ of 0.21. Data are means ± SE; n = 5 animals.

Hypoxic and hypercapnic gas mixtures were prepared with a Wostoff gas mixing pump (Bochum, Germany). The DNP (Sigma) was prepared as a 1.5% solution in sodium bicarbonate at a pH of 7.5.

Experimental protocol. Experiments were begun after a 30–40 min period to ensure that expired gases were in steady-state conditions. The experiment was divided into three phases. In the first phase, the animals were exposed to normoxia [fractional inspired O$_2$ (FIO$_2$) = 0.21, balanced N$_2$] for 30–40 min. This was followed by a 30-min exposure to hypoxia (FIO$_2$ = 0.05, balanced N$_2$). The FIO$_2$ was then increased (FIO$_2$ = 0.10, balanced N$_2$) for an additional 30 min. Finally, the animals were returned to normoxic levels for an additional 30 min. In the second phase of the experiment, the animals were exposed to a normoxic-hypercapnic gas mixture [FIO$_2$ = 0.21, fractional inspired CO$_2$ (FICO$_2$) = 0.05, balanced N$_2$] for up to 1 h. The order of administration of the hypercapnic hypoxic gases was the same as in the first phase. The final phase of the experiment was conducted at the end of the FIO$_2$ = 0.1, FICO$_2$ = 0.05 exposure. A single dose of DNP (20 mg/kg) was injected intravenously during hypoxia (FIO$_2$ = 0.1, FICO$_2$ = 0.05), and all measurements were made 20–30 min after injection. After the experimental protocol was complete, all turtles were killed by intravenous injections of KCl.

Data analysis and statistics. All recordings of blood flows were analyzed with AcqKnowledge data analysis software (version 3.2.3; Biopac). For each oxygen level mean values for QLAo, fH, ventilation, and arterial saturation were taken for the last 5 min of the exposure period. A two-way ANOVA for repeated measures was employed to assess the effects of reductions in FIO$_2$ and increased FICO$_2$ on the reported parameters. Mean values that were significantly different from the control condition (FIO$_2$ = 0.21 and FICO$_2$ = 0.00) were identified by a subsequent post hoc Dunnett's test. For each animal, the relationship between V$_{O2}$ and arterial and venous oxygen levels was determined by regression analysis. From this regression analysis, the effects of DNP injections on V$_{O2}$ were compared with the V$_{O2}$ predicted by the measured blood gases. Differences between predicted and measured values were tested by means of a one-tailed paired t-test. A fiducial limit for significance of P ≤ 0.05 was applied, and all data are presented as means ± SE.

RESULTS

Effects of hypoxia. Reductions in FIO$_2$ and the associated decrease in PO$_2$ and arterial and venous ctO$_2$ (Table 1) were accompanied by a significant decrease in oxygen uptake (P = 0.017). In normocapnia, V$_{O2}$ was maintained at the normoxic level at a FIO$_2$ of 0.10, but a further reduction to 0.05 elicited a significant reduction to 73% of the normoxic value. In all animals, the reduction in V$_{O2}$ at the lowest FIO$_2$ was reversed on exposure to normoxia (Fig. 1). Hypercapnia increased PaO$_2$, and venous PCO$_2$ approximately threefold and was associated with a 0.4% reduction of pH (Table 1). Because plasma [HCO$_3$] remained unaffected, this acidosis was a result of the increased PCO$_2$. Hypercapnia alone did not reduce V$_{O2}$ during normoxia and did not enhance the effects of hypoxia (Fig. 2). During hypercapnia, a reduction of FIO$_2$ to 0.10 reduced V$_{O2}$ to 76% of the normocapnic-normoxic value, and V$_{O2}$ was further reduced to 62% at a FIO$_2$ of 0.05. The reductions in V$_{O2}$ during normocapnic-hypoxia and hypercapnic-hypoxia were not associated with significant changes in Qsys, fH, or systemic stroke volume (Table 2).

Effects of DNP injections. DNP caused a significant fall in arterial and venous ctO$_2$ and reduced P$_O2$, approaching the levels measured at FIO$_2$ of 0.05 (Table 1 and Fig. 2). Therefore, it was necessary to compare the measured V$_{O2}$ after DNP injections with the V$_{O2}$ that would have prevailed at these blood oxygen levels (Fig. 2). By this comparison, the V$_{O2}$ after DNP injection was significantly higher than predicted by blood oxygen
Table 2. Effects of hypoxia and hypercapnia on gas exchange and hemodynamic variables in anesthetized and artificially ventilated T. scripta

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.21 FIO₂</th>
<th>0.10 FIO₂</th>
<th>0.05 FIO₂</th>
<th>0.21 FICO₂</th>
<th>0.10 FICO₂</th>
<th>0.05 FICO₂</th>
<th>DNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂, ml·kg⁻¹·min⁻¹</td>
<td>0.82±0.04</td>
<td>0.83±0.07</td>
<td>0.60±0.05*</td>
<td>0.79±0.02</td>
<td>0.62±0.09</td>
<td>0.51±0.06*</td>
<td>0.90±0.19†</td>
</tr>
<tr>
<td>VC₇₀₂, ml·kg⁻¹·min⁻¹</td>
<td>0.87±0.07</td>
<td>0.80±0.07</td>
<td>0.77±0.07</td>
<td>0.57±0.04*</td>
<td>0.55±0.13*</td>
<td>0.27±0.06*</td>
<td>1.21±0.17†</td>
</tr>
<tr>
<td>RE</td>
<td>1.06±0.05</td>
<td>0.96±0.03</td>
<td>1.3±0.10</td>
<td>0.76±0.08</td>
<td>1.02±0.34</td>
<td>0.58±0.16</td>
<td>1.44±0.11†</td>
</tr>
<tr>
<td>Qsys, ml·kg⁻¹·min⁻¹</td>
<td>27.8±2.3</td>
<td>24.2±2.2</td>
<td>27.5±0.8</td>
<td>19.6±1.3</td>
<td>23.3±1.3</td>
<td>28.1±2.8</td>
<td>23.6±4.9</td>
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<tr>
<td>fᵢ, min⁻¹</td>
<td>45±1</td>
<td>49±1</td>
<td>49±1</td>
<td>48±2</td>
<td>48±2</td>
<td>50±3</td>
<td>44±1</td>
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<tr>
<td>V₇₀₂, ml/kg</td>
<td>0.7±0.04</td>
<td>0.56±0.02</td>
<td>0.52±0.01</td>
<td>0.37±0.01</td>
<td>0.50±0.02</td>
<td>0.51±0.02</td>
<td>0.33±0.10</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5 animals. VO₂, Oxygen consumption; VC₇₀₂, carbon dioxide excretion; RE, respiratory exchange ratio; Qsys, systemic blood flow; fᵢ, heart rate; V₇₀₂, systemic stroke volume. *Significantly different from normocapnic-normoxic condition (P ≤ 0.05); †significantly different from preceding condition of 0.10 FIO₂ and 0.05 FICO₂ (P ≤ 0.05; paired t-test).

DISCUSSION

This study shows that hypoxia induces a decrease in oxygen uptake in anesthetized turtles. This hypometabolic response is correlated with the reduction in arterial and venous oxygen levels, and was not associated with significant increases in plasma lactate. In all animals, increasing FIO₂ back to normoxic levels reversed the reduction in VO₂. In addition, injections of DNP increased VO₂ during hypercapnic hypoxia in some animals to levels greater than those measured during normoxia. We conclude that the reduction in VO₂ after DNP injection was most likely reflects downregulation of ATP turnover rates.

Comparison with data on conscious turtles and the choice of experimental preparation. Conscious turtles exhibit cardiorespiratory responses to reduced FIO₂ to compensate for the reduced oxygen availability and may increase activity in connection with escape behaviors (37). These responses are associated with some metabolic cost (21, 39) that may mask a hypometabolic state and confound the analysis of the data. This is not the case in the present study, because the in situ anesthetized preparation does not exhibit cardiopulmonary responses to hypoxia or changes in muscle activity during activity. Consequently, changes in oxygen consumption most likely reflect altered tissue metabolism. Nevertheless, as a potential disadvantage of this preparation, anesthesia generally reduces Qsys (9), and it is therefore possible that the reduced systemic oxygen delivery renders anesthetized turtles more sensitive than conscious animals to hypoxia. However, because our data concord with values for conscious turtles, and because our experimental design allows the confounding effects of activity to be dismissed, it is likely that the hypometabolic state reported here applies to conscious animals.

In conscious turtles, the effects of hypoxia on VO₂ are markedly augmented with increased temperature (12, 19, 23). Thus at 10°C, VO₂ is maintained at the normoxic value whenever PaO₂ falls to <10 mmHg, whereas VO₂ falls progressively to values as low as 50% of the normoxic value whenever PaO₂ is reduced to 12 mmHg at 30°C (12). Extrapolations of the gas exchange data obtained in these previous studies on conscious turtles (12, 19) to 25°C are similar to those reported in the present experiments.

Delivery vs. a controlled response: DNP. The reduced VO₂ during hypoxia may be caused by either an inability of the cardiopulmonary system to supply sufficient oxygen to the tissues or by a downregulation of metabolism, i.e., reduction of ATP demand. To distinguish between these two possibilities, we injected the metabolic uncoupler DNP and found that the hypoxic hypometabolism was reversed even though arterial and venous blood O₂ levels remained reduced and cardiac output remained constant. In some of the experimental animals, the level of VO₂ after DNP injection was greater than VO₂ measured during normoxia. The pharmacological stimulation of VO₂ measured in our study is qualitatively similar to the results reported for isolated cells and similar to results reported in other animals. In the aquatic turtle, Chrysemys picta, isolated hepatocytes undergo rapid metabolic depression during anoxia that is reversed by treatment with DNP (3). In adult rats, hypoxia (FIO₂ = 0.10)-induced hypometabolism is reversed by a single injection of DNP (17 mg/kg), and the pharmacologically stimulated VO₂ during hypoxia can exceed the normoxic value (30).

Fig. 3. Effects of reducing arterial PO₂ (PaO₂) on plasma lactate in Trachemys scripta (○). Injection of DNP significantly increased plasma lactate (●).
We conclude that the reduced VO$_2$ during hypoxia in the present study reflects a reduction in ATP turnover rate. This conclusion is based on the observations that 1) plasma lactate concentrations did not increase significantly in hypoxia, indicating that the net ATP production derived from anaerobic metabolism was not increased; and 2) that VO$_2$ could be pharmacologically stimulated by injection of DNP during hypoxia, suggesting that oxygen delivery did not limit aerobic metabolism. Similar conclusions have been reached previously with comparable data in both adult and newborn mammals during hypoxia (27, 29). In mammals, inhibition of the pathways involved in thermogenesis may be the most important contributor to the reduced metabolism, although other mechanisms play a role (10, 11, 27). In ectotherms, thermogenic processes are absent, and the reduction in VO$_2$ at the organismic level may therefore be caused by the same mechanisms that depress metabolism during anoxia. As originally proposed more than a century ago, low oxygen levels appear to be the causative factor that leads to the suppression energy turnover (16, 27).

Hypoxemia-induced hypometabolism: a possible physiological role for R-L cardiac shunts. In freshwater turtles, diving is often associated with significant bradycardia, increased pulmonary vascular resistance, reduction in pulmonary blood flow, and the development of a large R-L intracardiac shunt (32, 33, 35, 40). In turtles, the magnitude of the cardiac shunt is determined by factors that affect heart rate, myocardial contractility, and the vascular resistances in the pulmonary and systemic circulations, and is primarily under cholinergic and adrenergic control (13, 14). These cardiovascular changes can occur rapidly on diving (<30 s), and as a consequence the addition of venous admixture to the arterial circulation rapidly reduces arterial blood oxygen levels toward venous values, whereas lung PO$_2$ declines more slowly (4, 40). It has been suggested that the reduction of pulmonary blood flow associated with the R-L shunt increases aerobic dive times by prolonging the use of lung oxygen stores (5). However, a recent theoretical analysis indicates that as long as tissue metabolism remains at predive levels, the development of a R-L shunt does not necessarily improve aerobic dive times (15). In our experiment, the arterial blood oxygen levels that initiated metabolic depression are similar to the levels measured in conscious turtles after the development of a R-L shunt during diving (4, 40). Thus the results of our study suggest that development of a R-L shunt may trigger the rapid onset of a hypometabolic state in the tissues and therefore contribute to the prolongation of aerobic dive times in freshwater turtles.

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