Cardiovascular and thermoregulatory biomarkers of heat stroke severity in a conscious rat model

Carrie M. Quinn, Rocio M. Duran, Gerald N. Audet, Nisha Charkoudian, and Lisa R. Leon

U.S. Army Research Institute of Environmental Medicine, Thermal and Mountain Medicine Division, Natick, Massachusetts

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Quinn CM, Duran RM, Audet GN, Charkoudian N, Leon LR. Cardiovascular and thermoregulatory biomarkers of heat stroke severity in a conscious rat model. J Appl Physiol 117: 971–978, 2014. First published August 14, 2014; doi:10.1152/japplphysiol.00365.2014.—Multigorgan failure is a catastrophic consequence of heat stroke (HS) and considered the underlying etiology of mortality. Identifying novel biomarkers capable of predicting the extent of HS-induced organ damage will enhance point-of-care triage and treatment. Conscious male F344 rats (n = 32) were radiotelemetered for continuous core temperature (Tc), heart rate, and arterial pressure measurement. Twenty-two animals were exposed to ambient temperature of 37°C to a maximum Tc of 41.9 ± 0.1°C. Rats were euthanized at 24 h of recovery for analysis of plasma biomarkers [cardiac troponin I (cTnI), blood urea nitrogen (BUN), alanine aminotransferase (ALT), albumin, glucose] and histology. Tc profiles observed during recovery stratified HS severity into Mild, Moderate, and Severe. Eleven (50%) animals exhibited an acute compensatory hemodynamic response to heat exposure and a monophasic Tc profile consisting of sustained hyperthermia (>1°C). Five (23%) rats displayed hemodynamic challenge and a biphasic Tc profile with rapid return to baseline followed by rebound hyperthermia. All biomarkers were significantly altered from control values (P < 0.05). Four (18%) animals exhibited significant hemodynamic compromise during heat and a triphasic profile characterized by rapid cooling to baseline Tc, rebound hyperthermia, and subsequent hypothermia (<35°C) through 24 h. cTnI showed a 40-fold increase over CON (P < 0.001) and correlated with BUN (r = 0.912) consistent with cardiorenal failure. Hypoglycemia correlated with ALT (r = 0.824) suggestive of liver dysfunction. Histology demonstrated myocardial infarction, renal tubular necrosis, and acute liver necrosis. Two (9%) animals succumbed during HS recovery. This study identified novel biomarkers that predict HS severity and organ damage during acute recovery that could provide clinical significance for identifying key biomarkers of HS pathogenesis.

heat stroke; hemodynamic; thermoregulation; cardiac troponin I

HEAT STROKE (HS) is a debilitating illness characterized by myriad thermoregulatory, cardiovascular, and systemic inflammatory abnormalities whose severity and time course vary between individuals subjected to the same environmental conditions. Sustained exposure to uncompensable heat stress results in HS which manifests as profound central nervous system dysfunction, often complicated by coagulopathies and catastrophic multigorgan failure.

Several animal models have been developed in an effort to experimentally induce the pathogenesis and clinical manifestations of HS sequelae. Previously, our laboratory developed a mouse HS model that minimized the confounding influences of anesthesia and restraint on HS responses (16). This was accomplished using radiotelemetry in conscious, freely moving mice. This model has contributed importantly to our understanding of the pathophysiology of HS (9, 15, 17); however, the small animal size prevented instrumentation for measurement of physiological changes beyond core temperature [Tc; e.g., heart rate (HR), ECG, blood pressure] that are known to be altered during extreme heat exposure.

The pathophysiology of HS includes major cardiovascular involvement, which has been well documented for decades (4, 8, 13, 14, 21, 26–30, 33, 35). However, no controlled study in a conscious animal model has used cardiovascular parameters as predictive indexes of HS severity or as a correlate for prognostication. In addition to providing potential biomarkers of HS severity and prognosis, alterations in hemodynamic stability could provide key insights into the pathogenesis of this condition.

The goal of the present study was to expand the conscious rodent model of HS to the rat, enhancing the connection between experimental and clinical symptomatology by exploiting the larger body size and greater blood volume relative to the mouse. We sought to determine if differences in pathophysiological and thermoregulatory responses exist between the rat and mouse models. Additionally, we tested the central hypothesis that hemodynamic indexes can experimentally predict HS severity with greater accuracy than Tc and expose interindividual variability as an essential component of heat responsiveness.

METHODS

Animals

Thirty-two adult male Fischer 344 rats (Charles River Laboratories, Wilmington, MA) weighing 272.4 ± 4.7 g were used. Rats were housed individually in Nalgene polycarbonate cages (Ancare, Bellmore, NY) fitted with HEPA-filter cage tops and ALPHA-dri/Cob blend bedding (PharmaServ, Framingham, MA). Environmental enrichment consisted of a rat igloo (Nalgene Nunc, Rochester, NY), a maplewood product containing a food treat to encourage foraging (W0002, BioServ, Frenchtown, NJ), and stainless steel rings for the support of postural adjustments. Rats were housed under standard laboratory conditions (20 ± 2°C, 12:12-h light:dark cycle; lights on at 0600) in an Association for Assessment and Accreditation of Laboratory Animal Care-accredited facility. Rodent laboratory chow (Harlan Teklad, LM-485, Madison, WI) and water were provided ad libitum except during heat exposure. The Institutional Animal Care and Use Committee approved all experimental procedures, which were performed in accordance with the American Physiological Society’s guiding principles for research involving animals and adhered to the Guide for the Care and Use of Laboratory Animals.

Radiotelemetry Measurements

Ten days prior to arrival, rats were implanted intraperitoneally with TL11M2-C50-PXT Physiotel Multiplus Radiotelemetry Transmitters...
defined as a \( T_c \) of 20°C at the end of the interval), respectively. Hypothermia was reached at 20°C, which was the lowest \( T_c \) value observed in undisturbed rats before heat stress (data not shown). Hypothermia depth (°C) was the lowest 1-min \( T_c \) value during recovery. Time to \( T_{c,\text{Max}} \) represents the time from \( T_{c,\text{Max}} \) to the experimental maximum \( T_c \) (\( T_{c,\text{Max}} \)) of 41.9°C (12-h daytime average \( T_c \) of rats in this study) were weighed, food and water were removed from the cage, and the incubator \( T_a \) was increased to 37 ± 0.2°C. Heating continued until a predetermined experimental maximum \( T_c \) (\( T_{c,\text{Max}} \)) of 41.9°C (\( n = 22 \)) was attained. At \( T_{c,\text{Max}} \), rats were removed from the incubator, weighed, placed in a new cage with access to food and water ad libitum, and maintained at a \( T_a \) of 20 ± 2°C in their original cage location until the time at which animals were euthanized. Control (CON) animals were exposed to the same experimental conditions at \( T_a \) of 20 ± 2°C with the timing of all procedures matched to that of a heated rat.

**Heating Calculations**

Time to \( T_{c,\text{Max}} \) represents the total heat exposure time. Thermal strain (°C-min) during heating (ascending) and cooling (descending) were calculated as intervals \( \times 0.5 \) (°C above \( T_{c,\text{Max}} \) of 40.0°C at the start of the interval) and \( \Sigma \) of the time intervals \( \times 0.5 \) (°C above \( T_{c,\text{Max}} \) of 40.0°C at the end of the interval), respectively. Hypothermia was defined as a \( T_c \) < 37.3°C, which was the lowest \( T_c \) value observed in undisturbed rats before heat stress (data not shown). Hypothermia depth (°C) was the lowest 1-min \( T_c \) value during recovery. Time to reach hypothermia depth was calculated as the time from \( T_{c,\text{Max}} \) to the lowest \( T_c \) observed during recovery.

**Dehydration**

BW was measured on a top-loading balance with an accuracy of ±0.1 g. Percent dehydration was calculated as \([\text{preheat BW} - \text{postheat BW}] / \text{preheat BW}] \times 100\), which is an estimate that did not account for BW loss from feces or urine. Preheat BW was obtained immediately prior to heat exposure; postheat BW was obtained immediately upon removal from the heating chamber at \( T_{c,\text{Max}} \).

**Blood Chemistry and Hematology**

At 24 h of HS recovery, rats were rapidly (<1 min), deeply anesthetized with isoflurane (5% in 100% \( O_2 \); flow rate = 5 l/min). A thoracotomy was performed, and the rats were exsanguinated via cardiac puncture (5 ml syringe; 21-gauge needle). The blood was divided for immediate determination of biomarkers of cardiac damage (cardiac Troponin I; cTnl), renal function (blood urea nitrogen; BUN), and liver function/damage [glucose, albumin, and alanine aminotransferase (ALT)] via a handheld iSTAT clinical analyzer (Abbott Diagnostics, Abbott Park, IL) and VetScan VS2 modalities (Abaxis, Union City, CA).

**Histopathology**

Following cardiac puncture and exsanguination, the organs were perfused with cold heparinized (10 U/ml) 0.9% sterile saline. The heart, kidney, liver and brain were rapidly excised, sliced into transverse or longitudinal sections, and fixed in ExCell Plus (American MasterTech, Lodi, CA). A certified veterinary pathologist determined the extent of organ damage. Histopathological findings were reported using a standard grading system (20) whereby 0 = no significant damage, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe damage. Heart and kidney tissues of 18 animals were analyzed, while 17 liver samples and 19 brain samples were analyzed.

**Statistics**

Data are presented as means ± SE. One-way ANOVA with Tukey’s post hoc test determined group effects. Significance was set at \( P < 0.05 \).

**RESULTS**

Based on \( T_c \) profiles observed during acute recovery, results were stratified into mild HS (MILD), moderate HS (MODERATE), and severe HS (SEVERE) groups. Following stratification, hemodynamic, histopathological and circulating biomarkers were compared among groups.

**Heat Exposure**

**Thermoregulatory response during heat exposure.** Table 1 outlines the thermal characteristics of heat exposure per severity of HS. No between-group differences existed in time to \( T_{c,\text{Max}} \) or thermal strain during heat exposure (Table 1). CON rats maintained the normal daytime \( T_c \) of ~37°C during experimentation (data not shown).

**Hemodynamic adjustments during heat exposure.** Figure 1 illustrates HR and SBP responses during heat exposure per.
The severity of HS. The HR of heated animals began to significantly increase relative to CON values at ~60 min (P < 0.02) and remained elevated until time 0 (Tc,Max) (Fig. 1A). The HR of animals in the SEVERE group was significantly elevated relative to MILD at 30 min of heating (526 ± 5 vs. 464 ± 19, respectively; P < 0.02). At Tc,Max HR of SEVERE and MODERATE animals were elevated above MILD (637 ± 13 and 596 ± 8 vs. 540 ± 14 beats/min, respectively; P < 0.02); however, no difference existed between SEVERE and MODERATE (P < 0.11; Fig. 1A).

The SBP of all heated animals was elevated over CON at ~120 min and remained elevated throughout heating (P < 0.001; Fig. 1B). At ~30 min the SBP of MODERATE animals was significantly elevated over MILD (215 ± 6 vs. 192 ± 7 mmHg, respectively; P < 0.05) but was not different from SEVERE (207 ± 7 mmHg; P < 0.40). Between ~30 min and time 0 (Tc,Max), SEVERE and MODERATE animals incurred a
drop in SBP (−ΔSBP). The −ΔSBP resulted in similar SBP for MODERATE and MILD animals (200 ± 3 vs. 201 ± 4 mmHg, respectively; P < 0.89) at Tc,Max. The −ΔSBP was more substantial in SEVERE animals, resulting in a significantly lower SBP in those animals relative to MODERATE (178 ± 7 vs. 200 ± 3 mmHg, respectively; P < 0.05) and a trend toward significance compared with MILD (201 ± 4 mmHg; P < 0.055; Fig. 1).

**Recovery Profile**

**Thermal profile in acute recovery.** The Tc profile of HS rats during 24 h of recovery is shown in Fig. 2. All CON rats showed virtually identical Tc rhythms with low daytime and high nighttime values observed during the lights-on and lights-off period, respectively (grouped for ease of presentation; Fig. 2). Starting at Tc,Max (time 0), rats showed interindividual variability in their Tc recovery responses through 24 h, with three distinct profiles correlating with HS severity. Eleven (50%) animals displayed a monophasic profile during recovery that was characterized by rapid cooling to 38.5 ± 0.2°C, which was sustained throughout recovery and remained significantly elevated above CON rats (37.5 ± 0.1°C; P < 0.001; Fig. 2A). All monophasic rats survived through 24 h of recovery. Five (23%) rats displayed a biphasic recovery profile characterized by rapid cooling and a return to baseline Tc followed by rebound hyperthermia that was maintained throughout the remainder of the recovery period (Fig. 2B). The average Tc of biphasic animals following the rebound through 24 h of recovery was 38.5 ± 0.2°C, which was higher than CON values (P < 0.001), but was not different from the monophasic response. Three (14%) animals displayed a triphasic profile characterized by rapid cooling with a return to baseline Tc and a subsequent rebound that was similar in profile to the biphasic response. The hyperthermic rebound was followed by a hypothermic phase characterized by hypothermia depth of ~35°C (Fig. 2C). Figure 2D shows the average Tc profile of the three HS groups through 24 h of recovery, and Table 2 describes the timeline of Tc responses and acute recovery characteristics of each group. One (5%) postheat thermal dataset was unrecoverable, two (9%) rats (1 biphasic, 1 triphasic) succumbed during HS recovery, and the remaining 20 (91%) heated and all CON rats survived to study end point (Table 2).

All thermal profiles during acute recovery correlated with HR and SBP responses during heat exposure such that all animals displaying significant hemodynamic compromise during heat had a triphasic profile in recovery and therefore maintained characterization as Severe. All animals displaying strained hemodynamic challenge during heat exposure exhibited rebound hyperthermia on acute recovery and thus remained characterized as MODERATE severity. Likewise, animals displaying mild hemodynamic compensation during heat exposure exhibited a monophasic thermal profile on acute recovery and thus maintained classification as MILD.

**Biomarkers of tissue damage at 24 h of recovery.** Table 3 shows circulating biomarkers of organ damage for CON, MILD, MODERATE, and SEVERE HS rats at 24 h of recovery. MILD was not associated with any changes in circulating levels of cTnI, BUN, glucose, or ALT at 24 h of recovery, whereas albumin levels were significantly lower in this group compared with CON (Table 3). MODERATE was associated with significant increases in circulating cTnI and ALT, and decreased glucose and albumin compared with CON rats (P < 0.05; Table 3). SEVERE rats showed significant alterations in all biomarkers with cTnI, BUN, and ALT elevated and glucose and albumin decreased compared with CON rats (P < 0.05). BUN and glucose showed a similar trend as cTnI, but failed to reach statistical significance (P = 0.053 and P = 0.059, respectively; Table 3).

### Table 2. Thermal profile per heat illness severity as defined by the recovery profile

<table>
<thead>
<tr>
<th>Thermal profile</th>
<th>Nonheated Control (n = 10)</th>
<th>MILD (n = 11)</th>
<th>MODERATE (n = 5)</th>
<th>SEVERE (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to baseline, min</td>
<td>100.0</td>
<td>100.0</td>
<td>80.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Rebound from baseline, min</td>
<td>12.2 ± 2.0</td>
<td>18.4 ± 6.9</td>
<td>16.4 ± 3.2</td>
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<tr>
<td>Hypothermia initiated, min</td>
<td>37.2 ± 0.2*</td>
<td></td>
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<tr>
<td>Hypothermia depth, °C</td>
<td></td>
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<tr>
<td>Descending thermal area, °C·min</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Survival, %</td>
<td>100.0</td>
<td>100.0</td>
<td>80.0</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Data are means ± SE. *Control vs. SEVERE, P < 0.01.

### Table 3. Circulating biomarkers of organ damage at 24 h of HS recovery

<table>
<thead>
<tr>
<th></th>
<th>Nonheated Control (n = 10)</th>
<th>MILD (n = 11)</th>
<th>MODERATE (n = 5)</th>
<th>SEVERE (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI, ng/ml</td>
<td>1.3 ± 0.4</td>
<td>3.2 ± 1.3</td>
<td>13.9 ± 2.1†</td>
<td>39.1 ± 5.6*§</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>17.2 ± 0.7</td>
<td>17.3 ± 1.2</td>
<td>26.4 ± 5.7</td>
<td>33.5 ± 2.7†</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>193.3 ± 5.3</td>
<td>190.3 ± 7.8</td>
<td>155.0 ± 7.8*†</td>
<td>161.0 ± 5.1*†</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.6 ± 0.4</td>
<td>4.1 ± 0.1*</td>
<td>3.5 ± 0.1*†</td>
<td>3.6 ± 0.1*†</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>76.0 ± 2.3</td>
<td>535.2 ± 228.2</td>
<td>1,848 ± 369.2†</td>
<td>1,213.8 ± 474.4*</td>
</tr>
</tbody>
</table>

Date are means ± SE. Significance set at P < 0.05: *vs. Control; †vs. MILD; §vs. MODERATE. cTnI, cardiac troponin I; BUN, blood urea nitrogen; ALT, alanine aminotransferase; HS, heat stroke.
Histopathological analysis of organ damage at 24 h of recovery. Table 4 outlines the histopathological findings per organ per HS severity. At 24 h of recovery, 12 (67%) of the animals displayed moderate myocardial damage. Renal damage was concentrated in the mild to moderate grades with nine (50%) animals falling into these categories; six (33%) displayed severe damage. Liver damage was distributed equally between minimal (n = 4, 24%), moderate (n = 4, 24%), and severe (n = 3, 18%) gradients; however, six (35%) animals showed no liver damage. The majority of rats showing no liver damage were of MILD HS severity, whereas all animals with severe liver damage were SEVERE HS animals. However, it was not possible to definitively determine HS severity based on histopathology alone presumably due to the small sample size within each standard grading category.

Representative micrographs from one CON and one SEVERE rat are presented in Fig. 3. No significant abnormalities were detected in CON rats (Fig. 3, A, C, and E). The heart of the SEVERE rat shows myocardial necrosis and myofiber degeneration consistent with late-stage ischemic cardiomyopathy and infarction (Fig. 3B). Acute tubular necrosis and hyaline droplet degeneration in the kidney was consistent with kidney nephrosis (Fig. 3D), and acute, multifocal necrosis of the liver (Fig. 3F).

DISCUSSION

The major findings of our present study are threefold. First, we identified specific temporal patterns of $T_c$ responses that distinguished between MILD, MODERATE, and SEVERE pathophysiology in this novel, freely moving rat model of HS that differ significantly from the thermoregulatory patterns observed in mice. Second, we identified HR and SBP patterns during heat exposure that were closely linked to HS severity. Third, we identified associations between hemodynamic alterations during heat exposure, $T_c$ in acute recovery, high circulating cTnI levels, and histopathological changes in the heart at 24 h of recovery. These major findings are consistent with existing clinical information about HS responses in humans (2, 4, 5, 19, 24, 26, 34, 36, 37), and provide insight into biomarkers of HS severity.

The thermoregulatory profile during recovery consisted of distinct temporal patterns indicative of MILD, MODERATE, and SEVERE responses, respectively (Fig. 2). MILD and MODERATE rats displayed similar postheating hyperthermic plateaus, but in the MODERATE group, this response was preceded by a return to baseline $T_c$. This is the first study to show rebound hyperthermia as an early HS recovery response in an animal model and identify this response as a biomarker of severity. Rebound hyperthermia has been reported in HS patients (24, 34) and is regarded as a compensatory peripheral vasoconstrictor response to cooling of the skin surface. Interestingly, MODERATE rats showed rebound hyperthermia even though our model did not employ active cooling of the skin surface, suggesting this is a normal $T_c$ recovery response in this (and perhaps other) species.

Previously, we characterized the biphasic thermal response profile of mice during acute recovery (16). In that study, $T_{c, max}$ was immediately followed by a period of hypothermia that recovered into regulated hyperthermia persisting from −24–36 h of recovery. Mice that did not recover from hypothermia died prematurely. These results suggest that the development and transition out of hypothermia to produce an elevated $T_c$ is critical for survival in mice (16). In contrast, our current results have shown that hypothermia in rats is a biomarker of HS severity and is associated with increased morbidity compared with other $T_c$ patterns. Furthermore, the Severe rats developed a delayed hyperthermia only after a return to baseline $T_c$ and short rebound hyperthermia, unlike the mice which became hypothermic immediately. The mechanisms behind this species difference are unclear.

Case reports indicate patients vary in thermal characteristics following extreme heat stress, such that some individuals remain hyperthermic (and/or develop a fever) while others display hypothermia (19, 24, 34). Hypothermia is considered an adverse event in humans although the regulated nature of this response has not been investigated. In light of our present findings, it is possible that certain temporal patterns in patient $T_c$ responses during HS recovery may be predictors of subsequent pathological aftereffects. Ideally, incorporation of the acute $T_c$ recovery profile with the cardiovascular alterations observed at the time of collapse would aid in improved stratification and diagnosis of HS patients.

As noted above, an important aspect of our present findings was the interindividual variability in responsiveness to a standardized heating protocol. Heart rate and blood pressure responses to HS were also variable, and were stratified by response severity, such that MODERATE and SEVERE animals had higher final HR values compared with MILD animals, and blood pressure dropped in MODERATE and SEVERE animals but not in MILD animals (Fig. 1). These data point to important links between cardiovascular and thermoregulatory mechanisms during severe heat stress and suggest that hemodynamic responses are potentially useful biomarkers of the severity of heat stress responses.

Although cardiovascular responses to whole body hyperthermia have been documented in previous rat models of heat stress, certain aspects of experimental design have limited interpretation of the results. First, many studies have used anesthetized models of HS to evaluate cardiovascular patho-

Table 4. Histopathological analysis of organ damage at 24 h of recovery

<table>
<thead>
<tr>
<th></th>
<th>Standard Grading Scale</th>
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<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
</tr>
<tr>
<td>Nonheated control, % (n)</td>
<td>100 (10)</td>
</tr>
<tr>
<td>MILD, % (n)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>MODERATE, % (n)</td>
<td>60 (3)</td>
</tr>
<tr>
<td>SEVERE, % (n)</td>
<td>25 (1)</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
</tr>
<tr>
<td>Nonheated control, % (n)</td>
<td>100 (10)</td>
</tr>
<tr>
<td>MILD, % (n)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>MODERATE, % (n)</td>
<td>44 (4)</td>
</tr>
<tr>
<td>SEVERE, % (n)</td>
<td>60 (3)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
</tr>
<tr>
<td>Nonheated control, % (n)</td>
<td>100 (10)</td>
</tr>
<tr>
<td>MILD, % (n)</td>
<td>56 (5)</td>
</tr>
<tr>
<td>MODERATE, % (n)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>SEVERE, % (n)</td>
<td>56 (5)</td>
</tr>
</tbody>
</table>

Histopathological findings were reported using a standard grading system whereby 0 = no significant damage, 1 = minimal damage, 2 = mild damage, 3 = moderate damage, and 4 = severe damage.
However, the cardiosuppressant and sympathoinhibitory effects of anesthesia complicate interpretation of cardiovascular findings (10, 32). Furthermore, anesthetic agents generally exert a prophylactic, preconditioning-like effect on the myocardium (39). Second, existing studies in both conscious and anesthetized rats have used changes in arterial pressure to identify HS onset (1, 7, 21, 31, 38). In this context, the use of blood pressure data to define the onset of heat stroke varies widely among studies. Our present data suggest that HR is more strongly correlated with HS severity than arterial pressure to identify HS onset (1, 7, 21, 31, 38). In this context, the use of blood pressure data to define the onset of heat stroke varies widely among studies. Our present data suggest that HR is more strongly correlated with HS severity than arterial pressure. Third, many studies have used a predefined Tc,max to define HS onset (22, 23, 33, 35); however, our present data suggest that interindividual variability in responsiveness precludes the use of a predetermined Tc,max as the major indicator of HS severity. Our conscious rat HS model overcomes these experimental limitations and provides novel insight into the predictive value of cardiovascular, thermoregulatory and circulating biomarkers through 24 h of recovery.

A catastrophic consequence of HS is multiorgan failure, which is considered the underlying etiology of mortality. In the present study, high cTnI levels and damage to the heart substantiated the predictive value of the Tc and hemodynamic responses observed. cTnI was elevated nearly 40-fold at 24 h of recovery in SEVERE rats, whereas this biomarker generally peaks at 6–18 h (3, 11, 18) in patients experiencing myocardial injury. cTnI is not currently included in traditional clinical heat panels, which routinely consist of a complete blood count, metabolic profile, and markers of kidney and liver damage/dysfunction (6, 25). We propose that cTnI is a sensitive biomarker that could improve assessment and treatment of cardiac damage during HS recovery. It will be important in future studies to determine cTnI levels at several time points during recovery to identify the time course of changes and the predictive power of this biomarker throughout recovery. Interestingly, there was a strong correlation between circulating cTnI and BUN levels (at 24 h of recovery), suggesting acute dysfunction of the heart may have contributed to renal dysfunction. Dehydration and ischemia are known to induce kidney dysfunction with HS, but impaired cardiac function may be an additional factor that has not been previously considered.

MODERATE and SEVERE rats displayed ~20% reduction in blood glucose levels at 24 h of recovery. Hypoglycemia has
been observed in case reports and other experimental HS models (4, 15). However, we showed in a mouse HS model that glucose normalized to control levels within 24 h (15), whereas in the present study MODERATE and SEVERE rats remained hypoglycemic at this time point. A probable cause for the discrepancy between studies was the lack of liver damage in HS mice through 24 h of recovery (15). Consistent with this hypothesis, the liver of MILD rats was, at most, minimally damaged whereas the majority of MODERATE and SEVERE rats suffered substantial liver damage (Table 4). As such, thermal or ischemic injury to the liver in the current study may have compromised glucose homeostasis.

In summary, we have developed a conscious, freely moving rat model of HS in which we have identified Tc, cardiovascular, and circulating biomarkers of HS severity and organ damage. We propose that robust HR and SBP responses observed during heat exposure are more sensitive biomarkers of HS severity than core temperature or thermal strain. Finally, our data suggest that cTnI in combination with traditional clinical biomarkers of organ damage may improve diagnosis and treatment of organ damage during the early stages of HS recovery.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


