

CIRCULATORY IMPAIRMENT INDUCED BY EXERCISE IN THE LIZARD *IGUANA IGUANA*

COLLEEN G. FARMER* AND JAMES W. HICKS

Department of Ecology and Evolutionary Biology, 321 Steinhaus Hall, University of California at Irvine, Irvine, CA 92697, USA

Address for correspondence: Department of Biology, 201 S. Biology, 257 South 1400 East, University of Utah, Salt Lake City, UT 84112, USA (e-mail: farmer@biology.utah.edu)

Accepted 7 June; published on WWW 9 August 2000

Summary

Mechanical integration of the cardiac, muscular and ventilatory pumps enables mammals to vary cardiac output over a wide range to match metabolic demands. We have found this integration lacking in a lizard (*Iguana iguana*) that differs from mammals because blood flow from the caudal body and ventilation are maximal after, rather than during, exercise. Because *Iguana iguana* are constrained from ventilation during intense locomotion, they appear to be unable to recruit the abdomen and thorax as a pump for venous return. This constraint on simultaneous running and costal breathing arises from

their musculoskeletal design, which is similar to that of basal tetrapods, and so a constraint on venous return during exercise may be ancestral for tetrapods. We suggest that mechanical coupling of the pulmonary and cardiac pumps may have been important for the evolution of high-speed locomotor stamina in terrestrial vertebrates.

Key words: venous return, evolution, stamina, respiratory pump, lizard, *Iguana iguana*, green iguana.

Introduction

Vertebrates meet their long-term energy needs with aerobic metabolism. In amniotes, the movement of oxygen from the environment to working muscles involves a series of four steps known as the oxygen cascade: (i) convection of oxygen into the lungs by ventilation, (ii) diffusion of oxygen from the air in the lungs into the blood, (iii) convection of oxygen-rich blood to the peripheral tissues, and (iv) diffusion of oxygen to the mitochondria. Because the steps are in series, a limitation at any one of the steps has been thought to be a bottleneck for the flow of oxygen through the entire cascade. For a number of years, many workers thought that cardiovascular transport was the factor limiting maximal rates of oxygen consumption ($\dot{V}_{O_{2max}}$) in air-breathing vertebrates and that ventilation occurred in excess of what was needed to maintain arterial saturation of hemoglobin (Bennett, 1994; Saltin, 1985; for a review, see Wagner, 1988). In contrast, it has been suggested that rates of oxygen consumption in lizards are limited at the first step of the cascade, convection of oxygen into the lungs by ventilation (Carrier, 1987a,b). Lizards walk and run with a lateral undulatory gait in which the body flexes from side to side, requiring unilateral recruitment of muscles of the trunk, but costal ventilation requires the recruitment of these muscles in a bilaterally symmetrical manner (Carrier, 1989, 1990). Consequently, lizards are mechanically constrained from

simultaneous costal ventilation and locomotion, a constraint that becomes increasingly severe as running speeds increase (Carrier, 1987a,b, 1989, 1990; Owerkowicz et al., 1999; Wang et al., 1997).

In contrast to the view that a single step of the oxygen cascade is rate-limiting, a number of mammalian studies of oxygen transport have brought to light the importance of the interactive nature of the oxygen cascade. It has become increasingly clear that $\dot{V}_{O_{2max}}$ is set by an integrative interplay between each and every step of the cascade (Hoppeler and Weibel, 1998; Wagner, 1988; Wagner et al., 1997). In mammals, as locomotor speeds increase, mechanical integration of the cardiac, muscular and ventilatory pumps is important in enabling the adjustment of cardiac output over a wide range (Janicki et al., 1996). We wondered whether this would also be true of iguanid lizards, particularly at speeds that are faster than a slow walk. We found that the speed-dependent mechanical constraint on simultaneous costal ventilation and locomotion in the lizard *Iguana iguana* impairs not just convection of oxygen into the lungs, but also convection of blood to the peripheral tissues. Hence, a complex picture of the activity metabolism of ectotherms and endotherms is emerging in which the integrative nature of the physiological and morphological elements that determine rates of oxygen consumption needs to be considered.

Materials and methods

Animals

Green iguanas (*Iguana iguana* L.) were obtained from a commercial dealer and kept in cages with a thermal gradient and a full-spectrum light source. They experienced a photoperiod of 14h:10h light:dark. They were fed a diet of fresh green and yellow vegetables. The animals were trained to walk on a treadmill over the course of several weeks. The animals' mass ranged from 350 to 600 g.

Surgical procedure, blood flow and abdominal pressure

A lizard was anesthetized lightly by placing it in a container with a cloth soaked in Halothane. It was then intubated and artificially ventilated (SAR-830, CWE Inc., Ardmore, PA, USA) with air that had passed through a Halothane vaporizer (Dräger, Lubeck, Germany). Initially, the vaporizer was set at 3–4%, but this was reduced to 1% throughout most of the surgery. A ventral incision (approximately 3 cm long) was made in the abdomen, and a loose-fitting ultrasonic flow probe (2R, Transonic System, Inc., Ithaca, NY, USA) was placed around the posterior vena cava. In *Iguana iguana*, the heart is located in a cranial position in the trunk, just caudal to the clavicle, and blood from the hindlegs is carried directly through the trunk by the posterior vena cava. A pressure transducer (Millar Mikro-Tip; Millar Instruments, Inc., Houston, TX, USA) was sutured to connective tissue in the area of the flow probe placement. The purpose of the pressure transducer was to measure the effects of locomotion and ventilation on abdominal pressures before exercise, during graded exercise and during recovery. The incision was sutured and treated with cyanoacrylate tissue glue (Nexaband; S/C-TriPoint Medical, Raleigh, NC, USA).

The animals were treated daily with an antibiotic, enrofloxacin (Baytril, Bayer Corporation, Shawnee Mission, KS, USA), administered intramuscularly. They were given 1 or 2 days to recover from surgery.

Lung ventilation and gas exchange

To measure ventilation, a mask was constructed out of the tip of a 20 ml plastic syringe. Two ports were drilled into the syringe, and flexible tubing was glued to the ports. The mask was sealed over the nares and mouth with quick-setting epoxy glue. Flow control units (Ametek, Pittsburgh, PA, USA) were used to pull fresh air with a fractional concentration of inspired oxygen ($F_{I_{O_2}}$) of 0.2093 and a fractional concentration of inspired carbon dioxide ($F_{I_{CO_2}}$) of 0.0003 through the mask. A pneumotachograph (8311, Hans Rudolph, Inc., Kansas City, MO, USA) was placed in the line upstream from the mask; a portion of the gas flowing through the mask was diverted and pulled through Drierite (anhydrous calcium sulfate) and then through oxygen (Beckman OM-11, Fullerton, CA, USA) and carbon dioxide (Ametek CD-3A, Pittsburgh, PA, USA) analyzers. The pneumotachograph was calibrated by injecting known volumes of gas into the sealed mask before it was attached to the animal. The oxygen

analyzer was calibrated with a dry gas containing 21% oxygen. The carbon dioxide analyzer was calibrated with two dry gases, one containing 0.03% carbon dioxide and one containing 5% carbon dioxide. Subsequent to the calibration of the gas analyzers, known volumes of known gas mixtures were injected into the mask to generate a calibration curve for oxygen consumption and carbon dioxide excretion. Further details of this technique have been reported previously (Wang et al., 1997).

Experimental protocol

The animals were brought to the experimental chamber 3 h before data were collected. Measurements of rectal temperature indicated that the animals' body temperatures were the same as the room temperature (30 °C). A mask was glued to an animal, and it was given time on the treadmill to settle down from handling before data were collected. The treadmill was turned on, and the animal walked at 1 km h⁻¹ for approximately 3–4 min. During this time, it could be seen that the animals had reached a steady state with respect to blood flow, ventilation and rates of oxygen consumption and carbon dioxide excretion. The treadmill speed was then increased to 4 km h⁻¹ and maintained there for as long as the animal could match the belt speed, which was generally less than 1 min. A period of recovery was then monitored. Because the animals could not sustain 4 km h⁻¹ for a prolonged period, they were made to repeat this speed during recovery, after blood flow had reached a maximum, to determine whether blood flow, ventilation and rates of oxygen consumption and carbon dioxide excretion would remain elevated or decline.

Data collection and analysis

The analog signals from the pneumotachograph, the carbon dioxide and oxygen analyzers, the ultrasonic flow probe and the pressure transducer were converted to a digital format using BioPac (Goleta, CA, USA) and sampled at 50 Hz with Acqknowledge software (BioPac, Goleta, CA, USA). Means ($N=5$) and standard deviations for blood flow through the posterior vena cava, for ventilation and for rates of oxygen consumption and carbon dioxide excretion during the pre-exercise, sustainable exercise (1 km h⁻¹), unsustainable exercise (4 km h⁻¹) and recovery periods were computed. Mean values of these variables were obtained for a 1 min period before exercise, for a 0.5–1 min period after the values had reached steady state during exercise at the slower speed, over the entire time the animal could sustain locomotion at the highest speed, and for a 1 min period after blood flow had reached a maximum during recovery. During the periods analyzed, the volumes of individual breaths were calculated and then summed to obtain minute ventilation. Carbon dioxide excretion and oxygen consumption were not obtained on a breath-by-breath basis but were averaged over the time analyzed. A one-way analysis of variance (ANOVA, $N=5$) was used to determine whether there were significant ($P<0.05$) changes in these variables.

Results

Simultaneous measurements of blood flow through the posterior vena cava, lung ventilation and abdominal pressures showed that, at the start of exercise, ventilation and blood flow increased above pre-exercise values in spite of a slightly elevated abdominal pressure. When activity increased from a slow, sustainable walk (1 km h^{-1}) to a faster, unsustainable pace (4 km h^{-1}), ventilation decreased, abdominal pressure tended to increase and the flow of blood from the caudal body to the heart decreased (Figs 1–4). There was a significant reduction in the rate of oxygen consumption, ventilation and venous flow at unsustainable speeds compared with sustainable speeds ($P < 0.05$; ANOVA, $N = 5$). Rates of oxygen consumption and carbon dioxide excretion, ventilation and blood flow were also significantly ($P < 0.05$; ANOVA, $N = 5$) reduced at the higher speed compared with recovery. Blood flow at 1 km h^{-1} was significantly ($P < 0.05$; ANOVA, $N = 5$) less than that measured during recovery. Rates of oxygen consumption, carbon dioxide excretion, ventilation and blood flow were significantly different from pre-exercise values at both speeds

and during recovery ($P < 0.05$; ANOVA, $N = 5$). When exercise at the higher speed commenced during recovery, ventilation and blood flow dropped while abdominal pressure tended to increase. Although there was a consistent increase in pressure when exercise commenced, the absolute values varied from animal to animal, probably depending on the exact position of the pressure transducer. Consequently, rather than quantifying pressure, general trends were noted.

Discussion

We undertook this study to investigate whether the speed-dependent mechanical constraint on simultaneous ventilation and locomotion of green iguanas interferes with their ability to integrate the cardiac, ventilatory and muscular pumps. We used an ultrasonic blood flow probe placed around the posterior vena cava to monitor blood flow from the hindlegs and tail, a pressure transducer placed in the abdominal cavity to correlate changes in blood flow with changes in abdominal pressure, a pneumotachograph connected to a face mask with a biased

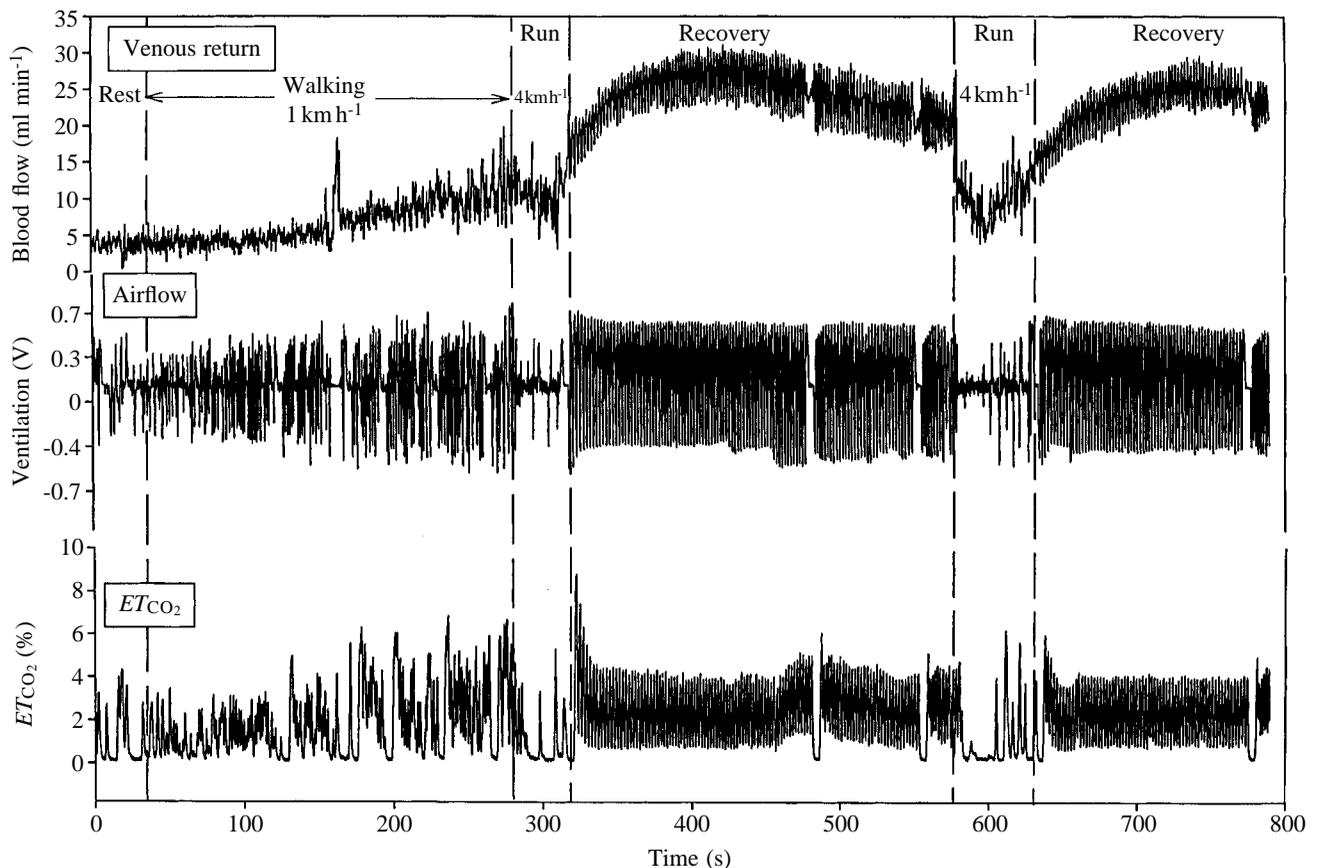


Fig. 1. Sample data illustrating the experimental protocol. The top trace is blood flow through the posterior vena cava recorded from the Transonic flow probe. The middle trace is from the pneumotachograph and indicates ventilation; exhalation is the negative portion of the trace. The bottom trace is the percentage of carbon dioxide (ET_{CO_2}) flowing through the gas analyzers. Exercise began at a slow pace, 1 km h^{-1} , and was maintained at this speed until blood flow and ventilation reached steady state, in this case at approximately 4.5 min. The treadmill speed was then increased to 4 km h^{-1} until the animal could no longer match the belt speed. Blood flow was monitored during recovery. After peak flows had been obtained, the treadmill was turned on again directly to 4 km h^{-1} to determine whether blood flow would remain elevated or decline.

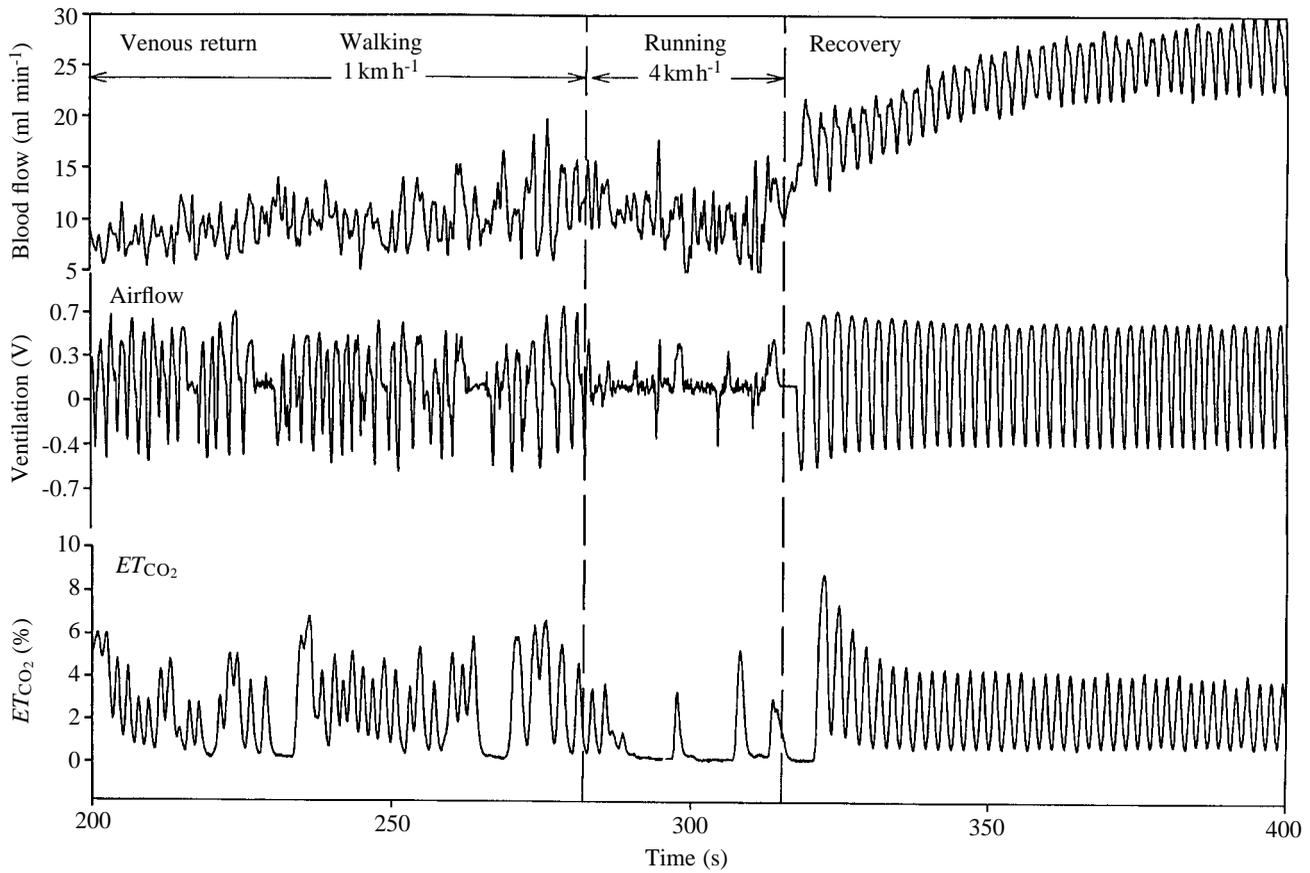


Fig. 2. The same data as in Fig. 1 but with an expanded time scale to provide more detail of the transition from exercise at 1 km h^{-1} to 4 km h^{-1} and the beginning of recovery.

flow to monitor ventilation, and oxygen and carbon dioxide analyzers to monitor gas exchange. We found that, at slow speeds (1 km h^{-1}), ventilation, blood flow and rates of oxygen consumption and carbon dioxide excretion were significantly elevated over pre-exercise values. Blood flow, ventilation and rates of oxygen consumption declined significantly when the speed increased to 4 km h^{-1} . In striking contrast to the pattern seen in mammals, the maximum values of blood flow were obtained during recovery, rather than during unsustainable exercise.

Blood flow through the posterior vena cava may be constrained by two mechanisms that result from the mechanics of running in these animals: (i) loss of the respiratory pump and/or (ii) elevated abdominal pressures. In mammals, ventilation-induced pressures in the abdomen and thorax have a dual effect, moving air into and out of the lungs and moving blood through the trunk (the respiratory pump) (Janicki et al., 1996). This pumping of blood is particularly important during exercise and, in conjunction with the skeletal muscle pump, supplements the pressure gradient generated by the heart to maintain the high cardiac outputs found during heavy exercise (Janicki et al., 1996). In contrast, the conflicting demands placed on the axial musculature of *Iguana iguana* during locomotion limit their recruitment for ventilation, causing ventilation to decline as locomotor speeds increase (Carrier,

1987b; Wang et al., 1997). We propose that the loss of the respiratory pump at the higher locomotor speeds contributes to the reduction of blood flow in the posterior vena cava.

An increase in pressure in the trunk during locomotion may also contribute to reduced blood flow from the caudal body during running in *Iguana iguana*. An elevation of abdominal pressure during locomotion is unavoidable given that all the hypaxial muscles (i.e. the muscles of the body wall) are active during locomotion (Carrier, 1990; Ritter, 1996). Increased abdominal pressures will tend to collapse the abdominal veins, increasing their resistance to flow and impeding the return of blood from peripheral veins into and through the posterior vena cava.

The hypothesis that elevated trunk pressures and a reduction in ventilation in *Iguana iguana* decrease venous return is consistent with data on exercising humans that voluntarily hold their breath. A 10 s breath-hold while exercising or during recovery from exercise causes a significant decrease in cardiac output due entirely to a progressive reduction in stroke volume; heart rate is unchanged (Miles et al., 1988). Breath-holding appears to reduce venous return both by the loss of the respiratory pump and by an increase in intrathoracic pressure (Miles et al., 1988). In a preliminary experiment, we measured cardiac output in one animal during high-speed exercise by placing an ultrasonic flow probe around the cardiac outflow

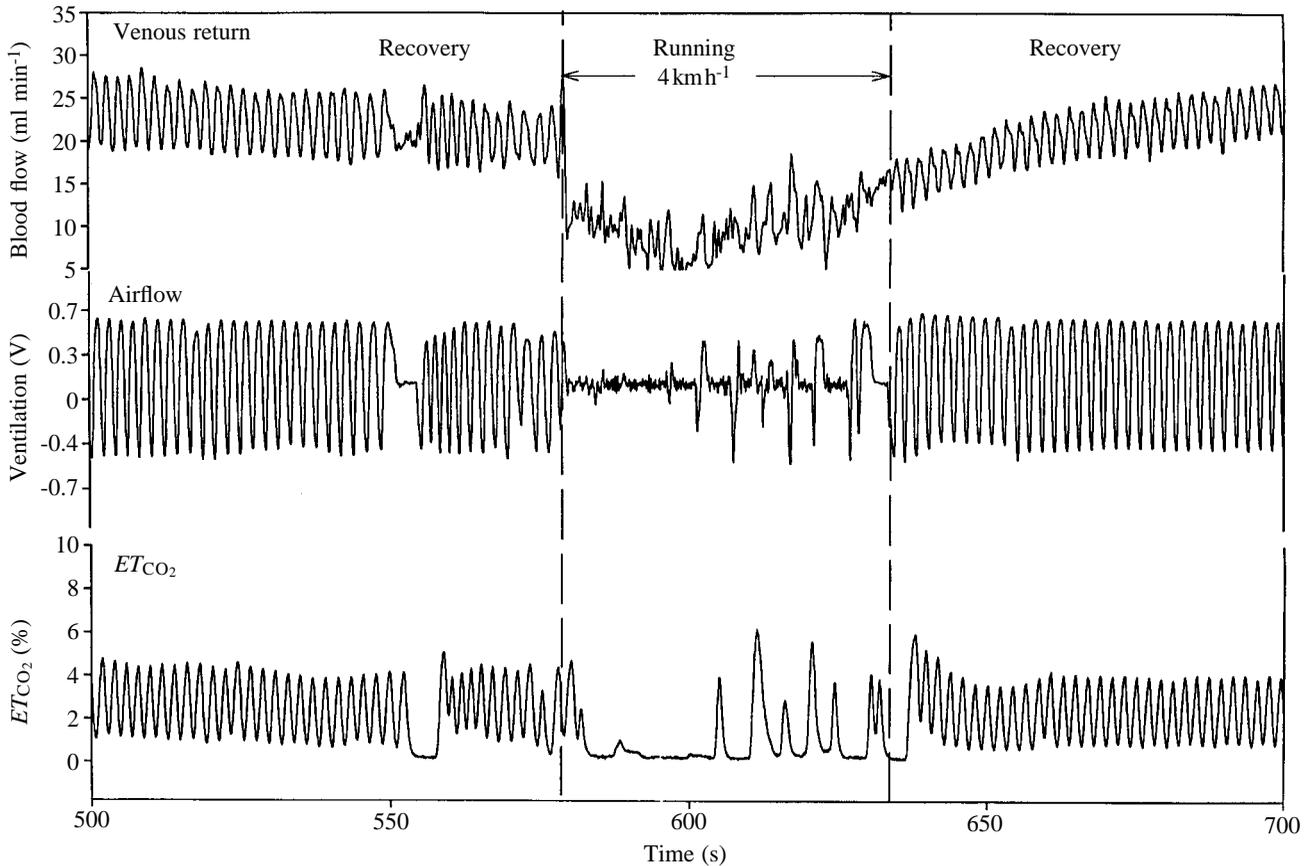


Fig. 3. The same data as in Fig. 1 but with an expanded time scale to illustrate the exercise period that occurred during recovery.

tracts (i.e. the pulmonary artery and the left and right aortas). We found a pattern identical to that produced by breath-holding in humans. As ventilation declined and pressure increased at the higher running speed, stroke volume fell by

7% while heart rate remained unchanged. It is not surprising to find that venous return affects cardiac output in lizards because it has long been known that, as with mammals, central venous pressures play a critical role in determining end-diastolic volumes and cardiac power in ectothermic tetrapods (Johansen and Burggren, 1984; Lillywhite, 1985).

Thus, our measurements of lung ventilation and blood flow in *Iguana iguana* suggest that both convective steps of the oxygen cascade begin to fail with unsustainable locomotion (i.e. locomotion that is faster than a slow walk). We believe there are several noteworthy points regarding these data. First, because locomotion curtails the convection of oxygen as a

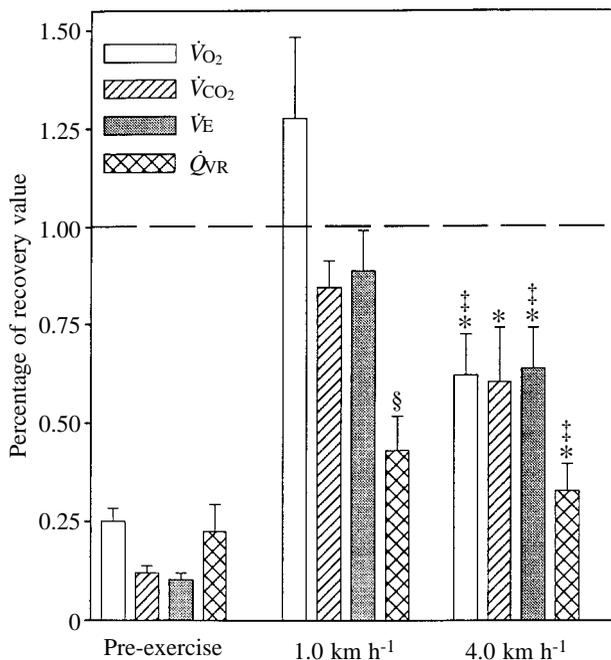


Fig. 4. Mean + s.d. ($N=5$) blood flow through the posterior vena cava (\dot{Q}_{VR}), ventilation (\dot{V}_E) and rates of oxygen consumption (\dot{V}_{O_2}) and carbon dioxide excretion (\dot{V}_{CO_2}) during the pre-exercise period, during sustainable exercise (1 km h^{-1}) and during unsustainable exercise (4 km h^{-1}) compared with recovery values. All values are expressed as a percentage of the maximal value measured during recovery. There was a significant reduction in the rate of oxygen consumption, ventilation and venous flow at unsustainable speeds compared with sustainable speeds ($P<0.05$; ANOVA), indicated with †. All values were significantly ($P<0.05$; ANOVA) reduced at the higher speeds compared with recovery, indicated by *. Blood flow at 1 km h^{-1} was significantly ($P<0.05$; ANOVA) less than that measured during recovery, indicated by §. All values were significantly different from pre-exercise values ($P<0.05$; ANOVA).

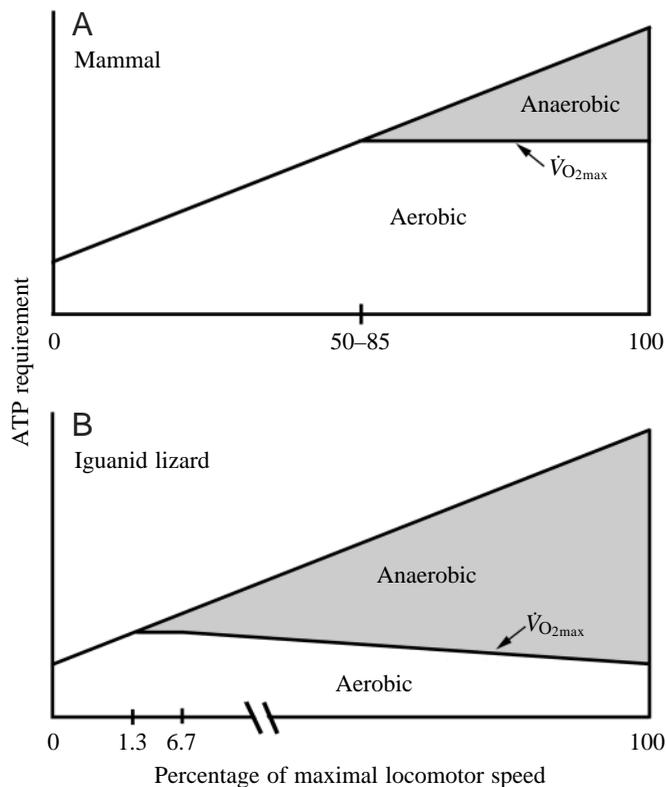


Fig. 5. Patterns of aerobic and anaerobic contributions to activity metabolism as a function of running speed postulated to occur in mammals and lizards. (A) The pattern typical of mammals; it has also been suggested that this pattern applies to ectothermic tetrapods. The rate of oxygen consumption (\dot{V}_{O_2}) increases as running speed increases until the maximum rate (\dot{V}_{O_2max}) is reached. At higher speeds, the rate of oxygen consumption stays maximal but the additional ATP required for muscular contractions is supplied by anaerobic metabolism. Maximum rates of oxygen consumption are generally reached at 50% or more of the maximum running speed. (B) The pattern expected when there is a constraint on ventilation that becomes more severe as running speed increases. Maximum rates of oxygen consumption of a 1 kg *Iguana iguana* are reached at approximately 1.3% of the maximum running speed. The rate of oxygen consumption reaches a maximum between 0.2 and 0.5 km h⁻¹ (Mitchell et al., 1981), but these animals are capable of short-duration running at 15 km h⁻¹ (Carrier, 1987b). A decline in the rate of oxygen consumption is seen at speeds between 1 and 2 km h⁻¹ (Wang et al., 1997), a small fraction (6.7%) of their running capacity.

function of locomotor speed, the mammalian paradigm of activity metabolism, in which the rate of oxygen consumption increases to a maximum and is maintained at that level as workload increases to its maximum or to near its maximum (see below), is not appropriate for these animals. Second, although the significance to oxygen flux of morphological variables such as pulmonary and tissue diffusive capacity are widely recognized, these data on *Iguana iguana* illustrate that axial morphology, posture and locomotor mechanics are also important determinants of oxygen consumption and high-speed stamina.

Speculation on the evolution of high-speed locomotor stamina

Tetrapods have diverse capacities to sustain activity; mammals and birds are well known for their high-speed endurance, whereas many species of lizard cannot maintain speeds faster than a slow walk for more than several minutes. A capacity for high-speed endurance is correlated with the maximal rate at which an animal can consume oxygen (\dot{V}_{O_2max}) (Taigen et al., 1982; Taigen and Pough, 1983), and many authors have linked the evolution of high-speed endurance to the evolution of elevated \dot{V}_{O_2max} (Bennett, 1991; Taigen et al., 1982; Taigen and Pough, 1983). In this paradigm, the distinction in high-speed endurance between an ectotherm and an endotherm can be attributed to the greater \dot{V}_{O_2max} of the endotherm (Bennett, 1991; Pough, 1980).

It has also been suggested that the absolute difference in \dot{V}_{O_2max} between an endotherm and a lizard does not fully account for their differences in exercise metabolism, but that the pattern of oxygen consumption as a function of running speed is strikingly different for endotherms and lizards (Carrier, 1987a,b). Lizards walk and run with a lateral undulatory gait in which the body flexes from side to side, requiring unilateral recruitment of muscles of the trunk, but costal ventilation requires the recruitment of these muscles in a bilaterally symmetrical manner (Carrier, 1989, 1990). Hence, lizards are mechanically constrained from simultaneous costal ventilation and locomotion, a constraint that becomes increasingly severe as running speeds increase. This speed-dependent constraint on costal ventilation is predicted to produce a very different pattern of oxygen consumption as a function of running speed from that seen in mammals (Fig. 5). In mammals, oxygen consumption increases with running speed until a maximum rate is reached, which generally occurs at 50% or more of the total running capability. For example, Thoroughbred racehorses reach \dot{V}_{O_2max} at approximately 58 km h⁻¹ (Landgren et al., 1991), but they are capable of running at approximately 68 km h⁻¹ (McWhirter and McWhirter, 1980). Hence, these animals reach \dot{V}_{O_2max} at approximately 85% of their maximum running speed. In striking contrast to this pattern, iguanid lizards weighing approximately 1 kg reach \dot{V}_{O_2max} when walking at between 0.2 and 0.5 km h⁻¹ (Mitchell et al., 1981), but they are capable of running at 15 km h⁻¹ (Carrier, 1987b). Hence, \dot{V}_{O_2max} is reached at approximately 1.3% of the total running speed. In *Iguana iguana*, oxygen consumption reaches a plateau and then decreases between 1 and 2 km h⁻¹ (Wang et al., 1997), which is only approximately 6.7% of their maximum running speed. It has been suggested this decrease in the rate of oxygen consumption at such a small fraction of their total locomotor speed is due to their inability to ventilate their lungs adequately (Carrier, 1987a,b).

Our results are consistent with the paradigm put forward by Carrier (1987a,b) in that oxygen transport is impaired by locomotor speeds that are faster than a slow walk. However, our results are also consistent with the idea that maximum rates of oxygen consumption are set by an integrative interplay between every step of the oxygen cascade (Hoppeler and

Weibel, 1998; Wagner, 1988; Wagner et al., 1997). It has long been appreciated that it is the mechanical integration of the cardiac, muscular and ventilatory pumps that enables mammals to adjust cardiac output over a wide range as locomotor speeds increase (Janicki et al., 1996) but, as far as we know, it has not been previously documented that this integration may be lacking in non-mammalian amniotes. In mammals, this mechanical integration is accomplished with a suite of characters, many of which are well studied and well known (e.g. Bainbridge and baroreceptor reflexes, venoconstriction, etc.). Although less well studied, the thoracic and abdominal pressure changes that occur during locomotion can affect both preload and afterload (Janicki et al., 1996). The phase relationships between the pressures of these compartments can vary depending on the patterns of ventilation and the speed of locomotion (Janicki et al., 1996). All these factors can play a role in determining cardiac output and oxygen consumption (Janicki et al., 1996). Keeping in mind, then, that oxygen consumption is determined not only by the capacity for oxygen flux in each step of the cascade, but is also a function of how well these steps are integrated and how this integration may change over a range of locomotor speeds, it is possible to speculate that the innovations that enable mammals and birds to integrate mechanically the cardiac, ventilatory and muscular pumps are little-appreciated aspects of the evolution of high-speed locomotor stamina.

We thank A. Bennett, D. Carrier, D. Jackson and three anonymous reviewers for comments on the manuscript and/or for the use of equipment. We are also grateful to D. Carrier for assistance in collecting portions of the data. This work was funded by an NSF doctoral dissertation improvement grant (IBN-9423297), an NIH individual national research service award (1F32-HL09796-01) to C.G.F. and NSF IBN-9630807 to J.W.H.

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