Forced running-induced rhabdomyolysis in the Sprague-Dawley rat: towards a rodent model of capture myopathy

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Abstract

Capture myopathy (CM) is a metabolic disease associated with mortality in mass boma captured (MBC) wildlife. The condition is induced by forced pursuit, capturing, and restraint of wild animals, although its causal biology remains to be confirmed. A core feature of MBC-CM is rhabdomyolysis, which is associated with myoglobinuria and hyperthermia. To develop a translational model of CM-associated rhabdomyolysis, we investigated forced treadmill running to induce physical exhaustion and trigger rhabdomyolysis in Sprague Dawley (SD) rats. Twenty-four (24) SD rats (12 per sex) were subjected to treadmill habituation in a speed-tiered approach. Forty-eight hours after the last habituation session, one strenuous exercise (SE) session was performed at 75% of the theoretical VO_{2MAX} (30m/min) until animals reached physical exhaustion. Core and skin surface temperatures were measured before the SE session and after rats reached exhaustion, after which a 1-hour - cumulative urine sample was collected, and the myoglobin content assayed. We show that most SE, but not control-exposed (non-exercise) rats presented with myoglobinuria, while core and surface body temperatures in both male and female rats were significantly higher post-exercise. This pre-clinical model framework shows potential for investigating the pathophysiology of MBC-CM.

Keywords: animal model; capture myopathy; myoglobin; treadmill running; rhabdomyolysis; hyperthermia

Introduction

Capture myopathy (CM) is a non-infectious metabolic syndrome that leads to significant mortality in wild animals (Breed et al. 2019; Paterson 2007). Muscle damage, or rhabdomyolysis, is a core feature of CM, which is primarily characterised by myoglobinuria and often also hyperthermia in the early stages of the condition (Meyer 2010; Paterson 2007). Under capture conditions, a relative reduction in oxygen and nutrient delivery to muscle fibres leads to physical injuries of the basal membranes and sarcolemma. This results in rhabdomyolysis of the skeletal myocytes (Paterson 2007), which is associated with myoglobin release. Under normal physiological conditions, myoglobin is loosely bound to plasma globulins and only small amounts reach the urine. However, when high concentrations of myoglobin are released into the circulation, it reaches the renal tubules, where it may precipitate under conditions of metabolic acidosis, a common manifestation of rhabdomyolysis. Breakdown of myoglobin also causes oxidative-stress (Vanholder et al. 2000) and vasoconstriction-induced (Liu et al. 2017) kidney damage. Multiple organ failure,

the terminal outcome of rhabdomyolysis, later ensues when haem proteins cause systemic oxidative stress and tissue injury (AlBasher et al. 2020; Nath et al. 1992).

In addition to myoglobinuria, hyperthermia is also regarded as an important underlying role player in rhabdomyolytic pathology (Meyer et al. 2008a; Meyer 2010) and is believed to contribute to the irreversible kidney damage and associated renal failure seen in CM (Meyer et al. 2008a). During wildlife capture, hypoxic conditions caused by a high metabolic demand resulting from intense escape-related activity are exacerbated by a hyperthermic state which increases cellular oxygen consumption (Meyer et al. 2008a). Hyperthermia also is directly associated with the magnitude of stress responses in animals (Meyer et al. 2008b; Meyer 2010; Oka et al. 2001), pointing to a bidirectional relationship between the central and peripheral neurobiological underpinnings of stress, and how these may act in concert to precipitate and/or worsen CM (Meyer et al. 2008b; Meyer 2010; Oka et al. 2001).

A handful of rodent models of rhabdomyolysis have been characterised with the intent of improving our understanding of rhabdomyolysis. However, these are often chemically induced (Korrapati et al. 2012; Nath et al. 1992), which somewhat cloud investigations of the naturalistic manifestation of the condition as it may transpire in wildlife during capture procedures. While studies in such models are informative of the cellular and molecular events that may lead to rhabdomyolysis during malignant hyperthermia or heat stroke (Chelu et al. 2006; Dainese et al. 2009; Michelucci et al. 2015), valuable insights into the naturalistic processes that may underlie CM, cannot be gained. Thus, towards the first step of constituting a platform for investigating the potential naturalistic triggers of rhabdomyolysis as it transpires in wildlife during capture and translocation procedures, the present work sought to standardize a laboratory procedure to induce stress- and forced running-associated rhabdomyolytic processes in the Sprague-Dawley rat.

Methods and materials

Animals

Twenty-four (24) adult SD rats of both sexes (12 per sex) and weighing 150 g ± 10 g (PND=40) at the onset of experimentation were randomly sourced from 12 different breeding pairs housed and maintained at the Vivarium of North-West University (NWU) (SAVC reg. no. FR15/13458; SANAS GLP compliance no. G0019). Rats were group-housed (3 same sex animals per cage; each rat from a different breeding pair) under identical conditions, i.e. in individually ventilated polypropylene cages (230 x 380 x 380 mm prepared with corncob bedding; Tecniplast®, Varese, Italy) which were maintained at a temperature of 21 ± 2 ºC and a humidity of 50 ± 10 %. Lights were operated on a normal 12 h light/dark cycle

(06:00/18:00) and animals had free access to food and water throughout the investigation. All animals were maintained, and procedures performed in accordance with the approval guidelines and prescriptions of the Animal Care Research Ethics Committee of the NWU (NHREC reg. no. AREC-130913-015).

Experimental procedure

Since the SD rats used in this investigation had no prior experience with respect to treadmill running, each rat was subjected to two weeks of daily forced treadmill habituation in a speed-tiered approach (**Figure 1**). Immediately prior to the onset of the first treadmill habituation session, all rats were allocated individually to a metabolic cage for one hour during which time accurate separation of faecal and urine samples could be achieved (Kurien et al. 2004) and the urine myoglobin content determined. Subsequently, animals were transferred to the treadmill room. Habituation on the treadmill was implemented as follows. Rats were exposed to the treadmill for five consecutive days during two weeks respectively. In week one, rats walked at a speed of 10 m/min for 10 min. In week two, they slowly jogged at a speed of 20 m/min for 10 min, i.e. 25 % and 50 % of the theoretical VO_{2MAX} in SD rats (Schoeman et al. 2017). Forty-eight hours after the last habituation session, rats were subjected to a single strenuous exercise (SE) session that began at a speed of 10 m/min for 5 min, after which the speed was suddenly increased to 30 m/min (75 % of VO_{2MAX} (30m/min). In a prior pilot probe, animals failed to reach a running speed of 40 m/min (100 % of VO_{2MAX}) and hence we chose 30 m/min as maximum exercise speed. Animals were forced to run at this speed until they reached physical exhaustion, which was defined as the inability to maintain a running pace that would prevent animals from being subjected to three electrical shocks within a 30-second window (Schoeman et al. 2017). For each animal, the time ran was recorded from the point of setting the pace at 30 m/min until exhaustion was reached. Immediately prior to the SE session (after animals were removed from the metabolic cages), both surface and core body temperatures were recorded (baseline values; see below). Once animals reached the point of exhaustion, they were removed from the treadmill and their surface and core temperature re-measured. Rats were once again individually transferred to metabolic cages and left for one hour after which urine samples were taken. On the following morning, rats were euthanized by means of carbon dioxide inhalation.

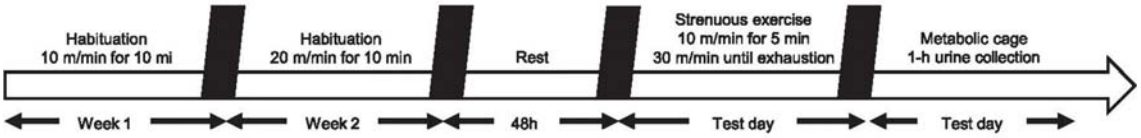

Fig. 1 Timeline detailing the course of events of each phase of the exercise protocol followed during each week of the investigation

Temperature and myoglobin measurement

Temperature

Temperature measurements were taken in the thermo-stable environment of the testing room immediately prior to and after the SE session. Surface temperatures were taken by scanning the dorsal surface of the neck area immediately behind the ears with a calibrated infrared thermometer (Fluke® 64 MAX Infrared Thermometer, Eindhoven, The Netherlands). Rectal temperatures were measured by gently inserting a lubricated and calibrated digital thermistor probe (Thermo Hygro®, Thermometer, BAMR®, Cape Town, South Africa) to a depth of 4 cm intra-rectally until a stable reading was obtained or for up to 20 s.

Myoglobin

To confirm myoglobinuria and quantify the urine myoglobin content, urine samples were collected over one hour prior to the onset of the first treadmill habituation session as well as over one hour after animals completed the SE protocol. All samples were immediately analysed using a validated photometric detection method (Indiko Plus® Benchtop Analyser, Thermo Fisher Scientific®, Waltham, Massachusetts, USA).

Statistical Analysis

All statistical analyses were performed with GraphPad® Prism® (version 9; GraphPad® Software, San Diego, California). The time ran until exhaustion on the treadmill by male and female rats was compared using Mann-Whitney *U*-tests. To analyse the pre- and post-SE surface and rectal body temperatures of male and female Sprague-Dawley rats, a three-way repeated measures analysis of variance (3-way RM ANOVA) was applied. Temperature was set as dependent variable, while body area, sex and time were set as independent variables. Two-way repeated measures ANOVA (2-way RM ANOVA) was applied to analyse the urine myoglobin content in male and female rats. Here, myoglobin concentration was set as dependent variable, while sex and time were set as independent variables. All ANOVA analyses were followed by Bonferroni multiple comparison tests to determine the significance of pairwise differences. Associations between the different variables measured, i.e. myoglobin concentration, surface and core body temperatures and total time ran during the SE session, were explored using Spearman's correlations. Statistical significance was set at $p < 0.05$ for all analyses. Data sets were assessed for normality applying Shapiro-Wilk tests.

Results

Time ran

No significant difference was demonstrated between the median running time of male (335.5 s) vs. female (530.0 s) rats (U = 41, z = -1.76, p = 0.08, 95CI: -14.0, 427.0).

Figure 2A: Baseline and post-SE surface and core body temperature

A 3-way ANOVA was used to examine the effects of body area, sex and time on the body temperatures (surface and rectal) of male and female rats before and after the SE session. No significant three-way interaction was observed [F(1, 44) = 2.9, p = 0.094]. Also, no two-way interactions existed between any of the independent factors. However, body area [F(1 44) = 435.0, p < 0.0001], sex [F(1 44) = 26.8, p < 0.0001], and time [F(1 44) = 160.3, p < 0.0001] all significantly impacted the results reported here. The mean surface and core temperatures of male [**Surface:** 31.6±1.5 °C vs. 28.7±0.8 °C, 95CI: -4.5, -1.99, p < 0.0001; **Core:** 35.4±1.0 °C vs. 33.5±0.5 °C, 95CI: -3.1, -0.63, p = 0.0003] and female rats [**Surface:** 32.1±1.2 °C vs. 29.9±0.8 °C, 95CI: -3.5, -1.0, p < 0.0001; **Core:** 37.8±0.8 °C vs. 34.8±1.0 °C, 95CI: -3.5, -0.94, p < 0.0001] were significantly higher after the SE session, compared to baseline. Further, while there were no differences in the surface body temperatures between male and female rats, female rats presented with significantly higher core body temperatures compared to male rats at baseline and post-SE [**Baseline:** 34.8±1.0 °C vs. 33.5±0.5 °C, 95CI: -2.7, -0.03, p = 0.04; **Post-SE:** 37.1±0.8 °C vs. 35.4±1.0 °C, 95CI: -2.99, -0.34, p = 0.003].

Figure 2B: Baseline and post-SE urine myoglobin concentration

A significant two-way interaction between sex and time was shown with respect to the post-SE urine myoglobin concentration [F(1, 22) = 6.10, p = 0.22]. While sex did not have an overall main impact on the myoglobin result [F(1, 22) = 2.2, p = 0.15], a significant main effect of time was demonstrated [F(1, 22) = 50.9, p < 0.0001]. Bonferroni post-hoc analysis subsequently revealed pairwise differences between the baseline and post-SE myoglobin concentration in male (0.54±0.51 vs. 1.68±1.67 µg/L, 95CI: -1.97, -0.31, p = 0.0065) and female (0.49±0.46 vs. 2.84±1.24 µg/L, 95CI: -3.18, -1.52, p < 0.0001) rats. Furthermore, female rats presented with a significantly higher post-SE myoglobin concentration (2.84±1.24 µg/L) than male rats (1.68±1.67 µg/L; 95CI: -2.20, -0.12, p = 0.026)

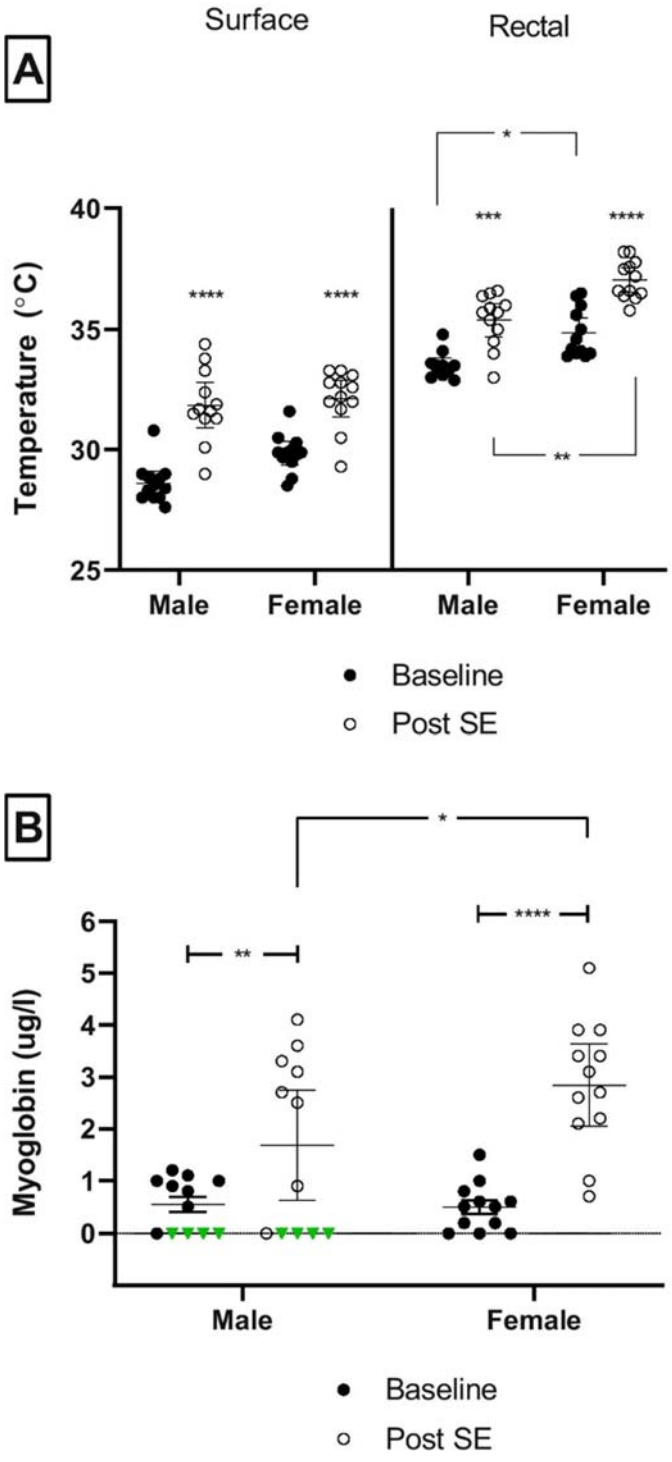

Fig 2 (A) Surface and rectal body temperatures (°C) and **(B)** urine myoglobin concentration (µg/L) of male and female rats at baseline (black dots) and after strenuous (open circles) exercise. Three- **(A)** and two-way **(B)** repeated measures analysis of variance followed by Bonferroni post-hoc tests. ****$p < 0.0001$; ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. SE: strenuous exercise. Green/downward pointing triangles: repeated measures data of male rats that presented with no urine myoglobin content at baseline and after strenuous exercise.

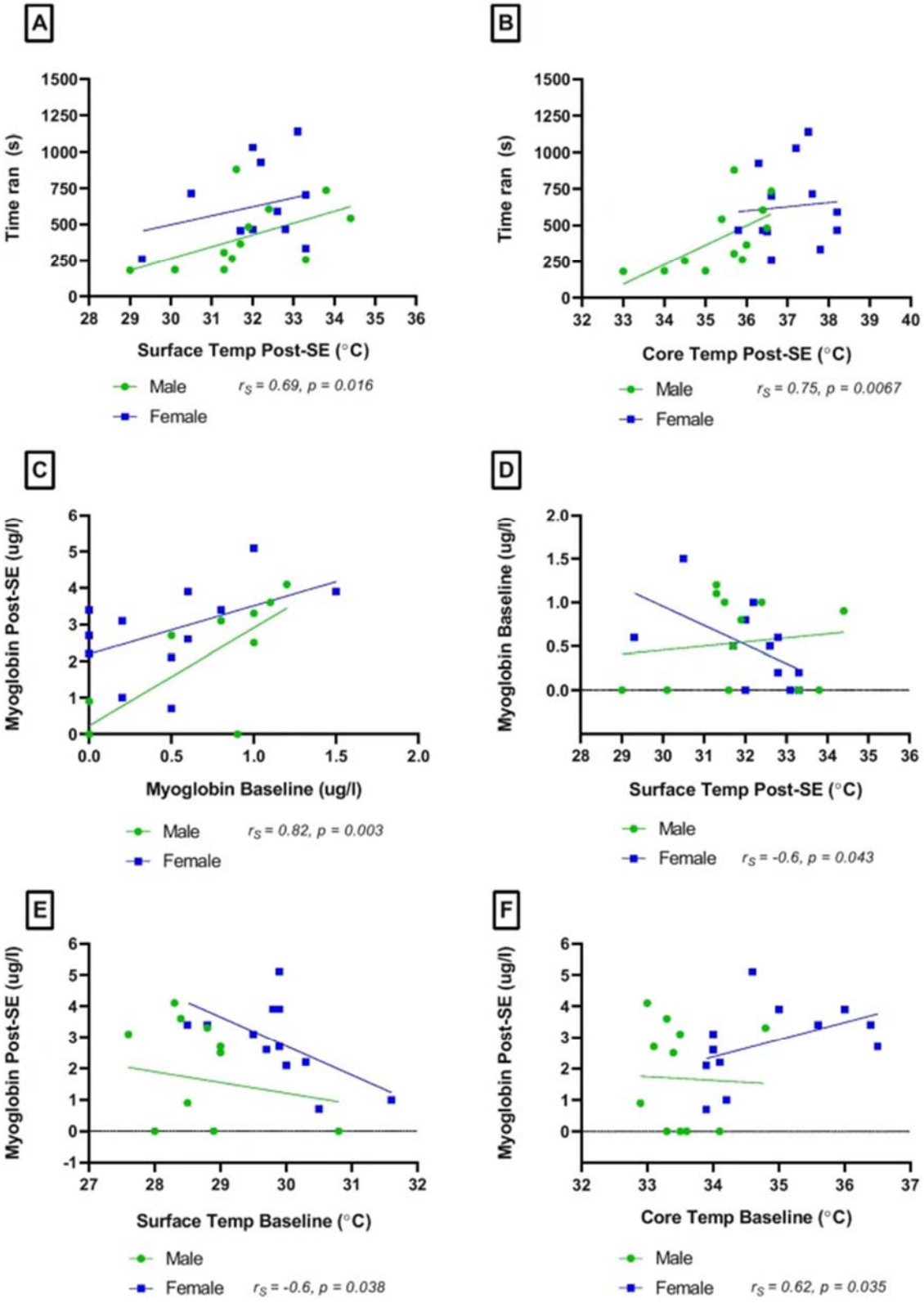

Fig 3 (A – F) Significant Spearman's correlations between the various parameters measured. Significance and Spearman's *r* is indicated next to the appropriate cohort in the respective figure legends. Green dots: male animals; blue squares: female animals.

Table 1 - Descriptive statistics and significance of Spearman's correlational analyses ran to explore the associations between urine myoglobin concentration ([MYO)], body temperature (temp.) and the total time ran. Significant correlations are highlighted in bold print.

Correlation	Male			Female		
	r_S	p	95CI	r_S	p	95CI
Baseline [MYO] vs. post-SE [MYO]	***0.817***	***0.003***	***0.44, 0.94***	0.51	0.09	-0.11, 0.84
Baseline [MYO] vs. baseline surface temp.	-0.068	0.83	-0.63, 0.54	-0.164	0.61	-0.68, 0.47
Baseline [MYO] vs. post-SE surface temp.	0.069	0.83	-0.63, 0.54	***-0.59***	***0.043***	***-0.88, -0.02***
Post-SE [MYO] vs. baseline surface temp.	-0.018	0.95	-0.60, 0.57	***-0.611***	***0.038***	***-0.88, -0.04***
Post-SE [MYO] vs. post-SE surface temp.	-0.323	0.30	-0.76, 0.32	-0.459	0.13	-0.82, 0.17
Baseline [MYO] vs. baseline core temp.	-0.154	0.63	-0.68, 0.48	-0.078	0.81	-0.64, 0.53
Baseline [MYO] vs. post-SE core temp.	0.204	0.52	-0.43, 0.71	-0.378	0.22	-0.79, 0.27
Post-SE [MYO] vs. baseline core temp.	-0.329	0.29	-0.77, 0.32	***0.620***	***0.035***	***0.06, 0.88***
Post-SE [MYO] vs. post-SE core temp.	0.225	0.47	-0.42, 0.72	-0.382	0.22	-0.79, 0.26
Time ran vs. baseline surface temp.	-0.092	0.78	-0.64, 0.52	-0.028	0.93	-0.61, 0.57
Time ran vs. post-SE surface temp.	***0.69***	***0.016***	***0.17, 0.91***	0.18	0.56	-0.45, 0.69
Time ran vs. baseline core temp.	0.46	0.13	-0.17, 0.82	0.42	0.17	-0.22, 0.81
Time ran vs. post-SE core temp.	***0.75***	***0.007***	***0.29, 0.93***	0.07	0.83	-0.54, 0.63
Time ran vs. baseline [MYO]	-0.02	0.96	-0.60, 0.57	-0.23	0.46	-0.72, 0.41
Time ran vs. post-SE [MYO]	-0.16	0.62	-0.68, 0.47	0.13	0.69	-0.50, 0.66
Baseline surface vs. post-SE surface temp.	-0.05	0.89	-0.62, 0.56	0.18	0.58	-0.46, 0.69
Baseline surface vs. baseline core temp.	-0.16	0.61	-0.68, 0.47	-0.41	0.18	-0.81, 0.23
Baseline surface vs. post-SE core temp.	-0.14	0.66	-0.67, 0.49	0.35	0.27	-0.30, 0.78
Baseline core vs. post-SE core temp.	0.43	0.16	-0.20, 0.81	-0.05	0.87	-0.62, 0.55

Figure 3: Correlations between urine myoglobin concentration, body temperature and time ran

Several Spearman's correlations were used to explore the associations between baseline and post-SE urine myoglobin concentrations, body temperature and the total time ran during the SE session (**Table 1**). Significant correlations were demonstrated for the following analyses: i) total time ran vs. post-SE surface temperature in male rats (**Fig 3A**, $r_S = 0.69$, $p = 0.016$), ii) total time ran vs. post-SE core temperature in male rats (**Fig 3B**, $r_S = 0.75$, $p = 0.0067$), iii) baseline myoglobin concentration vs. post-SE myoglobin concentration in male rats (**Fig 3C**, $r_S = 0.82$, $p = 0.003$), iv) baseline myoglobin concentration vs. post-SE surface temperature in female rats (**Fig 3D**, $r_S = 0.6$, $p = 0.043$), v) post-SE myoglobin vs. baseline surface (**Figure 3E**, $r_S = -0.61$, $p = 0.038$) and vi) core (**Fig 3F**, $r_S = 0.62$, $p = 0.035$) temperature in female rats (slopes differ significantly; $p = 0.016$).

Discussion

In this investigation, we aimed to describe and standardize a method to induce forced SE-induced rhabdomyolysis in the SD rat. Our data revealed several important findings. First, we showed that SE induced a significant increase in the surface and core body temperatures of male and female rats. Second, while rats of both sexes presented with significantly higher urine myoglobin concentrations after the SE session compared to baseline, this was significantly more pronounced in female rats. Third, male rats that did not present with urine myoglobin content at baseline generally remained resistant to the rhabdomyolytic effect of SE, while baseline myoglobin concentrations in male rats are a predictor of post-SE urine myoglobin values. Lastly, surface and core body temperature associated distinctly with urine myoglobin content in male rats, and with respect to total time ran by female rats.

Increased body temperature induced by psychobiological stress appears to be a consistent physiological phenomenon in various species, including mice (Olivier et al. 2003; Zethof et al. 1994), rats (Olivier et al. 2003), antelope (Breed et al. 2019; Meyer et al. 2008b) and humans (Bouwknecht et al. 2007). Here, we corroborate these findings in showing that both male and female SD rats are prone to develop SE-induced hyperthermia, as reflected in both surface and core body temperature. Further, the average increases in surface (male: 2.9 °C; female: 2.2 °C) and core (male: 1.9 °C; female 3.0 °C) **(Figure 2A)** body temperatures reported here are notably higher than that normally reported after moderate exercise (0.8 – 1.5°C) (Bouwknecht et al. 2007), highlighting the effectiveness of forced SE as a psychobiological-induced hyperthermic trigger. Importantly, core body temperatures were significantly higher in female compared to male rats both at baseline and post-SE. This finding is in line with previous research (Marrone et al. 1976) and agrees with clinical

data where women have been shown to be more likely to present with impaired thermoregulatory processes under conditions of exercise than their male counterparts (Nunneley 1978; Wyndham et al. 1965). Interestingly, time spent running is significantly and positively correlated with post-SE surface and core body temperatures in male, but not female rats **(Figure 3A & B)**, arguably pointing to unique underlying thermoregulatory processes in male, compared to female rats. Indeed, gender-related differences have also been described with respect to stress-induced hyperthermia in rabbits (Olivas and Villagrá, 2013). Although this finding needs further elucidation, it might inform future work regarding the role of hyperthermia in SE-induced rhabdomyolysis.

Myoglobin leakage is a common manifestation of rhabdomyolysis, while urine myoglobin content is commonly applied as a biomarker of rhabdomyolysis. Here we show that a single SE-session is sufficient to result in rhabdomyolysis and to significantly increase the urine myoglobin concentration in rats of both sexes. Further, this result was significantly more pronounced in female rats **(Figure 2B)**, indicating that SE had a greater effect on the muscle integrity of female, compared to male rats. Considering the difference in the relationship between workload and body temperature in male and female rats alluded to above, it should be considered that the ability of male rats to increase their metabolic energy turnover under conditions of SE, likely impart a myoprotective effect. Further, such protection might also be related to a sex-specific difference in muscle architecture, which warrants further research. Such a conclusion could be valid, especially since male rats that presented with no urine myoglobin content at baseline, also remained resilient to the effects of SE on muscle breakdown (**Figure 2B**, green/downwards pointing triangles). This view is further supported by the fact that baseline urine myoglobin content significantly predicted the post-SE content in male, but not female rats **(Figure 3C)**, potentially indicating that SE only fortified already inherent processes of muscular metabolism in male rats. Although our findings with respect to the manner in which pre- and post-SE urine myoglobin content in female rats predicted pre- and post-SE body temperatures **(Figure 3D – F)** are complex, it suffices to conclude that female rats do indeed present with notably distinct metabolic signatures in skeletal muscle under conditions of SE, compared to male rats.

Collectively, the findings reported here are informative for future studies of CM. Although extrapolation of findings from rodent studies to wildlife should be done with caution, valuable insights into illness-specific mechanisms can still be gained, especially since the mechanisms and mediators of stress-induced CM in wildlife are not yet fully understood (Giannoglou et al. 2007). Indeed, the present work aimed to develop and describe a standardized method to induce SE-related rhabdomyolysis which can be explored in future

as a naturalistic model of CM in wildlife. In this we believe we have succeeded. While the physiological response observed in male rats is more aligned with what we currently understand of rhabdomyolytic processes, our findings with respect to female rats might present research with a valuable avenue for future studies into other potential mechanisms underlying CM.

Declarations

Funding

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

All raw data presented in this work, are available from the corresponding author based on reasonable request.

Code availability

Not applicable.

Author contributions

DWW and CL conceptualised, planned and executed the work presented, wrote the draft version of this paper and did the final revision following co-author input. FPV assisted with myoglobin and temperature measurements and reviewed the draft paper. BHH and LM provided intellectual input, read and revised the draft and final versions of this paper.

Ethics Approval

This work was approved by the AnimCare Animal Research Ethics Committee of the North-West University (NHREC reg. no. AREC-130913-015), prior to onset (approval number: NWU-00576-19-A5).

Consent for publication

All authors provided consent for this work to be published in its present form.

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