The Journal of Experimental Biology 199, 2121–2129 (1996)
Printed in Great Britain © The Company of Biologists Limited 1996
JEB0591

REVIEW

THE INTERACTION OF PULMONARY VENTILATION AND THE RIGHT–LEFT SHUNT ON ARTERIAL OXYGEN LEVELS

TOBIAS WANG* AND JAMES W. HICKS

Department of Ecology and Evolutionary Biology, University of California at Irvine, Irvine, CA 92717, USA

Accepted 4 June 1996

Summary

In adult mammals, arterial blood gases closely reflect lung gas composition, and arterial blood gases can, therefore, be effectively regulated through changes in ventilation. This is not the case among most ectothermic vertebrates, where the systemic and pulmonary circulations are not completely separated, resulting in central vascular shunts. In the presence of a right-to-left shunt (R–L shunt), the O_2 levels (P_{O_2} and haemoglobin O_2-saturation) of systemic arterial blood are depressed relative to those of the blood returning from the lungs. Arterial blood gas composition is, accordingly, not determined only by ventilation, but also by the magnitude of admixture as well as the blood gas composition of systemic venous blood. Changes in the central shunt patterns, therefore, represent an alternative mechanism by which to control arterial blood gas levels. The primary aim of this report is to evaluate the relative importance of the R–L shunt and ventilation in determining arterial blood gas levels.

Using standard equations for gas exchange and the two-compartment model, we predicted arterial O_2 levels at physiologically relevant levels of ventilation, R–L shunt and blood flows. The analyses show that the effects of changing ventilation and the size of the R–L shunt on arterial O_2 levels vary with parameters such as the rate of O_2 uptake, the blood O_2-carrying capacity and the level of hypoxia. The relative importance of ventilation and the R–L shunt in determining arterial P_{O_2} values is largely explained by the sigmoidal shape of the O_2 dissociation curve. Thus, if lung P_{O_2} is high relative to blood O_2 affinity, a large change in ventilation may have little effect on pulmonary venous O_2 content, although P_{O_2} may have changed considerably. If an R–L shunt is taking place, this, in turn, implies that arterial O_2 content is affected only marginally, with a correspondingly small effect on P_{O_2}. These predictions are discussed in the light of the limited existing experimental data on cardiac shunts in lower vertebrates; we propose that, in future experiments, the measurement of both ventilatory and cardiovascular parameters must be combined if we aim to understand the regulation of arterial blood gas levels in lower vertebrates.

Key words: control of blood gas levels, ventilation, cardiac shunt, right–left shunt, gas exchange, two-compartment model, oxygen, reptile, amphibian, ectothermic vertebrates.

Introduction

In most fish as well as in adult mammals and birds, arterial blood gas levels closely reflect the gas composition at the gas-exchange organ, and systemic arterial blood gases can, therefore, be effectively regulated through changes in ventilation. This is not the case among reptiles, amphibians, many air-breathing fishes and embryonic mammals and birds. In these animals, the systemic and pulmonary circulations are not completely separated, resulting in the possibility of central vascular shunts. Central vascular shunts have traditionally been characterized by their direction as right-to-left shunts and left-to-right shunts (R–L shunt and L–R shunt, respectively), where an R–L shunt represents recirculation of systemic venous blood (pulmonary bypass), while an L–R shunt represents recirculation of O_2-rich blood within the pulmonary circulation (systemic bypass). In the presence of an R–L shunt, arterial systemic blood O_2 levels (P_{O_2}, O_2 content and haemoglobin O_2-saturation) are depressed relative to the O_2 levels in blood returning from the lungs (chorioallantoic blood in the case of embryonic mammals and birds). Similarly, an L–R shunt results in an increase in the oxygen levels in the pulmonary arterial blood relative to that in the systemic venous blood. Arterial blood gas composition in animals possessing central

*Present address: Department of Zoology, University of British Columbia, 6270 University Boulevard, Vancouver, British Columbia, Canada V6T 1Z4. e-mail: wang@zoology.ubc.ca.

vascular shunts is, accordingly, determined not only by ventilation but also by the magnitude of admixture as well as the blood gas composition of systemic venous blood. Changes in the shunt pattern, therefore, represent an alternative mechanism for arterial blood gas regulation and a means of altering systemic O_2 delivery (the product of blood flow and blood O_2 content) that is independent of ventilation and absolute levels of blood flows (Burggren, 1988; Hicks and Wood, 1989; Burggren *et al.* 1989).

It is the purpose of this paper to quantify and discuss the effects of the R–L shunt on arterial blood O_2 levels with the specific aim of comparing the effects of altered cardiac admixture with that of changes in pulmonary ventilation.

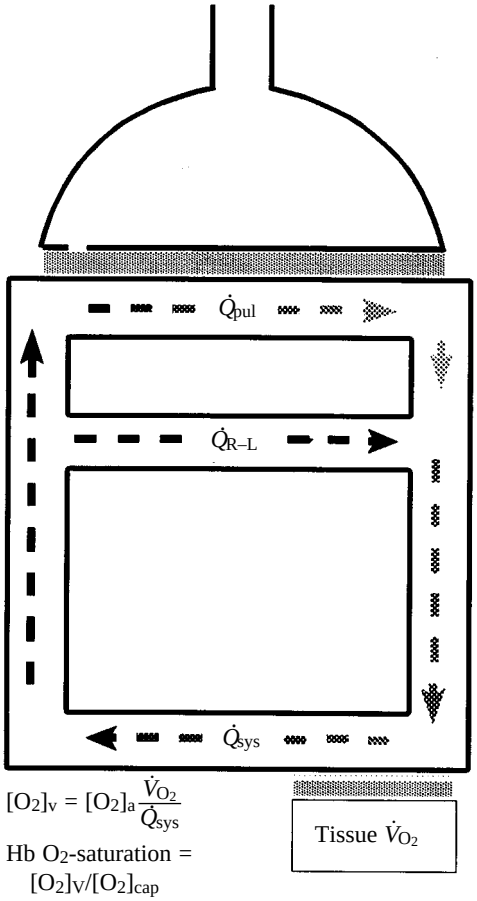
Design and description of the model

We have used the two-compartment model (Fig. 1) to analyze the effects of cardiac shunts on arterial O_2 levels. Pulmonary ventilation ($\dot{V}_A$) convectively transports O_2 from the environment to a single-compartment lung, where O_2 diffuses to the blood perfusing the lung. The circulatory system is characterized by the possibility of an R–L shunt, and O_2-poor blood returning from the tissues can flow to the lungs ($\dot{Q}_{pul}$) or may directly re-enter the systemic circulation and bypass the lung altogether ($\dot{Q}_{R-L}$). Oxygen uptake from the environment is assumed to occur exclusively at the lungs, and all O_2 consumption is assumed to occur in the tissue. At steady state, O_2 uptake in the lung is equal to tissue O_2 consumption.

All calculations are based on standard equations for mass transport, which have all been included in Fig. 1. Briefly, at a given inspired P_{O_2}, lung P_{O_2} (P_{LO_2}) is determined by ventilation relative to O_2 uptake, and pulmonary venous blood is assumed to achieve a P_{O_2} equal to P_{LO_2} minus a diffusion deficit which is considered constant at 10 mmHg. Hemoglobin (Hb) O_2-saturation of pulmonary venous blood is determined by blood O_2-binding characteristics (P_{50} and Hill's n_H) and pulmonary venous P_{O_2} (P_{PVO_2}). In turn, pulmonary venous blood O_2 content is given as the product of blood O_2-carrying capacity ($[O_2]_{cap}$) and Hb O_2-saturation. In the presence of an R–L shunt, arterial blood is a mixture of venous systemic and pulmonary venous blood, and arterial O_2 content ($[O_2]_a$) is given by the weighed mean of the O_2 content from these two circuits (Berggren, 1942). Under these conditions, arterial P_{O_2} depends on the resulting arterial Hb O_2-saturation and the O_2-binding characteristics of the blood. Finally, venous O_2 levels are determined by arterial O_2 delivery ($[O_2]_a \times \dot{Q}_{sys}$) relative to oxygen uptake ($\dot{V}_{O_2}$).

Critique of the model and assumptions

The predictions of the present model are inherently biased by the choice of values for any of the parameters included in



$$P_{LO_2} = (760\,\text{mmHg} - P_{H_2O}) \times F_{IO_2} \; (\dot{V}_{O_2}/\dot{V}_A)$$

$$P_{PVO_2} = P_{LO_2} - 10\,\text{mmHg}$$

$$\text{Hb } O_2\text{-saturation} = \frac{{P_{PVO_2}}^n}{{P_{PVO_2}}^n + {P_{50}}^n}$$

$$[O_2]_{PV} = \text{Hb } O_2\text{-saturation} \times [O_2]_{cap}$$

$$[O_2]_a = \frac{\dot{Q}_{pul} \times [O_2]_{PV} + \dot{Q}_{R-L} \times [O_2]_v}{\dot{Q}_{pul} + \dot{Q}_{R-L}}$$

$$\text{Hb } O_2\text{-saturation} = [O_2]_a/[O_2]_{cap}$$

$$Pa_{O_2} = P_{50}\left(\frac{\text{Hb } O_2\text{-saturation}}{1 - \text{Hb } O_2\text{-saturation}}\right)^{1/n}$$

Fig. 1. The two-compartment model used to describe O_2 transport in animals with intracardiac shunts. See text for further explanation (based on Rossoff *et al.* 1980; Wood, 1984). $[O_2]_{PV}$, pulmonary venous blood oxygen content; $[O_2]_v$, venous systemic blood oxygen content; $[O_2]_a$, arterial blood oxygen content; $\dot{V}_A$, pulmonary ventilation. See Table 1 for further explanation of abbreviations.

Table 1. *Values utilized for calculating blood oxygen levels in the four analyses (I–IV)*

Physiological variable	I	II	III	IV
P_{50} (mmHg)	25	25	25	25
Hill constant, n_H	2.5	2.5	2.5	2.5
Blood oxygen-carrying capacity, $[O_2]_{cap}$ (mmol O_2 l^{-1} blood)	5	2–10	5	5
$P_{LO_2} - P_{PVO_2}$ (mmHg)	10	10	10	10
Alveolar minute volume, $\dot{V}_A$ (ml kg^{-1} min^{-1})	20	20–100	20–100	20–100
Rate of oxygen uptake, $\dot{V}_{O_2}$ (ml kg^{-1} min^{-1})	1	1	0.5–6.5	1
Inspired oxygen fraction, F_{IO_2}	0.21	0.21	0.21	0.05–0.21
Systemic blood flow, $\dot{Q}_{sys}$ (ml kg^{-1} min^{-1})	30–90	60	60	60
Pulmonary blood flow, $\dot{Q}_{pul}$ (ml kg^{-1} min^{-1})	10–90	20–60	20–60	20–60
R–L shunt flow, $\dot{Q}_{R-L}$ (ml kg^{-1} min^{-1})	0–60	0–40	0–40	0–40
Fraction of cardiac outflow in the right–left shunt, $\dot{Q}_{pul}/\dot{Q}_{sys}$	0.33–1.0	0.33–1.0	0.33–1.0	0.33–1.0

P_{LO_2}, lung P_{O_2}; P_{PVO_2}, pulmonary venous P_{O_2}.

Fig. 1. The applied values (listed in Table 1) are based on published values for freshwater turtles (see, for example, Milsom and Chan, 1986; Wang and Hicks, 1996), but the general findings are applicable to all animals possessing a R–L shunt.

This analysis neglects the L–R shunt and, thus, assumes that the L–R shunt does not affect arterial blood gas levels. If the lung functions as a perfect gas exchanger, pulmonary venous blood gas levels would be equal to those of the lung, and recirculation of pulmonary venous blood to the lung (L–R shunt) would indeed have no effect. However, the lung is not a perfect gas exchanger and, if the P_{O_2} difference between lung gas and capillary blood is large, recirculation of blood to the lung may elevate pulmonary venous P_{O_2}. It has also been proposed that the L–R shunt and the associated increase in $\dot{Q}_{pul}$ improve ventilation–perfusion matching within the reptilian lung; recent experimental evidence supports this view (Hopkins *et al.* 1996).

In all analyses, we assume a constant P_{LO_2}–P_{PVO_2} deficit (equivalent of the mammalian alveolar–arterial difference) of 10 mmHg, which is similar to values determined experimentally in turtles (e.g. Burggren and Shelton, 1979). This P_{O_2} difference is the combined result of diffusion limitation, pulmonary shunts and ventilation–perfusion inequalities (for a review on reptiles, see Wang *et al.* 1996) and is, therefore, unlikely to remain constant *in vivo*. Furthermore, our predictions are based on the condition that gas exchange is in steady state. Although this assumption is rarely (if ever) fulfilled in lower vertebrates, the predicted importance of the R–L shunt as well as the predicted trends are valid even in the absence of a steady state. Finally, several studies on reptiles have documented higher O_2 levels in the right aortic arch than in the left aortic arch (Burggren and Shelton, 1979; Ishimatsu *et al.* 1988) but, for simplicity, the O_2 levels in the systemic circuit are assumed to be uniform in this study. Again, this assumption does not affect the qualitative predictions of the present analysis and could be modelled using the conceptually similar three-vessel model described by Tazawa and Johansen (1987) and Ishimatsu *et al.* (1988).

Analyses and predictions

As depicted in Fig. 1, arterial O_2 levels in the presence of an R–L shunt depend not only on the degree of the R–L shunt but also on the O_2 levels in the systemic and pulmonary venous blood. Since several of these parameters are mutually dependent, we performed several different analyses in which different parameters were varied. A summary of the four analyses (I–IV) is presented in Table 1. In all these analyses, we have assumed a fixed oxygen dissociation curve (P_{50}=25 mmHg; n_H=2.5).

Analysis I: effects of altering $\dot{Q}_{pul}/\dot{Q}_{sys}$ at several levels of blood flow

Fig. 2 shows the effects of increasing the R–L shunt at absolute levels of $\dot{Q}_{pul}$ and $\dot{Q}_{sys}$ during normoxia and at a fixed level of ventilation. At any value of $\dot{Q}_{sys}$, an increase in the R–L shunt (by a reduction in $\dot{Q}_{pul}$) reduces both arterial and venous Hb O_2-saturation and the accompanying P_{O_2} values. As the rate of oxygen uptake ($\dot{V}_{O_2}$) was constant in this analysis, the O_2 content difference between arterial and venous blood increases in proportion to the reduction in systemic blood flow.

In all the following analyses, $\dot{Q}_{sys}$ was kept constant at 60 ml kg^{-1} min^{-1}. At least in turtles, this premise seems to be valid, whereas other animals may alter $\dot{Q}_{sys}$ (e.g. Lillywhite and Donald, 1989).

Analysis II: effects of varying blood O_2-binding capacity

At constant $\dot{V}_{O_2}$ and $\dot{Q}_{sys}$, a reduction in blood O_2-binding capacity lowers venous Hb O_2-saturation. In the absence of an R–L shunt, this reduction does not affect arterial blood gas levels, which in this case are entirely determined by lung gas composition. However, in the presence of an R–L shunt, a reduction in venous Hb O_2-saturation proportionally reduce arterial Hb O_2-saturation and, thus, arterial P_{O_2} (Pa_{O_2}). These

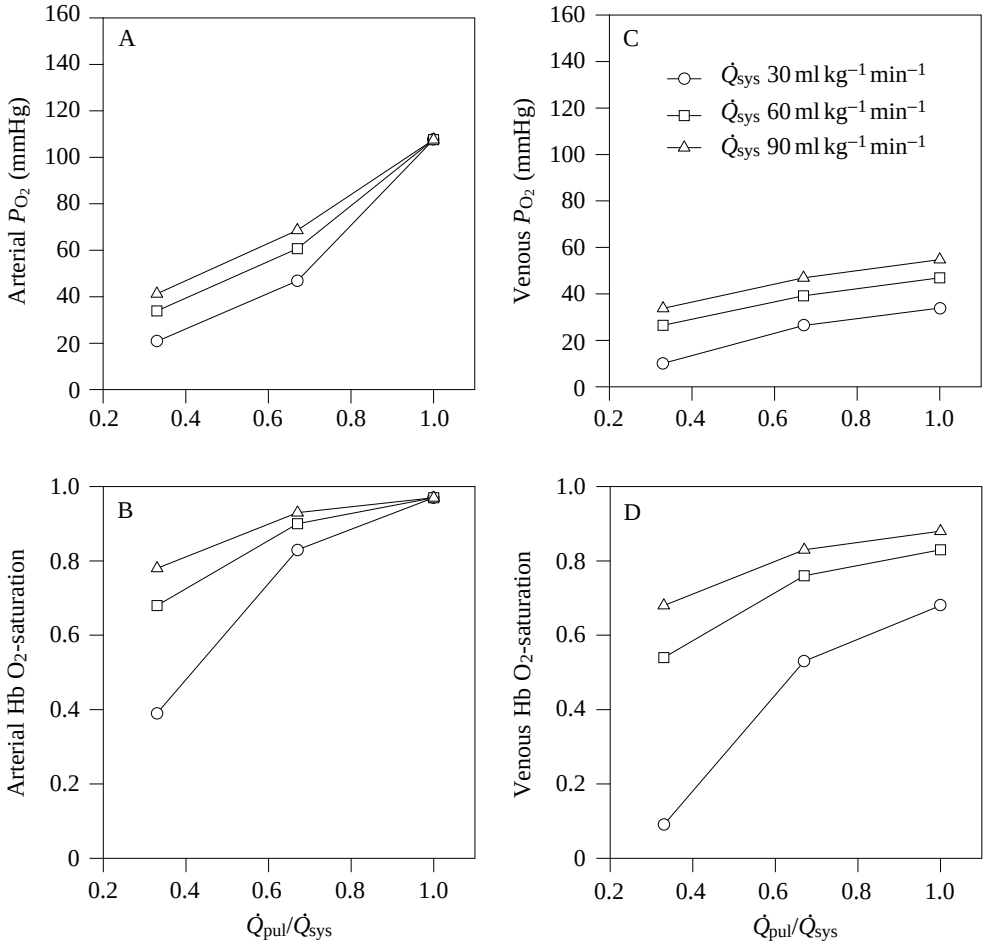


Fig. 2. The calculated effects of the R–L shunt on arterial P_{O_2} (A), arterial haemoglobin (Hb) O_2-saturation (B), venous P_{O_2} (C) and venous Hb O_2-saturation (D) at several levels of absolute blood flows (see text and Table 1 for further details and explanation). In Figs 2–5, values were obtained by substituting the values given in Table 1 into the relevant equations given in Fig. 1.

relationships are presented in Fig. 3 in the absence of an R–L shunt (circles), at a $\dot{Q}_{R-L}$ of 20 ml kg^{-1} min^{-1} (triangles) and at a $\dot{Q}_{R-L}$ of 40 ml kg^{-1} min^{-1} (squares) and at two rates of ventilation (20 and 100 ml kg^{-1} min^{-1}, represented by filled and open symbols, respectively). Note that an increased rate of ventilation has only a small effect on arterial Hb O_2-saturation and that only in the absence of an R–L shunt is the effect on arterial P_{O_2} sizable.

Analysis III: effects of increasing the rate of oxygen consumption

In this analysis, the effect of increasing metabolic rate was assessed at two rates of ventilation and three levels of R–L shunt (Table 1; Fig. 4). At constant ventilation, increasing $\dot{V}_{O_2}$ linearly decreased lung P_{O_2}, which, in the absence of an R–L shunt, resulted in a corresponding decrease in Pa_{O_2} (circles in Fig. 4A). In the presence of an R–L shunt, increasing $\dot{V}_{O_2}$

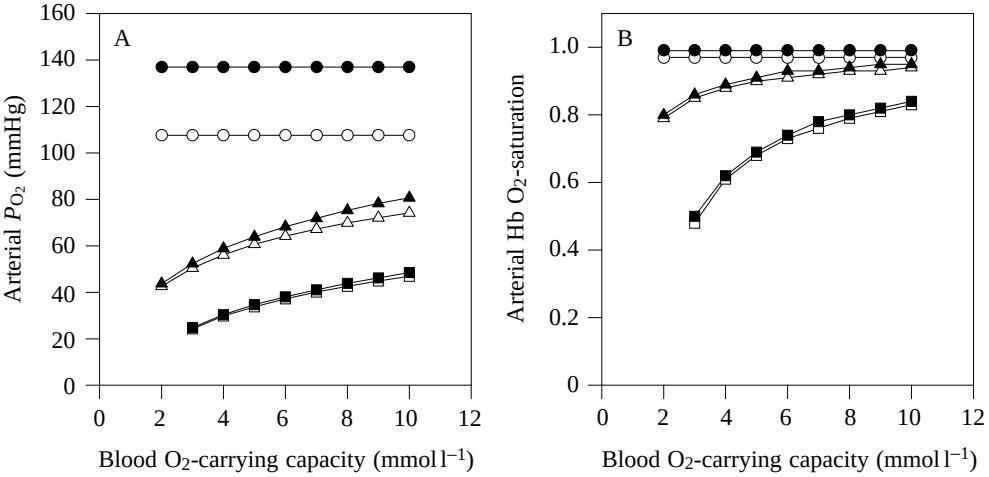


Fig. 3. The calculated effects of altering blood oxygen-carrying capacity on arterial P_{O_2} (A) and haemoglobin (Hb) O_2-saturation (B) in the absence and presence of an R–L shunt and at two rates of lung ventilation. Filled symbols represent high rates of ventilation (100 ml kg^{-1} min^{-1}), while open symbols depict low rates of ventilation (20 ml kg^{-1} min^{-1}). Circles represent no R–L shunt, triangles an R–L shunt of 33 % and squares an R–L shunt of 67 %. See text and Table 1 for further details and explanation.

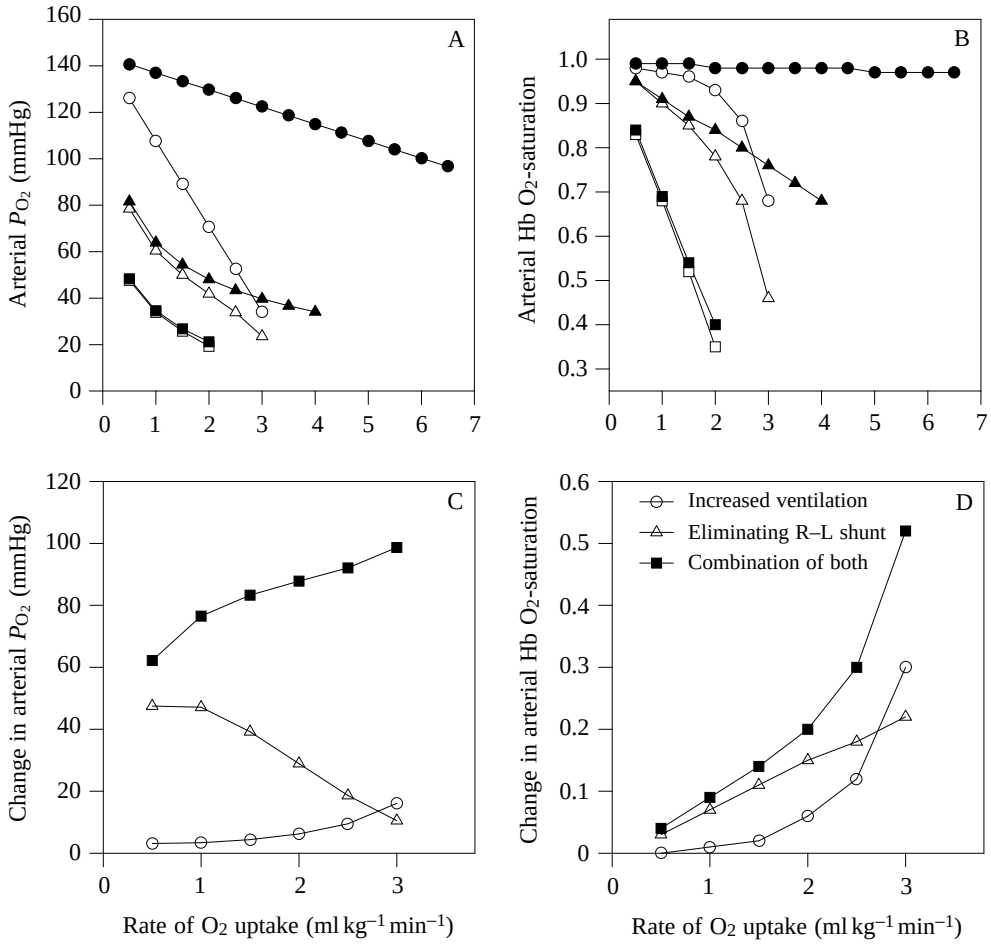


Fig. 4. The calculated effects of increasing the rate of oxygen uptake on arterial P_{O_2} (A) and arterial haemoglobin (Hb) O_2-saturation (B) in the absence and presence of an R–L shunt and at two rates of lung ventilation. Filled symbols represent high rates of ventilation (100 ml kg^{-1} min^{-1}), while open symbols depict low rates of ventilation (20 ml kg^{-1} min^{-1}). Circles represent no R–L shunt, triangles an R–L shunt of 33 % and squares an R–L shunt of 67 %. (C) The change in arterial P_{O_2} achieved by increasing ventilation (open circles), by eliminating the R–L shunt (open triangles) or by a combination of increasing ventilation and eliminating the R–L shunt (filled squares). Using identical symbols, D depicts the changes in arterial haemoglobin O_2-saturation. See text and Table 1 for further details and explanation.

decreased arterial O_2 levels because of the reduction in venous O_2 content. This relationship is depicted for two levels of R–L shunt (triangles and squares) and at two rates of ventilation (open and filled symbols) in Fig. 4A,B. Note that the highest levels of $\dot{V}_{O_2}$ can only be sustained if ventilation is high and the R–L shunt is eliminated.

The effects of increasing ventilation, eliminating the R–L shunt and the combination of both are presented in Fig. 4C,D, using a ventilation of 20 ml kg^{-1} min^{-1} and a $\dot{Q}_{pul}/\dot{Q}_{sys}$ of 40/60 as reference (open triangles in Fig. 4A,B). The increases in Pa_{O_2} and Hb O_2-saturation obtained by eliminating the R–L shunt, but maintaining ventilation constant, are depicted with open triangles, while the effects of increasing ventilation to 100 ml kg^{-1} min^{-1}, but maintaining the R–L shunt constant, are depicted with open circles (Fig. 4C,D). The filled squares represent the effect of both increasing ventilation and eliminating the R–L shunt. At low $\dot{V}_{O_2}$, increasing ventilation only modestly affected Pa_{O_2} and Hb O_2-saturation, while elimination of the R–L shunt had a pronounced effect on Pa_{O_2}. In contrast, at higher $\dot{V}_{O_2}$, an increase in ventilation had a larger effect on arterial oxygen levels than elimination of the R–L shunt. For any given condition, the combined effect of increasing ventilation and reducing the R–L shunt is larger than the effect of changing only ventilation or only the R–L shunt.

Analysis IV: effects of hypoxia

The effects of decreasing the inspired O_2 fraction (F_{IO_2}) were determined at two rates of ventilation and three levels of R–L shunt (Fig. 5). At constant ventilation, a reduction in F_{IO_2} linearly reduces P_{O_2} of pulmonary venous blood which, in the absence of an R–L shunt, is mirrored by a similar decrease in Pa_{O_2} (open and filled circles, respectively, in Fig. 5A,B). In the presence of an R–L shunt, this reduction in Pa_{O_2} is less pronounced (triangles and squares in Fig. 5A,B).

Fig. 5C,D shows the effects of increasing ventilation (open circles), eliminating the R–L shunt (open triangles) or a combination of both (filled squares) using a ventilation of 20 ml kg^{-1} min^{-1} and a $\dot{Q}_{pul}/\dot{Q}_{sys}$ of 40/60 as reference (open triangles in Fig. 5A,B). At normoxia (F_{IO_2}=0.21), the effect of increasing ventilation is virtually absent while the effect of eliminating the R–L shunt is maximal. As F_{IO_2} is lowered, the effect of increasing ventilation increases while the effect of eliminating the R–L shunt becomes progressively less pronounced. As in the previous analysis, the combined effect of changing both ventilation and the R–L shunt is always larger than that achieved by changing only one parameter.

Discussion

Our analyses emphasize that both ventilation and the R–L

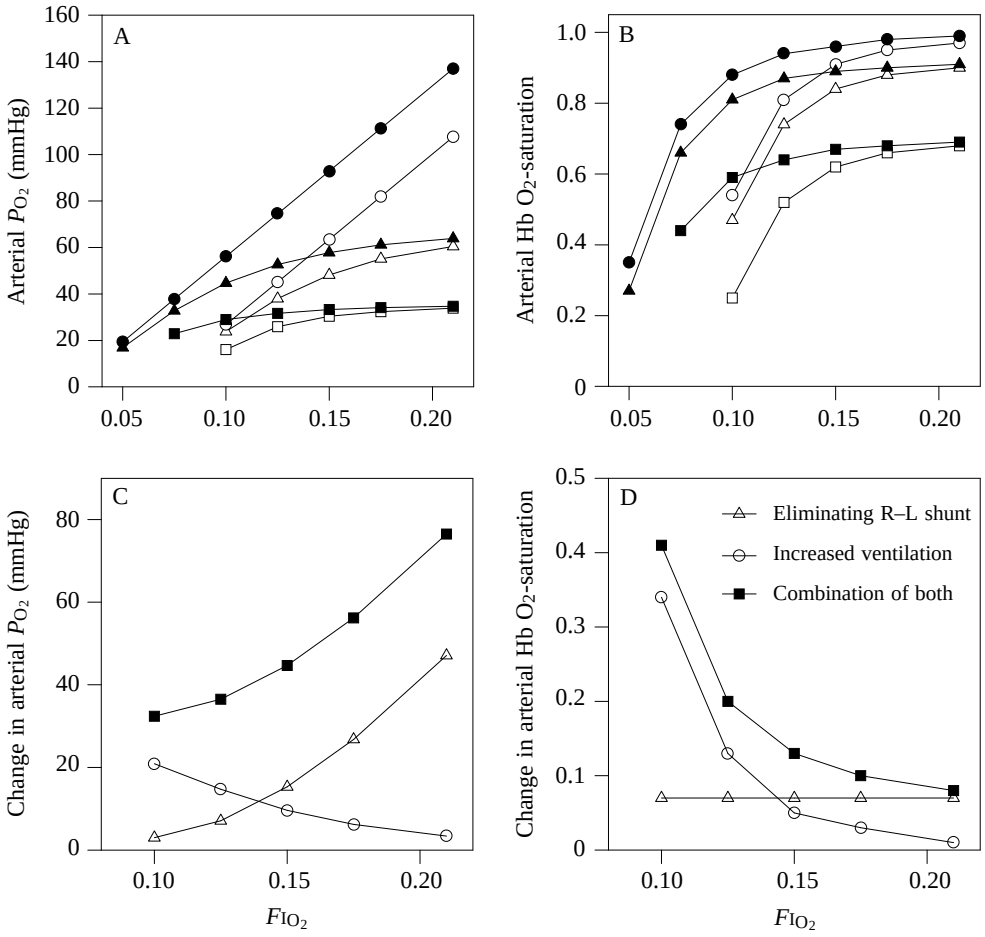


Fig. 5. The calculated effects of altering inspired oxygen fraction (F_{IO_2}) on arterial P_{O_2} (A) and arterial haemoglobin (Hb) O_2-saturation (B) in the absence and presence of an R–L shunt and at two rates of lung ventilation. Filled symbols represent high rates of ventilation (100 ml kg^{-1} min^{-1}), while open symbols depict low rates of ventilation (20 ml kg^{-1} min^{-1}). Circles represent no R–L shunt, triangles an R–L shunt of 33 % and squares an R–L shunt of 67 %. (C) The change in arterial P_{O_2} achieved by increasing ventilation (open circles), by eliminating the R–L shunt (open triangles) or by a combination of increasing ventilation and eliminating the R–L shunt (filled squares). Using identical symbols, D depicts the changes in arterial haemoglobin O_2-saturation. See text and Table 1 for further details and explanation.

shunt are important determinants of arterial O_2 levels. This observation is by no means novel, and the importance of the R–L shunt in determining arterial blood gas levels has long been recognized within both clinical and comparative physiology (see, for example, Rossoff *et al.* 1980; Wood, 1982, 1984). Nevertheless, most existing models for gas exchange in amphibians and reptiles have either ignored intracardiac shunts or assumed the R–L shunt to be fixed at a constant value (e.g. Boutilier and Shelton, 1986; Withers and Hillman, 1988). In addition, the principal focus of the present study was to quantify and compare the effects of altering ventilation and the R–L shunt within physiologically realistic limits. Such quantification has, at least to our knowledge, not been conducted prior to this study.

What determines the impact of changing the R–L shunt and ventilation on arterial O_2 levels?

This study demonstrates that the effect of changing ventilation and the R–L shunt on arterial O_2 levels varies with parameters such as inspired P_{O_2}, the rate of O_2 uptake and blood O_2-carrying capacity. These changes in the relative importance of altering ventilation and the cardiac R–L shunt in determining arterial blood gas levels are largely explained by the sigmoidal shape of the O_2 dissociation curve (ODC). If lung P_{O_2} is high relative to blood O_2 affinity, the O_2 levels of blood leaving the lung are positioned on the flat portion of the ODC and even a large increase in lung P_{O_2} (by increasing ventilation) has little effect on pulmonary venous O_2 content. If an R–L shunt is taking place, this implies that arterial O_2 content is affected only marginally, with a correspondingly small effect on arterial P_{O_2}. In contrast, if the O_2 levels of pulmonary venous blood are positioned on the step portion of the ODC, a small change in lung P_{O_2} affects pulmonary venous O_2 content markedly, and the resulting impact on arterial O_2 levels is accordingly more pronounced. This explains why, in the presence of an R–L shunt, an increase in ventilation from 20 to 100 ml kg^{-1} min^{-1} has only small effects on arterial O_2 levels at normoxia (Figs 3–5), whereas the impact of increasing ventilation is large when lung P_{O_2} is low. The converse argument explains the effect of the R–L shunt on arterial O_2 levels. As presented in Fig. 5D, the impact of eliminating the R–L shunt on arterial Hb O_2-saturation is independent of the level of hypoxia. Nevertheless, the corresponding change in Pa_{O_2} due to elimination of the R–L shunt is large (Fig. 5C) because the change in Hb O_2-saturation occurs on an increasingly steep portion of the ODC. The same arguments hold true in the analysis where the rate of oxygen uptake is altered (Fig. 4), although this situation is more complicated because the change in arterial Hb O_2-saturation for a given level of R–L shunt depends on the rate of oxygen uptake.

Because the effects of changing ventilation and/or the R–L shunt on arterial oxygen levels are determined by lung P_{O_2} relative to blood oxygen affinity, the most 'beneficial' cardiorespiratory response (in terms of improving O_2 transport) depends on the conditions of oxygen loading at the lungs. If lung P_{O_2} is high relative to blood O_2 affinity, a change in ventilation will have virtually no effect, while a decrease in the R–L shunt is relatively more powerful. Conversely, if lung P_{O_2} is low relative to blood O_2 affinity, the effect of changing ventilation is larger. Importantly, simultaneously increasing the ventilation and eliminating the R–L shunt always results in the largest increases in blood O_2 levels.

The R–L shunt invariably results in a decrease in arterial oxygen levels and, at a given $\dot{Q}_{sys}$, the R–L shunt therefore reduces the O_2 transport capacity of the cardiovascular system. As a result of this reduction, the presence of an R–L shunt reduces the maximum sustainable rate of O_2 consumption (Fig. 4) and reduces the tolerance to hypoxia (Fig. 5) and to reductions in blood O_2-carrying capacity (Fig. 3). Teleologically, it may therefore be argued that it is beneficial for gas exchange for the R–L shunt to be eliminated under circumstances where O_2 transport is challenged (hypoxia and hypoxaemia) or when metabolic rate is increased (during digestion and muscular exercise).

Is the R–L shunt eliminated in vivo *when oxygen transport is challenged?*

Detailed descriptions of cardiovascular responses under conditions other than rest are, unfortunately, scarce. In fact, not a single study has determined total systemic and pulmonary blood flows simultaneously during hypoxia, hypoxaemia or exercise in any animal possessing the possibility of cardiac shunting. This lack of simultaneous determinations of blood flows makes it difficult to assess the changes in intracardiac shunt in detail. Nevertheless, some studies have determined $\dot{Q}_{pul}$ in addition to blood flows in one or more systemic vessel, and the results from these studies seem to support our suggestion that the R–L shunt is eliminated, or at least reduced, during activity and hypoxia.

In the green sea turtle *Chelonia mydas*, $\dot{Q}_{pul}$ increases proportionately more than left aortic blood flow during swimming (West *et al.* 1992), which strongly suggests a reduction in the R–L shunt. Large increases in $\dot{Q}_{pul}$ compared with $\dot{Q}_{sys}$ and the development of a net L–R shunt during terrestrial exercise have also been noted by Burggren and Shelton (1979) for *Testudo graeca* and *Pseudemys scripta*, and large increases in $\dot{Q}_{pul}$ have been reported during movements under water in the turtle *Chelonia mydas* (Johansen *et al.* 1970). Detailed determinations of cardiac shunt patterns during different forms of activity are clearly needed, and studies on non-chelonian reptiles would be most welcome.

Compared with the considerable information on ventilatory responses to reductions in inspired oxygen levels, surprisingly few studies have investigated the effects of hypoxic hypoxia on central vascular blood flows. Nevertheless, in the aforementioned study on the green sea turtle, West *et al.* (1992) found a twofold increase in $\dot{Q}_{pul}$ at moderate hypoxia (10 % O_2), while left aortic blood flow increased by only 30 %. Similarly, Burggren *et al.* (1977) reported large increases in $\dot{Q}_{pul}$ during hypoxia in two other species of chelonians, but did not determine $\dot{Q}_{sys}$. In the Australian lungfish *Neoceratodus forsteri*, $\dot{Q}_{pul}$ increases two- to threefold during aquatic hypoxia (Fritsche *et al.* 1993) and, finally, hypoxia elicits increases in $\dot{Q}_{pul}$ in anaesthetized toads *Bufo marinus* (West and Burggren, 1984).

It has long been recognized that animals with low blood O_2-carrying capacity possesses high $\dot{Q}_{sys}$ (Lenfant *et al.* 1970), but the effects of reducing blood O_2-carrying capacity on cardiac shunting have received virtually no attention. Nevertheless, the possible role of arterial O_2 content as opposed to P_{O_2} as a regulated variable for ventilation has been discussed repeatedly (Wang *et al.* 1994). While this is an interesting question, our present analyses clearly show that an increased ventilation does not improve or safeguard O_2 transport in anaemic animals. Rather, an elimination of the R–L shunt and an increase in $\dot{Q}_{sys}$ are beneficial under these circumstances and future studies on the role of reduced blood O_2-carrying capacity should consequently address both the cardiovascular and the ventilatory events.

Are shunts actively controlled and do they participate in regulation of blood gases?

The potential role of the cardiovascular system in regulating arterial blood gas levels through changes in R–L shunting is undisputed. The existence of such potential, nevertheless, does not warrant the conclusion that the cardiovascular system is involved in this regulation. Chemoreceptors located in the arterial circulation and on the pulmocutaneous arches have been identified and recorded from several species of amphibians and reptiles. These chemoreceptors, like the peripheral chemoreceptors in mammals, increase their firing frequency during hypoxia (Ishii *et al.* 1985; Van Vliet and West, 1992). The afferent input from the receptors has mostly been studied from the viewpoint of ventilatory control, and its possible effects on the cardiovascular system are largely unknown.

Increases in $\dot{Q}_{pul}$ and the concomitant reductions in the R–L shunt are often associated with changes in ventilation. It can therefore be difficult to establish whether the cardiovascular performance changes independently or whether it is merely a function of the normal cardiorespiratory interaction. In several studies, Burggren and coworkers observed that turtles, while submerged and inactive, periodically increase $\dot{Q}_{pul}$ (Burggren and Shelton, 1979; Burggren, 1988; Burggren *et al.* 1989). It was therefore suggested that these transient perfusions of the lung serve to regulate arterial oxygenation, but it is imperative to emphasize that the involvement of arterial chemoreceptors and the appropriate afferent control of pulmonary perfusion remain to be demonstrated.

What do determinations of arterial blood gas levels reveal?

As discussed above and originally by Wood (1982, 1984),

arterial blood gas levels in the presence of an R–L shunt are dependent variables determined by all the parameters included in Fig. 1. As an example, $P_{a\mathrm{O}_2}$ increases with increased temperature in virtually all amphibians and reptiles, and this pattern is commonly interpreted as being primarily a result of decreased blood oxygen-affinity at elevated temperature (e.g. Glass *et al.* 1985). While these interpretations may provide an adequate explanation, alternatives exist, as illustrated by blood gas data from one of our own studies on toads (Branco *et al.* 1993). In these experiments, ventilation was stimulated by perfusing the central chemoreceptor with a mock cerebrospinal fluid solution of varying acidity while arterial blood gas levels were monitored. The increased ventilation resulted in a respiratory alkalosis (0.3 pH units at 35 °C) which, according to the interpretations above, should result in a decrease in $P_{a\mathrm{O}_2}$ because of the expected increase in blood O_2-affinity. In contrast to this 'expectation', $P_{a\mathrm{O}_2}$ increased significantly. This finding can be explained by a decrease in the R–L shunt, an increase in $\dot{Q}_{sys}$ and the resulting increase in mixed venous O_2 content, an increase in left atrial oxygenation level, a decrease in the rate of O_2 uptake or any possible combination of all these. Naturally, an evaluation of these possibilities requires that all, or at least most, of these parameters be determined. The point we would like stress is that, in the absence of detailed and simultaneous determinations of blood flows and blood gas levels from several central sites, interpretations of the causes of changing arterial blood gas levels are, at best, tenuous.

Conclusion and future directions for research on the control of arterial blood gas levels

The modelling of arterial O_2 levels in the present study unequivocally demonstrates the importance of intracardiac shunts for the determination of blood gas levels in lower vertebrates (and all embryonic vertebrates). It is, therefore, erroneous to view the control of arterial blood gas levels solely as a function of ventilation. Rather, arterial blood gas composition is the *combined* result of ventilation and cardiac shunts, and both the cardiovascular and the ventilatory systems must accordingly be evaluated if we aim to understand the control of arterial blood gas levels. Currently, only limited experimental data exist on cardiovascular performance in lower vertebrates and detailed studies on cardiac shunts are very scarce. Thus, although it is premature to conclude that the regulation of cardiac shunts is directly involved in the control of arterial blood gas levels, no data indicate the opposite. Clearly, future studies on lower vertebrates must combine measurements of cardiac shunts and ventilation.

T.W. was supported by a postdoctoral fellowship from the Carlsberg Foundation (Denmark) during the course of this study and J.W.H. received financial support from an NSF operating grant (IBN-9218936). We thank Dr S. C. Wood for critical comments on a previous version of this manuscript and Ole Wang for arithmetic advice.

References

BERGGREN, S. (1942) The oxygen deficit of arterial blood caused by nonventilating parts of the lung. *Acta. physiol. scand.* (Suppl.) **4**, 5–91.

BOUTILIER, R. G. AND SHELTON, G. (1986). Gas exchange, storage and transport in voluntarily diving *Xenopus laevis*. *J. exp. Biol*. **126**, 133–155.

BRANCO, L. G. S., GLASS, M. L., WANG, T. AND HOFFMANN, A. (1993). Temperature and central chemoreceptor drive to ventilation in toads (*Bufo marinus*). *Respir. Physiol.* **93**, 337–346.

BURGGREN, W. W. (1988). Cardiovascular responses to diving and their relation to lung and blood oxygen stores in vertebrates. *Can. J. Zool*. **66**, 20–28.

BURGGREN, W. W., GLASS, M. L. AND JOHANSEN, K. (1977). Pulmonary ventilation:perfusion relationships in terrestrial and aquatic chelonian reptiles. *Can. J. Zool*. **55**, 2024–2034.

BURGGREN, W. W. AND SHELTON, G. (1979). Gas exchange and transport during intermittent breathing in chelonian reptiles. *J. exp. Biol*. **82**, 75–92.

BURGGREN, W. W., SMITS, A. AND EVANS, B. (1989). Arterial O_2 homeostasis during diving in the turtle *Chelodina longicollis*. *Physiol. Zool*. **62**, 668–686.

FRITSCHE, R., AXELSSON, M., FRANKLIN, C. E., GRIGG, G. C., HOLMGREN, S. AND NILSSON, S. (1993). Respiratory and cardiovascular responses to hypoxia in the Australian lungfish, *Neoceratodus forsteri*. *Respir. Physiol*. **94**, 173–187.

GLASS, M. L., BOUTILIER, R. G. AND HEISLER, N. (1985). Effects of body temperature on respiration, blood gases and acid–base status in the turtle *Chrysemys picta bellii*. *J. exp. Biol*. **114**, 37–51.

HICKS, J. W. AND WOOD, S. C. (1989). Oxygen homeostasis in lower vertebrates: the impact of external and internal hypoxia. In *Comparative Pulmonary Physiology: Current Concepts* (ed. S. C. Wood), pp. 311–341. Marcel Dekker.

HOPKINS, S. R., WANG, T. AND HICKS, J. W. (1996). The effect of altering pulmonary blood flow on pulmonary gas exchange in the turtle *Trachemys* (*Pseudemys*) *scripta*. *J. exp. Biol.* **199**, 2207–2214.

ISHII, K., ISHII, K. AND KUSAKABE, T. (1985). Chemo- and baroreceptor innervation of the aortic trunk of the toad *Bufo vulgaris*. *Respir. Physiol*. **60**, 365–375.

ISHIMATSU, A., HICKS, J. W. AND HEISLER, N. (1988). Analysis of intracardiac shunting in the lizard, *Varanus niloticus*: a new model based on blood oxygen levels and microsphere distribution. *Respir. Physiol.* **71**, 83–100.

JOHANSEN, K., LENFANT, C. AND HANSON, D. (1970). Phylogenetic development of pulmonary circulation. *Fedn Proc. Fedn Am. Socs exp. Biol.* **29**, 1135–1140.

LENFANT, C., JOHANSEN, K. AND HANSON, D. (1970). Bimodal gas exchange and ventilation–perfusion relationship in lower vertebrates. *Fedn Proc. Fedn Am. Socs exp. Biol.* **29**, 1124–1129.

LILLYWHITE, H. B. AND DONALD, J. A. (1989). Pulmonary blood flow regulation in an aquatic snake. *Science* **245**, 293–295.

MILSOM, W. K. AND CHAN, P. (1986). The relationship between lung volume, respiratory drive and breathing pattern in the turtle, *Chrysemys picta*. *J. exp. Biol*. **120**, 233–247.

ROSSOFF, L., ZELDIN, R., HEW, E. AND ABERMAN, A. (1980). Changes in blood P_{50}: effects on oxygen delivery when arterial hypoxemia is due to shunting. *Chest* **77**, 142–146.

TAZAWA, H. AND JOHANSEN, K. (1987). Comparative model analysis of central shunts in vertebrate cardiovascular systems. *Comp. Biochem. Physiol*. **86**A, 595–607.

VAN VLIET, B. N. AND WEST, N. H. (1992). Functional characteristics of arterial chemoreceptors in an amphibian (*Bufo marinus*). *Respir. Physiol.* **88**, 113–127.

WANG, T., BRANCO, L. G. S. AND GLASS, M. L. (1994). Ventilatory responses to hypoxia in the toad *Bufo paracnemis* before and after decrease in HbO_2–capacity. *J. exp. Biol.* **186**, 1–8.

WANG, T. AND HICKS, J. W. (1996). Cardiorespiratory synchrony in turtles. *J. exp. Biol.* **199**, 1791–1800.

WANG, T., SMITS, A. W. AND BURGGREN, W. W. (1996). Lung function. In *Biology of Reptilia* (ed. T. Gaunt and C. Gans). Chicago: University of Chicago Press (in press).

WEST, N. H. AND BURGGREN, W. W. (1984). Factors influencing pulmonary and cutaneous arterial blood flow in the toad, *Bufo marinus*. *Am. J. Physiol.* **247**, R884–R894.

WEST, N. H., BUTLER, P. J. AND BEVAN, R. M. (1992). Pulmonary blood flow at rest and during swimming in the green turtle, *Chelonia mydas*. *Physiol. Zool.* **65**, 287–310.

WITHERS, P. C. AND HILLMAN, S. S. (1988). A steady-state model of maximal oxygen and carbon dioxide transport in anuran amphibians. *J. appl. Physiol.* **64**, 860–868.

WOOD, S. C. (1982). The effect of oxygen affinity on arterial P_{O_2} in animals with vascular shunts. *J. appl. Physiol.* **53**, 1360–1364.

WOOD, S. C. (1984). Cardiovascular shunts and oxygen transport in lower vertebrates. *Am. J. Physiol.* **247**, R3–R14.