

Elevated intra-abdominal pressure limits venous return during exercise in *Varanus exanthematicus*

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Summary

The effects of treadmill exercise on components of the cardiovascular (venous return, heart rate, arterial blood pressure) and respiratory systems (minute ventilation, tidal volume, breathing frequency, oxygen consumption, carbon dioxide production) and intra-abdominal pressure were investigated in the Savannah monitor lizard, *Varanus exanthematicus* B., at 35°C. Compared with resting conditions, treadmill exercise significantly increased lung ventilation, gular pumping, intra-abdominal pressure, mean arterial blood pressure and venous return (blood flow in the post caval vein). However, venous return declines at high levels of activity, and mean arterial pressure and venous return did not attain peak values until the recovery period, immediately following activity. Elevating intra-abdominal pressure in

resting lizards (*via* saline infusion) resulted in significant reductions in venous return when the transmural pressure of the post caval vein became negative (i.e. when intra-abdominal pressure exceeded central venous pressure). Together these results suggest that increments in intra-abdominal pressure compress the large abdominal veins and inhibit venous return. During locomotion, the physical compression of the large abdominal veins may represent a significant limitation to cardiac output and maximal oxygen consumption in lizards.

Key words: exercise, hemodynamics, intra-abdominal pressure, lizard, locomotion, oxygen consumption, reptile, venous return, ventilation.

Introduction

Movement of oxygen from the atmosphere to the mitochondria occurs *via* several convective and diffusive steps (Weibel et al., 1981). In mammals, maximal rate of oxygen consumption ($\dot{V}_{O_{2max}}$) is not limited by any one step of the oxygen cascade; rather limitations to $\dot{V}_{O_{2max}}$ are distributed across all steps (Hoppler and Weibel, 1998; Wagner, 1988; Wagner et al., 1997). However, this symmorphotic distribution of oxygen transport limitations (see (Taylor and Weibel, 1981; Weibel et al., 1991) may not be universal in vertebrates, and weak links in the oxygen transport cascade may be found in other animals, such as varanid lizards. Numerous studies have shown that almost all varanid lizards have high aerobic capacities and that they possess a number of physiological alterations that result in more efficient gas exchange and greater delivery of oxygen to the tissues relative to other lizards (for review, see Frappell et al., 2002b). In varanid lizards it has been suggested that limitations to $\dot{V}_{O_{2max}}$ occur within the cardiovascular, but not within the respiratory system (Bennett, 1994; Frappell et al., 2002a; Mitchell et al., 1981; Saltin, 1985; Wagner, 1988).

Recent studies have demonstrated that ventilation is constrained during exercise in some lizards. The laterally undulating gait employed by lizards requires unilateral

recruitment of hypaxial muscles, and costal ventilation requires bilateral recruitment of the same hypaxial muscles. This conflict may result in a speed-dependent constraint on ventilation (Carrier, 1987). Thus, effective lung ventilation may be compromised in exercising lizards by the lateral flexions that occur during locomotion (the axial constraint hypothesis). This constraint is overcome in varanid lizards due to the presence of an accessory ventilatory device, called the gular pump. Gular pumping enables varanid lizards to supplement costal ventilation during exercise, thus maintaining oxygen consumption despite a decrease in costal ventilation (Owerkowicz et al., 1999).

However, axial constraint may also have important implications for hemodynamics. Locomotion may elevate intra-abdominal pressure as a result of the activity of the hypaxial muscles that are recruited both during locomotion and ventilation (Carrier, 1990; Ritter, 1996). Elevated intra-abdominal pressures may act to compress the large veins in the abdomen and reduce venous return. An increase in intra-abdominal pressure and a reduction in blood flow from the caudal portions of the body occurred during high-speed running (4 km h^{-1}) in *Iguana iguana*, and suggests that venous return may be limited during exercise in iguanid lizards

(Farmer and Hicks, 2000). A reduction in blood flow returning to the heart may have important consequences for oxygen delivery to exercising muscles because systemic venous return and ventricular preload are the major determinants of cardiac output. Thus, in iguanid lizards, both ventilatory (axial constraint) and circulatory (venous return) constraints may act to limit $\dot{V}_{O_{2max}}$ during exercise. Varanid lizards circumvent the ventilatory constraints present in iguanid lizards by exploiting the gular pump; however, whether circulatory constraints similar to those in iguanid lizards exist in varanid lizards has not been investigated.

In mammals, venous return during exercise is the result of integration of the cardiac, skeletal muscle and respiratory pumps. Contraction of skeletal muscles can act as a circulatory pump in two ways: muscle contractions can compress intramuscular venous vessels, pushing blood towards the heart, and can reduce intramuscular venous pressure, creating an increased arterial–venous pressure gradient that aids blood flow in the muscle during relaxation (Rowland, 2001). Ventilation may also act to aid venous return. The negative intra-thoracic pressures created during inspiration increase the pressure gradient for blood flow back to the heart. During exercise, increased ventilation causes alternating distension of intra-thoracic vessels during inspiration and compression during expiration and may act to supplement cardiac output during exercise (Agostini and Butler, 1991). Thus, the pressure gradient generated by the heart is assisted by contraction of skeletal muscles and by the mechanical action of ventilation during exercise. However, the degree to which the cardiac, respiratory and skeletal muscle pumps are integrated in exercising reptiles has not been determined.

This study aimed to investigate the effects of exercise on venous return, intra-abdominal pressure, ventilation and gas exchange in *Varanus exanthematicus*. In addition, intra-abdominal pressure was increased using temperature-equilibrated saline in resting lizards. Saline-induced elevations in intra-abdominal pressure were designed to simulate the elevated intra-abdominal pressures measured in exercising lizards and, thus, to determine the hemodynamic and respiratory consequences of increased intra-abdominal pressures in the absence of the confounding effects of exercise.

Materials and methods

Animals

All Savannah monitor lizards (*Varanus exanthematicus* Bosc 1792) were obtained from a commercial dealer and kept in cages with a thermal gradient (28–38°C), full spectrum lighting (14 h:10 h L:D; Zoo Med, San Luis Obispo, CA, USA), free access to water and were fed a diet of whole mice, chicken meat and crickets. The six lizards used for the treadmill exercise experiment ranged in mass from 369 to 839 g (mean \pm S.E.M.=577 \pm 82 g). Five additional lizards ranging in mass from 859 to 1413 g (mean \pm S.E.M.=1033 \pm 110 g) were used to measure the effects of altered intra-abdominal pressure during rest.

Surgical procedure, blood flow, intra-abdominal pressure and blood pressure

Lizards were lightly anesthetised by placing them in a sealed container with gauze dampened with Isoflurane (Isoflo; Abbott laboratories, North Chicago, IL, USA). Lizards were then intubated and artificially ventilated (SAR-830; CWE Inc., Ardmore, PA, USA) with room air that had been passed through a vapourizer (Dräger, Lubeck, Germany). The vapourizer was initially set at 3–4%, and was then reduced to 1–2% for the majority of the surgery. A 3 cm ventral incision was made in the abdomen and a loose-fitting ultrasonic blood flow probe (2R; Transonic System Inc., Ithaca, NY, USA) was placed around the post caval vein (homologous to the mammalian inferior vena cava). In *Varanus exanthematicus* the two renal portal veins (carrying blood from the hind limbs, tail and pubic region) fuse to form the post caval vein just before its entry into the right lobe of the liver. The ultrasonic blood flow probe was placed around the post caval vein, anterior to the union of the two renal portal veins, but posterior to its entry into the right lobe of the liver. The intestinal, lienogastric, gastric and abdominal veins fuse to form the hepatic portal vein, which enters the left lobe of the liver (Schaffner, 1998). Thus, the venous return measured in this study comprises venous drainage from the hind limbs and tail, but excludes drainage from the gastrointestinal tract, which enters the liver anterior to the location of the blood flow probe. A pressure transducer (Millar Mikrotip; Millar Instruments Inc., Houston, TX, USA) was sutured to connective tissue adjacent to the flow probe. The probes were exteriorized through the lateral body wall approximately 5 cm anterior to the pelvis and secured using 3-0 silk sutures on the dorsal surface of the tail. In addition, the lizards used in the resting experiments had a 2–3 cm piece of sterile Tygon tubing inserted into the abdominal cavity; the remaining length of tubing (10–15 cm) was exteriorized *via* the same lateral incision used for the blood flow probes. This tubing served as a port for the introduction of saline and the direct alteration of intra-abdominal pressure.

The brachial artery was cannulated to measure arterial blood pressure. A 1–2 cm incision was made in the ventral surface of the upper fore limb. The brachial artery was exposed using blunt dissection techniques and the artery cannulated with polyethylene tubing (i.d. 0.023 cm, o.d. 0.038 cm; Harvard Apparatus, Inc., Holliston, MA, USA) and secured using 3-0 sutures. Blood pressure was measured using disposable pressure transducers (model MLT0670; AD Instruments, Colorado Springs, CO, USA).

In addition to the procedures detailed above, central venous pressure and right atrial pressure were also measured in resting *V. exanthematicus*. The femoral vein was exposed using the procedure detailed above for brachial artery cannulation. A 3.5F pressure transducer (Millar Mikrotip) was introduced into the femoral vein and advanced 5–7 cm into the central venous circuit. Another 3.5F pressure transducer was introduced into the right atria *via* a 1–2 mm incision in the atrial wall and secured using 4-0 silk.

All incisions were closed with intermittent sutures and treated with cyanoacrylate tissue adhesive (Vetbond; 3M, St Paul, MN, USA). Artificial ventilation with room air was continued until the lizard regained consciousness and reinitiated spontaneous breathing. Intramuscular injections of the antibiotic enrofloxacin (Baytril; Bayer Corporation, Shawnee Mission, KS, USA), and the analgesic flunixin meglumine (Flunixin; Fort Dodge, Madison, NJ, USA) were given at the conclusion of surgery. Enrofloxacin injections were repeated every second day after surgery. A minimum recovery period of 2 days was given before commencement of experimentation.

Lung ventilation and gas exchange

Ventilation was measured using a mask constructed from the base of a 50 ml polypropylene centrifuge tube (Corning Inc. Life Sciences, Acton, MA, USA). Flexible tubing was attached *via* two ports drilled into the mask. The mask was attached over the lizard's nostrils and the mouth sealed closed with a dental polyether impression material (Impregum F; 3M EPSE, St Paul, MN, USA). Impregum is non-toxic, easily removable and non-exothermic. Fresh room air was drawn through the mask using a sealed aquarium air pump at a constant flow rate of between 1.2 and 1.7 l min⁻¹ (depending on the size of the lizard). Care was taken to ensure that the flow rate through the mask exceeded the rate of inspiration, thus minimising the possibility of rebreathing. Air flow through the mask was controlled with rotameters (Brooks Instruments, Hatfield, PA, USA). Alterations in airflow due to ventilation were measured using a pneumotachograph (8311; Hans Rudolph, Inc., Kansas City, MO, USA) placed upstream of the mask, such that expirations caused an increase in airflow and inspiration caused a decrease in airflow. Pressure gradients induced by alterations in airflow across the pneumotachograph were monitored using a Validyne differential pressure transducer (MP-45-1-871; Validyne, Northridge, CA, USA). The signal from the differential pressure transducer was calibrated by injecting and withdrawing known volumes of gas from the sealed mask and was integrated to obtain tidal volumes. Costal ventilations were distinguished from gular pumps *via* visual observation of the lizards and the absence of expirations before the low volume gular pumps. Gas from the mask was sub-sampled and passed through Drierite (anhydrous calcium sulfate, Sigma-Aldrich Co., Milwaukee, WI, USA) before being passed through CO₂ (CD-3A; Applied Electrochemistry Inc., Sunnyvale, CA, USA) and O₂ (S-3A; Applied electrochemistry Inc., Sunnyvale, CA, USA) analyzers. The rates of oxygen consumption (\dot{V}_{O_2}) and carbon dioxide production (\dot{V}_{CO_2}) were determined using a technique described previously (Bennett and Hicks, 2001; Farmer and Hicks, 2000; Wang et al., 1997). Briefly, \dot{V}_{O_2} and \dot{V}_{CO_2} of single breaths were determined as the area below (\dot{V}_{O_2}) or above (\dot{V}_{CO_2}) the baseline signal for room air. Exhalations were simulated by injecting known volumes of known gas mixtures (21% O₂, 79% N₂; 100% N₂; 15% O₂, 5% CO₂, 80% N₂) into the mask to establish the relationship between this area and gas exchange. Minute ventilation and tidal volume are

reported at BTPS (body temperature and pressure, saturated) and metabolic gas values at STPD (atmospheric temperature and pressure, dry).

Experimental protocol

Treadmill exercise

Lizards were fasted for 7 days before surgery and were held at the experimental temperature (35°C) for 2–3 days before experimentation. A mask was attached over the lizard's nostrils and the lizard was placed on the treadmill belt. The lizard was left on the stationary treadmill belt for at least 1 h before the treadmill was started to obtain pre-exercise 'resting' measurements. All lizards rested quietly on the treadmill during the pre-exercise period. The exercise regime was similar to that used in the same species by Bennett and Hicks (2001) and consisted of a sequential step protocol with consecutive 4 min exercise bouts at each of four treadmill speeds: 0.5, 1.0, 1.5 or 2.0 km h⁻¹. Locomotion was initiated by gently tapping the treadmill belt behind the lizard or by lightly touching the lizard's tail. All lizards completed the exercise protocol, with exhaustion occurring between the third and fourth minute of exercise at 2.0 km h⁻¹. Exhaustion was defined as the failure of the lizard to keep pace with the treadmill belt despite tactile encouragement. At the lowest treadmill speed of 0.5 km h⁻¹, the lizard's locomotion was intermittent, but sustained locomotion was maintained consistently at all other treadmill speeds until exhaustion. Ventilatory and cardiovascular parameters reached a steady state by 3 min of treadmill exercise at each speed. To obtain blood pressure recordings that were unaffected by movement, the treadmill was stopped for 30 s at the end of each 4 min period, after which the treadmill was restarted at the next speed. After the exercise regime was completed, the lizards were allowed to rest on the treadmill for up to 2 h (termed the recovery period). Preliminary experiments suggested that venous return and mean arterial blood pressure may increase immediately after exercise ceased and, thus, the recovery period was included to allow determination of cardiovascular and respiratory parameters immediately after exercise.

Direct alteration of intra-abdominal pressure in resting lizards

Lizards were fasted for 7 days before surgery and were held at the experimental temperature (35°C) for 2–3 days before experimentation. A mask was attached over the lizard's nostrils and the lizard was placed in a darkened plastic holding container. The lizard rested quietly for at least 1 h before the alteration of intra-abdominal pressure. Intra-abdominal pressure was increased by the injection of temperature equilibrated sterile saline into the tygon port previously implanted. Intra-abdominal pressures of double and triple resting pressures were induced separately for 5 min, followed by a return to resting intra-abdominal pressure (by withdrawal of saline) for at least 1 h.

Data collection, analysis and statistics

All signals were collected on a computer at 120 Hz using

Acknowledge data-acquisition software (Biopac, Goleta, CA, USA). Owing to the intermittent and variable nature of reptilian ventilation and the low breathing frequencies at rest, ventilatory and cardiovascular parameters, and intra-abdominal pressure, were calculated from the last 10 min of the pre-exercise period before commencement of treadmill exercise. Minute ventilation, \dot{V}_{O_2} , \dot{V}_{CO_2} , intra-abdominal pressure (P_{IA}) and post caval blood flow (\dot{Q}_{PC}) were calculated from the last minute of treadmill exercise at each speed. Blood pressure and heart rate were calculated from the first 10 s of the 30 s pause between each treadmill speed. All recovery period data (except \dot{Q}_{PC} and blood pressure) were calculated from a 60 s window surrounding the maximal blood pressure response. Venous return peaked earlier than maximal blood pressure (40 s vs 140 s after exercise ceased), thus the recovery \dot{Q}_{PC} was calculated from a 10 s period at maximal blood flow. Blood pressure during recovery was measured from a 10 s period at the maximal response. Mean arterial blood pressure (\bar{P}_a) was calculated as:

$$\bar{P}_a = \frac{1}{3} P_S + \frac{2}{3} P_D,$$

where P_S is systolic blood pressure and P_D is diastolic blood pressure (Altimiras et al., 1998). The pattern of \dot{Q}_{PC} and \bar{P}_a during the recovery period was plotted by calculating the mean response of each parameter during consecutive 10 s periods as a percentage of end exercise values.

For experiments involving the direct manipulation of intra-abdominal pressure in resting lizards, all cardiovascular parameters were calculated from the last minute of the resting period and the last minute of the elevated intra-abdominal pressure period. Ventilatory parameters were calculated from the last 10 min of the resting period and the last minute of the elevated intra-abdominal pressure period.

The effect of increasing treadmill speed on all parameters was determined using paired Dunnett's tests with the rest period as the control ($P < 0.05$). Comparisons of the recovery period to the maximal treadmill speed were performed using a paired Student's t -test ($P < 0.05$). The effects of increased intra-abdominal pressure (via saline infusion) on all parameters were determined using paired t -tests ($P < 0.05$). All data presented are means \pm S.E.M.

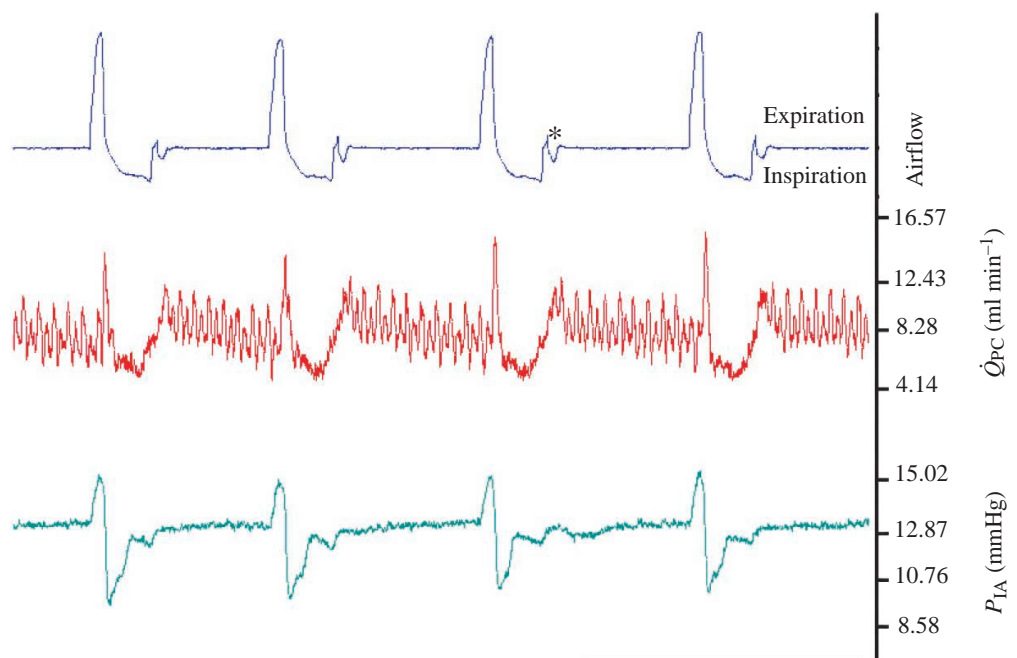
Results

The effects of treadmill exercise

Simultaneous measurements of ventilation, intra-abdominal pressure, arterial blood pressure and venous return (post caval blood flow) were made at rest and during progressive treadmill exercise. Blood flow in the post caval vein (\dot{Q}_{PC}) was pulsatile, the rate matching heart rate at rest and at all treadmill speeds. Ventilation caused fluctuations in \dot{Q}_{PC} and intra-abdominal pressure (P_{IA} ; Fig. 1). Ventilation always began with an expiration, which increased \dot{Q}_{PC} and P_{IA} , whereas costal inhalations caused a decrease in \dot{Q}_{PC} and P_{IA} . The respiratory cycle variations in \dot{Q}_{PC} are comparable to the action of the respiratory pump in mammals.

\dot{Q}_{PC} increased during the three lower treadmill speeds (0.5, 1.0 and 1.5 km h⁻¹) from 8.76 \pm 2.27 at rest to 19.64 \pm 5.77, 20.34 \pm 5.44 and 21.63 \pm 6.11 ml min⁻¹ kg⁻¹, respectively (Fig. 2). However, at the maximum treadmill speed of 2.0 km h⁻¹, \dot{Q}_{PC} decreased to 12.30 \pm 1.21 ml min⁻¹ kg⁻¹ and was not significantly different from that measured during rest. Systolic (P_S), diastolic (P_D) and mean arterial blood pressures (\bar{P}_a) were also elevated during treadmill exercise; however, neither \bar{P}_a nor \dot{Q}_{PC} showed any incremental increase with treadmill speed (Fig. 2). This trend was also observed in the heart rate response to exercise.

Fig. 1. A representative recording from one varanid lizard (post exercise) demonstrating that costal ventilation caused phasic alterations in post caval blood flow (\dot{Q}_{PC}) and intra-abdominal pressure (P_{IA}). A 25.0 ml expiration increased \dot{Q}_{PC} by 6.91 ml min⁻¹ and P_{IA} by 2.21 mmHg. A 23.3 ml inspiration decreased \dot{Q}_{PC} by 3.61 ml min⁻¹ and P_{IA} by 2.97 mmHg. The effect of respiratory cycle variations in P_{IA} was a net increase in \dot{Q}_{PC} , comparable to the respiratory pump in mammals. Note: \dot{Q}_{PC} blood flow was pulsatile with a rate that was strongly correlated with heart rate. Gular pumps (*) decrease P_{IA} slightly, but do not alter \dot{Q}_{PC} beyond fluctuations due to heart rate variability. Trace taken 10 min after exercise at 30°C in *V. exanthematicus* (mass 502 g). Scale bar, 15 s. 1 mmHg=133.3 Pa.



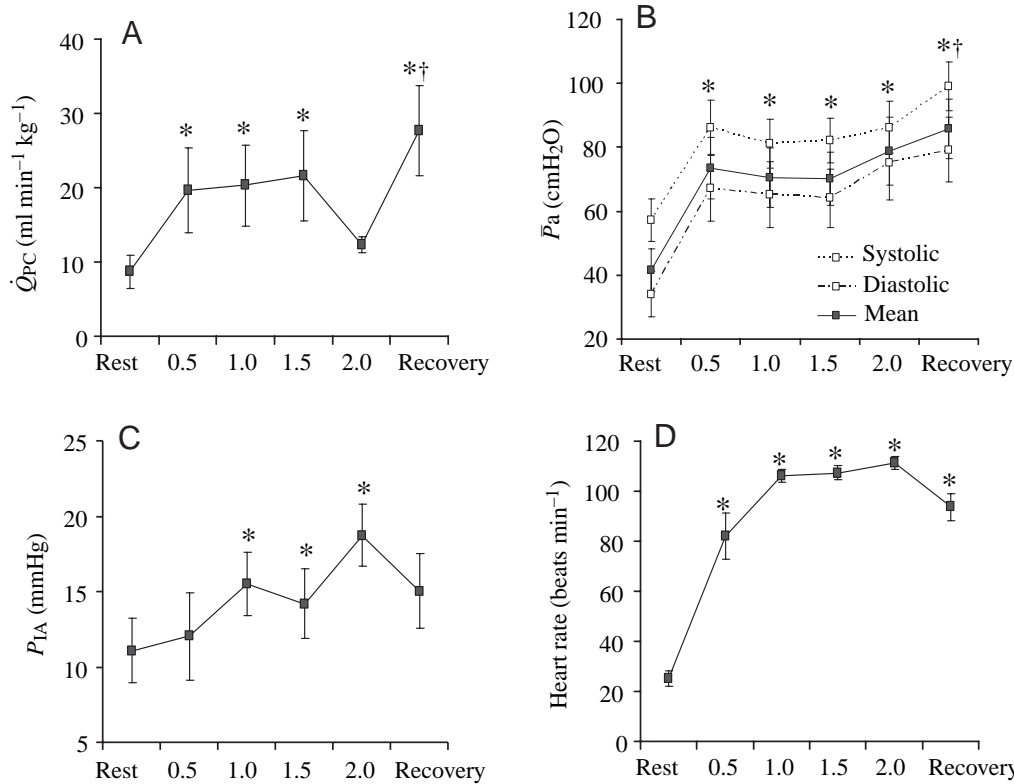


Fig. 2. The effects of treadmill exercise on (A) inferior vena cava blood flow (\dot{Q}_{PC}), (B) mean arterial blood pressure (\bar{P}_a), (C) intra-abdominal pressure (P_{IA}) and (D) heart rate in *Varanus exanthematicus*. *Indicates significance relative to rest (Dunnett's test, $P < 0.05$). †Indicates significance relative to 2.0 km h^{-1} (Student's paired t -test, $P < 0.05$). Data presented are means \pm S.E.M. ($N=6$). Note: statistical significances are shown only for mean arterial blood pressure for visual clarity; the statistical results for systolic and diastolic blood pressure follow the same trend as those for mean arterial blood pressure. 1 mmHg=133.3 Pa; 1 cmH₂O=98.1 Pa.

Heart rate increased from $25.11 \pm 2.99 \text{ min}^{-1}$ at rest to $82.05 \pm 9.17 \text{ min}^{-1}$ at 0.5 km h^{-1} (Fig. 2). Heart rate did not increase between 1.0 and 2.0 km h^{-1} (106.12 ± 2.50 , 107.43 ± 2.63 and $111.26 \pm 2.38 \text{ min}^{-1}$, respectively). Resting P_{IA} ($11.09 \pm 2.14 \text{ mmHg}$) was variable between individual lizards, predominantly due to body posture, degree of gastrointestinal tract filling and exact transducer position. P_{IA} was not significantly different from rest at 0.5 km h^{-1} ($12.03 \pm 2.88 \text{ mmHg}$), but increased to 15.48 ± 2.11 , 14.18 ± 2.29 and $18.74 \pm 2.09 \text{ mmHg}$ as treadmill speed increased from 1.0 to 2.0 km h^{-1} (Fig. 2). Peak P_{IA} was measured in response to treadmill exercise at 2.0 km h^{-1} , representing a 43% increase in P_{IA} relative to that measured at 1.5 km h^{-1} .

Inspiration can occur *via* two methods in *V. exanthematicus*; costal inhalation and gular pumping. Costal ventilation initially increased in response to treadmill exercise, but as treadmill speed increased to 1.5 and 2.0 km h^{-1} , costal ventilation decreased as a result of a decrease in tidal volume but no alteration in breathing frequency (Fig. 3). Gular pumping was not observed in resting *V. exanthematicus*. Gular pumping increased in response to treadmill exercise, due to increases both in gular pump volume (up to $8.3 \pm 0.4 \text{ ml kg}^{-1}$) and in gular pump frequency (up to $40.5 \pm 3.3 \text{ min}^{-1}$). The combined effects of treadmill exercise on costal and gular minute ventilation resulted in an increase in total ventilation, oxygen consumption and carbon dioxide production as treadmill speed increased.

Maximum \dot{Q}_{PC} and \bar{P}_a occurred during the recovery period, but the time course to peak responses differed. Maximal \dot{Q}_{PC} was measured at 40 s after exercise ceased, whereas maximal \bar{P}_a was measured 140 s after exercise ceased (Fig. 4).

The effects of increased intra-abdominal pressure in resting lizards

Increasing P_{IA} *via* infusion of temperature-equilibrated saline increased central venous pressure (P_{CV}), diastolic right atrial pressure (P_{RA}), and heart rate, but did not significantly alter \bar{P}_a (Table 1). Transmural pressure of the post cava (P_{TRANS}) was significantly reduced at both double and triple P_{IA} . P_{TRANS} became negative when P_{IA} was doubled due to P_{IA} exceeding P_{CV} , but remained positive when P_{IA} was tripled due to P_{CV} exceeding P_{IA} . Negative P_{TRANS} (at double resting P_{IA}) corresponded with a 52% reduction in \dot{Q}_{PC} , whereas no significant alteration in \dot{Q}_{PC} occurred when P_{IA} was tripled and P_{TRANS} remained positive (Fig. 5). Increasing P_{IA} significantly reduced inspired tidal volume (V_{TI}) and increased breathing frequency (f_b), resulting in no significant alteration in minute ventilation (\dot{V}_E) (Table 1).

Discussion

\dot{Q}_{PC} (venous return, i.e. post caval vein blood flow) increased with treadmill exercise in *V. exanthematicus*, but interestingly, peak venous return occurred during the recovery period, suggesting that venous return was suppressed during exercise. It is likely that the suppression of venous return during exercise was the result of an exercise-induced elevation of intra-abdominal pressure (P_{IA}). A doubling of P_{IA} in resting *V. exanthematicus*, an increase equivalent to that induced by maximal treadmill exercise, resulted in a 52% reduction in \dot{Q}_{PC} *via* reductions in P_{TRANS} (Fig. 5), further suggesting that compression of the post caval vein by elevated P_{IA} reduces \dot{Q}_{PC} .

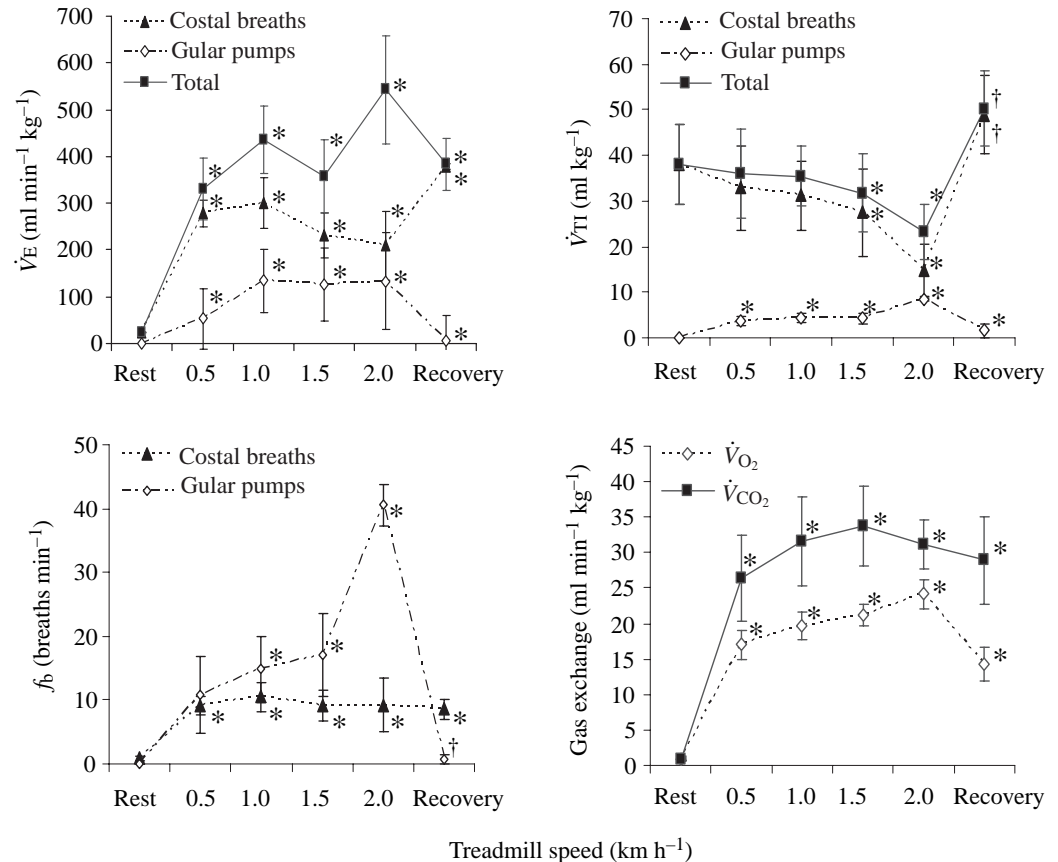


Fig. 3. The effects of treadmill exercise on (A) minute ventilation (\dot{V}_E), (B) tidal volume (\dot{V}_{TI}), (C) breathing frequency (f_b), (D) oxygen consumption and carbon dioxide production, in *Varanus exanthematicus*. *Indicates significance relative to rest (Dunnett's test, $P<0.05$). †Indicates significance relative to 2.0 km h⁻¹ (Student's paired t -test, $P<0.05$). Data presented are means \pm S.E.M. ($N=6$).

Elevations in P_{IA} during treadmill exercise have also been measured in *Iguana iguana* (Farmer and Hicks, 2000) and are probably the result of the hypaxial musculature being continuously active during exercise, serving a role both in lung ventilation and in lateral bending of the trunk (Carrier, 1990; Ritter, 1996). In *Iguana iguana*, treadmill exercise increased venous return at low speeds (1.0 km h⁻¹), but significantly reduced venous return while increasing P_{IA} at high speeds (Farmer and Hicks, 2000). High P_{IA} and reduced venous return during exercise may have broad hemodynamic ramifications, potentially limiting the increase in cardiac output and maximal oxygen consumption induced by exercise. Indeed, the 2–3-fold increases in venous return measured during exercise in this study are comparable with the 2–3-fold increases in systemic blood flow measured during a similar exercise regime in the same species of lizard (Wang et al., 1997), highlighting the interdependence of venous return and cardiac output.

The effects of elevated P_{IA} on hemodynamics have been studied in only one reptile (Farmer and Hicks, 2000), and variable results have been reported in mammals. Unlike mammals, reptiles do not possess a muscular diaphragm, so there is no separation of the abdominal and thoracic compartments. However, despite the presence of a muscular diaphragm in mammals, increases in P_{IA} do occur during inspiration due to descent of the diaphragm and displacement of the abdominal viscera (Decramer et al., 1984; Guyton and Adkins, 1954; Wexler et al., 1968). A P_{IA} below 10 mmHg is considered clinically normal in humans (Wittmann and

Iskander, 2000) and 8–12 mmHg is considered safe for laparoscopic surgery, thus avoiding the serious hemodynamic complications that arise from higher P_{IA} (Ishizaki et al., 1993; Neudecker et al., 2002). Low P_{IA} (<10 mmHg) and high P_{IA} (>20 mmHg) in combination with experimental manipulations, such as hypervolemia, increase venous return and cardiac output in anesthetized mammals (Kashtan et al., 1981; Richardson and Trinkle, 1976). However, high P_{IA} (>10 mmHg) decreases inferior vena cava blood flow resulting in a decrease in venous return (Barnes et al., 1985; Diamant et al., 1978; Ivankovich et al., 1975; Kashtan et al., 1981; Lynch et al., 1974; Richardson and Trinkle, 1976). A reduction in blood flow to the abdominal organs (renal, superior mesenteric and celiac vasculatures) has also been demonstrated in response to elevated P_{IA} (Barnes et al., 1985; Caldwell and Ricotta, 1987; Masey et al., 1985). At a P_{IA} of 15 mmHg (a pressure achieved during treadmill exercise in *V. exanthematicus*) gastrointestinal blood flow was reduced by 20–40% in anesthetized neonatal lambs (Masey et al., 1985). Similar reductions in gastrointestinal blood flow were found in anesthetized dogs at P_{IA} between 20 and 40 mmHg (Barnes et al., 1985; Caldwell and Ricotta, 1987).

In mammals, blood flow in the inferior vena cava represents approximately two thirds of total systemic venous return (Kitano et al., 1999; Scharf, 1995). Alterations in venous return have the potential to limit exercise performance because systemic venous return and ventricular preload are major determinants of cardiac output. Increases in P_{IA} in anesthetized

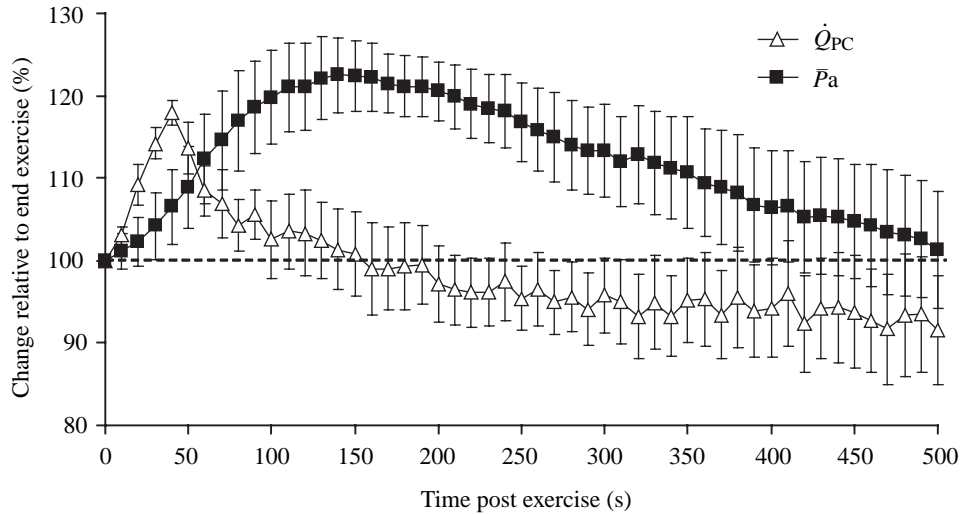


Fig. 4. Post cava blood flow (\dot{Q}_{PC}) and mean arterial blood pressure (\bar{P}_a) both peak during the recovery period after exercise. Maximal \dot{Q}_{PC} occurs at 40 s after exercise ceases, while \bar{P}_a peaks at 140 s. Data presented are mean percentage change relative to end exercise \pm S.E.M. ($N=6$).

mammals decrease cardiac output *via* decrements in stroke volume combined with more variable changes in heart rate [decreased heart rate (Masey et al., 1985); increased heart rate (Diamant et al., 1978; Ivankovich et al., 1975); no change in heart rate (Barnes et al., 1985)]. High P_{IA} of between 30 and 40 mmHg reduces cardiac output by 30–40% in anesthetized mammals (Barnes et al., 1985; Diamant et al., 1978; Lynch et al., 1974) and the degree of anesthesia may be responsible for the variability in heart rate responses.

Venous return is dependent on central venous pressure (P_{CV}), right atrial pressure (P_{RA}) and venous resistance. P_{CV} provides the upstream driving pressure for venous return and is determined by blood volume, vascular tone and the pressure

within the tissues surrounding the small veins and venules (capacitance vessels). P_{RA} provides the backpressure against venous return. Venous resistance is the hydraulic resistance of the veins between the capacitance vessels (site of mean systemic resistance) and the right atria. Thus, increases in P_{CV} act to augment venous return, while increases in P_{RA} or venous resistance act to decrease venous return. Large veins, such as the mammalian inferior vena cava or the lizard post caval vein, behave like collapsible tubes in which the cross-sectional area is largely a function of transmural pressure (Katz et al., 1969; Kresh and Noordergraaf, 1972; Moreno et al., 1970). When transmural pressure falls below zero, large alterations in vessel cross-sectional area occur, causing partial or complete collapse of the vessel and large increases in the viscous resistance to blood flow (Badeer and Hicks, 1992).

In resting *V. exanthematicus*, increasing P_{IA} significantly increased P_{RA} . However, concurrent increments in P_{CV} resulted in no significant alteration in the pressure gradient between the central venous circuit and the right atria (Table 1). A twofold increase in P_{IA} increased P_{CV} in resting lizards; however, P_{IA} exceeded P_{CV} , resulting in a negative P_{TRANS} and a 52% reduction in \dot{Q}_{PC} due to the collapse of the post caval vein. The elevated P_{CV} caused by a threefold increase in P_{IA} resulted in a significantly reduced but, importantly, still positive P_{TRANS} , thus maintaining \dot{Q}_{PC} . The high P_{CV} induced by a threefold increase in P_{IA} may be due to compression of the splanchnic veins and movement of venous blood from the gastrointestinal capacitance vessels to the central venous circuit. While a twofold increase in P_{IA} simulated the increase in P_{IA} that occurred during treadmill exercise, it is unclear whether threefold increases in P_{IA} are achieved during exercise, and these elevations in P_{IA} may only be physiologically relevant in certain conditions, such as after consuming a large meal or in gravid females. While high P_{CV} during threefold increases in P_{IA} have been measured in this study, the mechanisms underlying this increase are outside the scope of this study.

The hemodynamic responses to elevated P_{IA} are the result of complex interactions between P_{CV} , venous resistance and

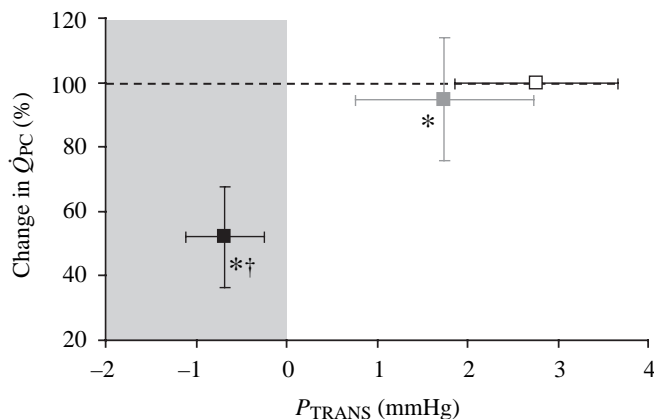


Fig. 5. A twofold increase in intra-abdominal pressure (P_{IA}) caused a decrease in post caval vein transmural pressure (P_{TRANS}) and a 52% decrease in flow through the post cava vein (\dot{Q}_{PC}). Despite inter-animal variation, a threefold increase in P_{IA} significantly decreased P_{TRANS} but did not alter \dot{Q}_{PC} . The gray panel indicates negative P_{TRANS} which theoretically correspond to the partial or complete collapse of the post cava vein. The open square represents resting P_{IA} , the black square represents double P_{IA} and the gray square represents triple P_{IA} . The dotted line indicates resting \dot{Q}_{PC} . *Indicates a significant decrease in P_{TRANS} and † indicates a significant decrease in \dot{Q}_{PC} (Bonferroni's corrected paired t -tests, $P<0.05$). Data presented are means \pm S.E.M. ($N=5$).

Table 1. *The effects of increasing intra-abdominal pressure in resting Varanus exanthematicus*

	Resting P_{IA} (3.27±1.13 mmHg)	Double P_{IA} (7.04±0.60 mmHg)	Triple P_{IA} (9.83±0.27 mmHg)
Heart rate	61.2±6.0	65.0±3.8	77.3±4.3*
P_{CV} (mmHg)	4.25±0.41	6.98±0.50 [†]	10.75±0.63 [‡]
\bar{P}_a (cmH ₂ O)	54.93±4.96	55.77±6.19	55.96±7.78
P_{RA} (mmHg)	2.23±0.58	5.43±0.74 [†]	8.87±0.82 [†]
P_{TRANS} (mmHg)	2.76±0.90	-0.69±0.44 [†]	1.74±0.99*
\dot{Q}_{PC} (%Δ)	100	51.98±15.74*	94.84±19.09
VTI (ml kg ⁻¹)	16.83±1.53	9.95±2.76 [†]	10.03±3.09 [†]
f_b (min ⁻¹)	1.57±0.21	4.00±0.44*	5.50±1.80*
\dot{V}_E (ml min ⁻¹ kg ⁻¹)	27.22±5.63	36.94±9.92	38.55±11.56

The effects of increasing intra-abdominal pressure (P_{IA}) on heart rate, central venous pressure (P_{CV}), mean arterial pressure (\bar{P}_a), right atrial pressure (P_{RA}), post cava transmural pressure (P_{TRANS}), proportion (%) change in venous return (i.e. post caval vein blood flow, \dot{Q}_{PC}) relative to resting values, inspired tidal volume (VTI), breathing frequency (f_b) and minute ventilation (\dot{V}_E) in resting *Varanus exanthematicus*. Data presented are means ± S.E.M. ($N=5$). Asterisks represent results of Bonferroni's corrected paired t -tests between resting and elevated P_{IA} . * $P<0.05$, [†] $P<0.01$, [‡] $P<0.001$. 1 mmHg=133.3 Pa; 1 cmH₂O=98.1 Pa.

P_{RA} . If the increase in P_{IA} exceeds P_{CV} , P_{TRANS} becomes negative and post caval collapse will occur, resulting in an increase in venous resistance and a decrease in venous return. However, the effect of elevated P_{IA} on the driving gradient for venous return will be dependent on the interaction of P_{CV} and P_{RA} . The complex interactions of P_{IA} , P_{CV} , P_{RA} and \dot{Q}_{PC} have led to the use of 'abdominal vascular zone conditions' to describe the variable hemodynamic responses to elevated P_{IA} in mammals (Kitano et al., 1999; Takata et al., 1990). When right atrial pressure exceeds P_{IA} the abdominal compartment acts as a capacitor, and increases in P_{IA} result in an increase in venous return in the inferior vena cava (abdominal vascular zone 3). When P_{IA} exceeds right atrial pressure, the abdominal compartment acts as a Starling resistor, increases in P_{IA} collapse the inferior vena cava and decrease venous return (abdominal vascular zone 2). The results of the current experiments are consistent with the abdominal compartment acting as a Starling resistor in lizards in response to twofold increases in P_{IA} (induced by either treadmill exercise or saline infusion), and as a capacitor during threefold increases in P_{IA} .

The relationship between venous resistance, P_{CV} and P_{RA} is complicated even further during exercise due to the increasing contributions of the skeletal muscle and respiratory pumps. During exercise, skeletal muscle contractions compress venous vessels, forcing blood centrally and supplementing venous return. The resulting decrement in intramuscular venous pressure increases the arterial-venous pressure gradient and aids arterial inflow into the muscle (Madger, 1995; Rowland, 2001). Fluctuations in intrathoracic and intra-abdominal pressures also affect venous return due to their effects on the inferior vena cava.

In mammals, the vigorous inhalations associated with exercise distend the inferior vena cava, supplementing venous return and cardiac output during exercise (Rowland, 2001). Collapse of the inferior vena cava due to elevated P_{IA} would limit the increase in venous return associated with increasingly negative intra-thoracic pressures during vigorous breathing (Amoore and Santamore, 1994). In *V. exanthematicus*, the

phasic fluctuations in P_{IA} caused by ventilation and the tonically elevated P_{IA} induced by exercise had different effects on venous return. Exhalation caused an increase, and inspiration caused a decrease, in P_{IA} and \dot{Q}_{PC} (Fig. 1). In contrast, exercise was associated with tonically elevated P_{IA} , which suppressed \dot{Q}_{PC} . The sudden increase in \dot{Q}_{PC} at the cessation of exercise correlated with a decrease in P_{IA} (Fig. 2) and an increase in venous return from the peripheral circulation. Concurrently, ventilation increased during the recovery period (Fig. 3), thus increasing the supplementary action of expiration on venous return. These results suggest that exercise-induced increases in P_{IA} reduce venous return to the heart and cause both a pooling of blood in the peripheral circulation as well as an increase in cardiac afterload. The combined effects of increasing cardiac afterload and decreasing cardiac preload during exercise may act to decrease stroke volume by increasing end-systolic volume and decreasing end-diastolic volume, respectively. Stroke volume was not measured directly in this study, however, arterial pulse pressure decreased during maximal exercise (Fig. 2), suggesting a decrease in stroke volume (assuming that arterial compliance was unchanged).

In *V. exanthematicus*, maximal heart rate was achieved at 1.0 km h⁻¹ (106.1±2.5 beats min⁻¹). Comparable maximal heart rates have been measured in response to treadmill exercise in *V. mertensi* (rest 74±9; exercise 120±14 beats min⁻¹; Frappell et al., 2002a) and *V. exanthematicus* (rest 45.5±3.6; exercise 99.4±5.7 beats min⁻¹; Wang et al., 1997); (rest 50 beats min⁻¹, exercise 105–110 beats min⁻¹; Gleeson et al., 1980), despite these studies recording higher resting heart rates than the present study (rest 25.1±3.0 beats min⁻¹). Further increments in treadmill speed elicited no additional increase in heart rate in this or previous studies (Gleeson et al., 1980; Wang et al., 1997). Progressive increments in treadmill speed also failed to elicit graded increases in systemic blood flow (Wang et al., 1997) and venous return (present study) nor any increment in stroke volume (Frappell et al., 2002a). Thus, in contrast to the graded respiratory response to exercise in varanid lizards, the

cardiovascular response may be 'all or nothing', with maximal cardiac output, systemic blood flow, heart rate and venous return reached at relatively low exercise intensities. The 'all or nothing' response of \dot{Q}_{PC} at the three lowest treadmill speeds, combined with the maintenance of \dot{V}_{O_2} at the highest treadmill speed (despite a decrease in \dot{Q}_{PC}) may suggest that lung perfusion may be in excess at low treadmill speeds. The maintenance of \dot{V}_{O_2} despite a decrease in \dot{Q}_{PC} may be the result of alterations in cardiac or intrapulmonary shunting, decreases in perfusion to areas of the lung with low ventilation-perfusion ratios, or may simply reflect a reduction in the over-perfusion of the lungs present at lower treadmill speeds.

In contrast to the 'all or nothing' cardiovascular response elicited by exercise, the cardiovascular response to digestion in reptiles is graded, showing progressive increases in heart rate, stroke volume and cardiac output during the first 24–48 h after feeding (Hicks et al., 2000; Secor et al., 2000). Thus, the cardiovascular response in varanid lizards, like the respiratory response, appears to be state dependent and flexible, and not stereotyped as previously suggested (Hicks et al., 2000). The conclusion of a previous study that the cardiovascular response to exercise was graded and, therefore, similar to the graded responses induced by digestion (Hicks et al., 2000) was probably the result of applying a linear regression analysis to non-linear data. The original data presented (Wang et al., 1997) and interpreted by Hicks et al. (2000) for heart rate and relative change in cardiac output show no increase in either parameter at the three highest treadmill speeds, thus demonstrating a curvilinear, rather than a linear, response. Thus, the cardiovascular responses to exercise measured in Wang et al. (1997) and the present study are in agreement, and together with the cardiovascular response to digestion measured by Hicks et al. (2000) suggest that the cardiovascular response in varanid lizards is plastic.

Resting respiratory parameters measured in this study (minute ventilation, total tidal volume, breathing frequency, \dot{V}_{O_2} , \dot{V}_{CO_2}) were comparable to those measured at rest in the same species (Hicks et al., 2000). In contrast, studies on the same or closely related species reported fivefold higher resting minute ventilations and fourfold higher breathing frequencies resulting from shorter pre-exercise equilibration times (Frappell et al., 2002a; Wang et al., 1997). Treadmill exercise increased total minute ventilation and costal breathing frequency by 24-fold and 10.5-fold, respectively, in this study, matching the magnitude of responses shown previously in the same species (Bennett and Hicks, 2001), but exceeding the magnitude of change reported in studies with elevated resting minute ventilations and breathing frequencies (4–7-fold and 2.5-fold, respectively; Frappell et al., 2002a; Wang et al., 1997). In the present study, minute ventilation, breathing frequency and tidal volume were analyzed in terms of the contributions made by costal ventilation and gular pumping. At rest, gular pumping did not occur and costal ventilation was the sole contributor to total minute ventilation. As treadmill speed increased, the frequency of gular pumping increased up to 40 min⁻¹ and gular pump volume increased up to

8.3 ml kg⁻¹. The progressive increments both in gular pump volume and in frequency enabled overall minute ventilation to increase in response to increasing treadmill speed, despite the reduction in costal tidal volume and costal minute ventilation measured at high treadmill speeds. These results support the hypothesis that gular pumping supplements costal ventilation during exercise and compensates for the speed-dependent axial constraint present during high-speed running in lizard species that laterally undulate (Owerkowitz et al., 1999). Reductions in costal tidal volume were also associated with elevated P_{IA} in resting *V. exanthematicus* (Table 1). Minute ventilation was maintained during elevated P_{IA} due to an increase in breathing frequency. These results suggest that costal tidal volume may be limited during exercise due to the demands placed on the hypaxial musculature and as a direct result of elevated P_{IA} .

The recovery from exercise was marked with an increase in \dot{Q}_{PC} , peaking 40 s after the cessation of exercise, and an increase in $\bar{P}a$, peaking at 140 s (Fig. 4). The difference in the time course of these two responses may be due to their underlying causes. During recovery, P_{IA} and its compressive effect on the post caval vein decreases immediately. This sudden decrement allows blood pooled in the peripheral circulation to return to the heart, thus causing an increase in venous return. The movement of blood from the venous to the arterial compartment increases effective blood volume, thus driving up $\bar{P}a$. At the same time, pulse pressure increases with no concurrent change in heart rate, suggesting that any alterations in cardiac output during the recovery period are produced by increments in stroke volume alone.

Exercise increased P_{IA} up to 18.74±2.09 mmHg in *V. exanthematicus*. Similar P_{IA} in resting mammals induce broad hemodynamic alterations including decrements in splanchnic blood flow, heart rate, stroke volume and cardiac output. In this study, increments in P_{IA} suppress venous return from the hind limbs and tail, potentially limiting the increase in cardiac output that can be achieved during exercise. The limitation of venous return during exercise by elevated P_{IA} demonstrates that despite circumventing the respiratory constraints present in iguanid lizards, cardiovascular constraints do still exist in varanid lizards. Understanding the integration of the cardiac, respiratory and skeletal muscle pumps during exercise, as well as the impact of elevated P_{IA} , may provide insight into factors that determine cardiac output, maximal oxygen consumption and endurance performance in reptiles.

List of abbreviations

f_b	breathing frequency
$\bar{P}a$	mean arterial blood pressure
P_{CV}	central venous pressure
P_D	diastolic blood pressure
P_{IA}	intra-abdominal pressure
P_{RD}	diastolic right atrial pressure
P_S	systolic blood pressure
P_{TRANS}	transmural pressure of the post caval vein
\dot{Q}_{PC}	post caval vein blood flow

\dot{V}_{CO_2}	carbon dioxide production
\dot{V}_{O_2}	oxygen consumption
\dot{V}_E	minute ventilation
$\dot{V}_{\text{O}_{2\text{max}}}$	maximal oxygen consumption
V_{TI}	inspired tidal volume

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