TEMPERATURE
2020, VOL. 7, NO. 4, 304–306
https://doi.org/10.1080/23328940.2020.1741333

Taylor & Francis
Taylor & Francis Group

FRONT MATTER: DISCOVERY

Assessing the risk of acute kidney injury following exercise in the heat: Timing is important

Comment on: Chapman, C.L., Johnson, B.D., Vargas, N.T., Hostler, D, Parker, M.D., and Schlader, Z.J. Hyperthermia and dehydration during physical work in the heat both contribute to the risk of acute kidney injury, *J Appl Physiol (1985)*, 2020. DOI: https://doi.org/10.1152/japplphysiol.00787.2019

There has been a surge of studies published in the last 10 y examining the potential for pathology related to exercise (or physical work) in the heat and the kidneys. For instance, a PubMed search using the terms "acute kidney injury" AND "exercise" revealed there were ~250 manuscripts published since 2010, exceeding the number of published manuscripts from 1950 to 2009. This notable uptick is likely related to advances in detecting acute kidney injury using novel biomarkers, a growing interest in quantifying the acute kidney injury biomarker response to prolonged endurance exercise (e.g. marathon running), and the alarming epidemiological evidence suggestive of heat-related acute kidney injury or chronic kidney disease in workers in hot outdoor environments (e.g. agricultural workers) [1,2]. Moreover, a recent meta-analysis reported that 15% of individuals who frequently work in heat stress experienced kidney disease or acute kidney injury [3].

Despite the growing interest in understanding the potential for kidney pathology during exercise in the heat, we are likely in our infancy in our collective understanding of the kinetic response of these acute kidney injury biomarkers during such physiological stressors. Scientists and health-care providers are interested in using these biomarkers to determine the etiology of pathological responses and to develop interventions to mitigate these risks. Generally, it appears that biomarkers in the blood may indicate a systemic response that may also be representative of kidney pathology (e.g. changes in kidney function), whereas acute kidney injury biomarkers in the urine are likely more specific to pathology within the kidney. In nearly all laboratory and field-based studies, changes in acute kidney injury biomarkers in response to exercise (in various environments) have been examined using blood and urine samples obtained pre- and post-exercise. Some studies have also included measurements at 24-h post-exercise. Findings from our recent study call this practice into question and suggest that the measurement intervals likely influence the resulting conclusions [4]. Thus, the purpose of this commentary is to highlight the importance of the timing in which post-exercise biological samples are collected, in relation to the cessation of exercise, so that physiological and/or pathophysiological changes in the kidneys are not missed due to improper timing of sample collections. We also suggest additional analyses to be considered in future studies that may improve our understanding of pathophysiological response in the kidneys to exercise in the heat.

In this recent study [4], we hypothesized that preventing dehydration and/or attenuating the rise in core temperature attenuates increases in acute kidney injury biomarkers during physical work in the heat compared to a nonintervention control condition. We recruited a subject population with similar demographics to those at risk for kidney disease and/or acute kidney injury during physical work in the heat [1,3]. Subjects exercised for 2 h in a hot environment (~40°C, 30% relative humidity) and received water to remain euhydrated (Water), continuous cooling via water-perfused suit (Cooling), both interventions (Water + Cooling), or no intervention (Control). Larger relative increases in acute kidney injury biomarkers were interpreted as representing an increased risk of acute kidney injury for a given trial [2]. One of the findings from this study was that in the Control trial, which elicited the greatest increases in core temperature and dehydration, biomarkers of acute kidney injury in the blood (neutrophil gelatinase-associated lipocalin, serum creatinine) were increased immediately post-exercise. However, the

response of the urine biomarkers was comparatively delayed. While increases in urine neutrophil gelatinase-associated lipocalin were observed post-exercise, increases in insulin-like growth factor binding protein 7 and albumin in the urine were not observed until 80-min post-exercise (i.e. following a recovery period). Furthermore, by the recovery period neutrophil gelatinase-associated lipocalin, insulin-like growth factor binding protein 7, and albumin were still increasing, whereas plasma neutrophil gelatinase-associate lipocalin was returning toward pre-exercise concentrations. Our lab included this recovery time-point during data collection based on speculation from our previous work that we missed the post-exercise window to detect changes in acute kidney injury biomarkers following physical work in the heat, because biological samples were only collected immediately post-exercise, during an overnight collection (~18-h period), and 24-h post-exercise [5].

The findings from our recent study support that the kinetic response of acute kidney injury biomarkers following physical work in the heat is different between blood and urine samples. Therefore, there is the potential that in previously published work, the post-exercise recovery window to detect changes in acute kidney injury biomarkers have been missed because urine samples are typically collected immediately post-exercise and, to a lesser degree, 24-h post-exercise (Figure 1). Further investigation into post-exercise recovery window for collecting biological samples is critical for understanding either the transient nature of these biomarkers or the potential for increased risk of acute kidney injury if biomarkers remained elevated during a recovery period. It is not known when urine biomarkers should be collected during this recovery period (e.g. 60-min or 120-min post-exercise). Our previous study lends support that this recovery period may be important to detecting changes in these biomarkers that are reflective of an increased risk of acute kidney injury. Notably, there are likely differences within the kinetic response of the urine biomarkers, such that the cell cycle arrest markers of insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinase 2 appear to increase in the urine before injury occurs, whereas neutrophil gelatinase-

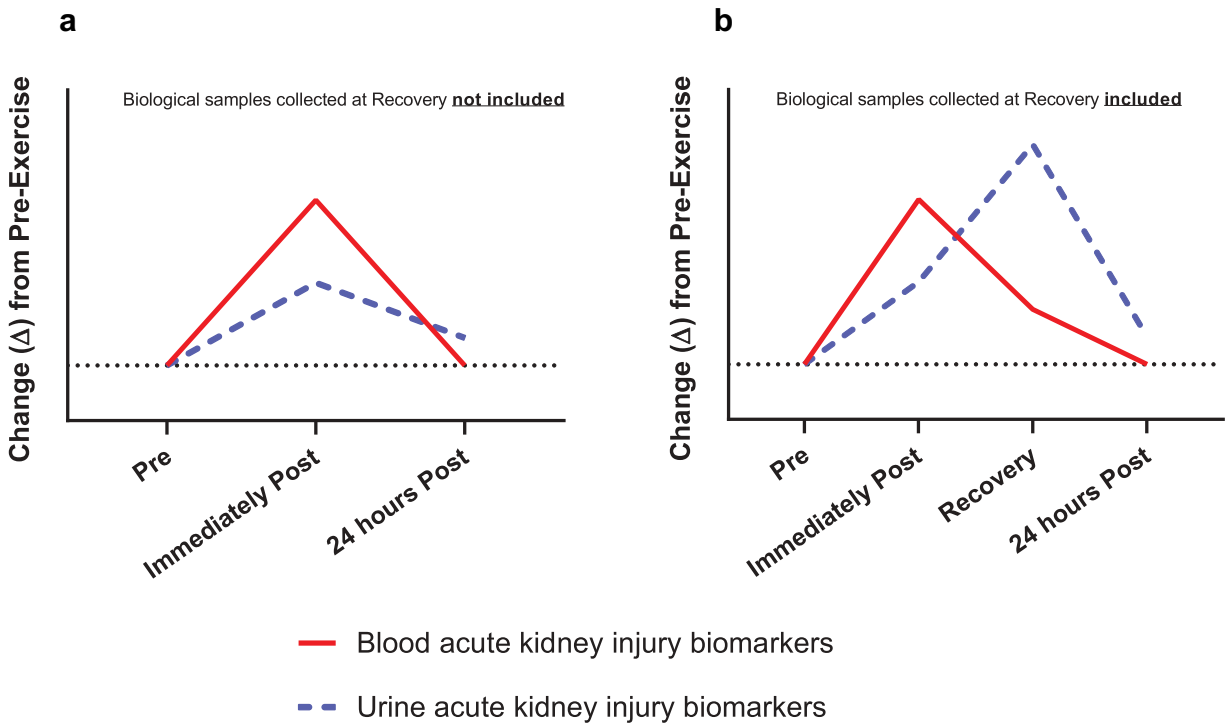

Figure 1. Illustrative model depicting the importance of the timing of when biological samples are collected for assessment of acute kidney injury biomarkers following exercise in the heat. Panel A shows a hypothetical kinetic response of acute kidney injury biomarkers based on data from our previous study in response to exercise in the heat without sample collection during a recovery period. Panel B is the same situation but includes biological sample collection during a recovery period. By contrasting Panel A with Panel B, it can be observed that the conclusions drawn regarding the influence of exercise in the heat on acute kidney injury biomarkers differ depending on when biological samples are obtained. This figure is not drawn to scale, but the illustration is modeled from data presented in Chapman et al. [4].

associated lipocalin may increase only after pathology has occurred [6]. Thus, care in study design is prudent to tease out the potential etiology of kidney pathology in response to exercise in the heat.

In addition to future studies including post-exercise recovery periods to collect biological samples, there may also be better techniques that are useful for quantifying if a pathological injury has occurred following exercise in the heat. For instance, microRNAs, which regulate protein translation, can be measured in the urine and plasma and have been previously shown to be involved with apoptosis of renal tubular epithelial cells following acute kidney injury. Interestingly, one of the mechanisms in which physical work in the heat is believed to increase the risk of acute kidney injury through reductions in renal blood flow, which creates localized hypoxia within the kidney and may exacerbate reductions in renal ATP [2]. Thus, future studies may consider testing the response of plasma miR-210, which is a microRNA upregulated by hypoxia-inducible factor-1α, to further examine a link between renal ischemia and the risk of acute kidney injury.

In summary, the purpose of this commentary was to highlight that the timing of when biological samples are collected following exercise in the heat is a critical consideration in study design. Due to the increased research examining the potential links between physical work in the heat and acute kidney injury, we suggest that future studies should include at least one recovery timepoint for collecting biological samples to decrease the risk that physiological and/or pathophysiological changes in urine acute kidney injury biomarkers are missed. We do not currently know what the kinetic response of the urine acute kidney injury biomarkers is during this recovery period. Thus, further studies are needed to determine when urine samples should be taken during the recovery period. Importantly, current workplace guidelines are in place to alleviate the heat strain and dehydration associated with physical work in hot environments, but the potential implications on the kidneys have been comparatively neglected. Therefore, understanding the recovery of these acute kidney injury biomarkers could better inform public health policies in relation to the safety of those undertaking manual labor in the heat.

References

[1] Johnson RJ, Wesseling C, Newman LS. Chronic kidney disease of unknown cause in agricultural communities. N Engl J Med. 2019;380:1843–1852.

[2] Schlader ZJ, Hostler D, Parker MD, et al. The potential for renal injury elicited by physical work in the heat. Nutrients. 2019;11:2087.

[3] Flouris AD, Dinas PC, Ioannou LG, et al. Workers' health and productivity under occupational heat strain: a systematic review and meta-analysis. Lancet Planet Health. 2018;2:e521–e531.

[4] Chapman CL, Johnson BD, Vargas NT, et al. Hyperthermia and dehydration during physical work in the heat both contribute to the risk of acute kidney injury. J Appl Physiol. 2020. DOI:10.1152/japplphysiol.00787.2019

[5] Chapman CL, Johnson BD, Sackett JR, et al. Soft drink consumption during and following exercise in the heat elevates biomarkers of acute kidney injury. Am J Physiol Regul Integr Comp Physiol. 2019;316:R189–R198.

[6] Zarbock A, Schmidt C, Van Aken H, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA. 2015;313:2133–2141.

Christopher L. Chapman
Center for Research and Education in Special Environments, Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, NY, USA
http://orcid.org/0000-0001-9717-4776

Zachary J. Schlader
Department of Kinesiology, School of Public Health, Indiana University, Bloomington, IN, USA
zschlade@indiana.edu
http://orcid.org/0000-0003-3590-3958