Natural Climbers: Insights from Avian Physiology at High Altitude

Nicole Parr,¹ Matt Wilkes,² and Lucy Alice Hawkes³

Abstract

Parr, Nicole, Matt Wilkes, and Lucy Alice Hawkes. Natural climbers: insights from avian physiology at high altitude. *High Alt Med Biol.* 20:427–437, 2019.—High altitudes are physiologically challenging: the hypobaric hypoxia, cold, and increased ultraviolet radiation mean humans ascending to high altitude faster than they acclimatize risk life-threatening illnesses. Despite such challenges, birds can thrive at high altitudes and some even complete metabolically costly migrations across the world's highest mountain ranges. We outline the aspects of avian anatomy and physiology that confer advantages at each level of the oxygen transport cascade and compare them with those of human and nonhuman mammals. We also discuss additional adaptations that have been described for high-altitude specialist species of birds and how these are mirrored in high-altitude adapted mammals.

Keywords: acclimatization; birds; comparative; hypoxia; physiology

Introduction

HIGH-ALTITUDE ENVIRONMENTS present a range of challenges to life, including cold, dehydration, increased exposure to solar radiation, malnutrition, and hypobaric hypoxia (Bouverot, 1985). Above 2000 m altitude, humans may begin to suffer from high-altitude illnesses (reviewed in Bärtsch and Swenson, 2013). Despite this, elite human mountaineers may spend years (and tens of thousands of dollars) preparing for ascents of the world's highest peaks (Fig. 1).

To survive in high-altitude environments, animals require a suite of physiological adjustments along the oxygen transport cascade to maintain an adequate supply of oxygen to respiring organs and tissues (Fig. 2). These adjustments may take any, or all, of three forms. First, those that are fixed as the result of generations of adaptation (the process of selection pressures increasing the expression of genes that alter physical or behavioral features at a species or population level) (Willmer et al., 2005). For example, some human populations have adapted to life at high altitude, and these adaptations vary with respect to geographical origin (e.g., Tibetan vs. Andean people, see reviews elsewhere; Beall, 2007; Azad et al., 2017). Second, short-term phenotypically plastic responses (referred to as “acute hypoxia responses” from now on), which are almost instantaneous responses to hypoxia exposure, but are usually temporary and reversible

(Piersma and van Gils, 2011). Third, longer-term plastic responses following continued exposure, also known as “acclimatization,” which can last for days to years. Acclimatization enables humans native to low altitudes to transiently visit extremely high altitudes, for example, to climb the world's 14 mountains over 8000 m without the use of supplementary oxygen (Wolfel et al., 1991).

Birds, regardless of the altitude at which they live, display essential features of their anatomy and physiology that put them at an advantage compared to mammals in hypoxic environments at high altitude. This was demonstrated by Tucker (1968) using a very simple hypoxic chamber experiment. After rapid ascent to a simulated altitude of 6100 m, a mouse was rendered comatose, while a house sparrow was able to maintain flight in a wind tunnel. The features of avian physiology that enabled this high tolerance for hypoxia are not necessarily the direct result of evolutionary adaptations following chronic hypoxic selection pressures, rather they likely evolved due to the high oxygen demands required to sustain flight. Flight is a very costly form of locomotion in terms of oxygen demand, requiring some 10–12 times resting metabolic rate (Bishop et al., 2002). Powered flight also evolved in bats, which (like birds) are also capable of high rates of oxygen consumption ($\dot{V}O_2$) (reviewed in Maina, 2000). High $\dot{V}O_2$ may therefore serve as a preadaptation for tolerating hypoxia in birds, and to some degree bats (Thomas

¹College of Life and Environmental Sciences, University of Exeter, Penryn Campus, Cornwall, United Kingdom.

²Centre for Altitude Space and Extreme Environment Medicine, Institute of Sport, Exercise and Health, London, United Kingdom.

³Hatherly Laboratories, College of Life and Environmental Sciences, University of Exeter, Exeter, United Kingdom.

FIG. 1. Schematic diagram showing records of humans and birds found at high altitude in relationship to commercial aircraft cruising altitude and some of the world’s highest mountains. High-altitude birds are, for the majority of the time, found at much lower altitudes, but make rare flights above 5500 m altitude. Sources: Noel (1927), Laybourne (1974), West (2002), Mukherjee et al. (2008), McCracken et al. (2009a), Borrás et al. (2010), Hawkes et al. (2011), Beall (2014), Dawson et al. (2016), Parr et al. (2017), and Everest by Numbers (2018).

et al., 1995), which weather radars have estimated to transiently visit altitudes up to 3000 m (Williams et al., 1973; Peurach, 2001).

In contrast to the majority of avian species, some species of birds spend a portion of their lives at high altitude (either

migrating or residing there, Fig. 1) and can thus tolerate hypoxia better, due to additional adaptations or greater ability to make further temporary physiological adjustments (such species will be referred to as “high-altitude adapted” birds from now on). The best studied high-altitude adapted avian

FIG. 2. Diagram of each stage (A–E) of the oxygen transport chain, detailing the physiological adjustments to high-altitude hypoxia that have been documented in low-altitude native humans ascending to high altitude, and details of preadaptations that are common across all birds and allow for a greater tolerance of hypoxia relative to mammals before any physiological adjustments occur upon exposure to hypoxia. Sources: Scheid and Piiper (1972), Grubb (1983), Faraci et al. (1984b), Maginniss et al. (1997), Maina (2000), Ward et al. (2002) Moudgil et al. (2005), West (2006), Grocott et al. (2009), McGuire and Guglielmo (2009), Scott et al. (2009), Wagner (2010), Scott (2011), Lague et al. (2016), and Hoiland et al. (2018).

species is the bar-headed goose (*Anser indicus*), which completes a trans-Himalayan migration, including a climb of 4000 to 5000 m from sea level in just 7–8 hours between wintering grounds in south Asia to breeding grounds in central China and Mongolia (Hawkes et al., 2011, 2012). On exposure to progressive hypoxia in laboratory studies (so removing the other stressors present at high altitude and the added costs of flight), bar-headed geese were able to remain standing and alert at a simulated altitude of 12,190 m, whereas lowland Canada geese were unable to stand at altitudes higher than 10,668 m (Black and Tenney, 1980a), although both altitudes were considerably higher than low-altitude mammals could tolerate (Tucker, 1968).

In addition to bar-headed geese, other avian migrants fly at very high altitudes (>5000 m), potentially in search of favorable conditions (Senner et al., 2018). However, to date, the highest altitudes directly recorded using tracking tags are 7290 m for a bar-headed goose, and 6800 m for a ruddy shelduck, although both species remain below 5500 m for the overwhelming majority (95%) of their migration (Hawkes et al., 2011; Parr et al., 2017). In addition to visitors to high altitude, several avian species that are resident at high altitude have become the subject of recent studies of high-altitude physiology and comparative transcriptomics. These species include passerines (perching birds) of the Himalayas (Grewal, 2017; Hao et al., 2019) and multiple species of waterfowl in the Andes, such as torrent duck (*Merganetta armata*, found up to 4500 m in riverain habitats of the Andes) (Dawson et al., 2016) and Andean geese (*Neochen melanoptera*, resident at 6000 m) (Fig. 1) (Maina et al., 2017).

Several mammalian species also reside at high altitude, including yak (*Bos grunniens*), llama (*Lama glama*), and vicuña (*Vicugna vicugna*). The high-altitude physiology of deer mice (*Peromyscus maniculatus*) has also been increasingly studied, given the large altitudinal ranges and possibility for translocation experiments between low- and high-altitude populations (reviewed in Storz et al., 2019). This review contrasts the mammalian and, in particular, human responses to high-altitude hypoxia with those of birds, at each level of the oxygen transport cascade, highlighting where the high-altitude environment has resulted in similar and divergent phenotypic adaptations.

Ventilation

In humans, the partial pressure of arterial oxygen (P_{aO_2}) falls within minutes of exposure to hypobaric hypoxia. Ventilation increases in response (Fig. 2A) and, while it may temporarily arrest the decline in P_{aO_2} , it also causes hypocapnia, a reduction in the partial pressure of arterial carbon dioxide (P_{aCO_2}), leading to respiratory alkalosis. Ultimately, this limits the initial hypoxic ventilatory response (HVR) (reviewed in Dempsey et al., 1974). Only over a period of days (duration dependent on altitude, ascent rate, and individual capacity) can ventilation rates slowly rise again in lowlanders visiting high altitude (reviewed in Hoiland et al., 2018). This is achieved by balancing respiratory alkalosis with (primarily) an increase in renal bicarbonate loss, offsetting the alkalemia, and allowing a progressive increase in ventilation and P_{aO_2} . Humans resident at high altitude generally have an HVR that is similar to that of lowlanders, although a blunting of HVR has been described in Tibetans living above 4000 m (Curran et al., 1995; but for review see Gilbert-Kawai et al., 2014). High-altitude nonhuman mam-

mals such as high-altitude deer mice and plateau pika (*Ochotona curzoniae*) are also able to increase total ventilation in response to acute hypoxia to a greater extent than low-altitude populations (Pichon et al., 2009; reviewed in Ivy and Scott, 2017), suggesting an evolved increase in capacity for acute hypoxia responses (reviewed in Storz et al., 2010).

Birds too display an HVR, increasing breathing rates as P_{aO_2} drops (Fig. 2A) (for review, see Ivy and Scott, 2014). However, it takes much longer for P_{aO_2} to fall in birds because of the remarkable avian respiratory system. In contrast to the mammalian lung, the avian lung is a unidirectionally ventilated structure, with a system of avascular air sacs distributed throughout the body that mechanically ventilate a relatively rigid lung (Fig. 2A) (Scheid, 1979). The consequence of this arrangement is a lung surface that is exposed to fresh oxygenated air on both inhalation when a body of air enters the lung in passage to the anterior air sacs and again on exhalation, as a separate body of air is expelled from the posterior air sacs through the lung (Banzett et al., 1987, 1991). Thus, the avian pulmonary gas exchange surface has twice the opportunity for oxygen extraction per unit of time as the mammalian lung (Scheid et al., 1972). In addition, when P_{aO_2} drops low enough to stimulate an HVR, birds are able to continue hyperventilating, despite hypocapnia either due to a greater capacity to buffer blood pH following respiratory alkalosis (Dodd et al., 2007; reviewed in Scott, 2011) or through insensitivity of avian brain tissue to hypocapnia (discussed below, Fig. 2D). As a result, ventilation rates are not suppressed to the same extent as in mammals.

In high-altitude adapted avian species, the HVR is more powerful than in lowland birds (Scott and Milsom, 2007). Bar-headed geese increase total ventilation on exposure to hypoxia by increasing tidal volume, in addition to respiratory frequency, a strategy that differs from low-altitude waterfowl that increase only ventilation rate (Scott and Milsom, 2007). Increasing tidal volume reduces the proportional contribution of anatomical dead space ventilation, and as a result, bar-headed geese sustain greater total ventilation for a given fraction of inspired oxygen than low-altitude geese, suggesting they have evolved a greater capacity for acute responses to hypoxia (Lague et al., 2016).

In addition, exposure to hypoxia during development appears to modify this response further: bar-headed geese raised at high altitude (3200 m) can sustain a greater HVR than bar-headed geese raised at sea level (Lague et al., 2016). Both groups of bar-headed geese in this case may respond to declines in P_{aO_2} similarly, but the response in low-altitude raised waterfowl is likely partially inhibited by responses to hypocapnia (Lague et al., 2016). This suggests that bar-headed geese in the wild (breeding grounds in Mongolia and the Tibetan-Qinghai Plateau are between 2000 and 4500 m) may have an enhanced capacity for acute hypoxia responses to high-altitude hypoxia. This increased capacity is likely the result of reduced sensitivity to hypocapnia (rather than increased response to hypoxic signals) relative to conspecifics, and so bar-headed geese have less restriction of minute ventilation (Scott and Milsom, 2007; Slessarev et al., 2010).

Pulmonary Oxygen Diffusion

At the pulmonary interface, oxygen must diffuse into the blood at a rate determined by the pulmonary oxygen diffusion capacity. This is increased in Tibetan and Andean human

populations through a larger pulmonary volume relative to lowlanders (Brutsaert, 2007). Larger lungs have also been found in mice (*Phyllotis darwini*) living at high altitudes (4660 m) relative to sea level populations (Pearson and Pearson, 1976). High-altitude adapted birds also have larger lungs relative to low-altitude species (Scott et al., 2011), but (regardless of altitude exposure) birds have on average 15% larger lung surface areas than mammals of equivalent body mass (reviewed in West, 2009). The blood-gas barrier is also considerably thinner in birds than mammals (Fig. 2B). Nonvolant mammalian blood-gas barriers can range from 0.33 μm (Etruscan shrew, *Suncus etruscus*) (Gehr et al., 1980) to 0.72 μm (domestic pig, *Sus scrofa domesticus*) (Meban, 1980), although heightened oxygen demand in bats has selected for a thinner blood-gas barrier (range 0.20 μm in the hairless bat, *Cheiromeles torquatus*, to 0.28 μm in the lesser short-nosed fruit bat, *Cynopterus brachyotis*) relative to nonvolant mammals (Maina and King, 1984). In contrast, blood gas barriers of 0.1 μm are not unusual in birds (such as waterfowl, sea birds, and passerines, but thickness can range from <0.1 μm (hummingbirds) to 0.56 μm in nonvolant birds such as ostriches) (Dubach, 1981; Maina and West, 2005; reviewed in West et al., 2007). Perhaps, surprisingly, given the thinness of the avian blood-gas barrier, the avian lung surface is much stronger compared with mammals. It is less susceptible to stress failures and more resistant to pressure than in the mammalian lung (Watson et al., 2007, 2008).

In the avian lung, gas exchange is also far more effective than in mammals, not only as the result of unidirectional air flow but also because of a cross-current gas exchange system (Fig. 2B) that theoretically allows $\text{P}_{\text{a}}\text{O}_2$ to exceed the partial pressure of oxygen (PO_2) of expired air (Scheid and Piiper, 1972). Air capillaries are intertwined with blood capillaries that deliver oxygenated blood to blood vessels running perpendicular to rigid parabronchioles, and therefore, the diffusion difference of oxygen is not diminished across the length of the avian parabronchioles (reviewed in Scott, 2011). Indeed, the cross-current arrangement of the air and blood capillaries in birds may be so significant that Powell and Scheid (1989) estimated that a human climber on Mount Everest could climb 780 m higher if they had an avian parabronchial lung arrangement (reviewed in Maina, 2015). Although it has been little studied in wild flying birds (given the technical challenges), the avian lung is likely overall a far more effective gas exchange organ than the mammalian lung (but see Thomas et al., 1984).

In addition to the general avian advantage over mammals, high-altitude adapted birds may be able to increase pulmonary oxygen extraction over that of low-altitude species (McCracken et al., 2009a; Natarajan et al., 2015; York et al., 2017). For example, work in waterfowl (Andean geese and crested ducks) has suggested that extraction efficiency can increase with altitude up to 90% (recorded at a simulated altitude of 11,000 m in Andean geese), but is $\sim 45\%$ at 12.2 kPa partial pressures of inspired oxygen (~ 4500 m). In contrast, bar-headed geese maintain a consistent extraction efficiency of $\sim 40\%$ across all altitudes (Laguë et al., 2017). The increased capillarity of the blood-gas interface, and a proportionally larger lung surface area of Andean geese relative to bar-headed geese (despite the relatively larger lung of bar-headed geese in comparison to lowland waterfowl) (Scott et al., 2011), has been suggested as a possible mechanism for this difference in extraction capabilities (Laguë et al., 2017;

Maina et al., 2017; York et al., 2017). Differences in Andean geese and bar-headed geese lung morphology and extraction efficiency in acute hypoxia highlight the variation in responses to high-altitude selection pressures present in waterfowl. This is potentially due to the differing nature of chronic or transient altitude exposure, or geographic origins (for review see Laguë, 2017), as when the same selection pressures are present across species in the same geographic area, a recent transcriptomic study found shifts in gene expression were similar across three high-altitude species relative to closely related low-altitude species (Hao et al., 2019).

High-altitude pulmonary edema

In humans at low altitudes, when regions of the lung become hypoxic (due to uneven or poor ventilation), pulmonary vascular resistance increases through hypoxic pulmonary vasoconstriction, an adaptive vasomotor response that redistributes blood to better-ventilated lung segments (reviewed in Moudgil et al., 2005). However, this response can be maladaptive at altitudes where hypoxia is ubiquitous. As a result of increased or uneven blood flow to localized regions of the alveolar capillary bed (Maggiorini et al., 2001), the gas exchange barrier can become damaged, allowing proteins and erythrocytes to leak into the alveoli, restricting the potential for gas exchange, thus amplifying the vasoconstriction and stimulating an inflammatory response (reviewed in Swenson et al., 2002). This has been well described in human mountaineers (reviewed in Basnyat and Murdoch, 2003) as a cause of noncardiogenic pulmonary edema, known as high-altitude pulmonary edema (HAPE) (Bartsch et al., 2005; reviewed in Dehnert et al., 2007). In prolonged exposure, pulmonary arteries may thicken in response to chronic vasoconstriction and the resulting increase in pressure may cause right ventricular hypertrophy and failure (Tucker et al., 1975). Similarly in cattle at high altitude (above 2100 m), hypoxic pulmonary hypertension has been linked to right heart failure (brisket disease) and is a major cause of livestock death in high altitudes (Rhodes, 2005). In contrast, yaks (a closely related bovine) appear to be well adapted to the high-altitude environments of Tibet (found up to 4500 m) (Dolt et al., 2007; Qiu et al., 2012). Generations of evolution appear to have eliminated hypoxic vasoconstriction in this species (Anand et al., 1986) and yaks have thin-walled pulmonary vessels, despite chronic altitude exposure (Durmowicz, 1993). In addition, to the authors' knowledge, large herbivores such as llamas, which have been domesticated in high altitudes of South America 6000–7000 years ago, do not develop right ventricular hypertrophy or pulmonary hypertension (Heath et al., 1974; Riek et al., 2019).

In contrast to the majority of mammals, birds are not known to suffer from HAPE, because, similar to the high-altitude adapted yak, avian pulmonary vessels do not vasoconstrict in response to hypoxia, regardless of previous exposure of high altitudes (reviewed in West et al., 2007). Instead, pulmonary pressure only increases in proportion to cardiac output (Burton et al., 1968; Black and Tenney, 1980b; Faraci et al., 1984a), and thus, pulmonary edema does not appear to occur in birds when exposed to high altitude. Even if it did, the unidirectional ventilation and a structural honeycomb network of support struts of avian airways would ensure they could not become closed or blocked (Watson et al., 2007). However, in commercial poultry production in

high-altitude environments, maladaptation from selective breeding of fast-growing chicks may have led to pulmonary arterial hypertension or “ascites syndrome” and cardiac failure (Yersin et al., 1992; Rostami et al., 2016). This is characterized by excessive accumulation of fluid in the abdominal cavity due to increased demands for cardiac output in hypoxic conditions, which is exacerbated by breeding programs for increased body size that is disproportional to heart and lung mass (Khajali and Wideman, 2016).

Circulatory Oxygen Delivery

Cardiac output

In addition to changes in ventilation, humans also respond to hypoxia by increasing cardiac output (Fig. 2C). Within 40 hours of exposure to a simulated altitude of 4600 m, heart rate increased by 34% in a study of resting lowlanders (Vogel and Harris, 1967). By comparison, high-altitude adapted humans from the Tibetan Plateau have a greater ability to increase heart rate, achieving higher maximal heart rates during exercise (for review, see Gilbert-Kawai et al., 2014). Similarly, high-altitude deer mice were found to sustain higher heart rates than low-altitude populations, both in high- and low-altitude conditions (reviewed in Ivy and Scott, 2017). Birds, in general, can sustain greater cardiac outputs; a 1 kg bird at rest has a cardiac output of ~290 mL/min compared to 166 mL/min for a mammal of the same mass; in addition, birds have proportionally larger hearts than mammals (Calder, 1968; Grubb, 1983) and can more than double their cardiac output in hypoxia through a combination of increased heart rate and stroke volume (Black and Tenney, 1980a; Lague et al., 2016).

On acclimatization to hypoxia, much like humans, birds can also increase cardiac output, even in species already adapted to high altitude; bar-headed geese that had undergone a 4-week period at a simulated altitude of 5450 m had a greater cardiac output than unacclimatized bar-headed geese (by ~200 mL/min) (Black and Tenney, 1980a). Similarly, bar-headed geese raised at high altitude increased cardiac output in response to diminished oxygen sooner than bar-headed geese raised at sea level (Lague et al., 2016), further demonstrating the importance of developmental phenotypic plastic responses, in addition to acclimatization for increasing the capacity to deliver oxygen through both increased ventilation and cardiac output (Monge and León-Velarde, 1991; Storz et al., 2010).

Blood properties

In addition to acute hypoxia responses, humans also make hematological adjustments after days to weeks at high altitude to sustain oxygen delivery to systemic tissue, typically by increasing hematocrit and total body hemoglobin mass (Fig. 2C), and therefore increasing arterial oxygen content (reviewed in Monge and León-Velarde, 1991). This also appears to occur as a fixed, evolved response to high-altitude hypoxia in humans native to the high-altitude Andes (Beall et al., 1998). The cost benefit of this is uncertain; despite the potential increase in arterial oxygen content, the resulting increase in blood viscosity creates a greater cardiac load, which may impair microcirculation, thus ultimately decreasing oxygen delivery to peripheral tissues (for reviews see Monge and León-Velarde, 1991; Storz et al., 2010; Barve

et al., 2016). At its extreme, prolonged elevation of hematocrit (secondary to central hypoventilation or increased bone marrow erythropoietin production) can be associated with chronic mountain sickness in humans (reviewed in Villafuerte and Corante, 2016) and may perhaps explain why this adaptation is not seen in humans native to Tibet (Beall et al., 1998) or other high-altitude adapted mammals such as Andean camelids (reviewed in Monge and León-Velarde, 1991).

Low-altitude species of birds also increase hematocrit when experimentally exposed to simulated high altitude for prolonged periods (e.g., 3 weeks or more) (Mcgrath, 1971; Weatheres and Snyder, 1974; Weinstein et al., 1985). A strong erythropoietic response was found in Pekin ducks that underwent a 4-week acclimatization to a simulated hypobaric hypoxia of 5450 m (Black and Tenney, 1980b), and hematocrit levels of wild citril finches (*Serinus citrinella*) increased by 6% after ascending to 2000 m (Borras et al., 2010). In addition to hypoxia, high-altitude environments impose multiple challenges on vertebrates that may moderate blood properties (Morton, 1976). For example, the increased oxygen demand for thermogenesis in the colder environment at high altitude may also play some role in inducing an erythropoietic response; indeed lower temperatures experienced by wild citril finches following ascents to 2000 m were suggested to contribute to the increase in hematocrit levels (Borras et al., 2010). Thus, hypoxia alone may not be the sole driver for hematological changes.

In contrast to the Pekin duck erythropoietic response, increases in hematocrit level were not seen in bar-headed geese when exposed to a simulated altitude of 5450 m (Black and Tenney, 1980b). This may be because other adaptations in bar-headed geese, as well as some other bird species, sufficed to maintain oxygen delivery (reviewed in Butler, 2010; Scott et al., 2015b; Monge and León-Velarde, 1991), thus avoiding the increased cardiac load that results from increasing hematocrit (Black and Tenney, 1980b). This also appears to be the case in Tibetan natives and other high-altitude nonhuman mammals that have a blunted erythropoietic response to acute hypoxia, such as deer mice (Lui et al., 2015).

A range of species living at high altitude have hemoglobin with an increased affinity for oxygen (McCracken et al., 2009b, 2010; Natarajan et al., 2015). Both bar-headed geese and Andean waterfowl have a lower P_{50} (the PO_2 at which hemoglobin is 50% saturated) relative to other avian species (Black and Tenney, 1980b; Liang et al., 2001; Meir and Milsom, 2013), although the mutation that causes this higher affinity in bar-headed geese differs from that in Andean waterfowl (Leu- $\beta 55$ to Ser- $\beta 55$ in Andean geese compared with Pro- $\alpha 119$ to Ala- $\alpha 119$ in bar-headed geese) (Weber et al., 1985). Camelids and high-altitude populations of deer mice have also been found to have hemoglobin with a higher affinity for oxygen than their low-altitude counterparts (Storz, 2007). However, the overall increase in oxygen consumption that can be achieved through a high oxygen affinity is the result of a trade-off between oxygen loading and unloading, sensitive to the altitude experienced (Storz, 2007). A recent comparative analysis demonstrated that there was ambiguous evidence for increased hemoglobin oxygen affinity in high-altitude mammals, although across avian species, there was a strong positive relationship between bird species' native elevation (taken as the mid-point of each species' elevation range) (Projecto-Garcia et al., 2013) and hemoglobin oxygen affinity (Storz, 2016). This suggests that

high-altitude selection pressures on birds act to increase hemoglobin oxygen affinity and this contributes to high-altitude birds' ability to sustain adequate oxygen supply without incurring the costs of elevated hematocrit levels that lowland birds and mammals experience.

Cerebral Oxygen Delivery and High-Altitude Cerebral Edema

Human lowlanders respond to hypoxia-induced decreased P_{aO_2} with temporarily increased cerebral blood flow. Upon initial exposure to high altitude, cerebral vasculature dilates and for a short period, blood flow and oxygen delivery to the brain increase to compensate for reduced P_{aO_2} (reviewed in Sanborn et al., 2015). However, this increase is subsequently diminished as a result of other acute hypoxia responses. First, increased ventilation leads to hypocapnia, which causes vasoconstriction of cerebral blood vessels (Fig. 2D). Second, other acclimatory changes, such as increased hematocrit, result in greater arterial oxygen content, so that cerebral blood flow can decrease without diminishing total cerebral oxygen delivery (for review see Hoiland et al., 2018). Birds' response to high-altitude hypoxia also begins with increased ventilation and a dilation of the brain vasculature so that cerebral blood flow is increased. However, an insensitivity of avian brain tissue to hypocapnia means that avian cerebral vasculature does not appear to vasoconstrict in response to the ensuing hypocapnia caused by increased ventilation, so cerebral blood flow is not diminished following prolonged hypoxic exposure (Faraci et al., 1985; Faraci, 1991) (Fig. 2D).

In humans, alterations to cerebral blood flow in response to hypoxia have been implicated in the onset of high-altitude cerebral edema (HACE) in climbers. HACE is thought to be a progression of acute mountain sickness that is marked by ataxia, headache, diminished conscious level, and ultimately, death (reviewed in Luks et al., 2017). It has been suggested that HACE may result from localized differences in cerebral blood flow, or where vasodilation and increased inflow are not matched to venous outflow (Wilson and Imray, 2016), leading to microhemorrhages and a diverse range of symptoms (Sagoo et al., 2017). In birds, the lack of vasoconstriction in response to hypocapnia means that cerebral blood pressure should not increase, despite the increase in cerebral blood flow (Grubb et al., 1977, 1978). Furthermore, avian neurons are less sensitive to hypoxia than mammalian neurons (Ludvigsen and Folkow, 2009); consequently, HACE is not known to occur in birds (Scott, 2011).

Skeletal Muscle Oxygen Delivery and Use

At the tissue and cellular level, further adaptations and acute hypoxia responses improve oxygen utilization in hypoxia in both mammals and birds. Human lowlanders visiting high altitude over a period of 1–2 months (i.e., the typical duration of an expedition in the Himalayas) undergo several muscular changes, including a reduction in cross-sectional surface area of muscle fibers (Hoppeler et al., 1990; MacDougall et al., 1991), and thus an improvement in oxygen diffusion as the capillary bed serves a smaller muscle volume (Hoppeler and Vogt, 2001). In addition, during a typical expedition to high altitude, the oxidative capacity of lowlanders' skeletal muscle also decreases. Oxidative capacity is the ability to consume oxygen and oxidize substrates, independent of the oxygen availability within the cell. One way

this can be reduced is through a smaller volume density of mitochondria, which has been found to occur in human lowlanders who undergo a reduction of up to 30% in the subsarcolemmal or interfibrillar mitochondria following expeditions to high altitude (Hoppeler et al., 1990). Furthermore, several respiratory enzymes, including citrate synthase, cytochrome oxidase (Howald et al., 1990), succinate dehydrogenase, and hexokinase activities, also decrease (Green et al., 1989; MacDougall et al., 1991). This serves to potentially reduce production of harmful reactive oxygen species (Hoppeler et al., 2003). For athletes wishing to incur some of the benefits of exposure to high altitude (i.e., increased oxygen-carrying capacity of the blood) without incurring these muscular costs, a schedule of intermittent hypoxia may be required (reviewed in Dempsey and Morgan, 2015). Total oxygen consumption in human high-altitude residents may be enhanced relative to that in lowlanders through increased oxygen delivery, achieved by greater capillary to muscle fiber ratios (Kayser et al., 1991) and higher rates of oxygen consumption per mitochondria. This may be the result of an enhanced efficiency in adenosine triphosphate (ATP) turnover achieved through coupling of ATP supply and demand pathways (Hoppeler and Vogt, 2001; Hoppeler et al., 2003).

However, birds have greater mass-specific $\dot{V}O_2$ than mammals, and this is supported by up to twice the capillarity in locomotor muscles than mammals (Fig. 2D) (Faraci, 1991; Mathieu-Costello et al., 1992), meaning that oxygen delivery to the muscles is more effective, as diffusion distances are reduced. This advantage is increased further in bar-headed geese, which have significantly higher capillary densities and higher capillary to muscle fiber ratios at the surface of flight muscles, relative to those in low-altitude waterfowl species, facilitating higher levels of oxygen delivery required during high-altitude flights (Scott et al., 2009, 2011).

Furthermore, avian flight muscle has a higher oxidative capacity and greater ability to metabolize fat than mammals (Rosser and George, 1986; for reviews see McGuire and Guglielmo, 2009; Butler, 2016). When mammals are exercising at maximal rates, fatty acids supply ~15% of the fuel metabolized (Weber et al., 1996). However, in birds, 90% of energy demand may be derived from fatty acids, made possible by a heightened capacity to transport fatty acids through an increase in fatty acid transport proteins on the membranes of the muscles relative to mammals (Fig. 2E) (reviewed in Guglielmo, 2010). This appears to be an adaptation necessary to sustain the high oxygen demands of flight (Tucker, 1970), rather than a response to hypobaric hypoxia *per se*. It is yet to be shown if greater fatty acid metabolism is beneficial at high altitudes, given the higher oxidative cost of metabolizing fatty acids; oxidizing lipids becomes increasingly expensive relative to glycogen with increasing altitude (Melzer, 2011; Yap et al., 2018). Enzymes involved in the metabolism of fatty acids were not found to vary across the locomotor muscles of high- and low-altitude populations of torrent duck (Dawson et al., 2016). However, high-altitude populations of deer mice have been found to have greater proportions of type I muscle fibers than low-altitude populations, which may increase their capacity to transport fatty acids (Lui et al., 2015). Furthermore, relative to low-altitude cattle, yaks have been shown to undergo modifications in five key genes in nutrition pathways relating to fatty acid metabolism (Qiu et al., 2012). These studies suggest that fatty

acid metabolism may be selected for or enhanced in high-altitude environments in mammals, but it is not yet clear if the same is true in birds, which already have a higher capacity to metabolize fatty acids than mammals (Lui et al., 2015; for review see Storz et al., 2019).

Avian high-altitude species can further increase oxidative capacity at the cellular level. High-altitude resident populations of torrent duck have significantly increased activities of cytochrome oxidase, phosphofructokinase, pyruvate kinase, and malate dehydrogenase in the locomotor muscles relative to those in ducks living at low altitude (Dawson et al., 2016). It is unknown whether these adaptations are common among other high-altitude adapted bird species (respiratory enzyme activity has not been studied in many other species to date), but other adaptations at the cellular level have been described in bar-headed geese. These include a redistribution of mitochondria closer to the capillaries, relative to those in low-altitude waterfowl, which is the opposite response of low-altitude humans acutely exposed to high altitude, who undergo a reduction in subsarcolemmal mitochondria (Hoppeler et al., 1990; Scott et al., 2009, 2011).

Similar adaptations have also been described in high-altitude populations of deer mice, including increased capillarity, a redistribution of mitochondria to reduce the intracellular oxygen diffusion distances, and increased activity of key respiratory enzymes (Lui et al., 2015; Scott et al., 2015a; Mahalingam et al., 2017; for review see McClelland and Scott, 2018). Therefore, chronic high-altitude hypoxia exposure appears to have acted in both birds and mammals to enhance the oxidative capacity as well as oxygen delivery to skeletal muscle. Such increases in oxidative capacity at the skeletal muscle contribute to greater overall maximum oxygen consumption ($\dot{V}O_{2\max}$). At the taxon level, birds appear to be able to support a higher $\dot{V}O_{2\max}$ than mammals (Fig. 2), which is beneficial at high altitudes characterized by both reduced oxygen availability and increased thermoregulation demands, given the cold challenge.

Conclusion

Birds' ability to sustain the high metabolic rates to facilitate the demands of flight likely confer benefits that allow birds to better tolerate hypoxia relative to mammals, including humans. Species and populations of birds and mammals that are regularly exposed to high altitudes have adaptations to enhance oxygen delivery, including greater HVR and greater oxygen-carrying capacity of the blood (reviewed in Butler, 2010; Scott, 2011; Ivy and Scott, 2014; Scott et al., 2015b). More recent research has shown that high altitude can also act as a strong selection pressure for greater oxidative capacity at the cellular level across both birds (Dawson et al., 2016; Yap et al., 2018; Hao et al., 2019) and mammals (Storz, 2007; McClelland and Scott, 2018). Despite these shared features, the advantages of the avian lung, hemoglobin with a high oxygen affinity and insensitivity to hypocapnia, triumph. Recent comparisons of high-altitude adaptations in resident waterfowl in the Andes and migratory bar-headed geese reveal that different mechanisms can serve to increase hypoxia tolerance (Laguë et al., 2017; reviewed in Laguë, 2017). However, there are common features unique to birds that visit high altitudes, which include more effective gas exchange with a greater HVR, larger lungs with higher capillarization, enhanced cardiac output, greater oxygen de-

livery to skeletal muscle due to increased hemoglobin oxygen affinity, and higher capillary to fiber ratios with increased oxidative capacity. Indeed, on rare occasions, several species of birds have been detected flying at exceptional altitudes (Noel, 1927; Laybourne, 1974; Hawkes et al., 2012; Parr et al., 2017). While extreme high-altitude flight may not represent their typical behavior, the question remains as to how high the best adapted avian species could reach, possibly with the assistance of orographic lift (Bishop et al., 2015).

Authors' Contributions

All authors contributed to the conception of the article; research and first drafting of the article were conducted by N.P. M.W. and L.A.H. contributed to the subsequent writing and editing. All authors have reviewed and approved the article for submission.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

N.P. was supported by a PhD studentship from the University of Exeter.

References

- Anand IS, Harris E, Ferrari R, Pearce P, and Harris P. (1986). Pulmonary haemodynamics of the yak, cattle, and cross breeds at high altitude. *Thorax* 41:696–700.
- Azad P, Stobdan T, Zhou D, Hartley I, Akbari A, Bafna V, and Haddad GG. (2017). High-altitude adaptation in humans: From genomics to integrative physiology. *J Mol Med* 95: 1269–1282.
- Banzett RB, Butler JP, Nations CS, Barnas GM, Lehr JL, and Jones JH. (1987). Inspiratory aerodynamic valving in goose lungs depends on gas density and velocity. *Respir Physiol* 70: 287–300.
- Banzett RB, Nations CS, Wang N, Fredberg JJ, and Butler JP. (1991). Pressure profiles show features essential to aerodynamic valving in geese. *Respir Physiol* 84:295–309.
- Bartsch P, Mairba H, Maggiorini M, and Swenson ER. (2005). Physiological aspects of high-altitude pulmonary edema. *J Appl Physiol* 98:1101–1110.
- Bärtsch P, and Swenson ER (2013). Acute high-altitude illnesses. *N Engl J Med* 368:2294–2302.
- Barve S, Dhondt AA, Mathur VB, and Cheviron ZA. (2016). Life-history characteristics influence physiological strategies to cope with hypoxia in Himalayan birds. *Proc Biol Sci* 283: 20162201.
- Basnyat B, and Murdoch DR. (2003). High-altitude illness. *Lancet* 361:1967–1974.
- Beall CM. (2007). Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *Proc Natl Acad Sci U S A* 104:8655–8660.
- Beall CM. (2014). Adaptation to High Altitude: Phenotypes and Genotypes. *Annu Rev Anthr* 43:251–272.
- Beall CM, Brittenham GM, Strohl KP, Blangero J, Williams-blanger S, Goldstein MC, Decker MJ, Vargas E, Villena M, Soria R, Alarcon AM, and Gonzales C. (1998). Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am J Phys Anthropol* 400:385–400.

- Bishop CM, Hawkes LA, Chua B, Frappell PB, Milsom WK, Natsagdorj T, Newman SH, Scott GR, Takekawa JY, Wikelski M, and Butler PJ. (2015). The roller coaster flight strategy of bar-headed geese conserves energy during Himalayan migrations. *Science* 347:250–254.
- Bishop CM, Ward S, Woakes AJ, and Butler PJ. (2002). The energetics of barnacle geese (*Branta leucopsis*) flying in wild and captive conditions. *Comp Biochem Physiol* 133: 225–237.
- Black CP, and Tenney SM. (1980a). Oxygen transport during progressive hypoxia in high-altitude and sea-level waterfowl. *Respir Physiol* 39:217–239.
- Black CP, and Tenney SM. (1980b). Pulmonary hemodynamic responses to acute and chronic hypoxia in two waterfowl species. *Comp Biochem Physiol* 67A:291–293.
- Borras A, Cabrera J, and Senar J. (2010). Hematocrit variation in response to altitude changes in wild birds: A repeated-measures design. *Condor* 112:622–626.
- Bouverot P. (1985). General introduction. In: *Adaptation to Altitude-Hypoxia in Vertebrates*. B Heinrich, K Johansen, H Langer, G Neuweiler and DJ Randall, eds. Springer-Verlag, Berlin. pp. 1–2.
- Brutsaert TD. (2007). Population genetic aspects and phenotypic plasticity of ventilatory responses in high altitude natives. *Respir Physiol Neurobiol* 158:151–160.
- Burton RR, Besch EL, and Smith AH. (1968). Effect of chronic hypoxia on the pulmonary arterial blood pressure of the chicken. *Am J Physiol* 214:1438–1442.
- Butler PJ. (2010). High fliers: The physiology of bar-headed geese. *Comp Biochem Physiol Part A Mol Integr Physiol* 156: 325–329.
- Butler PJ. (2016). The physiological basis of bird flight. *Philos Trans R Soc Lond B Biol Sci* 371:20150384.
- Calder W. (1968). Respiratory and heart rates of birds at rest. *Condor* 70:358–365.
- Curran LS, Zhuang J, Droma T, Land L, and Moore LG. (1995). Hypoxic ventilatory responses in Tibetan residents of 4400 m compared with 3658 m. *Respir Physiol* 100:223–230.
- Dawson NJ, Ivy CM, Alza L, Cheek R, York JM, Chua B, Milsom WK, McCracken KG, and Scott GR. (2016). Mitochondrial physiology in the skeletal and cardiac muscles is altered in torrent ducks, *Merganetta armata*, from high altitudes in the Andes. *J Exp Biol* 219:3719–3728.
- Dehnert C, Berger MM, Mairbäurl H, and Bärtsch P. (2007). High altitude pulmonary edema: A pressure-induced leak. *Respir Physiol Neurobiol* 158:266–273.
- Dempsey J, Forster H, and Dopico G. (1974). Ventilatory acclimatization to moderate hypoxemia in man. *J Clin Invest* 53:1091–1100.
- Dempsey JA, and Morgan BJ. (2015). Humans in hypoxia: A conspiracy of maladaptation?! *Physiology* 30:304–316.
- Dodd GAA, Scott GR, and Milsom WK. (2007). Ventilatory roll off during sustained hypercapnia is gender specific in pekin ducks. *Respir Physiol Neurobiol* 156:47–60.
- Dolt KS, Mishra MK, Karar J, Baig MA, Ahmed Z, and Pasha MAQ. (2007). cDNA cloning, gene organization and variant specific expression of HIF-1 α in high altitude yak (*Bos grunniens*). *Gene* 386:73–80.
- Dubach M. (1981). Quantitative analysis of the respiratory system of the house sparrow, budgerigar and violet-eared hummingbird. *Respir Physiol* 46:43–60.
- Durmowicz A. (1993). Functional and structural adaptation of the yak pulmonary circulation to residence at high altitude. *J Appl Physiol* 74:2276–2285.
- Everest by Numbers. (2018). The blog on alanarnette.com. Available at: <http://www.alanarnette.com/blog/> (accessed October 1, 2019).
- Faraci FM. (1991). Adaptations to hypoxia in birds: How to fly high. *Annu Rev Physiol* 53:59–70.
- Faraci FM, Kilgore Jr. DL, and Fedde MR. (1984a). Attenuated pulmonary pressor response to hypoxia in bar-headed geese. *Am J Physiol* 247:R402–3.
- Faraci FM, Kilgore Jr. DL, and Fedde MR. (1984b). Oxygen delivery to the heart and brain during hypoxia: Pekin duck vs. bar-headed goose. *Am J Physiol Regul Integr Comp Physiol* 247:R69–75.
- Faraci FM, Kilgore Jr. DL, and Fedde MR. (1985). Blood flow distribution during hypocapnic hypoxia in pekin ducks and bar-headed geese. *Respir Physiol* 61:21–30.
- Gehr P, Sehovic S, Burri P, Claassen H, and Weibel E. (1980). The lung of shrews: Morphometric estimation of diffusion capacity. *Respir Physiol* 40:33–47.
- Gilbert-Kawai ET, Milledge JS, Grocott MPW, and Martin DS. (2014). King of the mountains: Tibetan and sherpa physiological adaptations for life at high altitude. *Physiology* 29: 388–402.
- Green HJ, Young PM, Sutton JR, Cymerman A, and Houston CS. (1989). Operation Everest II: Adaptations in human skeletal muscle. *J Appl Physiol* 66:2454–2461.
- Grewal B. (2017). *Birds of the Himalayas*. London, England: Bloomsbury Publishing.
- Grocott M, Martin D, Levett D, McMorro R, Windsor J, and Montgomery H. (2009). Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 360: 140–149.
- Grubb B, Colacino JM, and Schmidt-Nielsen K. (1978). Cerebral blood flow in birds: Effect of hypoxia. *Am J Physiol* 234: H230–H234.
- Grubb B, Mills CD, Colacino JM, and Schmidt-Nielsen K. (1977). Effect of arterial carbon dioxide on cerebral blood flow in ducks. *Am J Physiol Circ Physiol* 232:H596–H601.
- Grubb BR. (1983). Allometric relations of cardiovascular function in birds. *Am J Physiol* 245:567–572.
- Guglielmo CG. (2010). Move that fatty acid: Fuel selection and transport in migratory birds and bats. *Integr Comp Biol* 50: 336–345.
- Hao Y, Xiong Y, Cheng Y, Song G, Jia C, Qu Y, and Lei F. (2019). Comparative transcriptomics of 3 high-altitude passerine birds and their low-altitude relatives. *Proc Natl Acad Sci U S A* 116:11851–11856.
- Hawkes L, Balachandran S, Batbayar N, Butler PJ, Chua B, Douglas DC, Frappell PB, Hou Y, Milsom WK, Newman SH, Prosser DJ, Sathiyaselvam P, Scott GR, Takekawa JY, Natsagdorj T, Wikelski M, Witt MJ, Yan B, and Bishop CM. (2012). The paradox of extreme high-altitude migration in bar-headed geese *Anser indicus*. *Proc Biol Sci* 280:20122114.
- Hawkes L, Balachandran S, Batbayar N, Butler PJ, Frappell PB, Milsom WK, Tseveenmyadag N, Newman SH, Scott GR, Sathiyaselvam P, Takekawa JY, Wikelski M, and Bishop CM. (2011). The trans-Himalayan flights of bar-headed geese (*Anser indicus*). *Proc Natl Acad Sci U S A* 108:9516–9519.
- Heath D, Smith P, Williams D, Harris P, Arias-Stella J, and Krüger H. (1974). The heart and pulmonary vasculature of the llama (*Lama glama*). *Thorax* 29:463–471.
- Hoiland RL, Howe CA, Coombs GB, and Ainslie PN. (2018). Ventilatory and cerebrovascular regulation and integration at high-altitude. *Clin Auton Res* 28:1–13.
- Hoppeler H, Kleinert E, Howald H, Claassen H, Cerretelli P, Kayar S, and Schlegel C. (1990). Morphological adaptations

- of human skeletal muscle to chronic hypoxia. *Int J Sports Med* 11:3–9.
- Hoppeler H, and Vogt M. (2001). Muscle tissue adaptations to hypoxia. *J Exp Biol* 204:3133–3139.
- Hoppeler H, Vogt M, Weibel RE, and Fluck M. (2003). Response of skeletal muscle mitochondria to hypoxia. *Exp Physiol* 88:109–119.
- Howald H, Cerretelli P, Pette D, Uber A, Simoneau J-A, and Hoppeler H. (1990). Effects of chronic hypoxia on muscle enzyme activities. *Int J Sports Med* 11:10–14.
- Ivy CM, and Scott GR. (2014). Control of breathing and the circulation in high-altitude mammals and birds. *Comp Biochem Physiol A Mol Integr Physiol* 186:66–74.
- Ivy CM, and Scott GR. (2017). Control of breathing and ventilatory acclimatization to hypoxia in deer mice native to high altitudes. *Acta Physiol* 221:266–282.
- Kayser B, Hoppeler H, Claassen H, and Cerretelli P. (1991). Muscle structure and performance of Himalayan Sherpas. *J Appl Physiol* 70:1938–1942.
- Khajali F, and Wideman RF. (2016). Nutritional approaches to ameliorate pulmonary hypertension in broiler chickens. *J Anim Physiol Anim Nutr (Berl)* 100:3–14.
- Laguë SL. (2017). High-altitude champions: Birds that live and migrate at altitude. *J Appl Physiol* 123:942–950.
- Laguë SL, Chua B, Alza L, Scott GR, Frappell PB, Zhong Y, Farrell AP, McCracken KG, Wang Y, and Milsom WK. (2017). Divergent respiratory and cardiovascular responses to hypoxia in bar-headed geese and Andean birds. *J Exp Biol* 220:4186–4194.
- Laguë SL, Chua B, Farrell AP, Wang Y, and Milsom WK. (2016). Altitude matters: Differences in cardiovascular and respiratory responses to hypoxia in bar-headed geese reared at high and low altitudes. *J Exp Biol* 219:1974–1984.
- Laybourne R. (1974). Collision between a vulture and an aircraft at an altitude of 37,000 feet. *Wilson Bull* 86:461–462.
- Liang Y, Hua Z, Liang X, Xu Q, and Lu G. (2001). The crystal structure of bar-headed goose hemoglobin in deoxy form: The allosteric mechanism of a hemoglobin species with high oxygen affinity. *J Mol Biol* 313:123–137.
- Ludvigsen S, and Folkow LP. (2009). Differences in vitro cerebellar neuronal responses to hypoxia in eider ducks, chicken and rats. *J Comp Physiol A Neuroethol Sensory Neural Behav Physiol* 195:1021–1030.
- Lui MA, Mahalingam S, Patel P, Connaty AD, Ivy CM, Chevion ZA, Storz JF, McClelland GB, and Scott GR. (2015). High-altitude ancestry and hypoxia acclimation have distinct effects on exercise capacity and muscle phenotype in deer mice. *Am J Physiol Regul Integr Comp Physiol* 308:R779–R791.
- Luks AM, Swenson ER, and Bärtsch P. (2017). Acute high-altitude sickness. *Eur Respir Rev* 26:1–14.
- MacDougall JD, Green HJ, Sutton JR, Coates G, Cymerman A, Young P, and Houston CS. (1991). Operation Everest II: Structural adaptations in skeletal muscle in response to extreme simulated altitude. *Acta Physiol Scand* 142:421–427.
- Maggiorini M, Mélot C, Pierre S, Pfeiffer F, Greve I, Sartori C, Lepori M, Hauser M, Scherrer U, and Naeije R. (2001). High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation* 103:2078–2083.
- Maginniss LA, Bernstein MH, Deitch MA, and Pinshow B. (1997). Effects of chronic hypobaric hypoxia on blood oxygen binding in pigeons. *J Exp Zool* 277:293–300.
- Mahalingam S, McClelland GB, and Scott GR. (2017). Evolved changes in the intracellular distribution and physiology of muscle mitochondria in high-altitude native deer mice. *J Physiol* 595:4785–4801.
- Maina JN. (2000). What it takes to fly: The structural and functional respiratory refinements in birds and bats. *J Exp Biol* 203:3045–3064.
- Maina JN. (2015). The design of the avian respiratory system: Development, morphology and function. *J Ornithol* 156:41–63.
- Maina JN, and King AS. (1984). Correlations between structure and function in the design of the bat lung: A morphometric study. *J Exp Biol* 104:43–61.
- Maina JN, McCracken KG, Chua B, York JM, and Milsom WK. (2017). Morphological and morphometric specializations of the lung of the Andean goose, *Chloephaga melanoptera*: A lifelong high-altitude resident. *PLoS One* 12:e0174395.
- Maina JN, and West JB. (2005). Thin and strong! The bioengineering dilemma in the structural and functional design of the blood-gas barrier. *Physiol Rev* 85:811–844.
- Mathieu-Costello O, Suarez RK, and Hochachka PW. (1992). Capillary-to-fiber geometry and mitochondrial density in hummingbird flight muscle. *Respir Physiol* 89:113–132.
- McClelland GB, and Scott GR. (2018). Evolved mechanisms of aerobic performance and hypoxia resistance in high-altitude natives. *Annu Rev Physiol* 81:561–583.
- McCracken KG, Barger CP, Bulgarella M, Johnson KP, Kuhner MK, Moore AV, Peters JL, Trucco J, Valqui TH, Winker K, and Wilson RE. (2009a). Signatures of high-altitude adaptation in the major hemoglobin of five species of Andean Dabbling Ducks. *Am Nat* 174:631–650.
- McCracken KG, Barger CP, Bulgarella M, Johnson KP, Sonsthagen SA, Trucco J, Valqui TH, Wilson RE, Winker K, and Sorenson MD. (2009b). Parallel evolution in the major hemoglobin genes of eight species of Andean waterfowl. *Mol Ecol* 18:3992–4005.
- McCracken KG, Barger CP, and Sorenson MD. (2010). Phylogenetic and structural analysis of the HbA and HbD hemoglobin genes in two high-altitude waterfowl from the Himalayas and the Andes: Bar-headed goose (*Anser indicus*) and Andean goose (*Chloephaga melanoptera*). *Mol Phylogenet Evol* 56:649–658.
- Mcgrath J. (1971). Acclimation response of pigeons to simulated high altitude. *J Appl Physiol* 31:23–25.
- McGuire LP, and Guglielmo CG. (2009). What can birds tell us about the migration physiology of bats? *J Mammal* 90:1290–1297.
- Meban C. (1980). Thickness of the air-blood barriers in vertebrate lungs. *J Anat* 131:299–307.
- Meir JU, and Milsom WK. (2013). High thermal sensitivity of blood enhances oxygen delivery in the high-flying bar-headed goose. *J Exp Biol* 216:2172–2175.
- Melzer K. (2011). Carbohydrate and fat utilization during rest and physical activity. *Eur J Clin Nutr Metab* 6:e45–e52.
- Monge C, and León-Velarde F. (1991). Physiological adaptation to high altitude: Oxygen transport in mammals and birds. *Physiol Rev* 71:1135–1172.
- Morton ML. (1976). Aspects of circulatory physiology of montane and lowland birds. *Comp Biochem Physiol A Comp Physiol* 54:61–74.
- Moudgil R, Michelakis ED, Archer SL, Michelakis ED, and Hypoxic SLA. (2005). Hypoxic pulmonary vasoconstriction. *Pulm Circ Hypoxia* 390–403.
- Mukherjee A, Borad C, and Parasharya B. (2008). White-winged Diuca Finch (*Diuca speculifera*) Nesting on Quelccaya Ice cap, Peru. *Wilson J Ornithol* 120:89–94.

- Natarajan C, Projecto-Garcia J, Moriyama H, Weber RE, Munoz-Fuentes V, Green AJ, Kopuchian C, Tubaro PL, Alza L, Bulgarella M, Smith MM, Wilson RE, Fago A, McCracken KG, and Storz JF. (2015). Convergent evolution of hemoglobin function in high-altitude Andean waterfowl involves limited parallelism at the molecular sequence level. *PLoS Genet* 11:1–25.
- Noel J. (1927). *Through Tibet to Everest*. E. London, England: Arnold & Company.
- Parr N, Bearhop S, Douglas DC, Takekawa JY, Prosser DJ, Newman SH, Perry WM, Balachandran S, Witt MJ, Hou Y, Luo Z, and Hawkes LA. (2017). High altitude flights by ruddy shelduck *Tadorna ferruginea* during trans-Himalayan migrations. *J Avian Biol* 48:1–6.
- Pearson OP, and Pearson AK. (1976). A stereological analysis of the ultrastructure of the lungs of wild mice living at low and high altitude. *J Morphol* 150:359–368.
- Peurach SC. (2001). High-altitude collision between an Airplane and a Hoary Bat, *Lasiurus cinereus*. *Bat Res News* 44:2–3.
- Pichon A, Zhenzhong B, Favret F, Jin G, Shufeng H, Marchant D, Richalet J-P, and Ge R-L. (2009). Long-term ventilatory adaptation and ventilatory response to hypoxia in plateau pika (*Ochotona curzoniae*): Role of nNOS and dopamine. *Am J Physiol Integr Comp Physiol* 297:R978–R987.
- Piersma T, and van Gils JA. (2011). *The Flexible Phenotype*. Oxford University Press, Oxford.
- Powell F, and Scheid P (1989). Physiology of gas exchange in the avian respiratory system. In: *Form and Function in Birds*. A King and J McLelland, eds. Academic Press, London. pp. 393–437.
- Projecto-Garcia J, Natarajan C, Moriyama H, Weber RE, Fago A, Cheviron ZA, Dudley R, McGuire JA, Witt CC, and Storz JF. (2013). Repeated elevational transitions in hemoglobin function during the evolution of Andean hummingbirds. *Proc Natl Acad Sci U S A* 110:20669–20674.
- Qiu Q, Zhang G, Ma T, Qian W, Wang J, Ye Z, Cao C, Hu Q, Kim J, Larkin DM, Auvi L, Capitanu B, Ma J, Lewin HA, Qian X, Lang Y, Zhou R, Wang L, Wang K, Xia J, Liao S, Pan S, Lu X, Hou H, Wang Y, Zang X, Yin Y, Ma H, Zhang J, Wang Z, Zhang Y, Zhang D, Yonezawa T, Hasegawa M, Zhong Y, Liu W, Zhang Y, Huang Z, Zhang S, Long R, Yang H, Wang J, Lenstra JA, Cooper DN, Wu Y, Wang J, Shi P, Wang J, and Liu J. (2012). The yak genome and adaptation to life at high altitude. *Nat Genet* 44:6–11.
- Rhodes J. (2005). Comparative physiology of hypoxic pulmonary hypertension: Historical clues from brisket disease. *J Appl Physiol* 98:1092–1100.
- Riek A, Stölzl A, Marquina Bernedo R, Ruf T, Arnold W, Hambly C, Speakman JR, and Gerken M. (2019). Energy expenditure and body temperature variations in llamas living in the High Andes of Peru. *Sci Rep* 9:1–11.
- Rosser BWC, and George JC. (1986). The avian pectoralis: Histochemical characterisation and distribution of muscle fiber types. *Can J Zool* 64:1174–1185.
- Rostami A, Moghaddam AKZ, Hassanpour H, and Khajali F. (2016). Pulmonary hypertension and right ventricular failure in broiler chickens reared at high altitude is affected by dietary source of n-6 and n-3 fatty acids. *J Anim Physiol Anim Nutr (Berl)* 100:701–706.
- Sagoo RS, Hutchinson CE, Wright A, Handford C, Parsons H, Sherwood V, Wayte S, Nagaraja S, Ng'Andwe E, Wilson MH, and Imray CH. (2017). Magnetic Resonance investigation into the mechanisms involved in the development of high-altitude cerebral edema. *J Cereb Blood Flow Metab* 37: 319–331.
- Sanborn MR, Edsell ME, Kim MN, Mesquita R, Putt ME, Imray C, Yow H, Wilson MH, Yodh AG, Grocott M, and Martin DS. (2015). Cerebral hemodynamics at altitude: Effects of hyperventilation and acclimatization on cerebral blood flow and oxygenation. *Wilderness Environ Med* 26: 133–141.
- Scheid P. (1979). *Mechanisms of Gas Exchange in Bird Lungs*. Springer, Berlin, Heidelberg.
- Scheid P, and Piiper J. (1972). Cross-current gas exchange in avian lungs: Effects of reversed parabronchial air flow in ducks. *Respir Physiol* 16:304–312.
- Scheid P, Slama H, and Piiper J. (1972). Mechanisms of unidirectional flow in parabronchi. *Respiration* 14:83–95.
- Scott GR. (2011). Elevated performance: The unique physiology of birds that fly at high altitudes. *J Exp Biol* 214:2455–2462.
- Scott GR, Egginton S, Richards JG, and Milsom WK. (2009). Evolution of muscle phenotype for extreme high altitude flight in the bar-headed goose. *Proc Biol Sci* 276:3645–3653.
- Scott GR, Elogio TS, Lui MA, Storz JF, and Cheviron ZA. (2015a). Adaptive modifications of muscle phenotype in high-altitude deer mice are associated with evolved changes in gene regulation. *Mol Biol Evol* 32:1962–1976.
- Scott GR, Hawkes LA, Frappell PB, Butler PJ, Bishop CM, and Milsom WK. (2015b). How bar-headed geese fly over the Himalayas. *Physiology* 30:107–115.
- Scott GR, and Milsom WK. (2007). Control of breathing and adaptation to high altitude in the bar-headed goose. *Am J Physiol Regul Integr Comp Physiol* 293:379–391.
- Scott GR, Schulte PM, Egginton S, Scott ALM, Richards JG, and Milsom WK. (2011). Molecular evolution of cytochrome c oxidase underlies high-altitude adaptation in the bar-headed goose. *Mol Biol Evol* 28:351–363.
- Senner NR, Stager M, Verhoeven MA, Cheviron ZA, Piersma T, and Bouten W. (2018). High-altitude shorebird migration in the absence of topographical barriers: Avoiding high air temperatures rather than searching for profitable winds. *Proc Biol Sci* 285:20180569.
- Slessarev M, Prisman E, Ito S, Watson RR, Jensen D, Preiss D, Greene R, Norboo T, Stobdan T, Diskit D, Norboo A, Kunzang M, Appenzeller O, Duffin J, and Fisher JA. (2010). Differences in the control of breathing between Himalayan and sea-level residents. *J Physiol* 588:1591–1606.
- Storz JF. (2007). Hemoglobin function and physiological adaptation to hypoxia in high-altitude mammals. *J Mammal* 88: 24–31.
- Storz JF. (2016). Hemoglobin-oxygen affinity in high-altitude vertebrates: Is there evidence for an adaptive trend? *J Exp Biol* 219:3190–3203.
- Storz JF, Cheviron ZA, McClelland GB, and Scott GR. (2019). Evolution of physiological performance capacities and environmental adaptation: Insights from high-elevation deer mice (*Peromyscus maniculatus*). *J Mammal* 100:910–922.
- Storz JF, Scott GR, and Cheviron ZA. (2010). Phenotypic plasticity and genetic adaptation to high-altitude hypoxia in vertebrates. *J Exp Biol* 213:4125–4136.
- Swenson ER, Maggiorini M, Mongovin S, Gibbs JSR, Greve I, Mairbäurl H, and Bartsch P. (2002). Pathogenesis of high-altitude pulmonary edema inflammation is not an etiologic factor. *JAMA* 287:2228–2235.
- Thomas SP, Follette DB, and Thomas GS. (1995). Metabolic and ventilatory adjustments and tolerance of the bat *Pteropus poliocephalus* to acute hypoxic stress. *Comp Biochem Physiol A Physiol* 112:43–54.

- Thomas SP, Lust MR, and Van Riper HJ. (1984). Ventilation and oxygen extraction in the bat *Phyllostomus hastatus* during rest and steady flight. *Physiol Zool* 57:237–250.
- Tucker VA. (1968). Respiratory physiology of house sparrows in relation to high-altitude flight. *J Exp Biol* 48:55–66.
- Tucker VA. (1970). Energetic cost of locomotion in animals. *Comp Biochem Physiol* 34:841–846.
- Tucker A, McMurtry I, Reeves J, Alexander A, Will D, and Grover R. (1975). Lung vascular smooth muscle as a determinant of pulmonary hypertension at high altitude. *Am J Physiol* 228:762–767.
- Villafuerte FC, and Corante N. (2016). Chronic mountain sickness: Clinical aspects, etiology, management, and treatment. *High Alt Med Biol* 17:61–69.
- Vogel JA, and Harris CW. (1967). Cardiopulmonary responses of resting man during early exposure to high altitude. *J Appl Physiol* 22:1124–1128.
- Wagner PD. (2010). Operation Everest II. *High Alt Med Biol* 11:111–119.
- Ward S, Bishop CM, Woakes AJ, and Butler PJ. (2002). Heart rate and the rate of oxygen consumption of flying and walking barnacle geese (*Branta leucopsis*) and bar-headed geese (*Anser indicus*). *J Exp Biol* 205:3347–3356.
- Watson RR, Fu Z, and West JB. (2007). Morphometry of the extremely thin pulmonary blood-gas barrier in the chicken lung. *Am J Physiol Lung Cell Mol Physiol* 292: L769–L777.
- Watson RR, Fu Z, and West JB. (2008). Minimal distensibility of pulmonary capillaries in avian lungs compared with mammalian lungs. *Respir Physiol Neurobiol* 160:208–214.
- Weatheres W, and Snyder G. (1974). Functional acclimation of Japanese quail to simulated high-altitude. *J Comp Physiol* 137:127–137.
- Weber JM, Roberts TJ, Vock R, Weibel ER, and Taylor CR. (1996). Design of the oxygen and substrate pathways. III. Partitioning energy provision from carbohydrates. *J Exp Biol* 199:1659–1666.
- Weber RE, Jessen T-H, Malte H, and Tame J. (1985). Mutant hemoglobins (Ala- α 119 and Pro- α 119): Functions related to high-altitude respiration. *J Appl Physiol* 75: 2646–2655.
- Weinstein Y, Bernstein MH, Bickler PE, Gonzales DV, Samaniego FC, and Escobedo M. (1985). Blood respiratory properties in pigeons at high altitudes: Effects of acclimation. *Am J Physiol Integr Comp Physiol* 249:R765–R775.
- West JB. (2002). Highest permanent human habitation. *High Alt Med Biol* 3:401–407.
- West JB. (2006). Human responses to extreme altitudes. *Integr Comp Biol* 46:25–34.
- West JB. (2009). Comparative physiology of the pulmonary blood-gas barrier: The unique avian solution. *Am J Physiol Regul Integr Comp Physiol* 297:R1625–R1634.
- West JB, Watson RR, and Fu Z. (2007). Major differences in the pulmonary circulation between birds and mammals. *Respir Physiol Neurobiol* 157:382–390.
- Williams TC, Ireland LC, and Williams JM. (1973). High altitude flights of the free-tailed bat, *Tadarida brasiliensis*, observed with radar. *J Mammal* 54:807–821.
- Willmer P, Stone G, and Johnston I. (2005). *Environmental Physiology of Animals*. Blackwell Publishing, Oxford.
- Wilson MH, and Imray CHE. (2016). The cerebral venous system and hypoxia. *J Appl Physiol* 120:244–250.
- Wolfel EE, Groves BM, Brooks GA, Butterfield GE, Mazzeo RS, Moore LG, Sutton JR, Bender PR, Dahms TE, McCullough RE, McCullough RG, Huang S, Sun S, Grover RF, Hultgren H., and Reeves JT. (1991). Oxygen transport during steady-state submaximal exercise in chronic hypoxia. *J Appl Physiol* 70:1129–1136.
- Yap KN, Dick MF, Guglielmo CG, and Williams TD. (2018). Effects of experimental manipulation of hematocrit on avian flight performance in high- and low-altitude conditions. *J Exp Biol* 221:jeb191056.
- Yersin AAG, Huff WE, Kubena LF, Elissalde MH, Harvey RB, and Giroir LE. (1992). Changes in hematological, blood gas, and serum biochemical variables in broilers during exposure to simulated high. *Avian Dis* 36:189–196.
- York JM, Chua BA, Ivy CM, Alza L, Cheek R, Scott GR, McCracken KG, Frappell PB, Dawson NJ, Laguë SL, and Milsom WK. (2017). Respiratory mechanics of eleven avian species resident at high and low altitude. *J Exp Biol* 220: 1079–1089.

Address correspondence to:

Lucy Alice Hawkes, PhD
Hatherly Laboratories
College of Life and Environmental Sciences
University of Exeter
Exeter EX4 4PS
United Kingdom

E-mail: l.hawkes@exeter.ac.uk

Received March 15, 2019;
accepted in final form September 2, 2019.