

CLASSICS

Early insights into the evolution of respiratory and cardiovascular physiology in vertebrates

RESPIRATION PHYSIOLOGY



Graham Scott discusses the impact of two classic *Respiration Physiology* papers by Kjell Johansen and Claude Lenfant, published in 1972, investigating the evolutionary continuum between water breathers and air breathers.

The fascinating diversity in respiratory and circulatory systems across vertebrates is well known to many biologists. Most undergraduate students of animal physiology are familiar with the variety of structures involved in gas exchange in different vertebrate groups, from the water-breathing gills of fish and amphibians to the many distinct forms of air-breathing lungs of terrestrial vertebrates. Equally familiar are the differences in heart structure across vertebrates – from the two-chambered heart of fish to the four-chambered hearts with fully divided ventricles that arose both in mammals and in crocodilians and birds – as well as the corresponding differences in their vascular systems. How these structures work has been a subject of immense interest to many of the great comparative physiologists. Kjell Johansen and Claude Lenfant in particular published a significant number of influential papers throughout the 1960s and 1970s on the structural and functional changes in gas exchange and transport associated with the evolution of air breathing. Their work emphasized the evolutionary continuum that exists between water breathers and air breathers, and it contributed to defining comparative physiology as a discipline that seeks to understand the diversity in how

physiological systems work (Prosser, 1991; Hochachka and Somero, 2002).

Johansen published two companion papers in *Respiration Physiology* in 1972 – collaborating with Lenfant on one of the publications – that together synthesized over a decade of work on the respiratory and cardiovascular physiology of a variety of vertebrate species. By reviewing the findings that they and several others (including Pierre Dejours, Hermann Rahn, Dave Randall and Graham Shelton) had made on distinct species of water- and/or air-breathers, they were able to examine the broad patterns of evolutionary variation that exists across vertebrates. The first paper examined how the transition from water breathing to air breathing affected ventilation and O₂ transport by the blood (Lenfant and Johansen, 1972), and the second examined how blood flow to gas-exchange organs is regulated across vertebrates (Johansen, 1972). They made several insights into the forces underlying physiological diversity.

In their joint paper, Lenfant and Johansen examined the relationships between the type of medium an organism breathes (water and/or air), its ventilatory and circulatory flow rates and O₂ transport by its blood (Lenfant and Johansen, 1972). The evolution of air breathing was clearly associated with a shift from water-breathing gills to various forms of air-breathing lungs, but it was not well appreciated at the time that air breathing had arisen repeatedly in vertebrates and that many ‘transitional’ forms exist among the air-breathing fish and amphibians that use both modes of gas exchange (Graham, 1997). Lenfant and Johansen showed how the gradual progression from strict water breathing, to transitional forms, to strict air breathing was associated with decreases in the breathing flow rates that are needed to support a given level of metabolism, in large part because the ≥ 20 -times greater abundance of O₂ in air than in water reduces the ventilation rates needed to move a given amount of O₂. This suggested that although metabolic rates are much higher in the air-breathing

endotherms (mammals and birds) than in ectotherms, the ventilatory flows needed to support those high metabolic rates are proportionally lower.

In addition, Lenfant and Johansen also explained how the transition to air breathing was associated with changes in blood physiology (Lenfant and Johansen, 1972). The effectiveness of the gas-exchange surfaces at loading O₂ into the blood increased with this transition, due both to the differences in O₂ content between air and water and to the evolved differences in the exchange capacity of the gas exchanger. High exchange capacity evolved in parallel in mammals, which possess tidally ventilated alveolar lungs, and in birds, which possess unique parabronchial lungs that create a cross-current (perpendicular) arrangement between air flow and blood flow (Piiper and Scheid, 1975). As a result, haemoglobin’s affinity for O₂ does not need to be as high in air breathers as in water breathers to fully saturate the blood. Lenfant and Johansen described how the transition to air breathing was associated with a decrease in haemoglobin’s affinity for O₂, as reflected by a rightward shift in the O₂ equilibrium curve, and suggested that this could have arisen to enhance O₂ unloading at the peripheral tissues. This is because a rightward shift in the O₂ equilibrium curve would increase the difference in O₂ pressure between the blood travelling through capillaries and the tissues, and thus increase the rate of O₂ diffusion into the tissue (Scott and Milsom, 2006). Lenfant and Johansen also described how the haemoglobin content of the blood increased with the transition to air breathing, possibly to increase the capacity for O₂ transport and to support the higher metabolic rates that are generally observed in air breathers (particularly mammals and birds) compared with water breathers.

In the second paper, published by Johansen alone in the same issue, he examined the underlying mechanisms controlling blood flow to gas-exchange organs across vertebrates (Johansen, 1972). It was well known at the time that vertebrates evolved from having

Classics is an occasional column, featuring historic publications from the literature. These articles, written by modern experts in the field, discuss each classic paper’s impact on the field of biology and their own work.

two-chambered hearts, such as exist in fish, to having three- and four-chambered hearts, as exist in the tetrapods. In the two-chambered heart of water-breathing fish, blood is pumped only once before it travels through the gills, is oxygenated, and then travels through the systemic tissues before returning again to the heart. In the fully divided four-chambered hearts of mammals and birds, blood is pumped by the right side of the heart through the lungs and then it returns to the left side of the heart where it is pumped again to the systemic tissues. Between these extremes are the amphibians – whose hearts have three chambers so that blood returning from the lungs and systemic tissues can mix in a single ventricle – and the non-crocodilian reptiles – whose hearts possess four chambers but can exhibit mixing of blood between the right and left ventricles. Therefore, with the evolutionary progression from two- to four-chambered hearts arose the ability to separate the circuit of blood flowing to the gas-exchange surfaces from that flowing to the systemic tissues and to drive these separate flows with separate pumps (i.e. the right and left sides of the heart, respectively).

Despite this variation across vertebrates, Johansen showed that there is a strong relationship between O_2 consumption rate and the flow rate of blood through the gas exchanger across fish, reptiles and mammals. He further explored this observation, first in vertebrates in which the gas-exchange and systemic circulations are arranged sequentially (such as those found in strictly water-breathing fish, mammals and birds). In these groups, blood flow through the gas exchanger is equal to the cardiac output, which is dictated by the blood pressures driving flow and the vascular resistances opposing flow. Because the two-chambered heart of fish pumps blood through the gills before it travels to the systemic circulation, branchial vascular resistance must remain low in order to minimize the drop in blood pressure across the gills to ensure there is enough pressure remaining to drive blood flow through the systemic tissues – a constraint that does not exist in mammals and birds by virtue of their divided right and left ventricles that pump blood separately through the pulmonary gas-exchange and systemic circulations. However, Johansen highlighted the alternative challenge

posed by the high blood-flow rates needed to support the high metabolic rates of mammals and birds – systemic vascular beds must be supported by high blood pressures in order to promote capillary filtration, but gas exchangers must be perfused by low blood pressures in order to minimize oedema and tissue damage. Correspondingly, Johansen showed that vascular resistance of the gas exchange circuit is dramatically reduced in mammals and birds compared with other vertebrates. In doing so, pulmonary blood pressures can remain low even at the high blood-flow rates in these groups. Furthermore, although cardiac output and systemic arterial blood pressures are much higher in birds and mammals than in other vertebrates, the metabolic work needed to pump a given amount of blood is minimized by an overall decrease in vascular resistance of both systemic and gas-exchange circuits.

Next, Johansen explored the regulation of blood flow through the gas exchangers of air-breathing fish, amphibians and reptiles (Johansen, 1972). These groups are more complex because blood that leaves a heart ventricle (e.g. the single ventricle of air-breathing fish and amphibians, or the left ventricle of non-crocodilian reptiles) can flow into either the systemic circuit or the gas-exchange circuit, which are therefore said to operate in parallel. Perfusion (the process of delivering blood) of the air-breathing organ can be metered to adjust to O_2 availability inside the organ by regulating the proportion of the blood flowing from the heart that enters the gas-exchange circuit. In amphibians and some reptiles, this can result in a right–left shunt (shunting of deoxygenated blood from the systemic circulation away from the lungs and directly back into the systemic circulation) or a left–right shunt (shunting of blood returning from the gas-exchange circuit back through the lungs for a second pass through the exchanger). Johansen explained that the shunts are regulated largely by changing the relative resistances to flow in the gas-exchange and systemic circuits. For example, in bowfin, a primitive air-breathing fish, changes in vascular resistance are entirely responsible for regulating the relative flows to the primitive lung and the systemic circulation, because a similar blood pressure drives perfusion of each vascular bed. Changes in vascular resistance are also important for regulating the relative flows to the lungs

and systemic tissues in amphibians and reptiles, but the additional capacity to regulate flows by creating a pressure differential between the pulmonary and systemic circuits becomes more pronounced from amphibians to reptiles to birds and mammals. Therefore, the overall decline in the vascular resistance of gas-exchange circuits in the transition from fish to amphibians to reptiles to mammals and birds is overlaid by a dramatic capacity to regulate this resistance in vertebrates with a pronounced capacity to shunt.

Kjell Johansen and Claude Lenfant pioneered our appreciation of the evolution of respiratory and circulatory systems across vertebrates. As stated by Bill Milsom – a former graduate student of Kjell Johansen – from the University of British Columbia (UBC), Canada: ‘Amongst the greatest strengths of these two was their ability to see subtleties in the data lost to most and to synthesize the data into a cohesive story’. The work of Johansen and Lenfant also had a tremendous impact on a broad spectrum of comparative physiologists, including Chris Wood at UBC. Wood was about a year into his PhD with Graham Shelton at the University of East Anglia, UK, when the papers by Johansen and Lenfant were published, and Wood recollects Shelton telling him in his always-understated fashion, ‘I think you should take a look at these papers by Johansen. He publishes far too much, but sometimes he has interesting ideas.’ The paper made a strong impression on Wood and influenced much of his early work on the regulation of gill blood flow in fish (Wood, 1974). Many others have followed in the footsteps of Johansen and Lenfant, and our appreciation of the comparative and evolutionary physiology of function, control and molecular underpinnings of respiratory and circulatory systems continues to grow (e.g. Milsom, 2010; Scott, 2011; Mairbaurl and Weber, 2012; Burggren et al., 2014; Randall et al., 2014, to name just a few examples). Comparative physiologists owe a great debt of gratitude to Johansen and Lenfant for the insight and ground-breaking research that laid the foundations for many exciting advances in our discipline, then and now.

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