The Journal of Experimental Biology 213, 78-88
Published by The Company of Biologists 2010
doi:10.1242/jeb.034058

Prioritizing blood flow: cardiovascular performance in response to the competing demands of locomotion and digestion for the Burmese python, *Python molurus*

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Accepted 14 September 2009

SUMMARY

Individually, the metabolic demands of digestion or movement can be fully supported by elevations in cardiovascular performance, but when occurring simultaneously, vascular perfusion may have to be prioritized to either the gut or skeletal muscles. Burmese pythons (*Python molurus*) experience similar increases in metabolic rate during the digestion of a meal as they do while crawling, hence each would have an equal demand for vascular supply when these two actions are combined. To determine, for the Burmese python, whether blood flow is prioritized when snakes are digesting and moving, we examined changes in cardiac performance and blood flow in response to digestion, movement, and the combination of digestion and movement. We used perivascular blood flow probes to measure blood flow through the left carotid artery, dorsal aorta, superior mesenteric artery and hepatic portal vein, and to calculate cardiac output, heart rate and stroke volume. Fasted pythons while crawling experienced a 2.7- and 3.3-fold increase, respectively, in heart rate and cardiac output, and a 66% decrease in superior mesenteric flow. During the digestion of a rodent meal equaling in mass to 24.7% of the snake's body mass, heart rate and cardiac output increased by 3.3- and 4.4-fold, respectively. Digestion also resulted in respective 11.6- and 14.1-fold increases in superior mesenteric and hepatic portal flow. When crawling while digesting, cardiac output and dorsal aorta flow increased by only 21% and 9%, respectively, a modest increase compared with that when they start to crawl on an empty stomach. Crawling did triggered a significant reduction in blood flow to the digesting gut, decreasing superior mesenteric and hepatic portal flow by 81% and 47%, respectively. When faced with the dual demands of digestion and crawling, Burmese pythons prioritize blood flow, apparently diverting visceral supply to the axial muscles.

Key words: arterial system, blood flow, cardiac output, digestion, intestinal hyperemia, postprandial, *Python molurus*, reptile, snake.

INTRODUCTION

The increase in activity of any tissue is met by increases in substrate utilization and oxygen consumption, both of which are supported by an elevation in vascular blood flow. For the whole organism, such a response is manifested by elevations in ventilation, gas exchange and cardiac output. This set of responses stemming from physical activity (i.e. skeletal muscle contraction) is well documented and apparent during bouts of exercise (Armstrong et al., 1987; Fletcher, 1994). Of a more modest magnitude are the metabolic and cardiovascular responses that accompany the digestion and assimilation of a meal. For vertebrates, digestion characteristically generates 25–200% increase in oxygen consumption, 10–100% increase in cardiac output, and 50–250% increase in gastrointestinal blood flow (i.e. postprandial hyperemia) (reviewed by Fara, 1984; Kearney et al., 1995; Seth et al., 2008; Secor, 2009). For the small intestine, postprandial hyperemia serves to provide the additional oxygen and metabolites to the active epithelium, to receive absorbed nutrients (amino acids, simple sugars and lipids) and transport them to the liver, and to deliver a host of regulatory peptides that signal the modulation of gastrointestinal performance (Farrell et al., 2001; Pappenheimer and Michel, 2003).

The magnitude of intestinal hyperemia can be dependent upon the composition of the meal, meal size and whether the gut is competing with other tissues for available blood. Meals high in protein or fat produce a more pronounced intestinal hyperemia than meals high in carbohydrates (Siregar and Chou, 1982; Sidery et al., 1991; Sidery et al., 1994). A 3-fold increase in meal size for humans results in nearly a 100% greater increase in superior mesenteric blood flow (Sidery and MacDonald, 1994). Because it is assumed that the cardiovascular system lacks the capacity to fully perfuse the gastrointestinal tract and locomotory muscles simultaneously, blood flow to one set of tissues will be compromised when an animal is digesting and moving (Farrell et al., 2001). For Chinook salmon (*Oncorhynchus tshawytscha*) induced to swim while digesting food, elevated visceral blood flow is preserved, whereas swimming performance is depressed, suggestive of a loss of axial muscle perfusion (Thorarensen and Farrell, 2006). Alternatively in such situations, perfusion priority is given to locomotory muscles, and it is blood flow to the gut that is reduced. For the sea bass, *Dicentracrchus labrax*, an increase in swimming speed reduces the magnitude of the postprandial intestinal hyperemia (Altimiras et al., 2008). A third scenario, one counter to the above assumption, is that there does exist adequate reserve capacity of the cardiovascular system enabling both locomotory muscles and the gut to be fully perfused during episodes of digestion and movement. Support for such a reserve capacity stems from human studies and the finding that the cardiovascular effects of digestion are additive to those of exercise (Yi et al., 1990).

Identifying which of the above scenarios is played out would be best determined using an organism whose metabolic response and cardiac performance during digestion matches that during locomotion. We therefore studied the cardiovascular responses of

the Burmese python (*Python molurus* L.) to the individual and simultaneous demands of digestion and crawling. Burmese pythons experience monumental increases in metabolic, cardiovascular and gastrointestinal performance during the digestion of their large intact meals (Secor and Diamond, 1997a; Secor and Diamond, 1977b; Secor et al., 2000). The digestion of a rodent meal weighing 25% of the snake's body mass, generates as much as a 16-fold increase in oxygen consumption, a 2.4-fold increase in heart rate, and a 4.5-fold increase in cardiac output (Secor and Diamond, 1997a; Secor et al., 2000). While crawling, fasted Burmese pythons experience similar 17-, 2.3- and 2.9-fold increases in oxygen consumption, heart rate and cardiac output, respectively (Secor et al., 2000). Hence, a digesting and crawling python would expectedly face a conflict in delivering the needed oxygen and nutrients to both the active gut and contracting axial muscles (Bennett and Hicks, 2001).

Our primary objectives in undertaking this study were to first document the postprandial profile of cardiovascular performance for the Burmese python and second, address the question of whether or not pythons divert blood flow from the quiescent or active intestine during bouts of activity. To achieve the first objective, we used perivascular blood flow probes to measure arterial (left carotid artery, dorsal aorta and superior mesenteric artery) and venous (hepatic portal vein) blood flow and cardiac performance (cardiac output, heart rate and stroke volume) of pythons fasted and up to 15 days after feeding. The second objective was undertaken by comparing blood flow patterns and cardiac performance of fasted and fed snakes at rest and when crawling. Given the python's large meal size and dramatic upregulation of intestinal performance, we predicted that they also experience a significantly large postprandial intestinal hyperemia. Such a large vascular response combined with the circulating demands of movement would support the prediction that pythons need to prioritize blood flow to either the gut or axial muscles when simultaneously digesting and moving. In this study, we found pythons to experience: (1) unprecedented postprandial increases in superior mesenteric arterial and hepatic portal venous flow; (2) the near cessation of intestinal blood flow when fasted animals begin to crawl; (3) a modest increase in cardiac output and sever depression of intestinal blood flow in sedentary digesting snakes that start to crawl. We found that when pythons are faced with the dual demands of digestion and movement, they prioritize blood flow, diverting much of visceral supply apparently to the axial muscles.

MATERIALS AND METHODS

Pythons, their maintenance, and description of arterial system

Burmese pythons used in this study were purchased as hatchlings (Bob Clark Captive Bred Reptiles, Oklahoma City, OK, USA) and maintained on a biweekly diet of rodents or rabbits with water available *ad libitum*. We used six adult pythons (6–9.5 years old) that averaged (mean ± s.e.m.) 253±7 cm snout–vent length (SVL), 289±9 cm total length, and 11.7±1.0 kg in mass to measure cardiovascular responses to fasting, movement and digestion. Prior to the surgical implantation of blood flow probes, snakes were fasted for 3–4 weeks with water available. Python care and study were conducted under approval from the University of Alabama Institutional Animal Care and Use Committee.

We dissected six additional pythons (206±16 cm SVL, 234±19 cm total length, 5.6±1.3 kg mass) that had been killed for other studies, to describe the major elements of the Burmese python's cardiovascular system. We noted the major systemic vessels attached to the heart and those extending from the dorsal aorta. We recorded the distance from the snake's snout of the major branches of the dorsal aorta and used digital calipers to measure their diameter. We relied on earlier sources of snake anatomy for vessel identification (Jacquart, 1855; O'Donoghue, 1912; Atwood, 1918; Van Bourgondien and Bothner, 1969).

Surgical procedures

Pythons were sedated with an intramuscular injection of ketamine (45 mg kg^{-1}, Ketaset®, Fort Dodge, Fort Dodge, IA, USA). Once relatively flaccid, we inserted an intubation tube into the snake's glottis and started the administration of anesthetic (4% Isoflurane, Forane®, Ohmeda Caribe Inc., Liberty Corner, NJ, USA). Once anesthetized, the snake was placed on its dorsum, held in position with cranial and caudal restraints, and scrubbed with Betadine solution (Purdue Frederick Co., Norwalk, CT, USA) at the sites of surgery. Areas around the surgical sites were covered with sterile drapes. We made a 10- to 20-cm incision at three locations on the snake's body: 10 cm cranial to the heart, 20 cm caudal to the heart, and 60% of SVL from the snout (approximate start of the small intestine). Incisions were made between the ventral scales and the first set of lateral scales and retracted open to expose the underlying organs and blood vessels. We attached perivascular ultrasound flow probes (Models 3R, 4R and 6R, Transonic Systems Inc., Ithaca, NY, USA) to the following four blood vessels; left carotid artery (anterior most incision; Fig. 1A, Fig. 2), dorsal aorta, immediately distal to the junction of the left and right systemic arteries (middle incision, Fig. 2), superior mesenteric artery, immediately after it branches from the dorsal aorta (distal incision; Fig. 1B, Fig. 2), and the hepatic portal vein, just anterior to the start of the small intestine (distal incision, Fig. 2). The wire leads from each flow probe was exteriorized through small incisions in the body wall and sutured to the external scales. The incisions were closed with an inner (muscular layer) and outer (scales) set of interrupted sutures (2-0 Vicryl®, Ethicon, Somerville, NJ, USA). Immediately following surgery, snakes were injected intramuscularly with a single dose of antibiotic (1 ml kg^{-1} enrofloxacin, Baytril®, Bayer, Shawnee Mission, KS, USA), and then injected several more times during the subsequent 2 weeks. Snakes were allowed to recover for a minimum of 1 month before the start of measurements, during which they had access to water but were not fed.

Experimental protocol

We measured blood flow (ml min^{-1}) of pythons while, (1) fasted and at rest (minimum of two months since last meal), (2) crawling while fasted, (3) digesting at rest, and (4) crawling while digesting. Blood flow was measured simultaneously for two of the four vessels by a dual-channel blood flow meter (model T206, Transonic Systems). Signals from the flow meter were continuously retrieved and stored by a computer-linked data-acquisition system (MP100, Biopac Systems, Santa Barbara, CA, USA). We measured blood flow of fasted and digesting snakes at rest while they were housed at 30°C within an environmental chamber (Fig. 1C,D). Blood flow of the four vessels of each snake fasted and at rest was recorded for 30 min in the morning (between 08:00 and 10:00 h) and in the evening (between 20:00 and 22:00 h) for four to five consecutive days. Following these sets of measurements, the snake was removed from the environmental chamber and allowed to crawl on the floor while its flow probes were connected to the flow meter and data acquisition system that was on a cart and pushed alongside the crawling snake (Fig. 1E). We measured twice for each vessel, the flow during steady episodes of crawling. Several days after the crawling blood flow measurements, the snake was fed a rodent meal

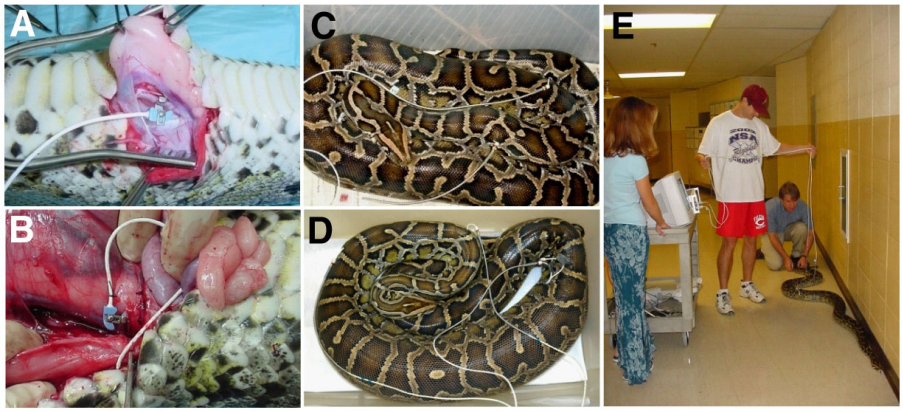

Fig. 1. Perivascular blood flow probe attached to left carotid artery (A) and superior mesenteric artery (B) of an adult Burmese python. Blood flow measurement being taken of an adult Burmese python at rest while fasting (C), at rest while digesting a rodent meal equal in mass to 25% of snake body mass (D), and crawling while fasting (E).

equal in mass to 24.7±0.3% of the snake's body mass. Blood flow measurements were resumed at 8-h intervals for 4 days, at 12-h intervals for another 4 days, and then once daily (between 08:00 and 10:00 h) thereafter for 7 more days. On day 5 of digestion and following the morning measurements of blood flow, the snake was removed from the environmental chamber and blood flow through each of the vessels was measured twice while the snake crawled on the floor.

We defined cardiac output as the volume of blood ejected into systemic circulation in a 1-min span and calculated it as the sum of dorsal aorta flow plus 1.94 times left carotid flow. Prior to its junction with the left systemic artery, three major vessels exit the right systemic artery: the right carotid, left carotid and vertebral arteries (Fig. 2). We measured the diameter of each of these blood vessels for the six dissected snakes. Based on the diameter of each of these vessels and assuming equal flow with respect to cross-sectional area, we estimated that blood flow through the right carotid and vertebral arteries are, respectively, 39% and 55% of flow through the left carotid artery. Hence, combined flow through these three vessels is approximately 1.94 times flow through the left carotid artery. For each measurement period, we calculated stroke volume (the volume of blood pumped into the right and left aortic arches with each heart beat) by dividing cardiac output by heart rate.

Data analysis

For resting snakes, fasting and digesting, we selected from each 30-min recorded trial a 5-min span of steady blood flow to calculate an average flow rate for each vessel. We quantified blood flow (presented as $ml\,min^{-1}\,kg^{-1}$) as well as heart rate (determined from dorsal aortic flow) using the software program AcqKnowledge (Biopac Systems, Inc., Santa Barbara, CA, USA). For crawling snakes, we selected a 1- to 2-min span of steady uninterrupted crawling to calculate blood flow, cardiac output, heart rate and stroke volume. From the multiple recordings for each snake fasting at rest, we selected the set of recordings that produced the lowest cardiac output to assign for that snake, resting and fasting blood flow, cardiac output, heart rate and stroke volume.

We used a repeated-measures designed analysis of variance (ANOVA) to test for significant effects of time (pre- and postfeeding) on cardiovascular parameters. An accompanying *post-hoc* pairwise means comparison allowed us to determine when variables were significantly different after feeding and when they differed from each other. Repeated-measures ANOVAs and pairwise comparisons were likewise used to test for significant differences among and between the five measurement treatments for each cardiovascular variable. The level of statistical significance is designated as $P<0.05$ and values are reported as means ± 1 s.e.m.

RESULTS

Brief description of cardiovascular system

For the six pythons dissected, the anterior edge of the heart was positioned at a distance of 21.4±0.6% of SVL from the snout. As is characteristic of reptiles, pythons possess a pair of aortic arches that originate from the ventricle. Near the start of the right aortic arch extends a short trunk that immediately splits into the right and left carotid arteries, both of which continue anteriorly on either side of the trachea (Fig. 2). The narrower right carotid artery branches to supply both the thyroid and thymus glands. The larger left carotid artery continues along the left side of the trachea to the head. The right aortic arch bends caudally while remaining dorsal to the heart, lungs, and esophagus. A short distance posterior to the bend, the vertebral artery extends cranially from the right aortic arch along the dorsal midline of the body before disappearing into the axial musculature (Fig. 2). Posterior to the vertebral artery, several small parietal arteries (i.e. intercostal arteries) extend from the right aortic arch into the axial musculature. The left aortic arch also curves caudally from the heart and continues on the left side of the body, ventral to the lungs and esophagus. Distal to the apex of the heart, the right and left aortic arteries join (28.7±0.5% of SVL) to form the dorsal aorta (Fig. 2). The dorsal aorta continues posteriorly along the dorsal midline of the body cavity ventral to the vertebral column. Along its full length are regularly spaced small parietal arteries that extend dorsally into the axial musculature. Anterior to the stomach, small arteries branch from the dorsal aorta to the liver (hepatic arteries) or esophagus (esophageal arteries), or to both.

At 51.0±0.6% of SVL an artery branches from the dorsal aorta to the proximal region of the stomach and continues caudally across the stomach. The distal stomach is supplied by the celiac artery (i.e. lieno-gastric artery), the origin of which, from the dorsal aorta is at 59.1±0.6% of SVL and immediately branches to the spleen and then continues cranially along the stomach (Fig. 2). Branching from the dorsal aorta, near the junction of the pyloric sphincter and small intestine, is the superior mesenteric artery (63.4±0.5% of SVL) that soon splits into an anterior branch supplying the pancreas, pyloric sphincter and adjoining small intestine and a posterior branch that continues alongside the small intestine with small branches that digitate around the small intestine (Fig. 2). Distal to the origin of the superior mesenteric artery are branches to the gonads (testicular or ovarian arteries; Fig. 2), small intestine (inferior mesenteric artery; Fig. 2), right kidney (right renal artery; 71.3±0.5% of SVL; Fig. 2), left kidney (left renal artery, 73.6±0.5% of SVL), and large intestine

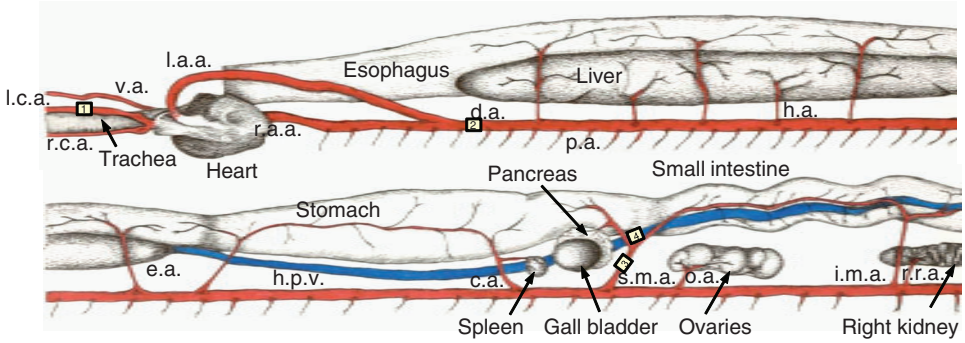

Fig. 2. Illustration of organs, major arteries and the hepatic portal vein of the Burmese python. The numbered boxes on vessels indicate the location of perivacular blood flow probes used in this study; (1) left carotid artery, (2) dorsal aorta, (3) superior mesenteric artery, and (4) hepatic portal vein. Vessel abbreviations: r.c.a., right carotid artery; l.c.a., left carotid artery; v.a., vertebral artery; l.a.a., left aortic arch; r.a.a., right aortic arch; d.a., dorsal aorta; p.a., parietal arteries; h.a., hepatic artery; e.a., esophageal artery; h.p.v., hepatic portal vein; c.a., celiac artery; s.m.a., superior mesenteric artery; o.a., ovarian artery; i.m.a., inferior mesenteric artery; r.r.a., right renal artery.

(additional inferior mesenteric arteries). At the base of the tail the dorsal aorta continues as the caudal artery and together with the caudal vein they are ventral to the caudal vertebrae.

Venous drainage of the posterior portion of the python's body is via the posterior vena cava (i.e. post-cava vein) that is formed from the junction of the efferent renal veins. The small intestine is drained by the hepatic portal vein which for the anterior portion of the small intestine, lies immediately beneath the superior mesenteric artery (Fig. 2). The hepatic portal vein separates from the small intestine just anterior to the start of the superior mesenteric artery and extends cranially to the caudal end of the liver (Fig. 2).

Cardiovascular response at rest and crawling while fasting

While at rest and fasting, adult Burmese pythons typically maintain a coiled position with their heads placed near the center of the coil (Fig. 1C). They will hold this position for several days, occasionally shifting the position of their head. At this time, minimum heart rate and cardiac output for this set of adult Burmese pythons averaged 16.8 ± 1.3 beats min^{-1} and 9.11 ± 1.02 ml min^{-1} kg^{-1}, respectively (Table 1). Of the calculated cardiac output, approximately 10% was delivered anterior to the heart through the right and left carotid arteries and the vertebral artery, and the remaining 90% delivered posterior to the heart. Of the flow traveling through the dorsal aorta,

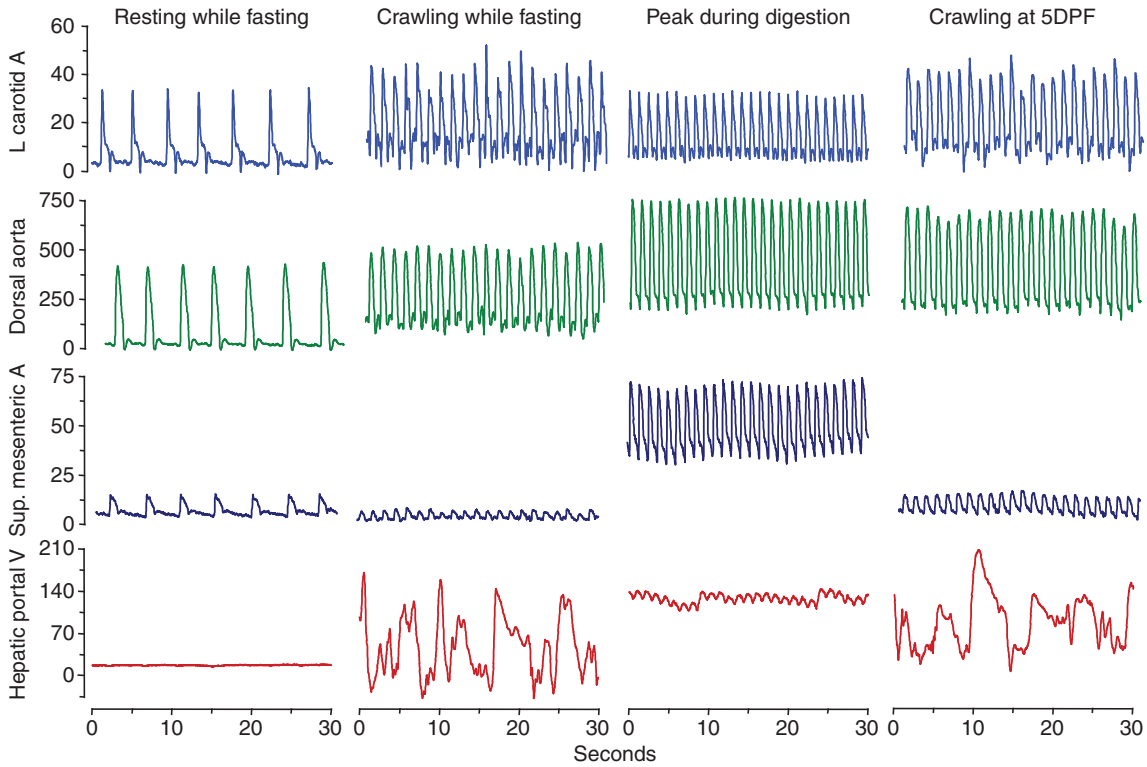

Fig. 3. Blood flow trace for the left carotid artery, dorsal aorta, superior mesenteric artery and hepatic portal vein for a 11.8 kg Burmese python resting while fasting, crawling while fasting, peak during digestion (2 days postfeeding), and crawling at 5 days postfeeding (5DPF). Note the increase in frequency and amplitude of flow pulses with crawling and digestion for the left carotid artery and dorsal aorta. Superior mesenteric and hepatic portal flow increased dramatically during digestion, the former dropping significantly and the latter showing an erratic flow pattern during crawling.

immediately distal to the junction of the right and left aortic arches, 7.7±1.0% entered the superior mesenteric artery (Table 1). For fasting and resting pythons, blood flow through the hepatic portal vein was nearly twice that of superior mesenteric arterial flow (Table 1). Characteristically, blood flow through the left carotid artery, dorsal aorta and superior mesenteric artery was pulsatile, whereas hepatic portal flow was smooth with no oscillations (Fig. 3).

When encouraged to crawl, pythons would stretch out on the floor, typically alongside a wall, and maintain steady movement using rectilinear locomotion (Fig. 1E). For these adult pythons, crawling generated significant (all $P<0.032$) increases in left carotid and dorsal aorta blood flow and heart rate, such that calculated cardiac output increased by 3.5-fold over fasting levels (Table 1, Fig. 3). This increase in cardiac output was due largely to a 2.8-fold increase in heart rate (Table 1). Mean stroke volume did rise by 25% but the increase was not statistically significant ($P=0.061$). By contrast, superior mesenteric flow decreased significantly ($P=0.0007$) with exercise (by 66±7%), such that only 0.8±0.2% of dorsal aorta flow was being delivered through the superior mesenteric artery (Table 1, Fig. 3). Crawling did generate an erratic flow pattern through the hepatic portal vein, and although hepatic portal flow while crawling averaged 70% greater than resting, the difference was not statistically significant (Table 1).

Postprandial cardiovascular response at rest

After feeding, pythons returned to a coiled position, though were not as tightly coiled because of the large bolus of food ingested (Fig. 1D). Among pythons, blood flow through the left carotid artery increased quickly after feeding and remained steady at approximately 75% above fasting levels for up to 15 days postfeeding (Fig. 4). Blood flow through the dorsal aorta, superior mesentery artery and hepatic portal vein varied significantly ($P<0.0001$) among the fasted and postprandial measurements (Fig. 4). Within 16 h after feeding, blood flow through these three vessels had significantly (all $P<0.009$) increased by 2.4-, 4.2- and 6.0-fold, respectively. Blood flow through the dorsal aorta continued to increase at a mean rate of $0.32\,ml\,min^{-1}\,kg^{-1}$ each hour for the next 48 h (Fig. 4). Dorsal aorta flow peaked at day 3, at 4.5-fold of the average resting prefeeding value (Table 1). Following this peak, dorsal aorta flow declined linearly, being reduced at an average rate of $2.0\,ml\,min^{-1}\,kg^{-1}$ every day for the next 12 days (Fig. 4). Blood flow through the superior mesenteric artery also continued to increase until day 3 (9.7-fold of fasting; Fig. 4), at which time flow through the superior mesentery artery represented 17.2±2.1% of the blood entering the dorsal aorta. Thereafter, superior mesenteric blood flow decline steadily and by day 12, flow rates did not differ from prefeeding values. For each of these adult python, postprandial peaks in superior mesenteric flow averaged 11.6±0.6 times flow when resting and fasting (Table 1). Matching the increase in blood supply to the small intestine was a very dramatic increase in hepatic portal drainage from the small intestine (Figs 3 and 4). Blood flow through the hepatic portal vein steadily increased after feeding; the average rate peaking at 80 h postfeeding at nearly 12-fold of resting values (Fig. 4). Individual postprandial peaks in hepatic portal flow averaged 15.4±2.8 times flow when snakes were resting and fasting (Table 1). Similar to other monitored vessels, blood flow through the hepatic portal vein decreased after its peak at a more gradual decline before reaching a rate not significantly greater than prefeeding flow at day 11 (Fig. 4). Interestingly during digestion, hepatic blood flow exhibited a subtle pulsatile pattern matching that of arterial flow (Fig. 3).

Digestion likewise generated significant ($P<0.0001$) variation in heart rate, which more than doubled ($P<0.0001$) within 8 h after feeding (Fig. 5). Mean heart rate among the six snakes peaked at 80 h postfeeding at $53.7\pm1.1\,beats\,min^{-1}$ (3.2-fold increase; Fig. 5) and individual peaks in heart rate averaged $55.4\pm1.2\,beats\,min^{-1}$ (3.3-fold of when resting and fasting; Table 1). Heart rates steadily declined after the peak and returned to levels not significantly greater than prefeeding rates by day 15. Cardiac output increased rapidly after feeding with mean output peaking at 64 h postfeeding following a 4.2-fold increase (Fig. 5). Cardiac output remained elevated for another 24 h before declining and returning to levels not significantly greater than fasting levels by day 15. Stroke volume varied ($P=0.0024$) among sampling times, increasing after feeding to plateau at 40 h postfeeding for the next 5 days at approximately 30% above resting and fasting values (Fig. 5).

Cardiovascular response to digestion and crawling

After five days of digestion, pythons still had food within their stomach as noted by the distention of their stomach region. While resting at this time, left carotid, dorsal aorta, superior mesenteric and hepatic portal blood flow of resting pythons were 1.6, 3.9, 8.5 and 11.3 times such values prior to feeding, respectively (Table 1). Heart rate, cardiac output and stroke volume at that time were 2.8, 3.6, and 1.3 times fasting values, respectively (Table 1). Although pythons were a little reluctant to move at this stage of digestion, we were able to observe during several minutes of steady crawling 251% and 9% increases (both $P<0.021$), respectively, in left carotid and dorsal aortic flow (Table 1). By contrast, blood flow through the superior mesenteric artery and hepatic portal vein decreased (both $P<0.007$) by a respective 81% and 47%. For digesting pythons, crawling resulted in respective 13% and 21% increases (both

Table 1. A comparison of blood flow and cardiac performance of six adult Burmese pythons, *Python molurus* when resting while fasted, crawling while fasted, peak during digesting, resting at 5 days postfeeding and crawling at 5 days postfeeding

Variable	Resting while fasted	Crawling while fasted	Peak during digestion	Resting at 5DPF	Crawling at 5DPF
Left carotid A ($ml\,min^{-1}\,kg^{-1}$)	0.38±0.04	2.44±0.91*	0.98±0.13***	0.62±0.10	2.27±0.69*
Dorsal aorta ($ml\,min^{-1}\,kg^{-1}$)	8.37±1.01	25.7±2.2***	39.1±2.5***	31.9±1.7	35.7±2.2*
Superior mesenteric A ($ml\,min^{-1}\,kg^{-1}$)	0.60±0.04	0.20±0.04***	6.99±0.50***	5.04±0.67	0.94±0.10*
Hepatic portal V ($ml\,min^{-1}\,kg^{-1}$)	1.16±0.31	1.91±0.69	14.6±1.5**	11.7±1.0	6.23±0.75**
Cardiac output ($ml\,min^{-1}\,kg^{-1}$)	9.10±1.03	30.5±3.8***	41.0±2.5***	33.1±1.8	40.1±3.0**
Heart rate ($beat\,min^{-1}$)	16.8±1.3	46.0±1.5***	55.4±1.2***	47.7±2.0	54.0±1.0**
Stroke volume ($ml\,kg^{-1}$)	0.54±0.05	0.67±0.09	0.74±0.03**	0.70±0.03	0.74±0.05

Values are means±1 s.e.m.; DPF, days postfeeding.

Asterisks indicate level of statistical significance; *0.05>P>0.01, **0.01>P>0.001, ***P<0.001, resulting from paired t-tests between resting while fasting and crawling while fasted, between resting while fasted and peak during digestion, and between resting at 5DPF and crawling at 5DPF.

Mean mass was 11.7±1.0 kg.

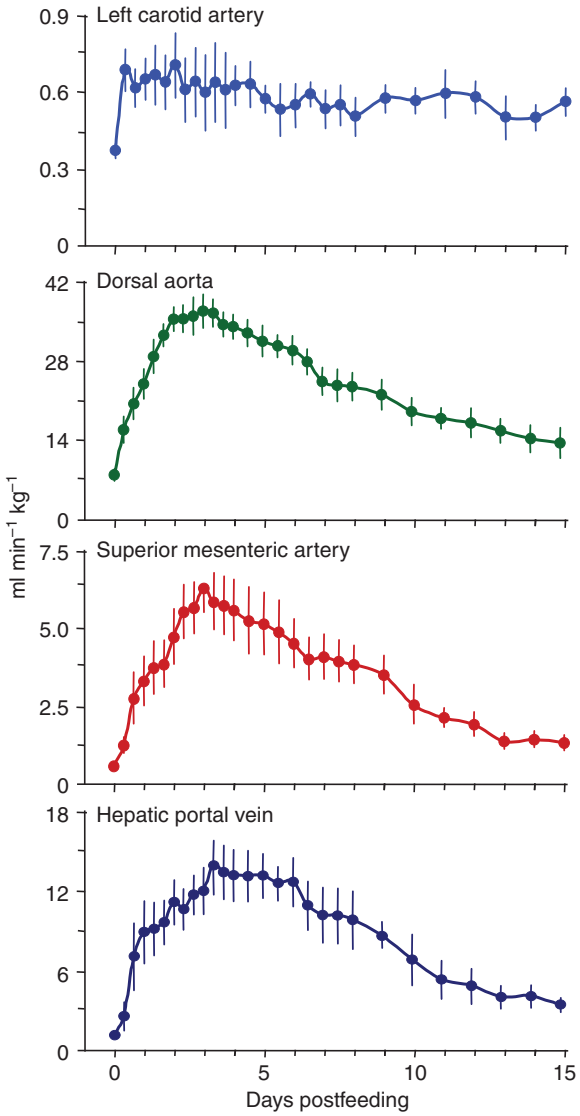

Fig. 4. Blood flow (ml min^{-1} kg^{-1}) through the left carotid artery, dorsal aorta, superior mesenteric artery and hepatic portal vein as a function of time postfeeding for six adult Burmese pythons that had consumed rodent meals equal in mass to 25% of the snake's body mass. Blood flow through each of these four vessels had significantly increased by 16 h after feeding.

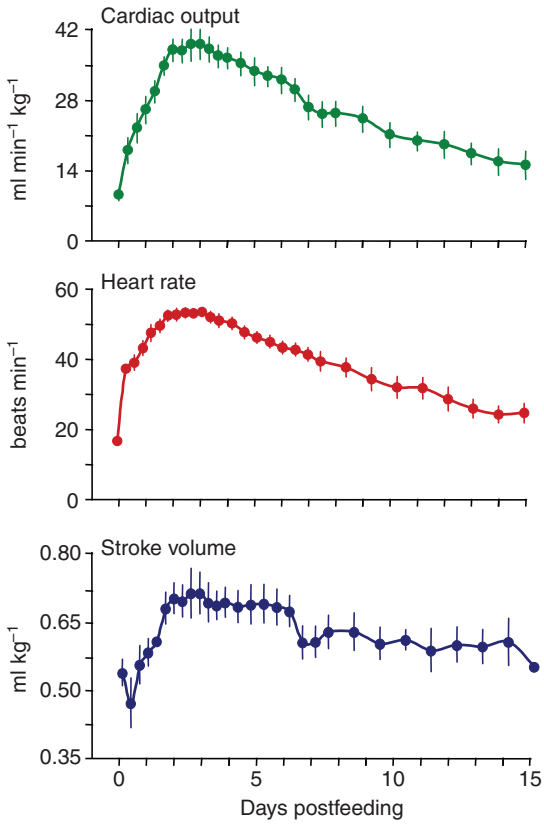

Fig. 5. Cardiac output (ml min^{-1} kg^{-1}), heart rate (beats min^{-1}), and stroke volume (ml kg^{-1}) as a function of time postfeeding for six adult Burmese pythons that has consumed rodent meals equal in mass to 25% of the snake's body mass. Postprandial increases in heart rate and stroke volume contributed to the impressive increase in cardiac output experienced by digesting pythons.

P<0.005) in heart rate and cardiac output. Stroke volume on average rose by 7.5%, but this increase was not significant (P=0.19).

DISCUSSION

In concert with their large postprandial metabolic response and upregulation of their gastrointestinal tract, Burmese pythons simultaneously experience a dramatic increase in cardiovascular performance. The postprandial increase in heart rate and stroke volume combine to generate as much as a 4.2-fold increase in cardiac output. For a python at rest digesting its meal, this increase in cardiac output serves to perfuse the active gut, evident by the near 11.6-fold increase in blood flow through the superior mesenteric artery and 15.4-fold increase in hepatic portal flow. When faced with the dual circulatory demands of a digesting gut and contracting axial muscles, priority for blood volume is apparently given to the locomotory muscles as suggested by the large reduction in intestinal blood flow when pythons crawl. In this Discussion we shall briefly compare the magnitudes of locomotion and postprandial cardiovascular performance, explore the mechanisms that trigger intestinal hyperemia for pythons, address how cardiac performance and regional blood flow respond to the combined needs of the gastrointestinal tract and locomotory muscles, and discuss the integration of metabolic, intestinal, and cardiovascular performance.

Cardiac output and regional blood flow during rest, locomotion and digestion

For fasted vertebrates (including humans) at rest, the gastrointestinal tract and other digestive organs receive a substantial percentage of cardiac output. Representing 5.3% of the rat's body mass, the stomach, small intestine, and large intestine receives 17.1% of the rat's cardiac output (Field et al., 1939; Malik et al., 1976). For unfed fish, 20–40% of cardiac output is delivered to the gut or splanchnic circulation (Axelsson and Fritsche, 1991; Axelsson et al., 2002; Altimiras et al., 2008). Similarly for unfed humans, 20–25% of cardiac output is allocated to the gut (Kearney et al., 1995; Matheson et al., 2000). Based on superior mesenteric blood flow and assuming that flow rate is equally proportional to organ mass for the stomach, pancreas, small intestine and large intestine, we estimate that the combined blood flow to these digestive organs for resting and fasting Burmese pythons is approximately 25% of their cardiac output.

Movement (e.g. swimming, crawling, running or flying) will generate increases in both cardiac output and the circulatory

Table 2. Cardiac output and gastrointestinal blood flow of vertebrates while fasted at rest, exercising while fasted, digesting at rest, and exercising while digesting

Species	Body mass (kg)	Meal mass (% of bm)	Cardiac output (ml min^{-1} kg^{-1})				Gastrointestinal blood flow (ml min^{-1} kg^{-1})				References
			Fasting	Exercise	Postprandial	Exercise and postprandial	Fasting	Exercise	Postprandial	Exercise and postprandial	
Rainbow trout, *Oncorhynchus mykiss*	0.81	2					4.2*		9.9		Eliason et al., 200
Chinook salmon, *Onchorhynchus tshawytscha*	0.2–0.4	2					12.0†	4.8	22		Thorarensen et al., 1993; Thorarensen and Farrell, 2006
Cod, *Gadus morhua*	0.55–1.05	2.5–3.5	18.0	27.0	22.1		7.60*	5.15	12.06		Axelsson and Fritsche, 1991
Sea bass, *Dicentrarchus labrax*	0.36	2.7	51.4	90.1	67.6	99.4	13.8*	10.4	25.1	14.1	Altimiras et al., 2008
Red Irish lord, *Hemilepidotus hemilepidotus*	0.3–1.2	10–15	24.4		47.3		9.0*		18.2		Axelsson et al., 2000
Sea raven, *Hemitripterus americanus*	0.67–2.3	10–20	18.8	30.9			2.9‡		5.8		Axelsson et al., 1989
Burmese python, *Python molurus*	11.7	25	9.1	30.5	33.1	40.1	0.60†	0.20	5.04	0.94	This study
Dog	12–20	2.5					1.8†		6.66		Fioramonti and Bueno, 1984
Baboon, *Papio anubis*	22–26						8.83†		14.3		Vatner et al., 1974
Human	78	0.4	85.5		96.4		16.8*		19.7		Brundin and Wahren, 1994
Human	81		76.5	216	111	210	19.8*	10.1	34.6	19.5	Perko et al., 1998

Gastrointestinal blood flow was measured from the *combined celiac and mesenteric (i.e. splanchnic), †superior mesenteric artery, or ‡celiac artery. For the Burmese python, postprandial and exercise, and postprandial cardiac output and gastrointestinal blood flow were measured at 5 days postfeeding.

perfusion of active muscles (Laughlin and Armstrong, 1982; Armstrong et al., 1987) (Table 2). On empty stomachs, the fish, *Hemitripterus americanus*, increases cardiac output by 65% with swimming and humans increase cardiac output by 185% with running (Axelsson et al., 1989; Yi et al., 1990). At maximum oxygen consumption rates ($\dot{V}_{O_2,max}$), cardiac output increases 3.5- and 4.7-fold of resting levels, respectively, for women and men, and 4.7-fold for pigs (Åstrand et al., 1964; Armstrong et al., 1987). When encouraged to crawl, fasted Burmese pythons experience nearly a 3.5-fold increase in cardiac output. As also observed for other animals and humans, the exercise-induced rise in cardiac output for the python is primarily generated from an increase in heart rate with a modest contribution from an increase in stroke volume (Åstrand et al., 1964; Sanders et al., 1976; Axelsson et al., 1989). On average, the increase in heart rate and stroke volume accounted for respective 87.5% and 12.5% of the elevation in cardiac output for crawling pythons.

Although not measured directly, we assumed that much of the increase in cardiac output for crawling pythons serves to elevate blood flow to the axial muscles. In support, blood flow through the left carotid artery and dorsal aorta increased by 490% and 220%, respectively, whereas flow through the superior mesenteric artery decreased by 66%. In assuming similar reduction in blood flow (relative to mass) to the liver, esophagus, stomach, distal small intestine, large intestine and kidneys while crawling, combined blood flow to these tissues is only 6% of cardiac output for moving pythons. Hence blood flow to other tissues (e.g. axial muscles) of the python is estimated to increase by 470% during locomotion. Declines in gut blood flow with exercise have also been documented for the cod, *Gadus morhua* (by 29–36%), pigs (by 89%) and humans (by 30–45%) (Armstrong et al., 1987; Axelsson and Fritsche, 1991; Perko et al., 1998) (Table 2).

The metabolic demands of digestion are met by an increase in cardiac output (Fara, 1984; Kearney et al., 1995). Postprandial increases in cardiac output, ranging from 11% to 94%, have been documented for fishes, dogs and humans (Vatner et al., 1970; Brundin and Wahren, 1994; Axelsson et al., 2000; Altimiras et al., 2008) (Table 2). In general, the cardiac response to digestion is minor compared with that of exercise, with the exception being the Burmese python. During the digestion of a meal nearly equal in mass to 25% of the snake's body mass, the coiled python experiences as much as a 4.4-fold increase in cardiac output. Individually, the pythons of this study experienced a 36±10% greater cardiac output during digestion than when crawling while fasted. In a previous study of Burmese pythons, combined blood flow through the right and left aortic arches increased by 2.9-fold with crawling and 4.5-fold during digestion (Secor et al., 2000). In the present study, the postprandial increase in cardiac output in general is a product of a 240% increase in heart rate and a 30% increase in calculated stroke volume. Similarly, postprandial increases in cardiac output for other vertebrates are largely generated by increases in heart rate with little or no contribution from changes in stroke volume (Vatner et al., 1970; Hicks et al., 2000; Axelsson et al., 2002). For the Burmese python, the increase in stroke volume can be explained in part by the 24–36% postprandial increase in their cardiac mass (Secor and Diamond, 1995; Andersen et al., 2005).

Postprandial intestinal hyperemia is a seemingly universal physiological phenomenon that has been documented for fishes, reptiles and mammals (Fioramonti and Bueno, 1984; Axelsson et al., 1989; Axelsson et al., 1991; Sieber et al., 1992; Starck and Wimmer, 2005; Altimiras et al., 2008). Among these organisms, blood flow to the gut generally increases by 50–150%, with the

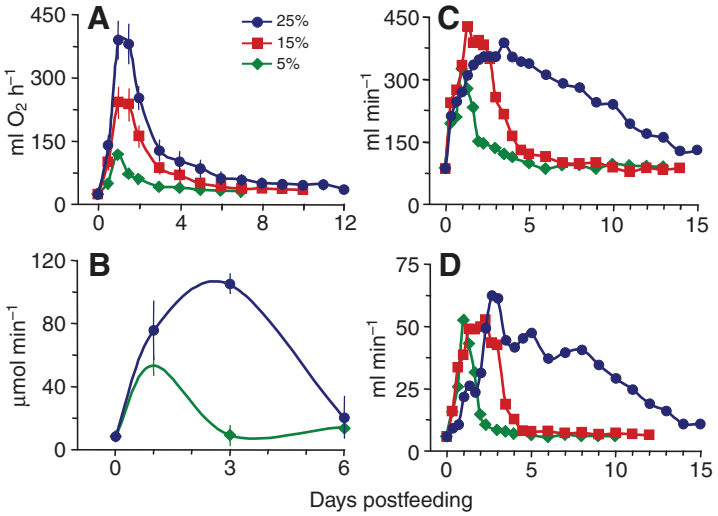

Fig. 6. The metabolic, digestive and cardiovascular responses of the Burmese python to different digestive loads. (A) Postprandial oxygen consumption, (B) intestinal uptake capacity for L-leucine, (C) dorsal aortic flow and (D) superior mesenteric flow for meal sizes equaling 5%, 15% and 25% of python body mass. Data for graphs A and B are from Secor and Diamond (Secor and Diamond, 1997a; Secor and Diamond, 1997b). Data for graphs C and D are from measurements taken from an 8.4 kg Burmese python.

largest previously recorded increase (270%) observed for dogs (Table 2). For the Burmese python, the postprandial increase in intestinal blood flow is much more dramatic, increasing by as much as 11.6-fold through the superior mesenteric artery and 15.4-fold through the hepatic portal vein. Understandably, the larger python response is due in part to their larger meals (25% *vs* 2–3% of body mass in other studies) which require a much greater metabolic demand and hence cardiovascular response. Since the relative increase in blood flow through the superior mesenteric artery after feeding is greater than that observed for cardiac output and dorsal aortic flow, this demonstrates that a proportionally greater amount of blood is diverted into the small intestine during digestion. For the first week of digestion nearly twice the percentage of cardiac output and dorsal aortic flow enters the superior mesenteric artery compared with prior to feeding. If we assume that blood flow is equally elevated to other gut tissues, proportional to their mass, then the combined blood flow to the stomach, pancreas, small intestine and large intestine within the first week of digestion is equivalent to approximately 36% of the python's cardiac output. A similar postprandial increase in the contribution of cardiac output to gut blood flow (24–34%) was observed for the sea bass, *Dicentrarchus labrax* (Axelsson et al., 2002).

Mechanisms underlying gastrointestinal hyperemia

Central to the studies of gastrointestinal hyperemia is an understanding of the mechanisms that mediate the cardiovascular changes accompanying digestion. Previously deemed complex and not well understood, these mechanisms include nutritive, metabolic, neural, hormonal and paracrine elements (Gallavan and Chou, 1985; Chou and Coatney, 1994; Matheson et al., 2000). The presence of food (chyme) within the gut may have a direct stimulatory effect on vascularization, as well as trigger a host of energy-consuming cellular activities, including ion and nutrient transport, intracellular trafficking and protein synthesis. Studies on dogs have demonstrated that micellar solutions of bile salts and oleic acid, as well as bile salts alone can generate a decrease in intestinal vascular resistance and hence increase blood flow (Kvietys et al., 1981; Chou et al., 1985). Pythons secrete bile during digestion and rapidly absorb luminal lipids. The former is evident by a 64% reduction after feeding in the mass of the full gall bladder, and the latter demonstrated by the postprandial appearance of large lipid droplets within intestinal enterocytes (Secor and Diamond, 1995; Starck and Beese, 2001; Lignot et al., 2005).

The presence of luminal nutrients stimulates a rapid increase in the activity, and hence oxygen consumption, of the gastric and intestinal epithelium (Pawlik et al., 1980). The resultant decrease in cellular oxygen partial pressure triggers vasodilation and an increase in tissue blood flow (Gallavan and Chou, 1985). For the Burmese python, digestion is characterized by a very large metabolic response (Secor and Diamond, 1997a). For example, pythons digesting rodent meals equal in mass to 25% of the snake's body mass experience as much as a 16-fold increase in oxygen consumption rates ($\dot{V}_{O_2}$) and eight days of elevated $\dot{V}_{O_2}$ (Secor and Diamond, 1997a). Pythons completely break down their intact meals within their stomach, experience as much as a 35-fold increase in pancreatic performance, and hydrolyze and absorb 90% of the ingested nutrients (Secor, 2003; Cox and Secor, 2007; Cox and Secor, 2008). Hence the large work load of the python's gastrointestinal tract during digestion, manifested as a large increase in $\dot{V}_{O_2}$, must be supported by matched increases in cardiac performance and gastrointestinal perfusion.

We can imagine neural mediation of the postprandial cardiovascular response operating at three sites: the heart, the gastrointestinal tract and the skeletal muscles. The heart, innervated by excitatory sympathetic and inhibitory parasympathetic fibers, would seemingly be responding to a postprandial increase in sympathetic and/or decrease in parasympathetic stimulation in increasing cardiac output. Expectedly, sympathetic stimulation is responsible in part for the pythons' increase in heart rate while crawling. In support, chemical blockade of the cholinergic and adrenergic receptors revealed for crawling boa constrictors (*Boa constrictor*) that the increase in heart rate was accompanied by an increase adrenergic tone and decrease cholinergic tone (Wang et al., 2001). Interestingly for the boa constrictor and ball python (*Python regius*), elevated heart rate during digestion is associated with a decrease in both cholinergic and adrenergic cardiac tone, and for the ball python, a transitory increase in histaminergic tone (Wang et al., 2001; Skovgaard et al., 2007). If this is the case for the Burmese python, then their postprandial tachycardia is apparently triggered by a circulating non-adrenergic, non-cholinergic (NANC) factor being released elsewhere in the body (Wang et al., 2001).

Although the small intestine is richly innervated by sympathetic and parasympathetic fibers, it is not clear what the role of the enteric nervous system is in moderating postprandial hyperemia (Sieber et al., 1991; Matheson et al., 2000). Originally it was suggested that cholinergic mechanisms were responsible for intestinal vasodilation

with feeding but experimental studies have demonstrated that parasympathetic, as well as sympathetic, innveration is not required for postprandial hyperemia (Nyhof and Chou, 1983; Nyhof et al., 1985).

Expectedly, the python's axial musculature receives an increase in sympathetic stimulation during exercise. The origin of this autonomic response may include the brain (central control), arterial baroreflex, and/or the local accumulation of chemicals released from the metabolically active tissue (e.g. nitric oxide) (Owlya et al., 1997; Delp and O'Leary, 2004). Although the sympathetically mediated response is vasoconstriction (hence serving to reduce gastrointestinal blood flow), there is conflicting evidence from mammalian studies regarding the impact of increased sympathetic tone on skeletal muscle blood flow (Delp and O'Leary, 2004). For the crawling Burmese python the seemingly opposing vasodilation within the skeletal muscle may reflect a decrease in responsiveness of α-adrenergic receptors or the dominance of a local chemically mediated vasodilator (Tateishi and Faber, 1995; Buckwalter and Clifford, 2001).

Given the apparent lack of a recognized neural pathway, postprandial cardiovascular performance may alternatively be modulated by humoral signals. Similar to other vertebrates, Burmese pythons possess a myriad of gastrointestinal hormones, which with feeding are released into the circulation (Secor et al., 2001). Within 24 h of feeding, plasma concentrations of cholecystokinin, neurotensin, glucose-dependent insulinotrophic peptide and glucagon have increased by 3.3- to 25-fold for the Burmese python (Secor et al., 2001). Studies on mammals and crocodilians have demonstrated that the administration of the gastrointestinal peptides, cholecystokinin, secretin, gastrin, neurotensin, substance P, neuropeptide Y and bombesin, stimulate vasodilation and/or an increase in blood flow within the gastrointestinal tract (Burns and Schenk, 1969; Premen et al., 1985; Holmgren et al., 1989; Kågström et al., 1998). In mammalian studies, peptide dosages that stimulated vascular response were much greater than endogenous levels (Premen et al., 1985; Matheson et al., 2000). The fact that dosages administered at physiological levels failed to induce gastrointestinal vasodilation or increase in blood flow calls into question whether any of these peptides are involved in the postprandial regulation of gastrointestinal blood flow (Sieber et al., 1991; Matheson et al., 2000). Two pieces of evidence suggesting humoral modulation of gut blood flow originate from studies on the ball python, *Python regius*. First, histamine, possibly released by cardiac mast cells, temporarily stimulate the postprandial heart, and second an administration of neurotensin at physiological levels (1 pmol kg^{-1}) induces a 150% increase in superior mesenteric blood flow (Skovgaard et al., 2007; Skovgaard et al., 2009).

Cardiovascular responses to the combination of digestion and locomotion

The assertion that vertebrates lack the cardiovascular capacity to provide elevated blood flow to a multitude of active tissues is supported by the findings of this study. When faced with the simultaneous circulatory demands of digestion and movement, Burmese pythons are unable to support both fully. If they could do so, cardiac output would represent an additive response to both locomotion and digestion, and hence increase by 5.9-fold for snakes crawling 5 days into meal digestion. Instead, we found pythons to experience a 4.4-fold increase in cardiac output at that time. Since digestion at day 5 and movement independently generate 3.6- and 3.3-fold increases in cardiac output, respectively, digesting and crawling pythons seemingly elevate blood flow to the axial muscles while maintaining reduced flow to the intestine. Pythons preferentially shunt blood away from the gut when moving, illustrating that the circulatory needs of the gut 'plays second fiddle' to that of the axial musculature. This pattern of response has also been observed for other vertebrates. For example, an increase in swimming speed of the sea bass, either fasting or digesting, results in a decrease in gut blood flow (Altimiras et al., 2008). At the other end of the vertebrate spectrum, humans reduce abdominal blood flow by 25–40% with exercise, regardless if they are fasting or digesting (Qamar and Reed, 1987). An adaptive explanation for prioritizing blood flow to skeletal muscles is that the immediate needs for heightened locomotory performance to elude predation, and thus survive, out-weighs the need to digest. Slowing or delaying digestion temporarily may have little consequence on meal assimilation and survival.

The above adaptive rationale for diverting blood away from the digesting gut to active skeletal muscle raises the question of how much is digestive performance inhibited by movement.

Many terrestrial vertebrates, especially snakes, are relatively sedentary after ingesting a meal; therefore normal gut activity is seldom interrupted. However, many species of fish are constant swimmers and therefore must digest their meals while swimming (Magnuson, 1973). We can imagine for such fishes a trade-off exists between provisioning adequate circulation to the axial muscles and to the gut, which depends on the demands of the axial muscles (Farrell et al., 2001). Although it has not been demonstrated experimentally, a fish swimming at near maximum capacity may experience sever depression or cessation of digestive performance. Although the pythons of this study may have experienced a decline of gastrointestinal performance when enticed to move 5 days into meal digestion, the effect was probably minor given they seldom continue moving for more than 10–15 min.

Integration of postprandial hyperemia

For the Burmese python, meal ingestion is immediately followed by the rapid upregulation of gastric, pancreatic, and small intestinal performance (Secor, 2008). The previously dormant stomach activates H^+/K^+ pumps to produce enough HCl to decrease luminal pH from 7 to 1.5 within 48 h and maintain a pH of 1.5 for an additional 4–6 days of digestion (Secor, 2003). The pancreas doubles in mass while increasing enzyme activity by 6- to 20-fold (Cox and Secor, 2008). Likewise the small intestine doubles in mass and experiences 4- to 20-fold increases in nutrient transport and hydrolase activity (Secor and Diamond, 1995; Cox and Secor, 2008). Faced with the daunting task of breaking down and absorbing such a large meal, these organs each require increases in vascular perfusion. The increase in gastric blood flow provides the H_2O, CO_2, and Cl^- needed for HCl formation and nutrients (glucose and fatty acids) to enhance the production of ATP which fuels the very active H^+/K^+ pumps. For the pancreas, increase flow provides the additional HCO_3^- that is released into the small intestine to buffer the acidic chyme exiting the stomach. Increased capillary flow in the intestinal mucosa with feeding is necessary to establish a strong epithelial–endothelial concentration gradient allowing nutrients to be rapidly absorbed (Pappenheimer and Michel, 2003). In addition to these organ-specific needs of postprandial hyperemia is the general requirement for increased oxygen delivery to the active digestive tissues. Although we did not specifically measure gastric and pancreatic blood flow (pancreatic arteries do originate from the superior mesenteric artery), postprandial increases in gastric and pancreatic blood flow have been studied in dogs (Gallavan et al., 1980; Kato et al., 1989). We suspect that the liver (independent of

hepatic portal flow) and kidneys also experience significant postprandial increases in blood flow, stimulated by their increase in mass, metabolism and function (Secor and Diamond, 1995). From cardiac output to vascular perfusion of gut tissues, to the cell–capillary interface, there is a coordinated bond between cardiovascular and gastrointestinal performance.

The link between cardiovascular and gut performance is illustrated by comparing the metabolic, digestive and cardiovascular responses of the Burmese python to different digestive loads. Meals equal in mass to 5%, 15% and 25% of the python's body mass generates corresponding increases in metabolic rate and specific dynamic action (Secor and Diamond, 1997a) (Fig. 6). With a 5-fold increase in meal size (5–25% of body mass), digestion is prolonged by an additional 3 days and the postprandial elevation in intestinal performance is increased by 100% (Secor and Diamond, 1997b) (Fig. 6). For an 8.4-kg python, increasing meal size (5% to 15% to 25%) generates matched increases in cardiac output and superior mesenteric flow (Fig. 6). The integrated area under the cardiac output profiles for 5%, 15% and 25% size meals is tightly correlated with the specific dynamic action (SDA) resulting from these meal sizes (Secor and Diamond, 1997a). Pythons respond to a 3-fold increase in meal size (5% to 15%) by increasing summed cardiac output and SDA by 2.5- and 3.2-fold, respectively. An additional 67% increase in meal size (15% to 25%) generates an added 80% and 75% increase in summed cardiac output and SDA, respectively (Fig. 6). For this range of meal sizes (5–25% of body mass), metabolic, gastrointestinal and cardiovascular performance of Burmese pythons increases accordingly with digestive demand. During the digestion of even larger meals (up to 65% of body mass), Burmese pythons further elevate metabolic and intestinal performance (Secor and Diamond, 1997a; Secor and Diamond, 1997b). Although predicted to match pace with the increase in metabolic response to larger meals, cardiac performance may at some point reach a plateau because of physiological or mechanical constraints underlying heart rate or stroke volume. Examining cardiac output and heart rate during the digestion of the larger meals would reveal whether pythons experience a functional bottleneck at the level of the heart in cardiovascular performance.

AKNOWLEDGEMENTS

We wish to thank for their assistance on this project Jason Barton, Scott Boback, Matthew Boehm, Hailey Clark, Brian Ott, Matthew May, and Shelley Spann. We are especially grateful to Joseph Robertson for Fig. 2. Financial support for this study was provided by the University of Alabama and the National Science Foundation (IOS 0446139 to S.M.S.).

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