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Recovery from an activity-induced metabolic acidosis in the American alligator, *Alligator mississippiensis*

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Abstract

The metabolic acidosis resulting from an intense exercise bout is large in crocodilians. Here we studied recovery from this pH perturbation in the American alligator. Metabolic rate, minute ventilation, arterial pH and gases, and strong ion concentration were measured for 10 h after exhaustion to elucidate the mechanisms and time course of recovery. Exhaustion resulted in a significant increase in lactate, metabolic rate, and ventilation, and a decrease in arterial P_{CO_2}, pH and bicarbonate. By 15 min after exhaustion, oxygen consumption returned to rest though carbon dioxide excretion remained elevated for 30 min. Arterial P_{O_2}, $[Na^+]$, and $[K^+]$, increased following exhaustion and recovered by 30 min post-exercise. Minute ventilation, tidal volume, $[Cl^-]$, and respiratory exchange ratio returned to resting values by 1 h. The air convection requirement for oxygen was elevated between 15 and 60 min of recovery. Breathing frequency and pH returned to resting values by 2 h of recovery. Lactate levels remained elevated until 6 h post-exercise. Arterial P_{CO_2} and $[HCO_3^-]$ were depressed until 8 h post-exercise. Compensation during recovery of acid-base balance was achieved by altering ventilation: following the initial metabolic acidosis and titration of bicarbonate, a relative hyperventilation prevented a further decrease in pH.

Keywords: Acid-base; Acidosis; *Alligator mississippiensis*; Arterial blood gases; Exercise; Metabolic rate; pH; Ventilation

1. Introduction

The activity capacity of many reptile species is largely supported by anaerobic metabolism (Bennett, 1978) and as a consequence, a metabolic acidosis results. A significant period of time is required to recover from this acid-base perturbation. Several factors influence recovery including duration of activity (Gleeson, 1991; Gleeson and Hancock, 2002) and body temperature (Tattersall and Boutilier, 1999; Wagner et al., 1999). Ventilatory adjustments and lactate levels during and following activity are fairly well described in reptiles (Gleeson and Bennett, 1982; Gleeson, 1991; Farmer and Carrier, 2000b,a; Nedrow et al., 2001), but changes in blood chemistry coupled with ventilatory adjustments throughout recovery have not been reported. In this experiment we address the following questions. What is the magnitude of the acidosis caused by an exhaustive activity bout? How long does it take for the acidosis to be recovered? What are the relative contributions of respiratory and metabolic (here, strong ion exchange) processes to recovering acid-base balance? We chose the American alligator (*Alligator mississippiensis*) as our model for this study because its acid-base regulation is well understood for a variety of physiological perturbations, namely digestion (Busk et al., 2000), varied gas tensions (Powell and Gray, 1989; Hicks and White, 1992; Wang and Warburton, 1995), graded exercise (Farmer and Carrier, 2000b), and temperature changes (Douse and Mitchell, 1991).

2. Materials and methods

2.1. Animals

American alligator eggs were collected from the Rockefeller Wildlife Refuge in Grand Chenier, LA, USA and were incubated at 30 °C. After hatching, alligators were housed in 1×4×1 meter fiberglass tanks with free access to

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water and basking sites; temperatures ranged from 28 to 32 °C. Animals were fed fish (goldfish or smelt), mice, and/or chicken pieces to satiation once weekly. Six alligators (mass = 479 ± 50 g) were used in this study. Approval for animal use in this study was given by the University of California, Irvine's Institutional Animal Care and Use Committee (protocol #2123).

2.2. Surgery

For serial blood sampling, a chronic arterial cannula was inserted into the femoral artery of the left hind limb. Alligators were lightly anesthetized by placing them in a container with gauze soaked in Isoflurane (Isoflo, Abbott laboratories, North Chicago, IL, USA), then intubated with a tracheal tube and artificially ventilated with 2% Isoflurane and room air (SAR-830, CWE Inc., Ardmore, PA, USA; Dräger, Lubeck, Germany). The incision site was scrubbed with Prepodyne (Iodine scrub, WestAgro, Kansas City, MO, USA), and a 3 cm incision was made through the skin. Superficial muscle groups were separated by blunt dissection, exposing the femoral artery. Flexible tubing (polyethylene tubing, I.D. 0.023, O.D. 0.038 cm Harvard Apparatus, Inc., Holliston, MA, USA) was inserted into the artery, and secured with 3-0 silk suture (Ethicon, Somerville, NJ, USA). The incision was stitched and sealed with a cyanoacrylate adhesive (Vetbond, 3M, St Paul, MN, USA). The cannula was looped and sutured at intervals to the skin to prevent tangling during subsequent activity. Analgesics (Flunixamine, Fort Dodge, Madison, NJ, USA) were administered for pain relief and antibiotics (Baytril, Bayer Corporation, Shawnee Mission, KS, USA) to prevent infection. Following surgery, the animal was ventilated with room air until voluntary breathing resumed. Animals were then allowed to recover from surgery for at least 48 h at 30 °C prior to experimentation.

2.3. Protocol

To collect expired gases, a mask was made from the end of a falcon tube (Corning Inc. Life Sciences, Acton, MA, USA) cut to 4 cm. Two holes were drilled in the mask, and flexible tubing (Tygon® tubing, Saint-Gobain Performance Plastics, Akron, OH, USA) was glued into these holes. The mask was then affixed over the alligator's nostrils and was secured to the head with polyether impression material (Impregum F, 3M EPSE, St. Paul, MN, USA). The sides of the mouth were sealed with Impregum to prevent the loss of expired gases. Room air was pulled through the mask by aquarium pumps, passing through a Drierite (anhydrous calcium sulfate, Xenia, OH, USA) column to remove water vapor. Flow rate (1.2–2.6 L min^{-1}, depending on the size of the animal) was controlled with rotameters (Brooks Instruments, Hatfield, PA, USA). Alligators were then placed in a darkened plastic container with holes drilled in the lid through which the tubing from the mask and the cannulae were exteriorized. A minimum of 12 h of quietly resting in the box was allowed to alleviate the effects of handling stress. Metabolic rate, breathing frequency and tidal volume data were collected by Acknowledge data acquisition software (Biopac, Goleta, CA, USA). Ventilation was measured by pneumotachography (8311, Hans Rudolph, Inc., Kansas City, MO, USA); oxygen consumption and carbon dioxide excretion were measured with oxygen and carbon dioxide gas analyzers (S-3A, Applied electrochemistry Inc., Sunnyvale, CA, USA; CD-3A, Applied Electrochemistry Inc., Sunnyvale, CA, USA, respectively). Calibration curves for $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were made by injecting known volumes of varied gas mixtures through the mask. Minute ventilation and tidal volume are reported at BTPS, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ at STPD. Air convection requirement for oxygen and carbon dioxide were calculated from measured minute ventilation and metabolic rate values ($\dot{V}_E\ \dot{V}_{O_2}^{-1}$, $\dot{V}_E\ \dot{V}_{CO_2}^{-1}$). Blood gases, pH, and strong ion concentration were measured by a NOVA blood gas analysis system (Waltham, MA, USA) corrected for temperature with a Radiometer blood gas analysis system (Copenhagen, Denmark). Two 0.25 mL blood samples separated by at least 1 h were

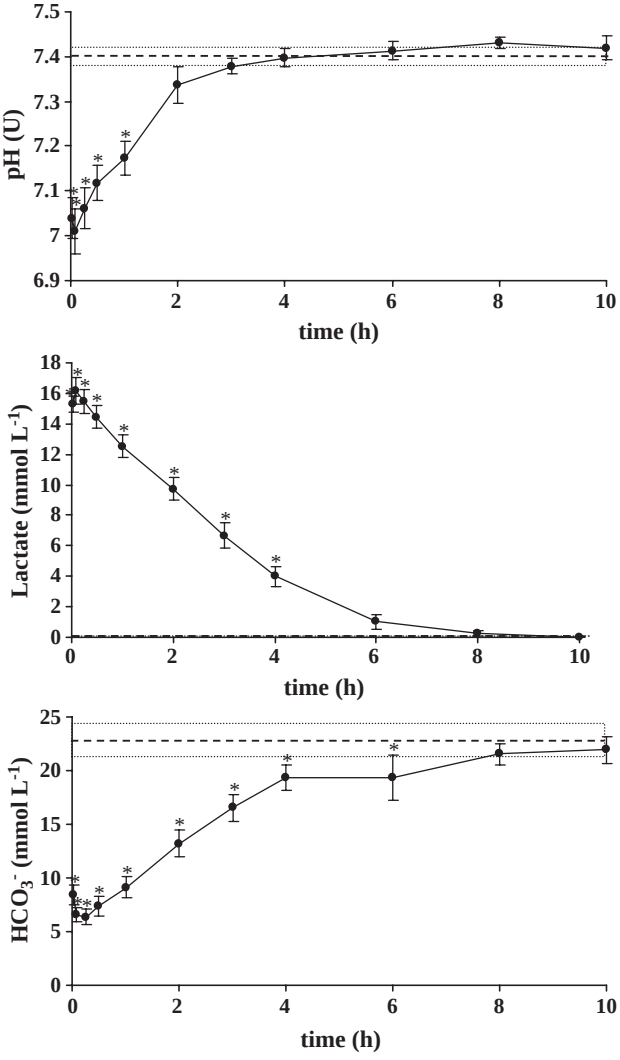

Fig. 1. Arterial pH, lactate, and bicarbonate levels throughout 10 h of recovery from exhaustive activity. Dashed line and dotted lines represent mean and standard error of the mean for resting levels, respectively. * indicates $P < 0.05$.

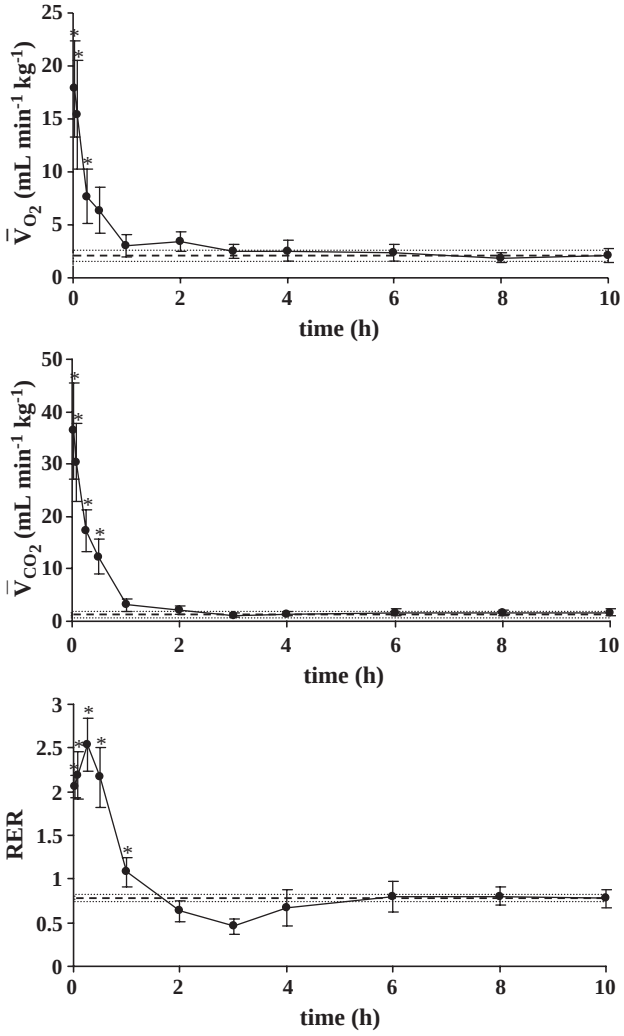

Fig. 2. Oxygen consumption, carbon dioxide excretion, and respiratory exchange ratio throughout 10 h of recovery from exhaustive activity. Dashed line and dotted lines represent mean and standard error of the mean for resting levels, respectively. * indicates $P<0.05$.

taken to ascertain resting blood values. The alligator was then removed from box and exercised to exhaustion. This exhaustive activity was achieved by turning the alligator onto its back from which position it struggled and turned itself back upright. Three to four minutes were required to exhaust an alligator to the point of being unable to right itself; at which point it was returned to the holding container, and the analysis of recovery begun. Metabolic rate and ventilation were measured continuously, and blood samples were taken at 1, 5, 15, 30, and 60 min, 2, 4, 6, 8, and 10 h of recovery. Alligators were kept in a walk-in environmental chamber maintained at 30±0.5 °C throughout the experiment.

2.4. Statistical tests

Repeated measures ANOVA (with post hoc Dunnett Test for Multiple Comparisons versus Control Group) was used to analyze time course data (Graphpad Software, San Diego, CA, USA). Time to recovery was determined for each variable where measured values were no longer significantly elevated from rest. Levels of significance were assumed with *p*-values less than 0.05. Values are reported as means±standard error of the mean. $N=6$ for blood chemistry, $N=5$ for respiratory variables.

3. Results

Struggle to exhaustion resulted in a large acidemia (with a maximal decrease of 0.39 pH units) which returned to resting levels 2 h into the recovery period. Lactate (Lac) accumulation from the exhaustive activity was also large (peak value of 16.2 mmol L^{-1} at 5 min recovery) and was accompanied by a 15 mmol L^{-1} drop in bicarbonate concentration ($[HCO_3^-]$) at 15 min recovery (Fig. 1).

This exhaustive activity was followed by a 10-fold increase in oxygen consumption ($\dot{V}_{O_2}$) and a 28-fold increase in carbon dioxide excretion ($\dot{V}_{CO_2}$). The larger $\dot{V}_{CO_2}$ relative to $\dot{V}_{O_2}$

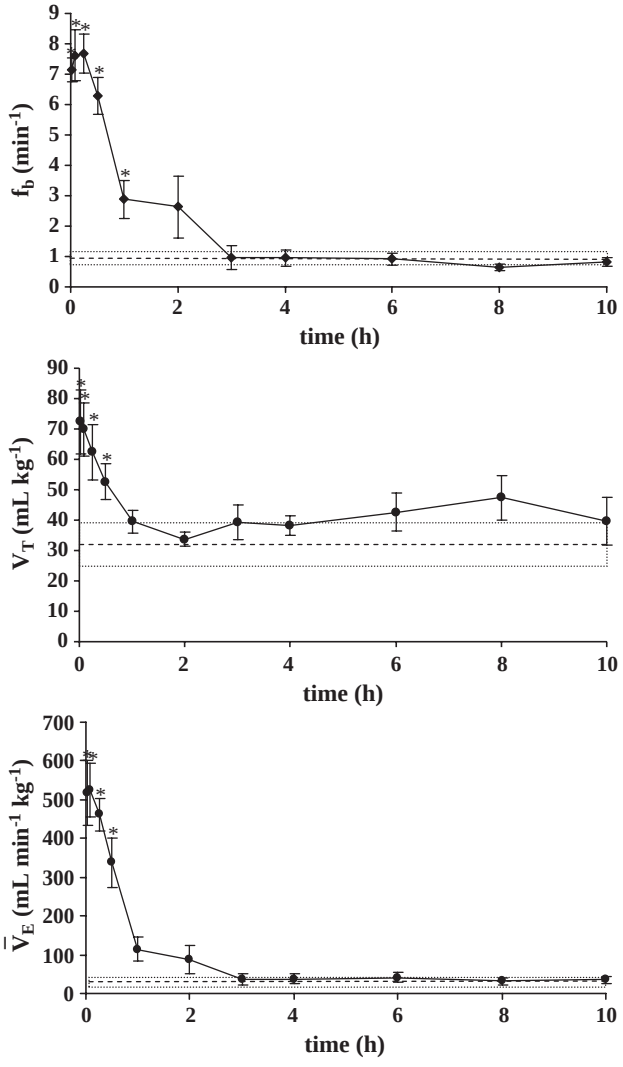

Fig. 3. Breathing frequency, tidal volume, and minute ventilation throughout 10 h of recovery from exhaustive activity. Dashed line and dotted lines represent mean and standard error of the mean for resting levels, respectively. * indicates $P<0.05$.

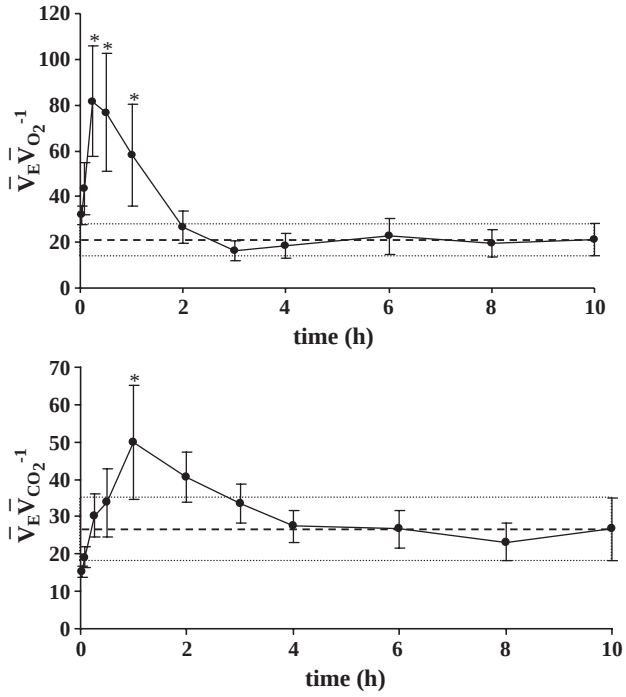

Fig. 4. Air convection requirement for oxygen and carbon dioxide throughout 10 h of recovery from exhaustive activity. Dashed line and dotted lines represent mean and standard error of the mean for resting levels, respectively. * indicates $P<0.05$.

resulted in a respiratory exchange ratio (R) of over 2 for the first half hour of recovery from exhaustion (Fig. 2). This three-fold increase in R is indicative of the titration of bicarbonate by increased $[H^+]$. An increase in both tidal volume (V_T) and breathing frequency (f) resulted in an 18-fold increase in minute ventilation ($\dot{V}_E$) (29.4±9.3 mL min^{-1} kg^{-1} at rest to 525.6 mL min^{-1} kg^{-1} 5 min into recovery) (Fig. 3).

The exercise induced metabolic acidosis was accompanied by a relative hyperventilation (a greater increase in $\dot{V}_E$ than that required to match the increased metabolic rate: an elevated $\dot{V}_E\ \dot{V}_{O_2}^{-1}$ and $\dot{V}_E\ \dot{V}_{CO_2}^{-1}$, Fig. 4), and a significantly decreased arterial partial pressure of carbon dioxide (Pa_{CO_2}) and increased arterial partial pressure of oxygen (Pa_{O_2}) (Fig. 5). By the second hour into the recovery period, resting pH and Pa_{O_2} were restored. There were significant changes in strong ion concentration (Na^+, K^+, and Cl^-) in the initial recovery period, but these ions were restored to resting levels by the first half-hour of recovery. There was a striking increase in $[K^+]$ of 2 meq L^{-1} immediately following the exhaustive activity bout (Fig. 6).

Metabolic rate and the strong ions were the first to recover (by 0.5 h), followed by R and $\dot{V}_E$ recovered by the first hour into recovery, pH was recovered by 2 h. Lactate concentrations

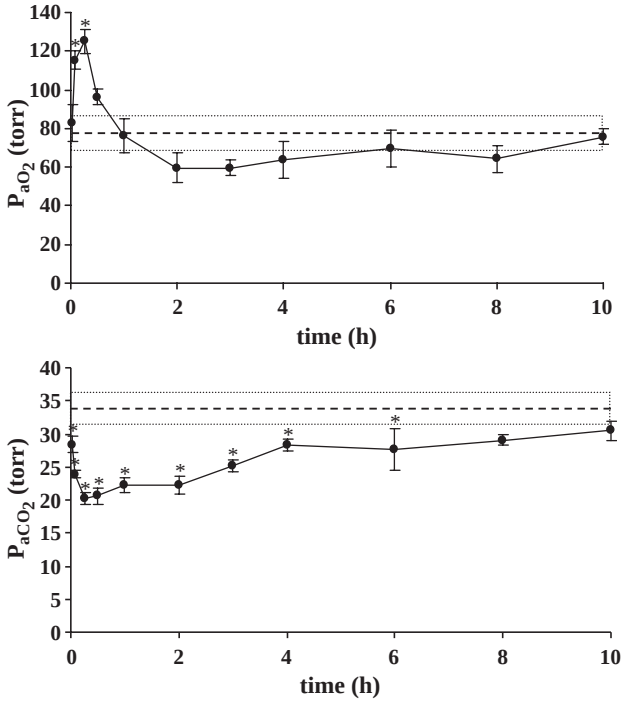

Fig. 5. Arterial partial pressures of oxygen and carbon dioxide throughout 10 h of recovery from exhaustive activity. Dashed line and dotted lines represent mean and standard error of the mean for resting levels, respectively. * indicates $P<0.05$.

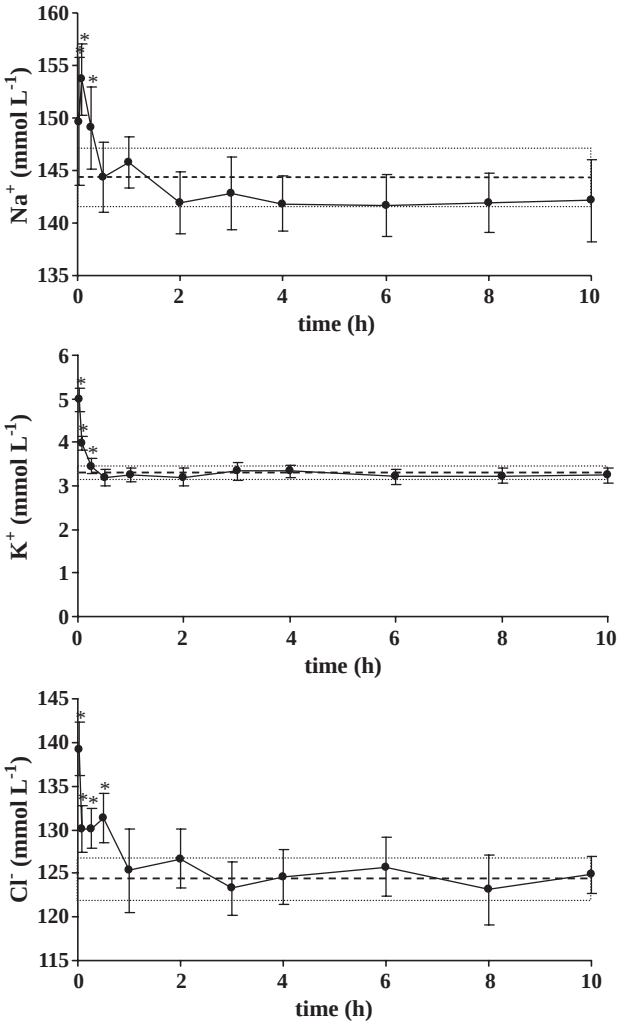

Fig. 6. Strong ions (Na^+, K^+, and Cl^-) throughout 10 h of recovery from exhaustive activity. Dashed line and dotted lines represent mean and standard error of the mean for resting levels, respectively. * indicates $P<0.05$.

did not recover until 6 h after exhaustion, and [HCO_3^-] and Pa_{CO_2} did not recover until 8 h after exhaustion.

4. Discussion

Much of the activity capacity of reptiles is supported by anaerobic metabolism (Bennett, 1994) with the consequent need of a significant recovery period to restore resting physiological state. Oxygen consumption remains elevated for a period of time following the activity bout (di Prampero and Ferretti, 1999; Gleeson and Hancock, 2002). Recovery from anaerobic exercise bouts has been examined for a number of vertebrate ectotherms, with a focus on crocodilians (Bennett et al., 1985; Seymour et al., 1985; Baldwin et al., 1995; Lance and Elsey, 1999; Farmer and Carrier, 2000b) and a variety of lizard species (Bennett, 1973; Gleeson and Bennett, 1982; Bickler and Anderson, 1986; Garland et al., 1987; Nedrow et al., 2001; Gleeson and Hancock, 2002). The recovery periods described in previous studies have generally been for only the first hour of recovery, and have described either ventilatory parameters or blood chemistry. Here we examined a longer time course for recovery and the interaction of ventilatory and blood chemistry parameters after a metabolic acidosis.

Patterns of post-exercise oxygen consumption ($\dot{V}_{O_2}$) and air convection requirement for oxygen ($\dot{V}_E\ \dot{V}_{O_2}^{-1}$) in these forcibly exercised alligators are similar to those reported for these animals after graded exercise (Farmer and Carrier, 2000a). High air convection requirements are tied to the large CO_2 load resulting from HCO_3^- titration. It is interesting to note that most of the ventilatory parameters measured were recovered by the first hour after exhaustion (Fig. 3), yet lactate remained elevated and Pa_{CO_2} and [HCO_3^-] remained depressed for 4 to 6 h (Figs. 1 and 4). It is this depressed Pa_{CO_2} which partially compensates for the metabolic acidosis (Fig. 7). As indicated by the arrows, there is a sharp acidosis (A) immediately following the exercise bout which then slows even though HCO_3^- continues to be titrated (B). This relative hyperventilation (as reflected by depressed Pa_{CO_2}) continues as pH returns to resting levels (C); after pH recovers, [HCO_3^-] and Pa_{CO_2} slowly return to resting levels (D).

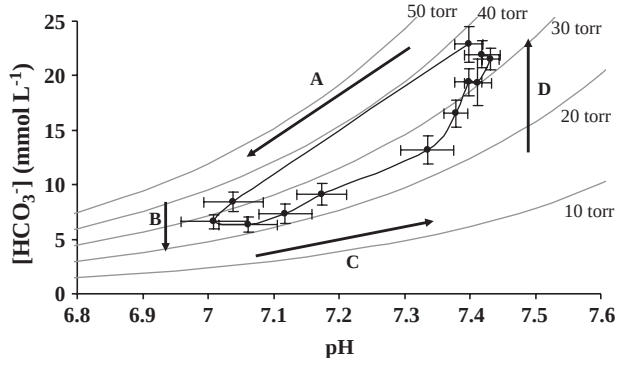

Fig. 7. Davenport diagram illustrating the acid-base perturbation and recovery from exhaustive activity. Arrows indicate the initial metabolic acidosis (A) from the resting state to the first minute of recovery; relative hyperventilation (B) from the first minute to 5 min into recovery; return of pH to resting levels (C) from the first 5 min into recovery until the second hour into recovery; and recovery of [HCO_3^-] and Pa_{CO_2} (D) from the second hour on through the recovery period.

The byproduct of anaerobic metabolism is lactate, and the amount released into the extracellular fluid depends on a variety of physiological circumstances: e.g. the amount generated, released from the muscle tissue, and/or reconverted through glycogenesis, and the rate of lactate oxidation. An exhaustive exercise bout such as experienced by the alligators in this study results in the shifting of large amounts of lactate into the extracellular fluid (Fig. 1). Besides intense (anaerobic) exercise, other situations (such as dives, forced submergences, and anoxic conditions) may also require anaerobic metabolism and the subsequent production of lactate. However, the production of lactate is not limited to anaerobic conditions, and significant increases in blood lactate have been reported for rattlesnakes in which aerobic capacity is maintained (Kemper et al., 2001). The 16-fold increase in arterial blood lactate measured in this experiment is similar to that increase reported for alligators worked to exhaustion or given exogenous catecholamines (Coulson and Hernandez, 1986), and for crocodiles (Baldwin et al., 1995) though larger caimans (Jackson et al., 2003) and larger crocodiles can produce more lactate (per kg body mass) during exhaustive exercise (Bennett et al., 1985). Besides size influences on lactate production, exercise intensity (Nedrow et al., 2001), activity patterns prior to exercise (Scholnick and Gleeson, 2000), submergences (Bagatto and Henry, 1999; Reese et al., 2001; Jackson et al., 2003); aggression (Schuett and Grober, 2000), catecholamines (Schuett and Grober, 2000), training (Warren and Jackson, 2004), and restraint techniques (Franklin et al., 2003) all impact the level of lactate production in various reptiles.

The metabolic acidosis resulting from an exhaustive exercise bout caused a drop in arterial pH of nearly 0.4 pH units (U) (in this case, an increase in [H^+] of 58 nmol L^{-1}). The variability in exercise-induced metabolic acidosis among reptiles is remarkable: *Iguana iguana* (−0.44 U) and *Sauromalus hispidus* (−0.22 U) after exhaustive exercise while smaller increases were measured in two varanid species: no change in *Varanus salvator*, and a decrease of 0.27 units in *Varanus exanthematicus* (Bennett, 1973; Gleeson and Bennett, 1982). Short dives elicited a decrease of 0.09 pH units in the water snake *Liophis miliaris* (Abe, 1987), while 1 h of forced submergence elicited a decrease of 0.20 pH units in *Trachemys scripta*, and 0.31 pH units in *Apalone ferox* (Bagatto and Henry, 1999). In these same species, exercise to exhaustion resulted in a decrease in pH of 0.18 units (Bagatto and Henry, 1999). In other crocodilians, a 30-min dive caused a decrease of 0.45 units in *Caiman latirostris* (Jackson et al., 2003), exhaustive activity in *Crocodylus porosus* caused a decrease in pH of 0.32 units, and the struggle during capture of a 32 kg *C. porosus* resulted in a drop in pH to 6.42 units recovering after 29 h having removed an incredible 334 nmol L^{-1} H^+ during this recovery period (Seymour et al., 1985). The degree of decrease in pH during a metabolic acidosis scales with body mass where larger animals

(at least *C. porosus*) had a greater decrease in pH and also cleared H^+ at a greater rate (Bennett et al., 1985; Baldwin et al., 1995).

Exhaustion caused the largest change in pH of any other acid-base disturbance reported for *Alligator mississippiensis*. For comparison, a 3-h exposure to hypoxia caused an increase of 0.31 pH units (Branco et al., 1993), which is slightly less than the disturbance caused by exhaustion in this experiment. Digestion did not cause a significant increase in pH due to a relative hypoventilation that increased Pa_{CO_2} by nearly 8 Torr (Busk et al., 2000). A 10 °C drop in body temperature in alligators caused an increase in pH of 0.18 units (Douse and Mitchell, 1991).

During the initial recovery period, there is an increase in all of the arterial strong ions, but while $[Na^+]$ increases by 7% and $[Cl^-]$ increases by 12%, there is an increase in $[K^+]$ of 36% (Fig. 6). The impact of increased $[K^+]$ is controversial. Potassium released from muscle during activity may reduce muscle performance, i.e. force production and excitability (Cairns et al., 1997), but see Overgaard and Nielsen (2001). It has been suggested that the acidosis caused by lactic acid generation may counterbalance the negative effects of increased $[K^+]$ (Nielsen et al., 2001). Paterson (1992) suggested that an alternative interpretation for the increased $[K^+]$ is that it is one of the cues triggering increased ventilation. Previous studies have shown that changes in ventilation happen too quickly to be due solely to the change in blood lactate (Asmussen and Nielsen, 1946), and that arterial $[K^+]$ and $\dot{V}_E$ are correlated (Paterson, 1992); however, in this experiment both arterial blood $[K^+]$ and [Lac] increased immediately after exhaustion. In the alligators in this experiment, $[K^+]$ increased to 5 mmol L^{-1}, a value comparable to that seen in humans with prolonged exercise (5.5 mM) though less than that in humans during exhaustive work (8–9 mM) and at maximal oxygen consumption (Paterson, 1996; Barlow et al., 1999; Overgaard et al., 2002).

Metabolic acidosis induced by intense activity increases $[H^+]$ 41% compared to rest. This acidemia is recovered within 2 h following the cessation of activity. A relative hyperventilation largely compensates the metabolic acidosis suggesting that respiratory mechanisms play a larger role in acid-base balance following activity than metabolic processes (such as lactate reconversion through glycogenesis, lactate oxidation, $[HCO_3^-]$ modification by the kidneys) that occur over a longer period of time.

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