Am J Physiol Renal Physiol 327: F224–F234, 2024.
First published June 13, 2024; doi:10.1152/ajprenal.00089.2024

american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
RENAL PHYSIOLOGY

RESEARCH ARTICLE

Creatinine clearance is maintained in a range of wet-bulb globe temperatures and work-rest ratios during simulated occupational heat stress

Hayden W. Hess,[1,3] Tyler B. Baker,[1] Macie L. Tarr,[1] Roger S. Zoh,[2] Blair D. Johnson,[1] David Hostler,[3] and Zachary J. Schlader[1]

[1]*Department of Kinesiology, School of Public Health-Bloomington, Indiana University, Bloomington, Indiana, United States;* [2]*Department of Epidemiology and Biostatistics, School of Public Health-Bloomington, Indiana University, Bloomington, Indiana, United States; and* [3]*Center for Research and Education in Special Environments, Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, New York, United States*

Abstract

We tested the hypothesis that compliance with the National Institute for Occupational Safety and Health (NIOSH) heat stress recommendations will prevent reductions in glomerular filtration rate (GFR) across a range of wet-bulb globe temperatures (WBGTs) and work-rest ratios at a fixed work intensity. We also tested the hypothesis that noncompliance would result in a reduction in GFR compared with a work-rest matched compliant trial. Twelve healthy adults completed five trials (four NIOSH compliant and one noncompliant) that consisted of 4 h of exposure to a range of WBGTs. Subjects walked on a treadmill (heat production: approximately 430 W) and work-rest ratios (work/h: 60, 45, 30, and 15 min) were prescribed as a function of WBGT (24°C, 26.5°C, 28.5°C, 30°C, and 36°C), and subjects drank a sport drink ad libitum. Peak core temperature (T_C) and percentage change in body weight (%ΔBW) were measured. Creatinine clearance measured pre- and postexposure provided a primary marker of GFR. Peak T_C did not differ among NIOSH-compliant trials ($P = 0.065$) but differed between compliant versus noncompliant trials ($P < 0.001$). %ΔBW did not differ among NIOSH-compliant trials ($P = 0.131$) or between compliant versus noncompliant trials ($P = 0.185$). Creatinine clearance did not change or differ among compliant trials ($P \geq 0.079$). Creatinine clearance did not change or differ between compliant versus noncompliant trials ($P \geq 0.661$). Compliance with the NIOSH recommendations maintained GFR. Surprisingly, despite a greater heat strain in a noncompliant trial, GFR was maintained highlighting the potential relative importance of hydration.

NEW & NOTEWORTHY We highlight that glomerular filtration rate (GFR) is maintained during simulated occupational heat stress across a range of total work, work-rest ratios, and wet-bulb globe temperatures with ad libitum consumption of an electrolyte and sugar-containing sports drink. Compared with a work-rest matched compliant trial, noncompliance resulted in augmented heat strain but did not induce a reduction in GFR likely due to an increased relative fluid intake and robust fluid conservatory responses.

exercise; glomerular filtration rate; heat stress; kidney function

INTRODUCTION

Outdoor workers are regularly exposed to hot environments (1)—a prominent public health problem given that the magnitude of extreme environmental temperature is predicted to increase due to climate change (2). In addition to the labor productivity loss (1, 3, 4) and heat-related illness (5), there are acute and long-term health implications of such heat exposures. Among the most notable is the epidemic of chronic kidney disease of nontraditional origin (CKDnt) documented in outdoor workers who frequently undertake physical labor in the heat (6–8). There is contention regarding the etiology of CKDnt; however, a prevailing hypothesis is that CKDnt is mediated, at least in part, by frequent and intense heat exposure that can cause reductions in glomerular filtration rate (GFR) and increase the risk of acute kidney injury (AKI) (9). The recurrent reductions in GFR and/or development of AKI are likely contributing factors to the development of CKDnt (7, 9).

A rapidly growing body of literature supports this phenomenon including several field studies (10, 11) and laboratory-based studies from our laboratory (12–16) and others (17, 18). The pathophysiological mechanisms of this heat-related kidney pathology have been reviewed in detail (7, 9, 19). To this end, a recent review by Masoud et al. (20) outlined strategies to mitigate the risk of AKI and loss of GFR during physical work in the heat. It was concluded that such strategies should include reducing heat strain (via reduction in metabolic heat production, total work, or environmental exposure limits) and dehydration. Indeed, field-based interventions in Mesoamerica have demonstrated efficacy in reducing AKI and loss of GFR across a harvest in sugarcane cutters by

Correspondence: Z. J. Schlader (zschlade@iu.edu).
Submitted 19 March 2024 / Revised 7 May 2024 / Accepted 6 June 2024

implementing rest, shade, and adequate access to hydration (10).

In the United States, the National Institute for Occupational Safety and Health (NIOSH) provides heat stress recommendations to maintain peak core temperature below 38.0°C in unacclimatized workers (21). The recommendations prescribe work-rest ratios based on environmental factors [e.g., wet-bulb globe temperature (WBGT)] and work intensity (i.e., metabolic heat production), and adherence largely ensures that core temperature is ≤38.0°C in unacclimatized adults (22). Given that the NIOSH heat stress and hydration recommendations (21) were not developed with consideration for maintenance of GFR, the purpose of the present study was to examine the changes in GFR following 4 h of simulated occupational heat stress. To do so, we examined GFR and fluid regulation following occupational heat stress that consisted of half workday exposures at a fixed work intensity but across a range of WBGTs and work-rest ratios that complied with the NIOSH recommendations. In addition, we examined a single scenario that was noncompliant with the NIOSH recommendations by exceeding WBGT limits for a given work intensity and work-rest ratio. Based on our previously reported findings (15, 22), we hypothesized that adhering to the NIOSH recommendations would maintain GFR, relative to preexposure, by preventing core temperature from exceeding 38.0°C when paired with ad libitum drinking that prevents dehydration (<2% body wt loss). We also hypothesized that violating the NIOSH recommendations would reduce GFR compared with a work-rest matched NIOSH-compliant scenario.

MATERIALS AND METHODS

Participants

Twelve healthy adult nonsmokers [6 women and 6 men; age: 28 yr (range: 21–38); body mass index: 24 kg/m^2 (range: 18–29)] participated in this study. All subjects were free of chronic disease, were not heat acclimatized (23), and regularly engaged in physical activity. All had normal GFR at screening (i.e., estimated GFR >60 mL/min/1.73 m^2) measured via a point-of-care device (StatSensor Creatinine, Nova Biomedical). Women were not pregnant confirmed via urine pregnancy test before each visit, self-reported to be normally menstruating, and had no diagnosis of a menstrual cycle disorder. Women were tested at any point during their menstrual cycle to maintain external validity, as in real-world settings women work across their entire menstrual cycle. The study was approved by the Institutional Review Board at Indiana University (IRB No. 1902420140), conformed to the Declaration of Helsinki, and was registered at clinicaltrials.gov (NCT04767347). Before participation, each subject was informed of the procedures and risks before providing informed written consent. The data presented here represent a secondary outcome, while a portion of these data has been previously published in reports that tested unique hypotheses (15, 22).

Experimental Protocol

The study design and experimental protocol have been described in detail previously (15, 22) Participants visited the laboratory on six occasions separated by at least 7 days (all subjects completed the study in 6–12 wk). The *visit 1* involved screening and *visits 2–6* were the experimental trials. The five experimental trials consisted of 4 h (half a workday) of exposure to WBGTs of 24.1 ± 0.3°C (*trial A*), 26.6 ± 0.2°C (*trial B*), 28.4 ± 0.2°C (*trial C*), 29.7 ± 1.6°C (*trial D*), and 36.1 ± 0.3°C (*trial E*). Subjects walked on a treadmill evoking an average rate of metabolic heat production (H_{prod}) of 430 W, the average H_{prod} for activities commonly completed by outdoor workers (24). Average measured H_{prod} was 431 ± 101 W (*trial A*), 461 ± 106 W (*trial B*), 462 ± 91 W (*trial C*), 453 ± 105 W (*trial D*), and 453 ± 113 W (*trial E*), which did not differ among trials ($P = 0.954$). NIOSH-compliant (21) work-rest ratios were prescribed as a function of WBGT and H_{prod} (work:rest min/h= *trial A*: 60:0, *trial B*: 45:15, *trial C*: 30:30, and *trial D*: 15:45). In *trial E*, the work-rest ratio was 15:45. *Trial E* was not NIOSH compliant but was used as a positive control with the work-rest ratio matched with *trial D*. In *trial E*, the environmental conditions reflected what was previously known as the ceiling limit, defined as the threshold WBGT that NIOSH would stipulate that work would be contraindicated (21), thereby rendering *trial E* noncompliant with the NIOSH recommendations. It is important to note that 10 subjects did not complete all 4 h of exposure in *trial E* ($n = 7$ exhaustion, $n = 3$ core temperature of 39.5°C). The average exposure duration for the 10 subjects that did not complete the entire exposure was 132 ± 12 min (range: 120–150 min). Thus, the total work completed was different between *trial D* and *trial E* (151 ± 52 vs. 97 ± 34 kJ, respectively; $P < 0.001$), despite being work-rest matched (15). The experimental trials were completed in a block-randomized order, and subjects were blinded to the environmental conditions where possible.

All subjects were euhydrated upon arrival, defined as urine specific gravity ≤ 1.020 (25). Following urine collection, subjects drank 376 ± 61 mL (0.5% body mass) of cool tap water. Subjects then rested supine for approximately 60 min in an approximately 22°C environment. A blood sample was then obtained followed by a renal ultrasound measurement of renal blood velocity (see *Instruments and Measurements*). Subjects then voided their bladder, were weighed nude, and then donned long pants and long shirt, a short sleeve cotton t-shirt that served as an undershirt, and athletic shoes. Subjects then entered the environmental chamber and the 4-h exposure commenced. Compliant with the NIOSH guidelines (21), subjects were provided 237 mL of a cool (9.2 ± 4.0°C) flavor preferred sport drink (Gatorade; 248 kcal/L; 62 g CHO/L; 450 mg Na/L) every 15 min and were permitted to drink ad libitum. Total volume consumed across the 4-h exposure was calculated. In addition, we calculated the percentage of potential volume (i.e., if participants drank all potential provided fluids up to 237 mL every 15 min) as [(total volume ÷ potential volume) × 100]. During rest periods, subjects sat on a mesh chair in the environmental chamber. Following the exposure, subjects were weighed nude, voided their bladder, and then rested supine for 20 min before a venous blood sample was obtained and a postexposure renal ultrasound completed. Subjects then completed a 60-min recovery period where an additional fluid replacement equal to the preexposure fluid bolus outlined above [i.e., 376 ± 61 mL (0.5% body mass)] but of their flavor preferred sports drink. Subjects then rested supine for approximately 60 min before measurements were repeated.

Instruments and Measurements

Height and nude body mass were measured using a stadiometer and scale. Percentage changes in body mass were calculated as [(postexposure − preexposure nude body mass)/preexposure body mass] × 100. Core temperature was measured via a telemetry pill (HQ) swallowed approximately 6–8 h before each experimental trial ($n = 8$) or a rectal temperature probe inserted approximately 10 cm beyond the anal sphincter ($n = 4$) for subjects contraindicated for taking the telemetry pill. Heart rate was measured using a wireless monitor (Polar Electro, Bethpage, NY). Systolic and diastolic blood pressures were measured manually in duplicate by the same member of the research team throughout the study.

Renal blood velocities were obtained via Doppler ultrasound (Toshiba Aplio 300, Canon Medical Systems) in the distal segment of the right renal artery (renal artery) and in the middle portion of the segmental arterial in the right kidney (segmental artery) as a surrogate for renal blood flow (26), using methods that have been published previously (27). The specific segmental artery and the location of the measurement within the renal and segmental arteries were the same at all time points within a participant. With the participant in the left lateral recumbent position and using the coronal approach, a phased-array transducer (2.5–3.5 MHz) was held in the same location for all measurements after marking the transducer location on the skin with indelible ink during the baseline measurements in each trial. In all instances, the focal zone was set to the artery's depth, and the insonation angle was <60°. Mean renal and segmental artery blood velocities were indexed from the waveform envelop by the time-averaged maximum velocity and reported as the average of three cardiac cycles (12, 27, 28). All renal measurements were obtained and extracted by the same sonographer [H.W.H; within-subject, test-retest coefficients of variation (CV) were 4.3 ± 0.3% (renal artery) and 4.3 ± 2.0% (segmental artery)]. Renal and segmental artery blood velocities were normalized to mean arterial pressure, providing an index of vascular resistance (i.e., mean arterial pressure/blood velocity).

Changes in plasma volume were calculated from hemoglobin and hematocrit using standard equations (29). Serum creatinine (sCr; inter-assay CV: 8.6 ± 3.4%; intra-assay CV: 2.9 ± 0.7%) and urine creatinine (uCr; inter-assay CV: 2.3 ± 0.5%; intra-assay CV: 0.9 ± 0.4%) were measured via human creatinine ELISA kits (Eagle Bioscience). Urine flow rate was calculated as urine volume divided by time (minutes between each bladder void). GFR was estimated from creatinine clearance (i.e., urinary creatinine × urine flow rate ÷ serum creatinine). Urine specific gravity was measured using refractometry (Atago, Tokyo, Japan). Urine and plasma osmolality (Advanced Instruments, Norwood, MA), and sodium and potassium concentrations (Medica, Bedford, MA) were measured in duplicate using commercially available systems. Fractional excretion (FEx) was calculated as $100 \times [(U_x \times sCr) \div (S_x \times uCr)]$, where U_x and S_x represent concentrations of "x" in the urine and serum and uCr and sCr are serum and urinary creatinine concentrations (9). Free water clearance was calculated as UFR × [1 − (Uosm ÷ Posm)], where UFR is urine flow rate and Uosm and Posm are the osmolality of the urine and plasma. Osmolar clearance was calculated as (Uosm ÷ Posm) × UFR (30).

Data and Statistical Analysis

Three unique statistical analyses were undertaken. *1*) We examined dependent variables (peak core temperature, percentage change in body weight, fluid intake, and baseline fluid and electrolytes and creatinine clearance) across the NIOSH-compliant trials using repeated measures one-way linear mixed models. *2*) We compared dependent variables (peak core temperature, percentage change in body weight, fluid intake, and baseline fluid and electrolytes and creatinine clearance) between the NIOSH-compliant (*trial D*) and noncompliant (*trial E*) conditions using two-tailed paired *t* tests. This permitted direct assessment of whether compliance with NIOSH recommendations modified any of the dependent variables when work-rest ratios were matched. The first two analyses were completed to compare fluid and electrolyte homeostasis and creatinine clearance between trials at preexposure (Table 1), so that we could then examine changes from pre- to postexposure and following a 1-h recovery if a significant time effect or interaction was identified. *3*) We then examined all dependent variables over time (pre- to postexposure and following a 1-h recovery) using two-way (time × trial) linear mixed models. This was completed among NIOSH-compliant trials (*trials A–D*) and between a NIOSH-compliant trial (*trial D*) and the noncompliant trial (*trial E*). When there was a main effect of time or interaction effect, postexposure and recovery data were compared with preexposure to better identify changes in fluid and electrolytes, and creatinine clearance following the simulated occupational heat stress under both NIOSH-compliant and noncompliant scenarios. In all instances, when a significant effect or interaction was identified, multiple comparisons were carried out using Sidak's test. Data were analyzed with GraphPad Prism software (v. 10.2.0). All data are presented as absolute or change (from preexposure) values using means ± SD; $n = 12$ unless otherwise reported (see Figs. 1–4). There are several reasons for missing data: *1*) failure to obtain a blood draw or urine sample within a given subject/trial/timepoint, *2*) limited or no sample available due to prior analyses on the blood and urine [see Hess et al. (15)], and/or *3*) samples were outside of the range of the assay kit (i.e., for urine and serum creatinine) or of the osmometer and/or electrolyte analyzer. A priori statistical significance was set at $P \leq 0.05$.

RESULTS

Thermoregulation and Hydration

Peak core temperature did not differ among NIOSH-compliant trials (*trial A*: 38.1 ± 0.4°C, *trial B*: 37.9 ± 0.4°C, *trial C*: 37.9 ± 0.3°C, and *trial D*: 37.7 ± 0.4°C; $P = 0.065$). However, peak core temperature differed between work:rest ratio matched compliant versus noncompliant trials (*trial D*: 37.7 ± 0.4°C vs. *trial E*: 39.1 ± 0.3°C; $P < 0.001$). Similarly, percentage change in body weight did not differ among NIOSH-compliant trials (*trial A*: −0.8 ± 0.7%, *trial B*: −0.7 ± 0.4%, *trial C*: −0.5 ± 0.3%, and *trial D*: −0.3 ± 0.6%;

Table 1. *Fluid consumption and composition during each experimental trial*

	NIOSH Compliant				Noncompliant	*P* Values	
	Trial A	*Trial B*	*Trial C*	*Trial D*	*Trial E*	LMM (*trials A–D*)	Paired *t* test (*trial D* vs. *trial E*)
Total volume, mL	1,743 (752)	1,680 (703)	1,574 (521)	1,435 (555)	1,668 (546)	0.4788	0.2101
Potential volume, %	49 (21)	48 (20)	44 (15)	40 (16)	73 (15)	0.4316	**<0.0001**
Total sodium, mg	784 (338)	755 (316)	708 (234)	644 (249)	745 (244)	0.4720	0.2301
Total CHO, g	108 (47)	104 (43)	97 (32)	89 (34)	103 (34)	0.4715	0.2301
Total kcal	431 (186)	416 (174)	390 (129)	354 (137)	410 (134)	0.4725	0.2302

Data are presented as means (SD). NIOSH, National Institute for Occupational Safety and Health. Bold text indicates statistically significant.

$P = 0.131$) or between work-rest ratio matched compliant versus noncompliant trials (*trial D*: −0.3 ± 0.6% vs. *trial E*: −0.7 ± 1.0%; $P = 0.185$). Ad libitum fluid intake is shown in Table 1. Briefly, there were no differences in total fluid intake among NIOSH-compliant trials (*trials A–D*; $P = 0.4788$) or between *trial D* and *trial E* ($P = 0.2101$). However, percentage of potential total volume (i.e., if participants drank all potential provided fluids up to 237 mL every 15 min) was greater in *trial E* than in *trial D* ($P < 0.0001$). There were no differences in total sodium, total carbohydrate, or total kcal consumption among NIOSH-compliant trials (*trials A–D*; $P \geq 0.4316$) or between *trial D* and *trial E* ($P \geq 0.2301$).

Fluid and Electrolyte Balance

Baseline fluid and electrolyte data collected at preexposure are shown in Table 2. Fluid and electrolyte homeostasis are shown in Figs. 2, *A–H* and 3, *A–H*.

NIOSH-compliant trials.

Urine specific gravity (Fig. 1*A*) was increased from pre- to postexposure in *trial D* ($P = 0.0259$) and at from preexposure at recovery in *trial A* ($P = 0.0442$). Serum osmolality (Fig. 1*B*) did not change over time or differ among NIOSH-compliant trials (time × trial: $P = 0.6548$). However, urine osmolality

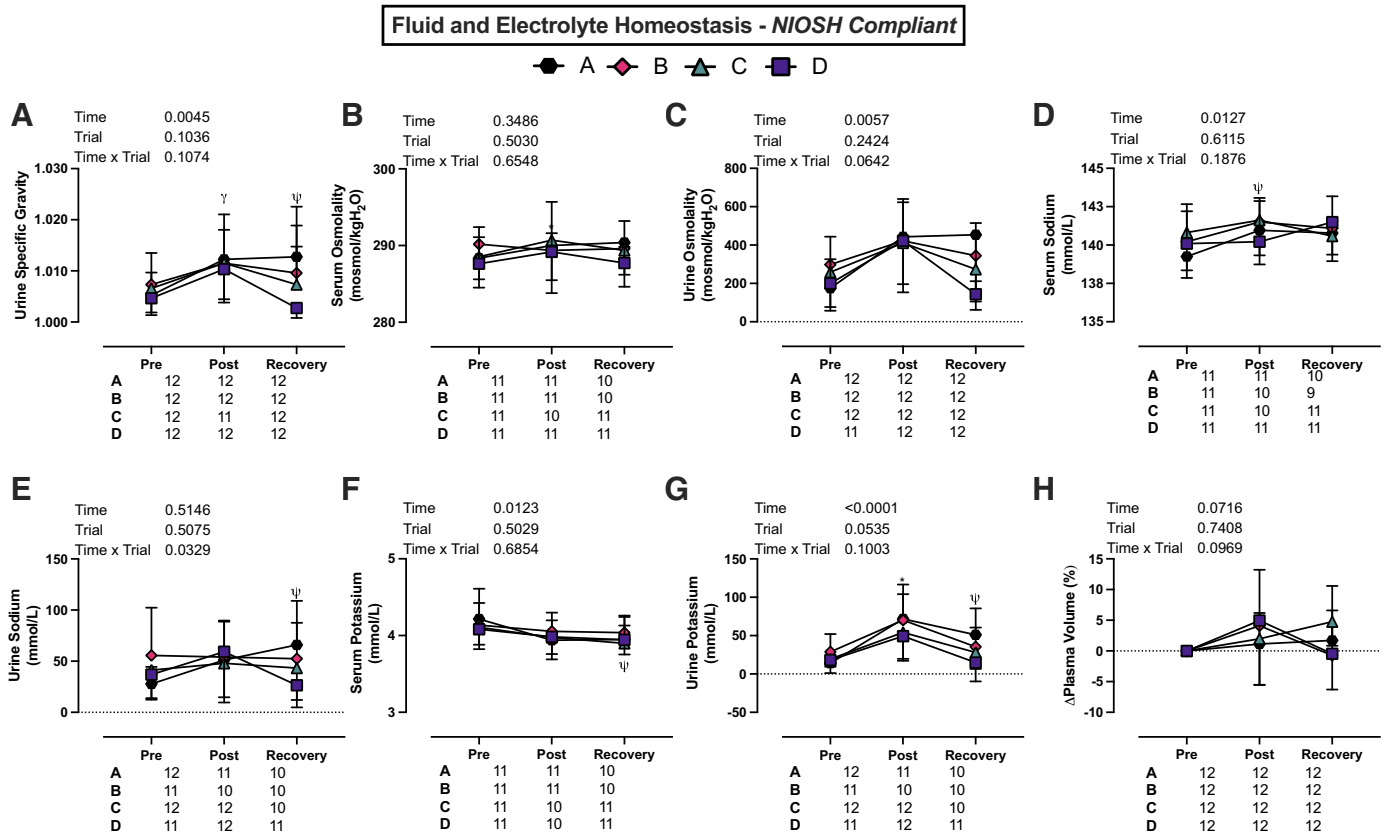

Figure 1. *A–H*: indices of fluid and electrolyte status measured preexposure (Pre), postexposure (Post), and following a 1-h recovery period during the NIOSH-compliant trials. Data are presented as means ± SD. Data were analyzed using a linear mixed model and post hoc analyses were completed using Sidak's multiple comparisons. Actual *P* values are reported. *n* is presented for trial and timepoint under each figure. *All trials different from Pre ($P < 0.05$); $^{\Psi}$*trial A* different from Pre ($P < 0.05$); $^{\gamma}$*trial D* different from Pre ($P < 0.05$). NIOSH, National Institute for Occupational Safety and Health.

Table 2. *Baseline (preexposure) data*

	NIOSH Compliant				Noncompliant	*P* Values	
	Trial A	*Trial B*	*Trial C*	*Trial D*	*Trial E*	LMM (*trials A–D*)	Paired *t* test (*trial D* vs. *trial E*)
Water and electrolyte homeostasis							
24-h sodium excretion, g/day	11.0 (4.9)	9.3 (2.6)	11.7 (8.5)	9.4 (3.8)	9.7 (4.2)	0.4865	0.8531
Urine specific gravity	1.005 (0.004)	1.007 (0.006)	1.007 (0.005)	1.005 (0.003)	1.005 (0.004)	0.2753	0.7100
Serum osmolality, mosmol/kgH_2O	288 (4)	290 (5)	289 (3)	287 (5)	287 (3)	0.4213	0.8542
Urine osmolality, mosmol/kgH_2O	175 (118)	298 (221)	259 (185)	259 (185)	218 (135)	0.2088	0.6324
Serum sodium, mmol/L	139.3 (1.4)	140.2 (1.9)	140.8 (1.4)	140.1 (2.6)	139.3 (1.2)	0.2886	0.7150
Urine sodium, mmol/L	27.7 (16.7)	55.7 (46.6)	41.2 (28.9)	37.0 (23.1)	34.7 (20.2)	0.1542	0.7483
Serum potassium, mmol/L	4.2 (0.4)	4.1 (0.3)	4.1 (0.3)	4.1 (0.2)	4.2 (0.2)	0.5067	0.0677
Urine potassium, mmol/L	14.2 (7.3)	28.9 (23.1)	19.6 (18.5)	18.2 (8.7)	18.3 (9.4)	0.1582	0.9844
Creatinine clearance and fluid conservation							
Urine flow rate, mL/min	6.2 (3.3)	3.9 (2.2)	4.8 (2.9)	5.7 (3.1)	5.2 (3.1)	**0.0545**	0.5829
Urine creatinine, mg/dL	33.4 (35.8)	58.9 (58.5)	44.9 (35.0)	35.0 (31.7)	38.4 (33.6)	0.3379	0.8117
Serum creatinine, mg/dL	1.1 (0.2)	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	0.3932	0.2291
Creatinine clearance, mL/min	112.8 (42.1)	118.1 (34.3)	120.9 (45.9)	102.1 (52.7)	114.0 (51.7)	0.1645	0.2979
Free water clearance, mL/min	3.6 (3.0)	1.0 (2.1)	1.8 (3.0)	2.8 (2.8)	3.1 (2.9)	**0.0265**	0.8320
Osmolar clearance, mL/min	2.8 (0.8)	2.7 (0.7)	2.7 (0.6)	3.0 (0.6)	2.8 (0.6)	0.5246	0.5060
Fractional excretion of sodium, %	1.0 (0.7)	1.0 (0.4)	0.9 (0.5)	1.5 (1.1)	0.9 (0.4)	0.1772	0.1707
Fractional excretion of potassium, %	16.9 (9.8)	17.9 (8.4)	16.4 (10.8)	22.9 (13.6)	17.1 (6.9)	0.2556	0.1365

Data are presented as means (SD). Data were analyzed using either a linear mixed model (LMM; *trials A–D*) or as two-tailed paired *t* tests (*trial D* vs. *trial E*). Actual *P* values are reported. All data are $n = 12$ unless otherwise reported. NIOSH, National Institute for Occupational Safety and Health. Bold text indicates statistically significant.

(Fig. 1*C*) increased from pre- to postexposure in *trials A* and *D* ($P \leq 0.0309$). Serum sodium (Fig. 1*D*) was elevated from preexposure in *trial A* ($P = 0.0064$). Urine sodium (Fig. 1*E*) was elevated from preexposure at recovery in *trial A* ($P = 0.0280$) and higher than *trial D* ($P = 0.0169$) at recovery. Serum potassium (Fig. 1*F*) was different from preexposure at recovery in *trial A* ($P = 0.0289$). Urine potassium (Fig. 1*G*) was elevated from pre- to postexposure in all trials ($P \leq$

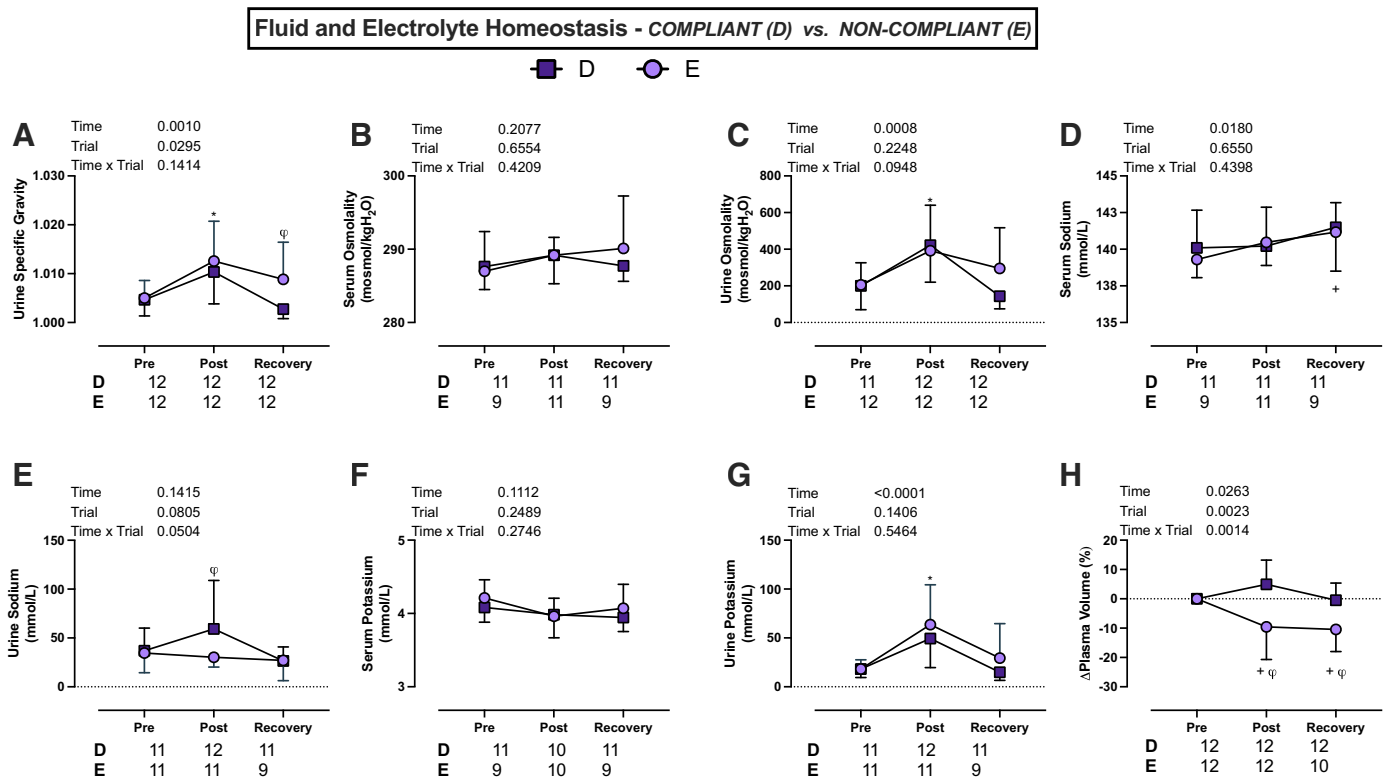

Figure 2. *A–H*: indices of fluid and electrolyte status measured preexposure (Pre), postexposure (Post), and following a 1-h recovery period during the NIOSH-compliant (*trial D*) and noncompliant (*trial E*) trials. Data are presented as means ± SD. Data were analyzed using a linear mixed model and post hoc analyses were completed using Sidak's multiple comparisons. Actual *P* values are reported. *n* is presented for the trial and timepoint under each figure. + *Trial E* different from Pre ($P < 0.05$); $^{\varphi}$*trial E* different from *trial D* ($P < 0.05$); *all trials different from Pre ($P < 0.05$). NIOSH, National Institute for Occupational Safety and Health.

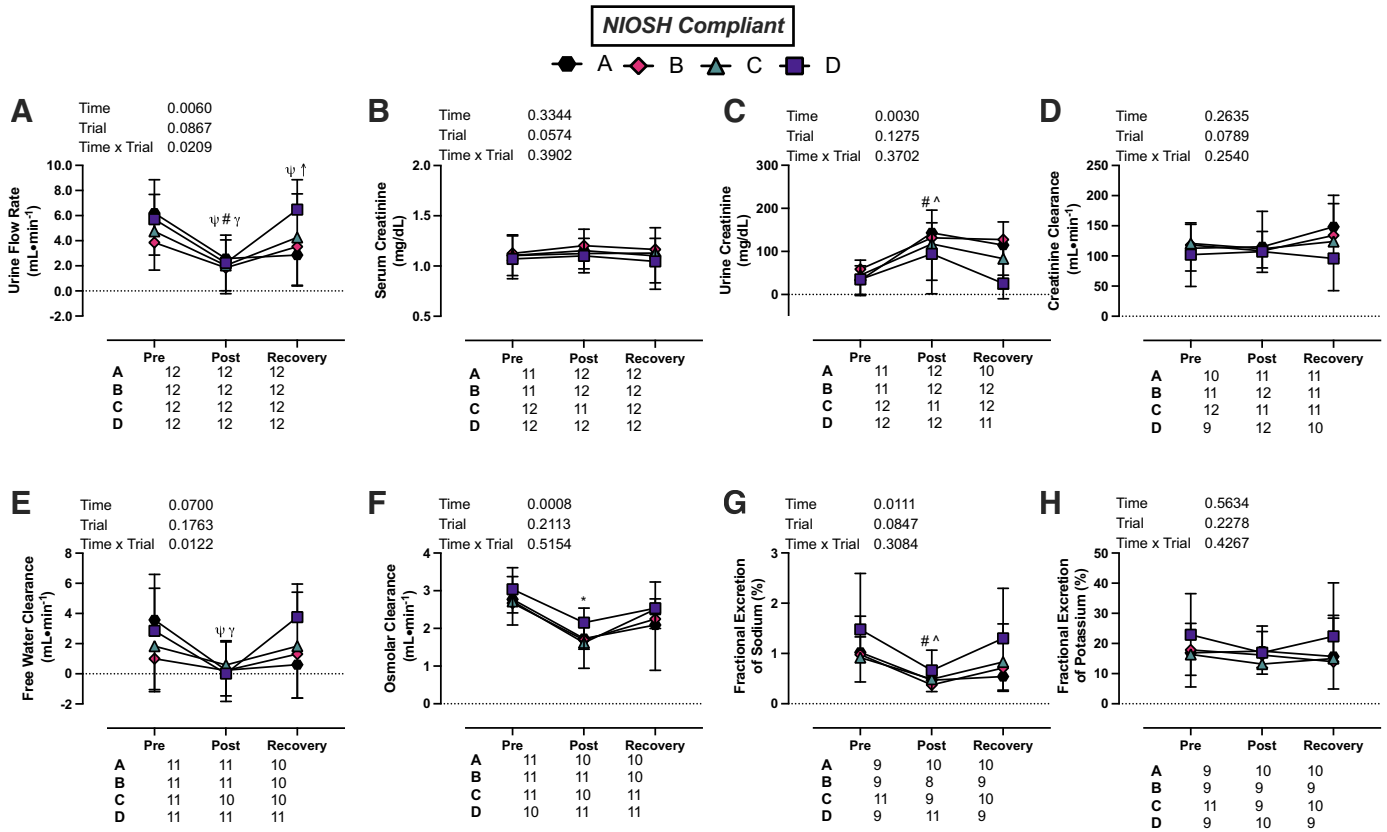

Figure 3. *A–H*: indices of creatinine clearance and fluid conservation measured at preexposure (Pre), postexposure (Post), and following a 1-h recovery period during NIOSH-compliant trials. Data are presented as means ± SD. Data were analyzed using a linear mixed model and post hoc analyses were completed using Sidak's multiple comparisons. Actual *P* values are reported. *n* is presented for the trial and timepoint under each figure. *All trials different from Pre ($P < 0.05$); $^{\psi}$*trial A* different from Pre ($P < 0.05$); $^{\gamma}$*trial D* different from Pre ($P < 0.05$); $^{\#}$*trial B* different from Pre ($P < 0.05$); ^*trial C* different from Pre ($P < 0.05$); ↑*trial A* different from *trial D* ($P < 0.05$). NIOSH, National Institute for Occupational Safety and Health.

0.0106) and at recovery in *trial A* ($P = 0.0152$). Plasma volume (Fig. 1*H*) did not change over time or differ among NIOSH-compliant trials (time × trial: $P = 0.0969$).

Compliant vs. noncompliant trials (trial D vs. trial E).

Urine specific gravity increased from pre- to postexposure in both trials (Fig. 2*A*; $P \leq 0.0235$) and was higher at recovery in *trial E* compared with *trial D* ($P = 0.0138$). Serum osmolality (Fig. 2*B*) did not change over time or differ between *trials D* and *E* (time × trial: $P = 0.4209$). However, urine osmolality (Fig. 2*C*) increased from preexposure in both trials ($P \leq 0.0137$). Serum sodium (Fig. 2*D*) was elevated in *trial E* at recovery ($P = 0.0269$). In contrast, there was an interaction effect for urine sodium (Fig. 2*E*). However, post hoc analyses did not reveal any changes over time ($P \geq 0.0703$), but *trial D* was different than *trial E* at postexposure ($P = 0.0066$). This suggests that sodium reabsorption was greater in *trial E* compared with *trial D*. Serum potassium (Fig. 2*F*) did not change over time or differ between *trials D* and *E* (time × trial: $P = 0.2746$). However, urine potassium (Fig. 2*G*) increased from pre- to postexposure in both trials ($P \leq 0.0084$). Finally, plasma volume (Fig. 2*H*) was reduced from pre- to postexposure and at recovery in *trial E* and different from *trial D* (time × trial: $P = 0.0014$).

Creatinine Clearance and Fluid Conservation

Baseline creatinine clearance and fluid conservation data collected at preexposure are shown in Table 2. Indices of creatinine clearance and fluid conservation are shown in Figs. 3, *A–H* (NIOSH compliant) and Fig. 4, *A–H* [compliant vs. noncompliant trials (*trial D* vs. *trial E*)]. Renal hemodynamic measures are shown in Table 3 (NIOSH compliant) and Table 4 [compliant vs. noncompliant trials (*trial D* vs. *trial E*)].

NIOSH-compliant trials.

Urine flow rate (Fig. 3*A*) fell from pre- to postexposure in all trials ($P \leq 0.0364$) except for *trial C* ($P = 0.0954$). Urine flow rate remained lower than preexposure at recovery in *trial A* ($P = 0.0379$) and was different from *trial D* ($P = 0.0032$). Serum creatinine (Fig. 3*B*) did not change over time or differ among trials (time × trial: $P = 0.3902$). Urine creatinine (Fig. 3*C*) was elevated from pre- to postexposure in *trials B* and *C* ($P \leq 0.0432$). Creatinine clearance (Fig. 3*D*) did not change over time or differ among trials (time × trial: $P = 0.2540$). Free water clearance (Fig. 3*E*) fell from pre- to postexposure in *trials A* and *D* ($P \leq 0.0443$) and remained lower than preexposure at recovery in *trial A* ($P = 0.0447$). Osmolar clearance (Fig. 3*F*) fell from pre- to postexposure in all trials ($P \leq 0.0167$). Fractional excretion of sodium (Fig. 3*G*) decreased from pre- to postexposure in *trials B* and *C* ($P \leq 0.0470$).

Table 3. *Renal hemodynamics in NIOSH-compliant trials (trials A–D)*

	Trial A			Trial B			Trial C			Trial D			LMM		
	Pre	Post	Rec	Pre	Post	Rec	Pre	Post	Rec	Pre	Post	Rec	Time	Trial	Time × Trial
Mean arterial pressure, mmHg	87 (4)	86 (6)	89 (5)	87 (6)	88 (7)	89 (7)	90 (6)	87 (6)	88 (5)	88 (5)	87 (3)	89 (4)	0.0786	0.9302	0.2950
Renal artery															
Blood velocity, cm/s	33 (8)	39 (8)$^{\psi}$	37 (7)	35 (9)	39 (12)	41 (16)	33 (9)	39 (8)^	38 (9)	33 (10)	37 (9)	34 (10)	**0.0004**	0.3821	0.5989
Vascular resistance, mmHg/cm/s	2.8 (0.7)	2.3 (0.6)$^{\psi}$	2.5 (0.4)	2.6 (0.7)	2.5 (0.7)	2.5 (0.9)	2.9 (0.7)	2.3 (0.4)^	2.4 (0.6)	2.8 (0.9)	2.5 (0.6)	2.8 (0.7)	**0.0016**	0.2812	0.5805
Segmental artery															
Blood velocity, cm/s	19 (4)	19 (3)	18 (2)	20 (6)	20 (7)	21 (6)	19 (4)	20 (5)	20 (5)	19 (3)	20 (3)	20 (5)	0.3412	0.5577	0.7959
Vascular resistance, mmHg/cm/s	4.8 (0.9)	4.5 (0.6)	4.9 (0.7)	4.6 (1.0)	4.6 (1.2)	4.6 (1.0)	4.9 (0.9)	4.5 (0.8)	4.6 (1.0)	4.6 (0.6)	4.5 (0.5)	4.7 (0.9)	0.2275	0.8273	0.6078

Data are presented as means (SD). Data were analyzed using a linear mixed model (LMM). Actual P values are reported. All data are $n = 12$ unless otherwise reported. NIOSH, National Institute for Occupational Safety and Health; Post, postexposure; Pre, preexposure; Rec, recovery. $^{\psi}$*Trial A* different from Pre ($P < 0.05$); ^*trial C* different from Pre ($P < 0.05$). Bold text indicates statistically significant.

Finally, fractional excretion of potassium (Fig. 3*H*) did not change over time or differ among trials (time × trial: $P = 0.4267$).

Renal hemodynamics are shown in Table 3. Mean arterial pressure did not change over time or differ among trials (time × trial: $P = 0.2950$). There was an increase in renal blood velocity from pre- to postexposure in *trials A* and *C* ($P \leq 0.0018$) that paralleled a decrease in renal vascular resistance ($P \leq 0.0045$). Neither segmental blood velocity nor vascular resistance changed over time or differed among trials (time × trial: $P \geq 0.6078$).

Compliant vs. noncompliant trials (trial D vs. trial E). Urine flow rate (Fig. 4*A*) fell from pre- to postexposure in both trials ($P \leq 0.0005$). Urine flow rate remained lower than preexposure at recovery in *trial E* ($P = 0.0500$) and was different from *trial D* ($P = 0.0002$). Serum creatinine (Fig. 4*B*) increased from pre- to postexposure in *trial E* ($P < 0.0001$) and remained elevated at recovery ($P = 0.0296$). Furthermore, serum creatinine was different between trials at both postexposure and recovery ($P \leq 0.0359$). Urine creatinine (Fig. 4*C*) was elevated from pre- to postexposure in *trial E* ($P = 0.0003$) and was different from *trial D* ($P = 0.0194$). There was an interaction effect for creatinine clearance (Fig. 4*D*; time × trial: $P = 0.0478$); however, post hoc analyses did not reveal any change over time or differences between trials ($P \geq 0.1660$). Free water clearance (Fig. 4*E*) fell from pre- to postexposure in both trials ($P \leq 0.0031$) and was different between trials at recovery ($P = 0.0180$). Osmolar clearance (Fig. 4*F*) fell from pre- to postexposure and recovery in both trials ($P \leq 0.0343$) but was different between trials at both time points ($P \leq 0.0012$). Fractional excretion of sodium (Fig. 4*G*) decreased from pre- to postexposure in both trials ($P \leq 0.0125$) and differed between trials at recovery ($P = 0.0068$). Finally, fractional excretion of potassium (Fig. 4*H*) differed between trials at recovery ($P = 0.0053$).

Renal hemodynamics are shown in Table 4. Mean arterial pressure did not change over time or differ between trials (time × trial: $P = 0.2984$). There was an increase in renal blood velocity from pre- to postexposure in *trial E* ($P = 0.0181$) that paralleled a decrease in renal vascular resistance and was different from *trial D* ($P \leq 0.0524$). There was an interaction effect (time × trial: $P = 0.0506$) for segmental blood velocity. Segmental artery blood velocity was decreased from preexposure at recovery in *trial E* ($P = 0.0512$). There were no differences between trials ($P \geq 0.5712$).

DISCUSSION

We presented a secondary analysis of data from our registered clinical trial (NCT04767347) that aimed to examine indices of GFR (creatinine clearance) and fluid and electrolyte regulation following simulated occupational heat stress scenarios that were compliant with the NIOSH heat stress recommendations. We hypothesized that GFR would be maintained during the NIOSH-compliant trials and that responses would not differ among trials despite differences in WBGT and work-rest ratios, given that work intensity

Table 4. *Renal hemodynamics in work-rest matched NIOSH-compliant and noncompliant trials (trial D vs. trial E)*

	Trial D			Trial E			LMM		
	Pre	Post	Rec	Pre	Post	Rec	Time	Trial	Time × Trial
Mean arterial pressure, mmHg	88 (5)	87 (3)	89 (4)	85 (5)	87 (5)	90 (10)	0.4982	0.6922	0.2984
Renal artery									
Blood velocity, cm/s	33 (10)	37 (9)	34 (10)	33 (10)	33 (9)	36 (8) + $^{\varphi}$	0.0971	0.2160	**0.0566**
Vascular resistance, mmHg/cm/s	2.8 (0.9)	2.5 (0.6)	2.8 (0.7)	2.9 (0.9)	2.8 (0.7)	2.6 (0.6) + $^{\varphi}$	0.1884	0.2605	**0.0269**
Segmental artery									
Blood velocity, cm/s	19 (3)	20 (3)	20 (5)	19 (3)	20 (6)	18 (4) + $^{\varphi}$	**0.0498**	0.8510	**0.0506**
Vascular resistance, mmHg/cm/s	4.6 (0.6)	4.5 (0.5)	4.7 (0.9)	4.7 (0.9)	4.7 (1.0)	5.2 (0.8)	0.7590	0.8896	0.0662

Data are presented as means (SD). Data were analyzed using a linear mixed model (LMM). Actual P values are reported. All data are $n = 12$ unless otherwise reported. NIOSH, National Institute for Occupational Safety and Health; Post, postexposure; Pre, preexposure; Rec, recovery. + *Trial E* different from Pre ($P < 0.05$); $^{\varphi}$*trial E* different from *trial D* ($P < 0.05$). Bold text indicates statistically significant.

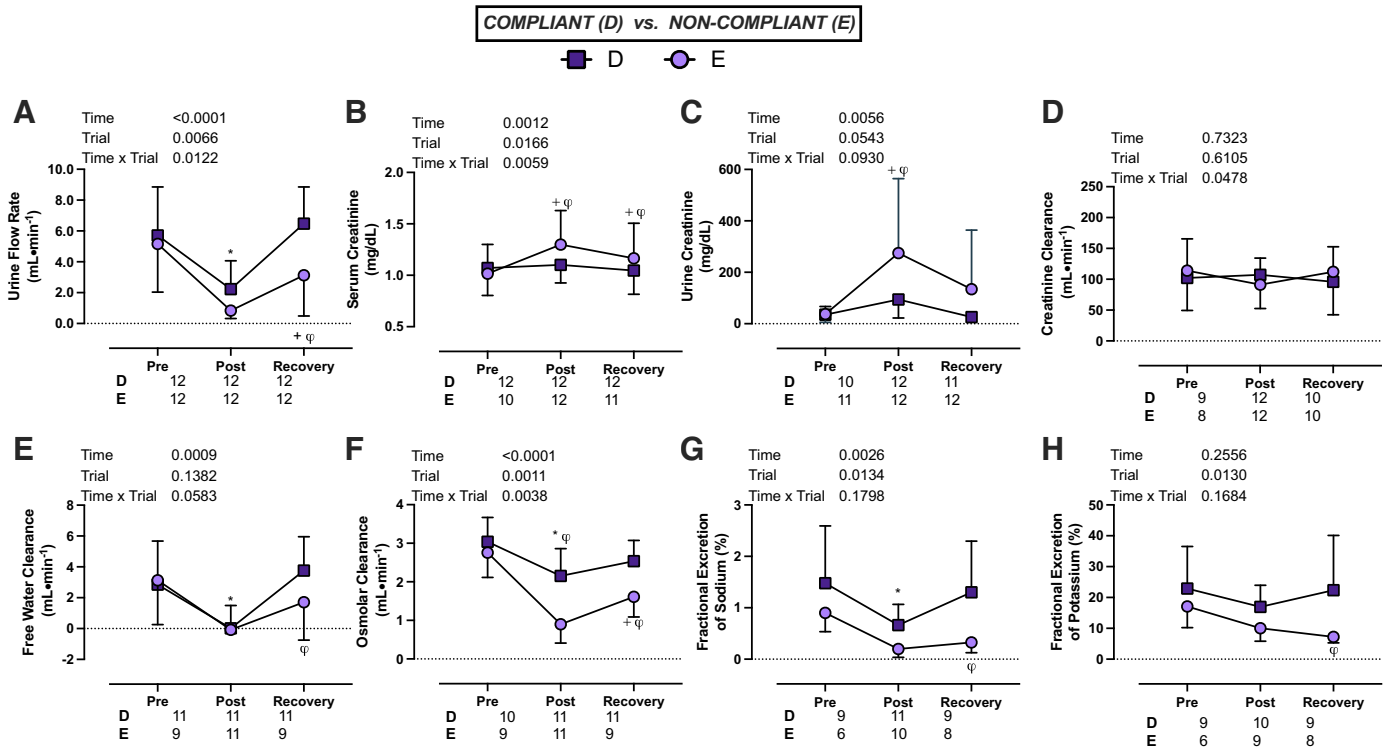

Figure 4. *A–H*: indices of creatinine clearance and fluid conservation measured at preexposure (Pre), postexposure (Post), and following a 1-h recovery period during the NIOSH-compliant (*trail D*) and noncompliant (*trial E*) trials. Data are presented as means ± SD. Data were analyzed using a linear mixed model and post hoc analyses completed using Sidak's multiple comparisons. Actual *P* values are reported. *n* is presented for the trial and timepoint under each figure. + *Trial E* different from Pre ($P < 0.05$); $^{\varphi}$*trial E* different from *trial D* ($P < 0.05$); *all trials different from Pre ($P < 0.05$). NIOSH, National Institute for Occupational Safety and Health.

(metabolic heat production) was the same among trials and similar peak core temperature and percentage changes in body weight were observed (15, 22). The findings in the present study support this hypothesis. Creatinine clearance (our measure of GFR) did not differ from pre-exposure following NIOSH-compliant trials and was not different among trials (Fig. 3*D*). Furthermore, measurements of fluid and electrolyte conservation and urine concentrating capacity remained intact (i.e., no observation of a paradoxical increase in free water clearance due to hyperfiltration to maintain GFR) and were largely not different among trials (Figs. 1 and 3).

A secondary purpose of the present study was to examine the indices of GFR and fluid conservation following a simulated occupational heat stress scenario that was noncompliant with the NIOSH recommendations (i.e., exceeded the allowable WBGT at that work intensity, work-rest ratio). As anticipated in a markedly higher environmental exposure (WBGT: approximately 36°C) resulting in greater heat strain, indices of fluid conservation and regulation revealed a more robust response compared with a work-rest ratio matched condition (Figs. 2 and 4), but creatinine clearance did not differ between these trials, which contrasted our hypothesis. Because the magnitude of dehydration (i.e., percent change in body wt) did not differ between these two conditions, this observation likely highlights the importance of maintaining adequate fluid intake during occupational heat stress scenarios that are noncompliant with the NIOSH heat stress recommendations.

As previously reported (15, 22), the magnitude of heat strain (i.e., peak core temperature) did not differ among NIOSH-compliant trials despite differences in WBGT, total work, and work-rest ratios. Furthermore, we observed that ad libitum drinking (Table 1) was sufficient in maintaining euhydration across the range of simulated occupational heat stress scenarios. To this end, we provide additional measurements of hydration status (see indices of fluid and electrolyte homeostasis in Fig. 1). In the NIOSH-compliant trials, there were no hydration status indices that met criteria for dehydration (22) [e.g., serum osmolality: +9 mosmol/kgH_2O; urine specific gravity: +0.010; percentage change in body wt: −2% (25)]. This was likely due to both sufficient drinking to replace fluid volume loss via sweating and the fluid-conservatory responses of the kidneys (9). This is highlighted by a reduction in urine flow rate, free water clearance, and fractional excretion of sodium that did not differ across NIOSH-compliant trials (see Fig. 3). Finally, in the NIOSH compliant trials, there was no change in plasma volume, which further highlights that fluid replacement and/or fluid conservatory mechanisms were sufficient in maintaining plasma volume despite sweat rates of approximately 0.5 L per hour (22). This is important with regards to the maintenance of blood volume and preventing reductions in renal blood flow, and subsequently GFR, due to dehydration (31). To this end, it is important to note that there were no changes in creatinine clearance (our marker of GFR in the present study) from pre- to postexposure or differences among NIOSH compliant trials (Fig. 3*D*). This is in contrast to previous work in

our laboratory that has demonstrated a reduction in creatinine clearance following physical work in the heat (12, 16), even when water is consumed equal to sweat loss (12). However, the differences in these findings are likely due to differences in experimental design (e.g., environmental conditions, total work and intensity) (12) or the composition of the available fluids (i.e., water vs. sports drink). Therefore, GFR is not uniformly reduced during/following physical work in the heat and appears to be modified by exercise parameters, duration, magnitude of heat strain, and/or dehydration (9, 31, 32).

To test our secondary hypothesis, we assessed the fluid regulatory and GFR responses following an occupational heat stress scenario that was noncompliant with the NIOSH recommendations. Interestingly, there were no differences in indices of hydration status among the NIOSH compliant and noncompliant trials (see Fig. 2), likely due to increased fluid intake per unit time. However, there was a reduction in plasma volume from pre- to postexposure that was sustained even following a 1-h recovery that included additional fluid replacement (Fig. 2*H*). This occurred under conditions of a shorter exposure period (approximately 130 min vs. 240 min) but a greater peak core temperature and equal volume of fluid consumption (Table 1). In addition, the fluid conservatory responses (e.g., reduction in urine flow rate, free water clearance, and fractional excretion of sodium) did not differ among the NIOSH-compliant and noncompliant trials from pre- to postexposure. We speculate that this observation can be explained by a theoretical maximum reduction in urine flow rate, free water clearance, and/or fractional excretion of sodium, based on the neurohormonal responses to heat stress and dehydration (9). This fluid conservatory response was achieved by a greater urine concentrating response following the noncompliant trial (Figs. 2 and 4) and an increased relative fluid intake. In contrast, the fluid conservation responses were sustained following a 1-h recovery period in the noncompliant trial, whereas urine flow rate and associated indices of GFR had returned to preexposure values in the compliant trial. This includes an observed difference in the fractional excretion of potassium between the noncompliant and compliant trials following a 1-h recovery (Fig. 4*H*). This is an interesting finding. However, we can only speculate as to the potential mechanisms, which may include sustained reductions in urine flow rate, increased renin-angiotensin-aldosterone system activity, or modified acid-base disturbances, all of which are expected with prolonged physical work in the heat. Perhaps most interestingly, creatinine clearance was maintained following the noncompliant trial despite these marked differences in peak core temperature, fluid turnover, and blood volume loss. There was an increase in serum creatinine in the noncompliant trial that was associated with a greater risk of AKI as presented in our previous publication (15), but this may have been reflective of increased serum creatinine concentration (via reduction in plasma volume) or a normal physiological increase in creatinine from skeletal muscle during exercise and heat stress (9) and not necessarily a fall in GFR. This further highlights the limitations and clinical utility of serum creatinine as a marker of AKI following physical work in the heat (9).

Renal hemodynamics measured via renal ultrasound were largely unchanged following the NIOSH-compliant trials except for a few innocuous time points where there were very modest differences (i.e., increases in renal artery vascular resistance from pre- to postexposure in *trials A* and *C* and at recovery in *trial E*; Tables 3 and 4). This is consistent with our previous work that measured renal blood velocity before and following exertional heat stress (12). Therefore, it is unsurprising that we did not observe any meaningful changes in the renal and segmental artery hemodynamics in the absence of a concurrent stressor [e.g., cold pressor test (33) or following an oral protein load (34)]. Thus, these findings suggest that GFR is unlikely to be modified in the absence of changes in renal blood flow or during an active sympathetic stressor (35).

Experimental Considerations

Experimental considerations pertaining to the present study have been previously discussed (15, 22). Here, we will briefly discuss and expand upon these considerations. First, the strict adherence to the NIOSH heat stress recommendations was only permitted under laboratory-controlled conditions where environmental conditions and metabolic heat production remained constant during the 4-h exposure. This is an unlikely scenario given the fluctuation in environmental conditions during the workday and metabolic heat production due to variations in job tasks (10). That said, we could consider the present study representative of a peak exposure period that typically lasts 3–4 h midday (10). Second, the examination of kidney-related indices occurred after a simulated half workday, whereas typical workdays may consist of 6–12 h of exposure (7). It remains unknown if the kidney responses observed under such conditions would remain intact if the exposure duration was extended. This is particularly important in scenarios where workers are noncompliant with the NIOSH heat stress recommendations (15). Third, we assessed indices of fluid and electrolyte homeostasis preexposure, postexposure, and following a recovery period. This may have altered our results as the ambient heat stress had been lifted at the postexposure assessment, although we obtained these samples within approximately 10 min after the participant was removed from the environmental chamber. All indices required timed urine and blood samples and are not reflective of the likely dynamic changes in GFR during the simulated occupational heat stress. It is likely that dynamic alterations in GFR occurred during the work-rest cycles that were not captured but may be physiologically meaningful in the context of the risk of AKI given the fluctuation in heat strain (22). Finally, participants in the present study were self-reported to be healthy and aged 21–38 yr. The findings in the present study may not be broadly generalizable to the general population of workers exposed to heat stress that are aged across the entire adult lifespan (6) or carry traditional risk factors that may further challenge the kidneys during occupational heat stress (e.g., hypertension, diabetes, or obesity) (7).

Conclusions

In conclusion, GFR is broadly maintained with compliance to the NIOSH heat stress and hydration recommendations

[via adherence to work-rest ratios at a given WBGT and fixed metabolic heat production (work intensity)]. This observation occurred despite a range of WBGT exposures and total amount of physical work, which was likely mediated by similar core temperature, fluid intake, and fluid regulatory responses. However, under a noncompliant scenario, we demonstrate a greater magnitude of heat strain (e.g., peak core temperature) but no reduction in glomerular filtration rate (creatinine clearance), which was likely due to adequate fluid intake to prevent dehydration and robust fluid conservation responses. Therefore, the data from the present study serve to highlight that strategies that mitigate occupational heat strain should be taken (e.g., work-rest cycles, adequate fluid intake, and mitigation of environmental exposure) to prevent workday reductions in GFR, and subsequent risk of AKI, supporting interventions from field work in Mesoamerica.

DATA AVAILABILITY

Data will be made available upon reasonable request.

ACKNOWLEDGMENTS

We thank the subjects for participating in our study. In addition, we thank the research staff and other students for assistance during data collection. The methodological figure in the Graphical Abstract was republished from Fig. 1*A* in Hess et al. (15) with permission (License No. 5774870421783).

Present address of H. W. Hess: Center for Research and Education in Special Environments, Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, New York, United States.

GRANTS

This work was supported by the National Institute for Occupational Safety and Health (Grant R01OH011528, to Z.J.S.).

DISCLAIMERS

This article's contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute for Occupational Safety and Health.

DISCLOSURES

Z.J.S. has received consultant fees from Otsuka Holdings Co., Ltd. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

H.W.H., B.D.J., D.H., and Z.J.S. conceived and designed research; H.W.H., T.B.B., and M.L.T. performed experiments; H.W.H., T.B.B., R.S.Z., and Z.J.S. analyzed data; H.W.H. interpreted results of experiments; H.W.H. prepared figures; H.W.H. and Z.J.S. drafted manuscript; H.W.H., T.B.B., M.L.T., R.S.Z., B.D.J., D.H., and Z.J.S. edited and revised manuscript; H.W.H., T.B.B., M.L.T., R.S.Z., B.D.J., D.H., and Z.J.S. approved final version of manuscript.

REFERENCES

1. **Ioannou LG**, **Foster J**, **Morris NB**, **Piil JF**, **Havenith G**, **Mekjavic IB**, **Kenny GP**, **Nybo L**, **Flouris AD.** Occupational heat strain in outdoor workers: a comprehensive review and meta-analysis. *Temperature (Austin)* 9: 67–102, 2022. doi:10.1080/23328940.2022.2030634.
2. **IPCC.** *Climate Change 2021: the Physical Science Basis*. IPCC Sixth Assessment Report. Cambridge, UK: Cambridge University Press, 2021, p. 33–144.
3. **Flouris AD**, **Dinas PC**, **Ioannou LG**, **Nybo L**, **Havenith G**, **Kenny GP**, **Kjellstrom T.** Workers' health and productivity under occupational heat strain: a systematic review and meta-analysis. *Lancet Planet Health* 2: e521–e531, 2018. doi:10.1016/S2542-5196(18)30237-7.
4. **Havenith G.** *Solving the Health & Work Productivity Challenges Posed by Global Warming* [Online]. https://www.lboro.ac.uk/departments/design-school/research/projects/heat_shield/ [Accessed 17 November 2020].
5. **Leon LR**, **Bouchama A.** Heat stroke. *Compr Physiol* 5: 611–647, 2015. doi:10.1002/cphy.c140017.
6. **Johnson RJ**, **Wesseling C**, **Newman LS.** Chronic kidney disease of unknown cause in agricultural communities. *N Engl J Med* 380: 1843–1852, 2019. doi:10.1056/NEJMra1813869.
7. **Chapman CL**, **Hess HW**, **Lucas RAI**, **Glaser J**, **Saran R**, **Bragg-Gresham J**, **Wegman DH**, **Hansson E**, **Minson CT**, **Schlader ZJ.** Occupational heat exposure and the risk of chronic kidney disease of nontraditional origin in the United States. *Am J Physiol Regul Integr Comp Physiol* 321: R141–R151, 2021. doi:10.1152/ajpregu.00103.2021.
8. **Glaser J**, **Lemery J**, **Rajagopalan B**, **Diaz HF**, **García-Trabanino R**, **Taduri G**, **Madero M**, **Amarasinghe M**, **Abraham G**, **Anutrakulchai S**, **Jha V**, **Stenvinkel P**, **Roncal-Jimenez C**, **Lanaspa MA**, **Correa-Rotter R**, **Sheikh-Hamad D**, **Burdmann EA**, **Andres-Hernando A**, **Milagres T**, **Weiss I**, **Kanbay M**, **Wesseling C**, **Sánchez-Lozada LG**, **Johnson RJ.** Climate change and the emergent epidemic of CKD from heat stress in rural communities: the case for heat stress nephropathy. *Clin J Am Soc Nephrol* 11: 1472–1483, 2016. doi:10.2215/CJN.13841215.
9. **Chapman CL**, **Johnson BD**, **Parker MD**, **Hostler D**, **Pryor RR**, **Schlader Z.** Kidney physiology and pathophysiology during heat stress and the modification by exercise, dehydration, heat acclimation and aging. *Temperature (Austin)* 8: 108–159, 2020. doi:10.1080/23328940.2020.1826841.
10. **Glaser J**, **Hansson E**, **Weiss I**, **Wesseling C**, **Jakobsson K**, **Ekström U**, **Apelqvist J**, **Lucas R**, **Arias Monge E**, **Peraza S**, **Hogstedt C**, **Wegman DH.** Preventing kidney injury among sugarcane workers: promising evidence from enhanced workplace interventions. *Occup Environ Med* 77: 527–534, 2020. doi:10.1136/oemed-2020-106406.
11. **Hansson E**, **Glaser J**, **Weiss I**, **Ekström U**, **Apelqvist J**, **Hogstedt C**, **Peraza S**, **Lucas R**, **Jakobsson K**, **Wesseling C**, **Wegman DH.** Workload and cross-harvest kidney injury in a Nicaraguan sugarcane worker cohort. *Occup Environ Med* 76: 818–826, 2019. doi:10.1136/oemed-2019-105986.
12. **Chapman CL**, **Johnson BD**, **Vargas NT**, **Hostler D**, **Parker MD**, **Schlader ZJ.** Both hyperthermia and dehydration during physical work in the heat contribute to the risk of acute kidney injury. *J Appl Physiol (1985)* 128: 715–728, 2020. doi:10.1152/japplphysiol.00787.2019.
13. **Hess HW**, **Stooks JJ**, **Baker TB**, **Chapman CL**, **Johnson BD**, **Pryor RR**, **Basile DP**, **Monroe JC**, **Hostler D**, **Schlader ZJ.** Kidney injury risk during prolonged exposure to current and projected wet bulb temperatures occurring during extreme heat events in healthy young men. *J Appl Physiol (1985)* 133: 27–40, 2022. doi:10.1152/japplphysiol.00601.2021.
14. **Chapman CL**, **Johnson BD**, **Sackett JR**, **Parker MD**, **Schlader ZJ.** Soft drink consumption during and following exercise in the heat elevates biomarkers of acute kidney injury. *Am J Physiol Regul Integr Comp Physiol* 316: R189–R198, 2019. doi:10.1152/ajpregu.00351.2018.
15. **Hess HW**, **Baker TB**, **Tarr ML**, **Zoh RS**, **Johnson BD**, **Hostler D**, **Schlader ZJ.** Occupational heat stress recommendation compliance attenuates acute kidney injury risk compared to a work-rest matched, positive control scenario. *Kidney360* 4: 1752–1756, 2023. doi:10.34067/KID.0000000000000288.
16. **Schlader ZJ**, **Chapman CL**, **Sarker S**, **Russo L**, **Rideout TC**, **Parker MD**, **Johnson BD**, **Hostler D.** Firefighter work duration influences the extent of acute kidney injury. *Med Sci Sports Exerc* 49: 1745–1753, 2017. doi:10.1249/MSS.0000000000001254.

17. **Houck J**, **McKenna Z**, **Fennel Z**, **Ducharme J**, **Wells A**, **Mermier C**, **Deyhle M**, **Laitano O**, **Specht J**, **Amorim F.** The effect of interval and continuous work on markers of acute kidney injury in a hot environment. *Eur J Appl Physiol* 122: 2437–2450, 2022. doi:10.1007/s00421-022-05030-1.
18. **Li Z**, **McKenna Z**, **Fennel Z**, **Nava RC**, **Wells A**, **Ducharme J**, **Houck J**, **Morana K**, **Mermier C**, **Kuennen M**, **Magalhaes FC**, **Amorim F.** The combined effects of exercise-induced muscle damage and heat stress on acute kidney stress and heat strain during subsequent endurance exercise. *Eur J Appl Physiol* 122: 1239–1248, 2022. doi:10.1007/s00421-022-04919-1.
19. **Schlader ZJ**, **Hostler D**, **Parker MD**, **Pryor RR**, **Lohr JW**, **Johnson BD**, **Chapman CL.** The potential for renal injury elicited by physical work in the heat. *Nutrients* 11: 2087, 2019. doi:10.3390/nu11092087.
20. **Masoud A**, **McKenna ZJ**, **Li Z**, **Deyhle MR**, **Mermier CM**, **Schlader ZJ**, **Amorim FT.** Strategies to mitigate acute kidney injury risk during physical work in hot environments. *Am J Physiol Renal Physiol* 326: F499–F510, 2024. doi:10.1152/ajprenal.00350.2023.
21. **Jacklitsch B**, **Williams J**, **Musolin K**, **Coca A**, **Kim JH**, **Turner N.** *Occupational Exposure to Heat and Hot Environments*. Atlanta, GA: NIOSH, CDC, 2016.
22. **Hess HW**, **Tarr ML**, **Baker TB**, **Hostler D**, **Schlader ZJ.** Ad libitum drinking prevents dehydration during physical work in the heat when adhering to occupational heat stress recommendations. *Temperature (Austin)* 9: 292–302, 2022. doi:10.1080/23328940.2022.2094160.
23. **Bain AR**, **Jay O.** Does summer in a humid continental climate elicit an acclimatization of human thermoregulatory responses? *Eur J Appl Physiol* 111: 1197–1205, 2011. doi:10.1007/s00421-010-1743-9.
24. **Ainsworth BE**, **Haskell WL**, **Herrmann SD**, **Meckes N**, **Bassett DR Jr**, **Tudor-Locke C**, **Greer JL**, **Vezina J**, **Whitt-Glover MC**, **Leon AS.** 2011 Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 43: 1575–1581, 2011. doi:10.1249/MSS.0b013e31821ece12.
25. **Cheuvront SN**, **Ely BR**, **Kenefick RW**, **Sawka MN.** Biological variation and diagnostic accuracy of dehydration assessment markers. *Am J Clin Nutr* 92: 565–573, 2010. doi:10.3945/ajcn.2010.29490.
26. **Manoharan G**, **Pijls NHJ**, **Lameire N**, **Verhamme K**, **Heyndrickx GR**, **Barbato E**, **Wijns W**, **Madaric J**, **Tielbeele X**, **Bartunek J**, **De Bruyne B.** Assessment of renal flow and flow reserve in humans. *J Am Coll Cardiol* 47: 620–625, 2006. doi:10.1016/j.jacc.2005.08.071.
27. **Chapman CL**, **Johnson BD**, **Hostler D**, **Lema PC**, **Schlader ZJ.** Reliability and agreement of human renal and segmental artery hemodynamics measured using Doppler ultrasound. *J Appl Physiol (1985)* 128: 627–636, 2020. doi:10.1152/japplphysiol.00813.2019.
28. **Chapman CL**, **Grigoryan T**, **Vargas NT**, **Reed EL**, **Kueck PJ**, **Pietrafesa LD**, **Bloomfield AC**, **Johnson BD**, **Schlader ZJ.** High-fructose corn syrup-sweetened soft drink consumption increases vascular resistance in the kidneys at rest and during sympathetic activation. *Am J Physiol Renal Physiol* 318: F1053–F1065, 2020. doi:10.1152/ajprenal.00374.2019.
29. **Dill DB**, **Costill DL.** Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol* 37: 247–248, 1974. doi:10.1152/jappl.1974.37.2.247.
30. **Wesson LG Jr**, **Anslow WP Jr.** Effect of osmotic and mercurial diuresis on simultaneous water diuresis. *Am J Physiol* 170: 255–269, 1952. doi:10.1152/ajplegacy.1952.170.2.255.
31. **Smith JH**, **Robinson S**, **Pearcy M.** Renal responses to exercise, heat and dehydration. *J Appl Physiol* 4: 659–665, 1952. doi:10.1152/jappl.1952.4.8.659.
32. **Radigan LR**, **Robinson S.** Effects of environmental heat stress and exercise on renal blood flow and filtration rate. *J Appl Physiol* 2: 185–191, 1949. doi:10.1152/jappl.1949.2.4.185.
33. **Chapman CL**, **Benati JM**, **Johnson BD**, **Vargas NT**, **Lema PC**, **Schlader ZJ.** Renal and segmental artery hemodynamics during whole body passive heating and cooling recovery. *J Appl Physiol (1985)* 127: 974–983, 2019. doi:10.1152/japplphysiol.00403.2019.
34. **Freemas JA**, **Worley ML**, **Gabler MC**, **Hess HW**, **McDeavitt J**, **Baker TB**, **Johnson BD**, **Chapman CL**, **Schlader ZJ.** Glomerular filtration rate reserve is reduced during mild passive heat stress in healthy young adults. *Am J Physiol Regul Integr Comp Physiol* 323: R340–R350, 2022. doi:10.1152/ajpregu.00090.2022.
35. **Petersen JCG**, **Jonassen TEN**, **Holstein-Rathlou NH**, **Petersen LG**, **Sorensen CM.** Dynamic changes in renal sodium handling during sympathetic stimulation in healthy human males. *Auton Neurosci* 250: 103131, 2023. doi:10.1016/j.autneu.2023.103131.