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REVIEW

Unidirectional pulmonary airflow in vertebrates: a review of structure, function, and evolution

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Abstract Mechanisms explaining unidirectional pulmonary airflow in birds, a condition where lung gases flow in a consistent direction during both inspiration and expiration in some parts of the lung, were suggested as early as the first part of the twentieth century and unidirectional pulmonary airflow has been discovered recently in crocodilians and squamates. Our knowledge of the functional anatomy, fluid dynamics, and significance of this trait is reviewed. The preponderance of the data indicates that unidirectional airflow is maintained by means of convective inertia in inspiratory and expiratory aerodynamic valves in birds. The study of flow patterns in non-avian reptiles is just beginning, but inspiratory aerodynamic valving likely also plays an important role in controlling flow direction in these lungs. Although highly efficient counter and cross-current blood–gas exchange arrangements are possible in lungs with unidirectional airflow, very few experiments have investigated blood–gas exchange mechanisms in the bird lung and blood–gas arrangements in the lungs of non-avian reptiles are completely unknown. The presence of unidirectional airflow in non-volant ectotherms voids the traditional hypothesis that this trait evolved to supply the high aerobic demands of flight and endothermy, and there is a need for new scenarios in our understanding of lung evolution. The potential value of unidirectional pulmonary airflow for allowing economic lung gas mixing, facilitating lung gas washout, and providing for adequate gas exchange during hypoxic conditions is discussed.

Keywords Unidirectional airflow · Pulmonary · Diapsid · Lung · Cardiogenic

Introduction

The diverse pulmonary morphology of diapsids, including the specialized lungs of birds, has long fascinated scientists, but its function remains poorly understood. In contrast to the tidal motion of gases in the mammalian lung, which pause in alveolar cul-de-sacs before returning by the same path out of the trachea, pulmonary gases move in a consistent direction during both phases of ventilation in many of the regions of the avian lung, a condition termed unidirectional airflow. The history of anatomical and physiological investigation of airflow patterns in birds is rich, and well reviewed (King 1966; Bretz and Schmidt-Nielsen 1971; Scheid 1979; Maina and Africa 2000; Maina et al. 2009).

Traditionally, unidirectional airflow was associated with the energetic demands of flight and the use of compliant air sacs to effect ventilation in birds (for example, Maina 2006); however, the discovery of unidirectional pulmonary airflow in crocodilians, and two squamate lizards requires new thinking. Because these species do not ventilate the lung using avian-style air sacs, these structures are not necessary for unidirectional pulmonary airflow. Furthermore, unidirectional pulmonary airflow did not evolve associated with the energetic demands of flight, because it is present in non-volant ectotherms. Unidirectional airflow has been recorded in the following species of crocodilians, the American alligator *Alligator mississippiensis*, Nile crocodile *Crocodylus niloticus*, saltwater crocodile *Crocodylus porosus*, Morelet's crocodile *Crocodylus moreletti*, black caiman *Melanosuchus niger*, spectacled caiman *Caiman crocodilus*, and dwarf crocodile *Osteolaemus tetraspis* (Farmer 2015b),

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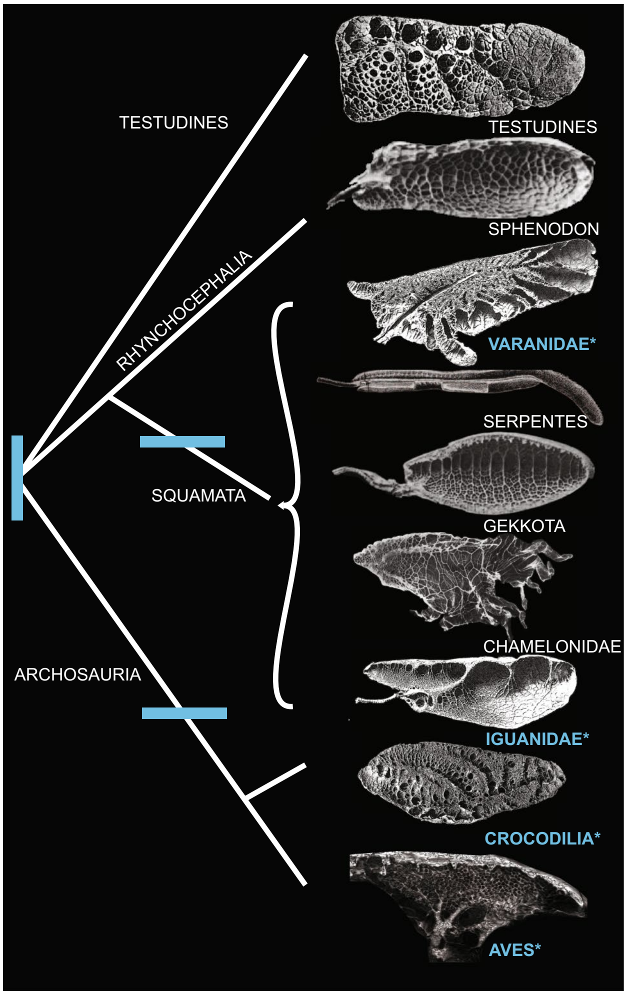


Fig. 1 Cladogram of reptiles summarizing the diversity of pulmonary morphology and the evolution of unidirectional airflow. Taxa where unidirectional flow has been documented are in *bold blue* and indicated with an *asterisk*. The presence of unidirectional airflow in squamates and archosaurs strongly suggests that this trait is basal to Diapsida (*vertical blue bar*), but it could also have evolved independently in squamates and archosaurs (*horizontal blue bars*) (Cieri et al. 2014). The determination of airflow patterns in Rhynchocephalia and Testudines is critical for determination of the evolutionary history of unidirectional pulmonary airflow. Lung images adapted from (Milani 1894a, b; Perry and Duncker 1978)

and two squamate lizards, the anguimorph savannah monitor *Varanus exanthematicus* (Schachner et al. 2013), and the green iguana *Iguana iguana* (Cieri et al. 2014) (Fig. 1). These recent discoveries implicate reconstruction of unidirectional airflow as a basal trait for diapsids, dating its evolution at least to the mid Permian period, and demand new hypotheses regarding its current and past physiological functions and evolution. This review will briefly summarize the history of the study of unidirectional airflow, the physical phenomena generating unidirectional airflow, and review the trait in an evolutionary context.

Although the complexity of lung structure in non-mammals has long been of interest to investigators, determination of airflow patterns has proceeded slowly. Because the mechanics of fluids are non-intuitive and the geometry of reptile and bird lungs is extremely complex, direct measurements or validated computational fluid dynamics models are necessary to understand how air flows in these organs. Inferences about airflow patterns based on lung anatomy alone have often turned out to be incorrect. For example, early workers hypothesized many incorrect patterns of flow in the bird lung, (Bretz and Schmidt-Nielsen 1971), and the remarkably bird-like lungs of crocodilians were first thought to have had tidal airflow (Bickler et al. 1985; Perry 1990).

Anatomy

In birds, where unidirectional airflow is by far the best studied, the gas exchange airways, termed avipulmosaccules (air capillaries), arise from tubular parabronchi (tertiary bronchi) (Maina 2015a). The parabronchi connect two groups of secondary bronchi: ventrobronchi, which branch from the primary bronchus near the hilum, and dorsobronchi, which branch at the distal end of the primary bronchus (Fig. 2). These air passages are ventilated by two groups of compliant air sacs. A caudal group of air sacs arises from the terminal end of the primary bronchi (the abdominal air sacs) and the laterobronchi (the caudal thoracic air sacs), a distal branch of the primary bronchus, and a cranial set of air sacs (the cervical, clavicular, and cranial thoracic sacs) branches from the ventrobronchi. During inspiration, the air sacs are expanded and air flows into the lungs through the primary bronchi, passing the more proximal openings to the ventrobronchi, and moves into the openings of the dorsobronchi and the caudal air sacs. Also during inspiration, air that was already in the parabronchi moves into the cranial air sacs. Upon commencement of exhalation, the air sacs are compressed, causing the air in the cranial sacs to move through the ventrobronchi and out into the trachea, and air stored in the caudal sacs courses into the dorsobronchi and parabronchi (Kuethe 1988).

Consequently, flow is unidirectional in much of the bird lung; air moves caudal to cranial in the dorsobronchi, parabronchi, and ventrobronchi (Hazelhoff's d–p–v system) during both phases of ventilation, as suggested by four lines of evidence (Table 1). First, the pattern of staining of the wall of the lung from inspired air laced with charcoal demonstrated to Hazelhoff (1943, English translation 1951) that flow must be unidirectional. Second, observations made with implantable flow probes (Fig. 3) record gas moving in the same direction during both phases of ventilation in dorsobronchi and ventrobronchi (Bretz and Schmidt-Nielsen

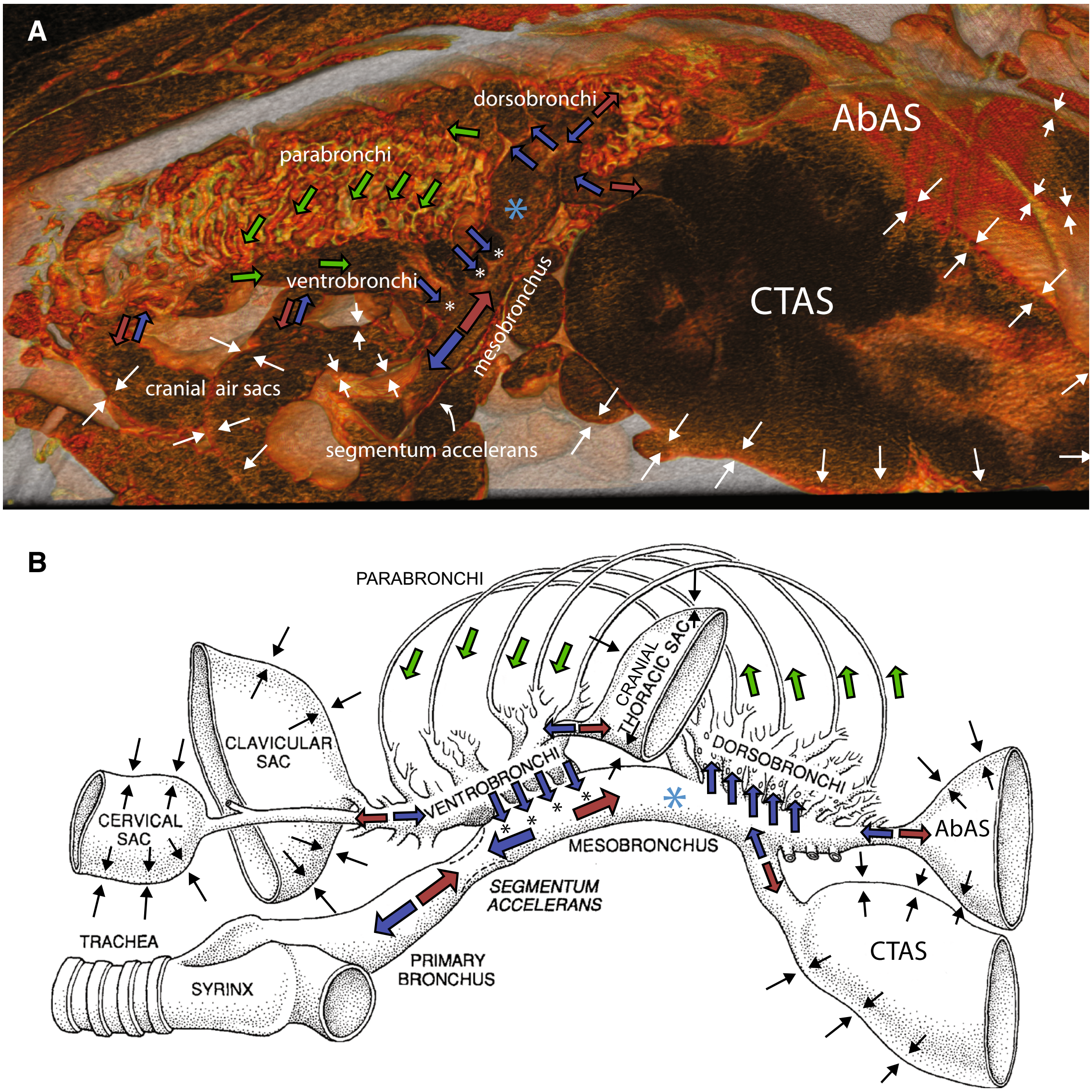


Fig. 2 Summary of unidirectional airflow in the avian lung. **a** Oblique computed tomography section of a parrot, craniomedial at *left*, caudolateral at *right*. **b** Diagram of avian pulmonary anatomy. Air flows through the largely isovolumetric lung as the air sacs are expanded and contracted (*small white arrows*). *Red arrows* depict flow during inspiration, *blue* during expiration, and *green* flow during both phases of ventilation. The inspiratory aerodynamic valves are *white* and *black asterisks*, and the expiratory aerodynamic valve is a *blue asterisk*. The cranial air sacs are ventilated through the ventrobronchi, and the abdominal (AbAS) air sacs are ventilated through the mesobronchus (primary bronchus). Diagram in **b** is modified from Wang et al. (1992)

1971; Scheid and Piiper 1971; Brackenbury 1971; Scheid et al. 1972). Third, gas analysis techniques (Bretz and Schmidt-Nielsen 1972; Powell et al. 1981) suggest that almost no inspired gas enters the cranial sacs without passing through the lung first, that almost all of the air from the caudal sacs moves through the parabronchi during expiration, and that almost no gas moves caudally through the parabronchi during inspiration. Finally, recent computational fluid dynamics and piecewise linear mathematical models yield unidirectional flow in simplified avian lung anatomies (Urushikubo et al. 2013; Harvey and Ben-Tal 2016). Two non-intuitive features of the established pattern of flow deserve investigation: inspired air bypasses the entrances to the ventrobronchi, termed the inspiratory valve, and air flowing from the caudal sacs during expiration enters the d–p–v system rather than taking the more direct path out of animal through the primary bronchus, termed the expiratory valve (Butler et al. 1988) (Fig. 2).

Three lines of evidence suggest that inspiratory and expiratory valving is more aerodynamic than mechanical in nature, as first suggested by Dotterweich (1936). First, no obvious valving structures such as flaps are present in the

Table 1 Summary of studies providing evidence for unidirectional pulmonary airflow

Animal	Method	Condition	Authors	Year
Crows, chickens, pigeons, herons	Study of charcoal deposits injected with air into trachea and air sacs	Dead	Hazelhoff	1943
Ducks	Thermistor probes implanted in the primary bronchus and a dorsobronchus	Anesthetized, anesthetized and panting	Bretz and Schmidt-Nielsen	1971
Ducks	Thermistor probe implanted in a dorsobronchus	Awake	Scheid and Piiper	1971
Geese	Manometric flow probe	Anesthetized	Brackenbury	1971
Ducks	Dual heated thermistors in dorsobronchi, ventrobronchi, and mesobronchus	Dead, before and after removal of the air sacs	Scheid, Slama, Piiper	1972
Ducks	Mass spectrometer analysis of CO_2 levels in dorsobronchi, ventrobronchi, and mesobronchus	Anesthetized	Powell, Geiser, Gratz, and Scheid	1981
Alligators	Visualization of microspheres, dual thermistor probes implanted into the cervical ventral bronchus and dorsal bronchus	Dead and excised lungs, awake and spontaneously breathing	Farmer and Sanders	2010
Savannah monitors	Visualization of microspheres, dual thermistor probes implanted into lateral bronchi	Dead and excised lungs, awake and spontaneously breathing	Schachner, Cieri, Butler, and Farmer	2013
Generic bird	Computational fluid dynamics model of simplified anatomy	Digital	Urushikubo, Nakamura, Hirahara	2013
Green iguanas	Visualization of inhaled aerosolized lipid, computational fluid dynamics simulations, dual thermistor probes	Excised lungs, awake and spontaneously breathing, digital	Cieri, Craven, Schachner, and Farmer	2014
Various crocodilians	Dual thermistor probes and visualization of microspheres and aerosolized lipid	Excised lungs, awake and spontaneously breathing	Farmer	2015b
Generic bird	Piecewise linear mathematical model	Digital	Harvey and Ben-Tal	2016

avian lung anatomy (Maina 2006). Second, patterns of unidirectional flow are largely preserved in fixed lungs (Hazelhoff 1943; Scheid et al. 1972) and static models (Wang et al. 1988). Finally, a cineradiographic study by Jones et al. (1981) found no significant change in the size of ostia connecting secondary to primary bronchi during the resting respiratory cycle in a lightly anesthetized duck, ruling out the action of sphincters.

The actual pattern of flow through bird lungs may vary from this generic model in a number of ways. During thermistor studies by Bretz and Schmidt-Nielsen (1971) and Mackelprang and Goller (2013), some inspired tracer gas was detected in the cranial sacs after the first inspiration with the tracer. This gas could have reached the cranial sacs through a partial failure of the inspiratory aerodynamic valve, an unknown anatomical connection between the cranial sacs and the primary bronchus, or by traveling through the d–p–v system in a single breath. Additionally, some caudal air sac gas may be expired through the mesobronchus, bypassing the d–p–v system, during phonation (Mackelprang and Goller 2013) or panting (Bretz and Schmidt-Nielsen 1971), representing an attenuation of the aerodynamic expiratory valve. The attenuation of valving effectiveness could be the passive result of changes in aerodynamics under certain conditions, or be the result of active changes in bronchial smooth muscle tone, as detailed below.

In the lungs of crocodilians, which change volume to effect inspiration and expiration, air moves in a pattern similar to that seen in birds (Farmer and Sanders 2010; Farmer 2015b). Air appears to flow tidally through the primary bronchus, unidirectionally craniad through the dorsobronchi, and caudad through the ventrobronchi (Fig. 4b). Small tubular parabronchi connect the dorsobronchi to the ventrobronchi (Sanders and Farmer 2012), and conduct air unidirectionally towards the ventrobronchi (Farmer 2015a). In *V. exanthematicus*, a long intrapulmonary bronchus is perforated with ostia giving rise to lateral and medial bronchi and terminates in a caudal sac-like bronchus. Air flows caudad in the primary bronchus upon inspiration and craniad across thin, perforated walls between adjacent laterobronchi during inspiration and expiration (Fig. 2c) (Schachner et al. 2013). The lungs of *I. iguana* are cavernous organs consisting of cranial and caudal chambers without an enclosed intrapulmonary primary bronchus. In both chambers, a high-speed jet of air flows caudad along the lateral aspect of the lung upon inspiration, but flow along the medial wall is craniad during both phases of ventilation (Fig. 4d, e) (Cieri et al. 2014).

Inspiratory aerodynamic valving

The inertia hypothesis for the inspiratory aerodynamic valve posits that if the inspired air has sufficient convective

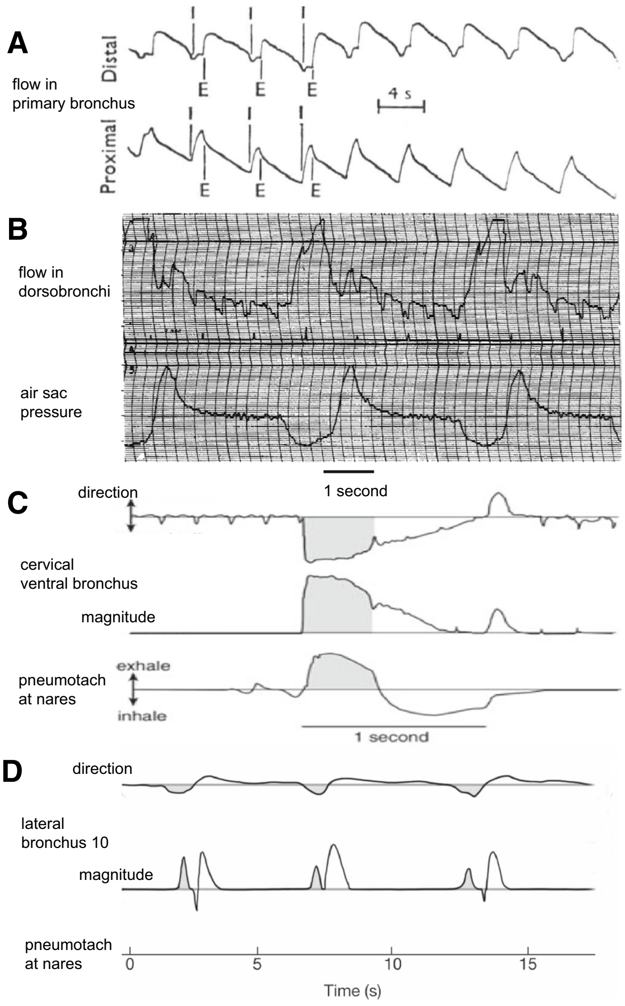


Fig. 3 Airflow tracings in lungs. **a** Traces from two thermistors in the primary bronchus of an unanesthetized duck (Bretz and Schmidt-Nielsen 1971) showing tidal flow in this region of the lung. During inspiration, the proximal thermistor receives the brunt of the airflow, and shows a strong peak in the signal. During expiration, when the flow direction is reversed, the distal thermistor receives more flow, resulting in a bigger signal. **b** Manometric flow probe recording (*top*) showing unidirectional airflow in the dorsobronchus of a goose and air sac pressure (Brackenbury 1972). Flow is unidirectional because it continues in the same direction during both expansion (negative air sac pressure; inspiration) and contraction (positive air sac pressure expiration) of the air sac. **c** Dual heated thermistor flow probe recording of unidirectional airflow in the cervical ventral bronchus of an American alligator. The *top* trace shows flow direction (calculated by which thermistor is heated first), the *middle* trace shows magnitude (as both thermistors are heated), and the *bottom* shows pneumotography recorded from breathing at the nares (Farmer and Sanders 2010). **d** Dual heated thermistor flow probe recording of unidirectional airflow in the tenth lateral bronchus of a savannah monitor lizard showing direction (*top*), magnitude (*middle*), and flow at the nares (*bottom*) (Schachner et al. 2013)

momentum, which is the product of gas density and velocity squared (Butler et al. 1988), it will continue past the openings of the ventrobronchi instead of making a sharp turn to enter them, overwhelming the influence of the possible pressure drop towards the ventrobronchi (Butler et al. 1988). This model is supported by studies that demonstrate increased flow of N_2 tracer gas into the ventrobronchi when inspiratory velocity or gas density is sufficiently reduced in mechanically ventilated geese (Banzett et al. 1987) and similar results from lung models (Wang et al. 1988). Indeed, these studied demonstrated that the valve is more effective than predicted analytically, when the velocity at the critical juncture was calculated from the local cross sectional area (Banzett et al. 1987, 1991; Butler et al. 1988).

The increased valve efficacy observed experimentally compared to initial analytical predictions is explained by a narrowing in the primary bronchus that accelerates the inspired air and was not included in the initial calculations of Butler et al. (1988). Further measurements detected a pressure drop indicating a narrowing of the primary bronchus (Banzett et al. 1991) just upstream from the inspiratory valve, which accelerates the inspired air sufficiently to predict from theory the nearly perfect valving observed experimentally. This constriction, termed the segmentum accelerans, which has been identified in *Gallus gallus domesticus*, *Columba livia*, and *Anser anser* (Maina and Africa 2000), consists of smooth muscle, and has been shown to dilate in the presence of heightened CO_2 levels in *A. anser* (Wang et al. 1992). Active constriction or dilation of the segmentum accelerans could control the efficacy of the inspiratory valve (Maina and Africa 2000; Wang et al. 1992). A microscopic study of the primary bronchus in *G. domesticus* and *C. livia* (Maina and Africa 2000) revealed epithelial swellings that may also act to constrict the air passage and accelerate inspired air. Morphology downstream from the inspiratory valve site also contributes to aerodynamic valving: a computational fluid dynamics simulation of a simplified ostrich trachea, and primary bronchus yielded complete inspiratory valving only when pathways representing the dorsobronchi were included (Maina et al. 2009).

Inspiratory aerodynamic valving in crocodilian lungs probably functions similarly, as inspired air largely bypasses the ostium to the cervical ventral bronchus. This bronchus then makes an immediate hairpin turn cranially (Farmer and Sanders 2010; Sanders and Farmer 2012). Experiments that measure valving efficacy while manipulating the convective inertia of inspired air by changing density or velocity are needed to assess the degree to which the inspiratory aerodynamic valve functions similarly across Archosauria. Although the direction of airflow in much of the lung in *V. exanthematicus* remains obscure, convective inertia likely contributes to air bypassing many of the laterobronchi and ventrobronchi as it courses caudad through the intrapulmonary bronchus.

Although there is no enclosed intrapulmonary bronchus in *I. iguana*, thin streams of inspired air continue largely laterocaudad and do not change direction until the caudal aspect of each chamber, causing craniad flow to continue along the medial walls. The presence of a qualitatively similar inspiratory flow pattern in a (comparatively) anatomically simple lung that does not have an enclosed intrapulmonary bronchus suggests that complex internal lung structure may have more to do with increasing internal, vascular surface area than directing overall airflow patterns. The influence of gross pulmonary morphology on airflow patterns clearly deserves much further study.

Expiratory aerodynamic valving

The avian expiratory aerodynamic valve, which directs air from the caudal sacs into the dorsobronchi and not back out the primary bronchus during expiration, has been the subject of comparatively much less study and remains poorly understood. Hazelhoff (1943) first suggested that the expiratory flow from the ventrobronchi, which must turn a sharp corner to flow out the trachea, creates a region of high pressure in the mesobronchus, which induces flow from the caudal sacs into the dorsobronchi instead. The role of this phenomenon could be assessed by pressure measurements made between the openings to the ventrobronchi and dorsobronchi during expiration. This hypothesis is supported by a study by Kuethe (1988) in which physical models where the ostia of the caudal sacs were not directed towards the dorsobronchial openings failed to produce expiratory valving.

Another hypothesized mechanism is that the convective inertia of flow out of the laterobronchi and caudal thoracic air sac, which are pointed directly at the dorsobronchial openings, entrains the air flowing from the larger abdominal air sac (Butler et al. 1988; Kuethe 1988). The convective inertial jet from the laterobronchi would be enhanced by narrowed laterobronchial openings. An experimental test of this hypothesis, however, found valve effectiveness to be sensitive only to flow velocity and not density (Brown et al. 1995). In this experiment, complete expiratory valving only occurred during flow rates exceeding resting ventilation, leading the authors to speculate that dynamic compression of the mesobronchus, which would depend on gas velocity but not density, could contribute to aerodynamic valving. Other studies, however, found incomplete expiratory valving during normal resting ventilation suggesting that the expiratory aerodynamic valve does not function perfectly during quiet ventilation in nature (Piiper et al. 1970; Powell et al. 1981). Expiratory aerodynamic valving in non-avian reptiles remains unexplored.

Recently, complete inspiratory and expiratory aerodynamic valving in birds was mathematically modeled by ascribing time-varying resistances to the mesobronchus, and ventrobronchi while holding the parabronchial and dorsobronchial resistances constant (Harvey and Ben-Tal 2016). In the model, inspiratory aerodynamic valving was simulated by setting mesobronchial to be less than ventrobronchial resistance and multiplying by the ratio of cranial to caudal air sac compliances during inspiration. Expiratory aerodynamic valving was simulated by setting mesobronchial resistance to be less than ventrobronchial during expiration. If inspiratory aerodynamic valving was modeled without expiratory valving (mesobronchial and ventrobronchial resistances set to be equal during expiration), or vice versa, the simulated flow through the parabronchi remained unidirectionally caudo-cranial. Without both valves included in the model, however, some air bypassed the d–p–v system.

The expiratory aerodynamic valve may be under active control, whereby birds could benefit by shunting gas away from the d–p–v system. The openings to secondary bronchi in bird lungs contain rings of smooth muscle (King and Cowie 1969) that contract spontaneously, but do not seem to be sensitive to intrapulmonary gas concentrations (Barnas and Mather 1978). Birds undergo less of a respiratory alkalosis than mammals during respiratory cooling (Calder and Schmidt-Nielsen 1966; Schmidt-Nielsen et al. 1969), show craniad flow in the mesobronchus during expiration while calling (Mackelprang and Goller 2013) and panting (Bretz and Schmidt-Nielsen 1971), and may actively shunt gas away from the d–p–v system during thermoregulatory hyperventilation or hyperventilation due to vocalization to avoid respiratory alkalosis (Calder and Schmidt-Nielson 1966 and references within).

Air sacs

Data from a radiographic study indicate that the duck lung is largely isovolumetric, changing in volume by less than 1 % during normal respiration (Jones et al. 1985). Thus, ventilation is caused mostly by air sac volume changes during normal respiration, but the effect of air sacs on the direction of pulmonary airflow warrants further investigation. Brackenbury (1979) found that the direction of dorsobronchial flow was consistently craniad when air was pushed or pulled through the cranial (interclavicular and cranial thoracic) sacs and into or out of the trachea, but that parabronchial airflow was tidal in the dorsobronchi upon ventilation through the caudal (caudal thoracic and abdominal) sacs. An elegant set of experiments that occluded combinations of the cranial thoracic, caudal thoracic, and abdominal air sacs in domestic fowl (Brackenbury 1989; Brackenbury and Amaku 1990a, b) detected no changes in total ventilation compared with control animals, though the birds compensated a loss of tidal volume with great increases in respiratory frequency. When the cranial thoracic, caudal thoracic, and abdominal air sacs were all occluded, the partial pressure of oxygen (P_{O_2}) was reduced and the partial pressure of carbon dioxide (P_{CO_2}) elevated in the clavicular sac (Brackenbury and Amaku 1990a). Brackenbury and Amaku (1990a) concluded that the inspiratory aerodynamic valve functioned well under these conditions, as fresh air was not reaching the clavicular sac. However, because tidal volume was reduced, the percentage of minute ventilation comprising dead space volume presumably increased, and could have contributed to the measured increase in clavicular P_{CO_2}. None of these studies completely rule out a valving function for the interclavicular sac, or an expiratory valving function for the caudal sacs.

Pressure oscillations between the air sacs and the atmosphere clearly lead to ventilation, but pressure differences among air sacs may also regulate the timing of parabronchial airflow. During ventilation, the same pattern of pressure variations occur in each air sac, but the magnitude of these variations differ such that there is greater pressure in the cranial than caudal sacs during inspiration, and greater pressure in the caudal sacs than cranial sacs during expiration (Brackenbury 1971). In a fixed duck lung, Kuethe (1988) manipulated the pressure gradient between caudal and cranial air sacs and found that higher gradients caused more parabronchial flow during exhalation than during inspiration, and lower gradients caused more flow during inspiration. Using a computational fluid dynamics model of a simplified avian airway, Urushikubo et al. (2013) found parabronchial airflow to be unidirectional when air sac compliances were such that the air sac pressures fluctuated in phase. In a recent abstract model, Harvey and Ben-Tal (2016) showed that the timing of parabronchial airflow was controlled by relative air sac compliance – the parabronchi were mainly ventilated during inspiration if the caudal sacs were made to be less compliant than the cranial sacs, and vice versa. These insights may indicate a functional role for differences in compliance between air sacs in the same animal (Scheid et al. 1974) and between species (Powell 2015).

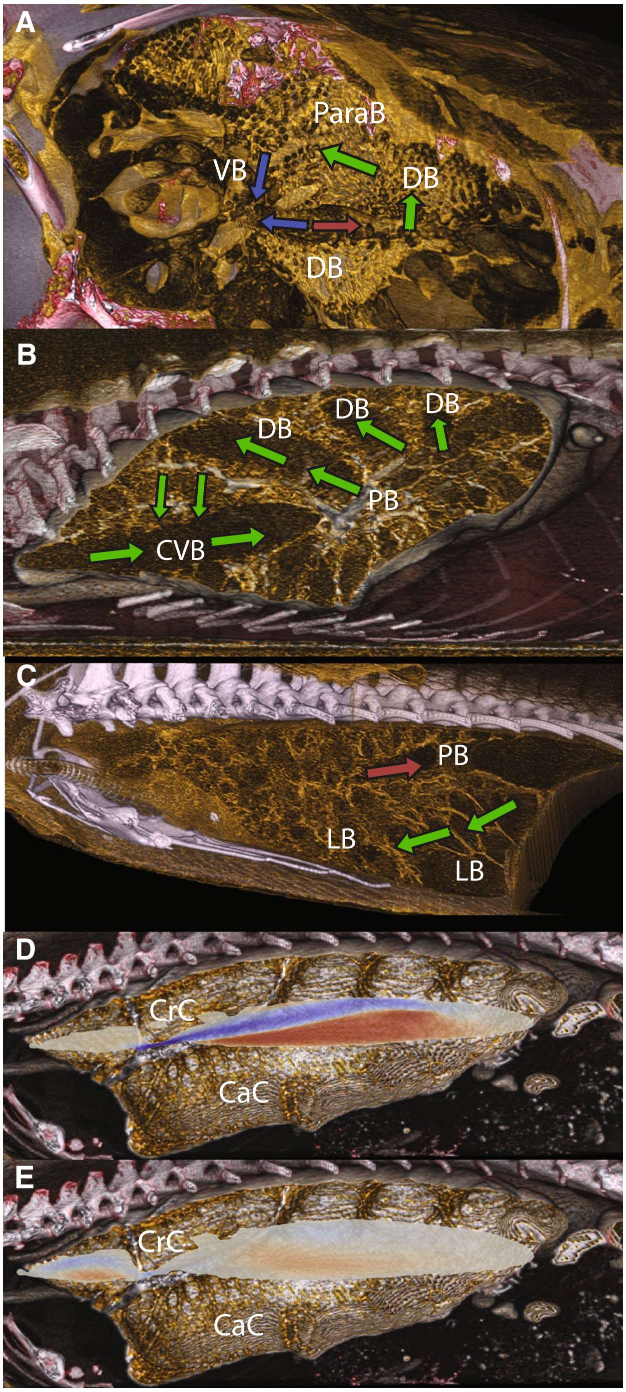
Study of the mechanisms driving unidirectional pulmonary airflow in other species is in its infancy, but a few points can be made. First, no other groups with unidirectional lungs have an avian-style air sac system, indicating that although this style of air sacs may or may not be important to flow direction in birds, they are not necessary for unidirectional airflow in lungs in general. Second, the arrangement of the proximal portion of the primary bronchus and the topography of secondary bronchi in crocodilians is strikingly similar to the avian condition (Farmer and Sanders 2010; Sanders and Farmer 2012; Farmer 2015a), suggesting that the topography of the conducting airways favoring aerodynamic valving as seen in birds is highly conserved and may be critical for unidirectional ventilation. Unidirectional flow in the specialized lungs of varanid lizards (Schachner et al. 2013) and simple lungs of iguanas (Cieri et al. 2014; Farmer 2015c) suggest that the mechanisms leading to basic unidirectional flow patterns may arise from a high-speed jet from inspiration, and that the elaborate anatomy and ventilatory mechanisms seen in other taxa are secondary adaptations with other functions besides directing the overall direction of lung gases.

Functional significance

Traditionally, the bird lung has been associated with an increased efficiency over the broncho-alveolar lung, and, although this is not generally explicitly defined in most studies it is implicated to be synonymous with extraction [oxygen consumed per product of the fraction of oxygen in inspired gas and volume of gas ventilated $= \dot{V}_{O_2}/(F_{I_{O_2}} \times \dot{V}_E)$]. It is thought that great extraction in birds is mandated by the heightened aerobic requirements of powered flight. However, few measurements of extraction on flying animals have been made. Instead, much has been made of broad differences in oxygen extraction rate between birds and mammals at rest, and these comparisons should be interpreted with caution because data were recorded under different experimental conditions, and they may not reveal true differences in exchange capacities between different lung designs. Extraction tends to fall rapidly if animals pant, for example (Tucker 1968). Further caution is warranted because most birds studied fly, while most mammals studied do not, and flight itself may be a confounding factor. Finally, the data offer only mixed support for greater extraction in birds compared to mammals. For example, a medium-sized bat, *Phyllostomus hastatus*, has a resting extraction of 0.29, which is greater than that of the average non-passerine bird of the same body mass, which is 0.21 (Thomas et al. 1984). During flight the budgerigar (*Melopsittacus undulatus*) and *P. hastatus* have the same extraction fraction (about 0.21) while flying at similar speeds (8 m $\sec^{-1}$ for the bat, 9.7 m $\sec^{-1}$ for *M. undulatus*) at similar temperatures in wind tunnels (Tucker 1968; Thomas et al. 1984). It is true that, theoretically, respiratory systems based on unidirectional airflow, if coupled with counter or cross-current gas exchange, have greater capacities for extraction than those that are ventilated tidally; however, empirical data are mainly consistent with this hypothesis under conditions of inspired hypoxia (Scheid and Piiper 1970).

Extraction aside, bat and bird lungs perform similarly in terms of rates of oxygen uptake during exercise, except during hypoxia (Maina 2000; Figueroa et al. 2007). For example, at sea level, a pigeon (*C. livia*) flying at 10 m/s

Fig. 4 Summary of known unidirectional pulmonary airflow patterns ▸ mapped onto CT images. *Green arrows* indicate airflow during both phases of ventilation, *blue arrows* indicate flow during expiration, and *red arrows* indicate flow during inspiration. **a** In the idealized bird lung, air moves unidirectionally through the dorsobronchi (DB), into the parabronchi (ParaB), and back to the tidal intrapulmonary bronchus (PB) through the ventrobronchi (VB) as a result of the air sacs being compressed and expanded. **b** In the lungs of crocodilians (*A. mississippiensis* pictured), air moves unidirectionally craniad in the dorsobronchi and caudad in the ventrobronchi, flowing between these chambers through the gas exchange tissue. Flow appears to be tidal in a portion of the primary bronchus (not pictured). **c** In *V. exanthematicus*, a monitor lizard, air moves unidirectionally craniad between laterobronchi after coursing caudad through the intrapulmonary bronchus during inspiration. **d** and **e** In the bicameral lungs of *I. iguana*, air moves largely unidirectionally in both chambers, craniad (*warm colors*) in the ventromedial portion and caudad (*cool colors*) in the dorsolateral portion as predicted by a CFD model (*pictured*), from (Cieri et al. 2014). *PB* primary bronchus, *DB* dorsobronchus, *CVB* cervical ventrobronchus, *LB* laterobronchus, *CrC* cranial chamber, *CaC* caudal chamber



consumes 200 mL O_2^{-1} min^{-1} kg^{-1} (Butler et al. 1977) while a bat *(P. hastatus)* flying at 8 m/s burns 286 mL O_2^{-1} min^{-1} kg^{-1} (Thomas et al. 1984). However, bats appear less tolerant of inspired hypoxia during exercise, while many birds can exercise at great altitudes. For example, bar headed geese ran on an inclined treadmill with inspired oxygen tension of 48 torr (Fedde et al. 1989) but when Thomas et al. (1995) subjected the grey-headed flying fox (*Pteropus poliocephalus*) at rest to hypoxia they found the bats could not tolerate an inspired oxygen partial pressure (P_{IO_2}) lower than 30 torr without homeostatic failure. Because the demands of resting metabolism were barely met when P_{IO_2} was 30 torr, sustained aerobic exercise at this level of hypoxia seems unlikely.

It is thus reasonable to propose that the generalized, broncho-alveolar lung is an inferior gas exchanger compared to the generalized, unidirectional parabronchial lung at low inspired oxygen concentrations (Farmer 2010). This may be due to the significantly thinner blood–gas barrier possible in parabronchial lung: the harmonic mean thickness of the blood–gas barrier is roughly 2.5 times smaller in birds compared to non-flying mammals, and about 1.5 times smaller compared to bats in birds (Maina 2000; Dubach 1981). Mammals achieve similar oxygen extraction rates at normoxia with a comparatively much greater lung surface area compared to those of birds (Maina 2000).

Another possible advantage to an unidirectionally ventilated lung design is that it could permit an optimized blood–gas exchange pattern. Counter-current and cross-current exchange patterns facilitate a reversal of the blood gas differential, such that pulmonary venous blood could have a higher oxygen and lower carbon dioxide tension than in exhaled air. However, gas exchange efficiency may also be limited by ventilation/perfusion heterogeneity, which may vary with changes in ventilation or blood flow during conditions such as exercise or exposure to hypoxia (Powell 2015).

A seminal study distinguished cross-current from counter-current gas exchange by reversing parabronchial airflow direction while monitoring blood–gas and inspired/expired gas tensions in anesthetized domestic ducks, and detected no change in the blood–air oxygen differentials before and after the reversal (Scheid and Piiper 1972), leading the experimenters to conclude that the avian blood–gas exchange is in fact a cross-current arrangement (Fig. 5). Although a counter-current exchange could theoretically be more efficient, the actual cross-current arrangement still effected a substantial (6 mmHg) reversal in the CO_2 differential (Scheid and Piiper 1972). On the other hand, other experiments (see Table 2) measured no reversal of the CO_2 differential in anesthetized fowl breathing room air (Piiper et al. 1970), but a small reversal in awake fowl breathing hypercarbic gas (Scheid and Piiper 1970). Reversals of the CO_2 gradient have also been observed in mammals (reviewed in Scheid and Piiper 1980), and can be caused by other factors, such as the slow equilibration of $CO_2/HCO_3^-/H^+$ in blood, or the Haldane effect (reviewed in Farmer 2015a). Furthermore, the preponderance of the studies do not show a reversed differential for oxygen tension (Table 2), which would be expected from counter and cross-current gas exchangers.

In the cross-current model for the avian lung, blood–gas exchangers run between intraparabronchial arteries and veins, which branch serially along interparabronchial vessels running parallel to the parabronchi (Fig. 5). Within the walls of the parabronchi, however, unabsorbed oxygen presumably moves outward through the atria and avipulmosaccules (air capillaries) while the deoxygenated blood moves centripetally through the avipulmoreteformis (blood capillaries), such that the blood–gas arrangement may be considered counter-current at this scale (Maina 2015b). Gas exchange, and air or blood flow direction at the scale of the avipulmoreteformes and avipulmosaccules have never been measured, and more research in this area is needed. Arrangement of the blood and air streams in non-avian unidirectional lungs is unknown, and investigation in this area is required to inform our understanding of the importance of this aspect of unidirectional pulmonary airflow in lung evolution.

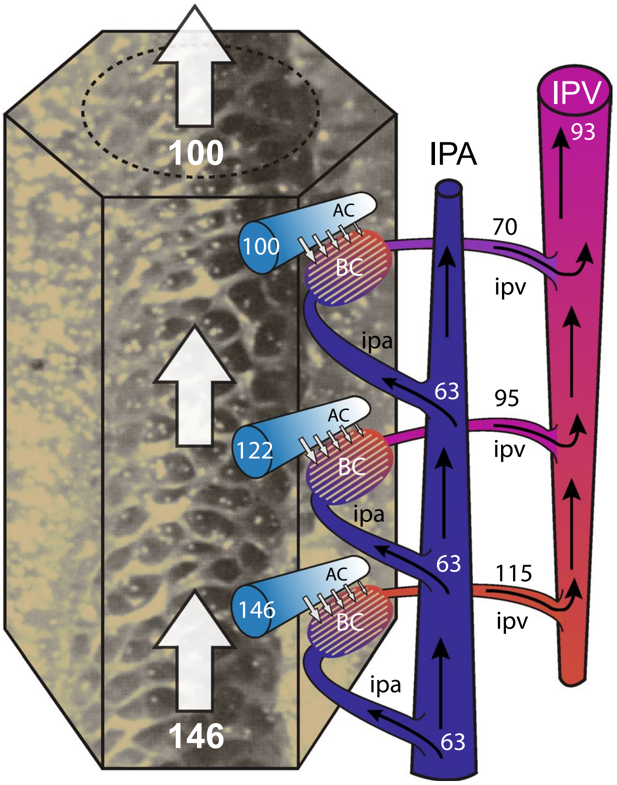


Fig. 5 The cross-current flow hypothesis for the avian lung theoretically can, but generally does not, cause a reversal in the difference between gas tensions in blood and air. Air travels unidirectionally through the central lumen (*dashed circle*) of the parabronchi (*white arrows*) and blood–gas exchange occurs in a series of anastomosing networks of air capillaries (avipulmosaccules) (AC), and blood capillaries (avipulmoreteformis) (BC), which connect to the interparabronchial veins (IPV) and arteries (IPA) through serially arranged intraparabronchial veins (ipv) and arteries (ipa). The airflow in the parabronchial lumen and blood flow in the intrapulmonary vessels are thus arranged perpendicularly, resulting in high rates of oxygen extraction because, since the blood in each ipa is fully de-oxygenated, the local blood–gas oxygen gradient is always maximized. Because oxygen diffuses from the ACs into the BCs, there is net oxygen flux distally (*blue arrows*), which may establish a local counter-current blood–gas arrangement as blood is flowing centripetally (Maina 2015b). Lung air and blood oxygen partial pressures (P_{O_2}) from a domestic duck, (*Anas sp.*) from Jones and Holeton (1972) are indicated in torr (ipv values are hypothetical). Because gas tensions in each ipv are averaged in the IPV, gas exchange differences are largely independent of parabronchial flow direction

Evolution

The presence of unidirectional airflow in squamates and crocodilians, as well as birds, indicates that the basic design of such lungs is probably quite ancient, and its evolution was not linked to the aerobic demands of flight. New hypotheses for the evolution of different lung designs in synapsids and diapsids that take into account the life-history traits of early members of these clades are necessary. Our understanding of the evolution of pulmonary morphology and airflow patterns in diapsids is significantly hampered by lack of data: more studies documenting the non-intuitive airflow patterns in lepidosaurs are required. Current knowledge of airflow patterns is summarized in this review (Figs. 2, 4). Although the few species that have been documented have very different airflow patterns, the main jet of inspired air completely bypasses a section of the lung in each animal studied, and the airflow in that region is opposed to the direction of inspired air. Therefore, each lung studied has an inspiratory aerodynamic valve, which takes the form of an unconfined inspiratory jet in the cavernous iguana lung.

One possible advantage to unidirectional ventilation among ectotherms is that it may allow minute ventilatory motions, such as cardiogenic oscillations, to contribute

Table 2 Experiments and observations on pulmonary blood–air gas differences in birds

Species	Inspired gas	Condition	O_2 differential	CO_2 differential	References
Gallus domesticus	Hypoxic and hypercarbic	Awake	Reversed	Reversed	Scheid and Piiper 1970
Gallus domesticus	Room air	Awake	Normal	Normal	Piiper et al. 1970
	Room air	Artificial ventilation	Normal	Normal	
Duck	Room Air	Anesthetized	Normal	Reversed	Scheid and Piiper 1972
		Anesthetized, parabronchial airflow reversed	Normal	Reversed	
Duck	Room Air	Awake	Normal	Normal	Jones and Holeton 1972
Cairina moschata and *Anas sp.*	Hypoxic		Normal	Normal	
Gallus domesticus	Room air	Anesthetized and spontaneously breathing	N/A	Reversed	Davies and Dutton 1975
	Hypercarbic		N/A	Reversed	
Gallus domesticus	Hypoxic/hypercarbic	Anesthetized and artificially ventilated	N/A	Reversed	Meyer et al. 1976
		Rebreathing	N/A	No difference	
Gallus domesticus (male)	Room air	Anesthetized hyperventilation, normal ventilation, hypoventilation	N/A	No difference	Paré et al. 2013

Normally, expired air has a higher oxygen and lower carbon dioxide concentration than blood leaving the lungs. When the blood-gas differential is reversed, the pulmonary venous blood has higher oxygen and lower carbon dioxide concentrations than the expired air

meaningfully to lung function. Unidirectional airflow due to the tugging motion of the heart on the lung surface, termed cardiogenic flow, has been documented in the lungs of alligators (Farmer 2010, 2015b) and birds (Brackenbury 1979), and slow rhythmic oscillations of the inner lung surface, probably the result of pulmonary blood flow or smooth muscle contraction have been observed in the tegu (Scheid et al. 1977), gecko (Perry and Duncker 1978), and *Chrysemys* turtles (Carlson and Luckhardt 1920).

Because inspired air theoretically moves in the unidirectional lung through chambers sequentially, instead of mixing evenly with the residual lung volume as occurs in the broncho-alveolar lung, small ventilatory motions may be more physiologically meaningful in unidirectional compared to tidal lungs. Making the most of airflow resulting from cardiogenic or other small oscillations could result in energy savings, reduced evaporative water and heat loss, and increased crypsis over animals employing greater ventilatory activity (Farmer 2015a). Furthermore, the additive result of many small breaths or several, extremely slow ventilations may effect significant ventilation of the unidirectional lung. Similarly, the unidirectional design may also facilitate a greater per-breath washout than the tidal lung. Ectotherms exhibit an intermittent breathing pattern (Milsom 1991), which provides adequate lung convection in a unidirectional lung, and may have cryptic advantages. Furthermore, among aquatic ectotherms, greater washout would mean less time needed for ventilation at the surface. This idea is consistent with the observation that the most common number of breaths taken by American alligators between periods of apnea is 2 (Hicks and White 1992) and unidirectional washout of the respiratory system is hypothesized to occur in about two breaths (Farmer 2015a), whereas resting humpback whales (*Megaptera novaeangeliae*) take an average of 12.9 breaths during breathing bouts (Dolphin 1987), although it is possible that their elevated myoglobin storage can partially explain this difference. The increased efficacy of the unidirectional avian-style pulmonary system at low inspired oxygen concentrations suggests that it may have evolved during a geologic period of relative hypoxia (Farmer 2010). This hypothesis, reviewed thoroughly by Farmer (2015a), posits that selection for a relatively thin blood–gas barrier in archosaurs, led to the evolution of a heterogenous lung of constant volume and relatively compliant ventilatory regions. This may explain the great florescence of archosaurs, unique to the hypoxic Mesozoic, into most of the aerobically demanding functional niches at the expense of synapsids.

In conclusion, the authors wish to emphasize the following main points. First, the functional significance of unidirectional flow remains an exciting mystery to be solved. Contrary to conventional wisdom, the oxygen and carbon dioxide tension in pulmonary venous blood is not significantly improved in the cross-current lung compared to the broncho-alveolar lung, except during inspired hypoxia. Also, the unidirectional lung lends itself to little, if any, improvement in extraction compared to the tidal bronchial-alveolar lung at normal levels of inspired oxygen for resting animals, and even during exercise the data on extraction are mixed. The decreased blood–gas barrier thickness made possible by an isovolumetric lung, however, might provide physiological advantages when the inspired gas is relatively hypoxic. Second, although the fluid dynamics responsible for unidirectional flow in sauropsid lungs are not fully understood, aerodynamic valving plays an important role in directing flow in all species studied. Third, because unidirectional pulmonary airflow is present in animals with and without avian-style air sacs, the presence of these air sacs in any extant or extinct species cannot be used to draw inferences regarding the design of that animal's lung. Finally, unidirectional lungs may be advantageous to ectotherms because minute movements of lung gases may additively result in ventilation and gas exchange. Unidirectional pulmonary airflow is likely a primitive trait for reptiles, and notions that it evolved to facilitate endothermy or flight should be discarded. Further study may shed light on evolutionary pressures leading to this remarkable trait.

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