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Heat Stress Nephropathy and Cardiovascular Surgery-Associated Renal Failure: Similarities and Implications

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ABSTRACT

Climate changes associated with global warming are producing challenges increasingly relevant to clinicians. Rising temperatures and extended heat waves are associated with a growing incidence of a recently described condition termed heat sensitivity nephropathy. Considering all causes of acute kidney injury and chronic kidney disease, those producing renal dysfunction consequent to cardiovascular surgery may most closely overlap those tied to kidney disease following excessive chronic or acute heat exposure.

In this review, heat sensitivity nephropathy and cardiovascular surgeryrelated renal injury are characterized and compared. While both are global in distribution, the former has highest prevalence in remote, rural areas and difficult to study and quantify. Renal injury following cardiovascular surgery, occurring by contrast in relatively controlled settings, is more amenable to evaluation of diagnostic approaches, prognostic indicators, and potential treatments. Such findings may ultimately apply not only to surgically related kidney damage but to heat sensitivity nephropathy as well.

Despite many studies addressing post-cardiovascular surgery renal failure, no single management method has emerged as definitively superior. Nonetheless, reasonably standardized worldwide conduct of cardiac and vascular surgery provides fertile conditions for research that could lead to improved diagnostic and therapeutic approaches. Such findings may ultimately apply to not only surgically related renal injury but perhaps also to heat sensitivity nephropathy.

Instead of anticipating discovery of major isolated preventative or treatment methods applicable to either cause of renal failure, it is more realistic that a series of marginally successful measures employed in combination will engender the most nearterm progress. Potentially complimenting currently available options is biomarker analysis that may better guide both renal injury diagnosis and treatment efficacy assessment.

Keywords: heat sensitivity nephropathy; cardiovascular surgery-associated acute kidney injury; chronic kidney disease; end stage renal disease; biomarkers

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Introduction:

Climate changes secondary to global warming are producing challenges increasingly relevant to clinicians. Rising temperatures and extended heat waves are closely associated with a growing incidence of the recently described condition termed *heat sensitivity nephropathy*. Though seemingly of disparate causation, renal damage consequent to cardiovascular surgery may more closely resemble that appearing in laborers exposed to excessively high environmental temperatures than renal injury produced by any other cause.

In this review, heat sensitivity nephropathy and cardiovascular surgery related renal injury are characterized and compared. While both are global phenomena, the former has highest prevalence in remote, rural areas and is difficult to study and quantify. Renal injury following cardiovascular surgery, occurring by contrast in relatively controlled settings, is more amenable to evaluation of diagnostic approaches, prognostic indicators, and potential treatments. Such findings may ultimately apply not only to surgically-related kidney damage but to heat sensitivity nephropathy as well.

Materials and Methods:

This article is based on review of the current literature pertaining to heat sensitivity nephropathy and renal injury occurring as a complication of cardiovascular surgery. Searches were conducted through PubMed (www.ncbi.nlm.nih.gov/pubmed) and Google using relevant key words, as well as consulting one recently published textbook.[5]

Results and Discussion:

Climate alterations due to a warming planet are progressively posing challenges to global clinical care provision.[1-3] Increasing duration and intensity of drought conditions compromise food production, with prevalence of malnutrition rising in numerous parts of the world. Closely related is the growing scarcity of potable water with harmful impact on populations across large geographic regions. Diminishing food and water availability is, in many countries, adversely affecting their population's general wellbeing, resistance to disease, and ability to recover from illness or injury.[3,4]

Moreover, the increasing number and worsening severity of extreme weather events across the globe are placing a considerable strain on healthcare systems that are in many instances already stretched thin. Hurricanes and other major environmental perturbations disrupt hospital and outpatient health center operations, wreak havoc on communications, and produce mass casualty situations—all exerting to varying degrees serious pressures on healthcare providers, their supporting infrastructures, and related ancillary services. Relevance of much of this to surgeons worldwide has recently been emphasized by leading surgical organizations[1, 2]

Beyond the destructive effects of anomalous weather patterns, the progressive rise in both mean global temperatures and unprecedented heatwaves is associated with spreading and/or new vector-borne diseases and other illnesses.[1] With respect to the latter, a disease entity termed *heat stress nephropathy* (HSN) has recently been described. Indeed, this might be considered one of the first non-infectious global epidemics resulting from climate change.[3, 5]

HSN connotes a circumstance whereby kidney injury results from an individual's chronic and/or acute exposure to excessively high environmental temperatures and concomitant dehydration. Predominantly striking outdoor workers, the deleterious effects of laboring under extremely hot conditions are compounded by inadequate water consumption, insufficient electrolyte replacement, infrequent rest breaks, and prolonged exposure to direct sunlight.[3, 5] Seemingly straightforward measures such as curtailing continuous heat exposure duration, reducing work pace, and increasing appropriate fluid intake are often at odds with sociopolitical forces operative in many locales.[5] Policies placing the onus on field workers to manage their own wellbeing, though perhaps well-intentioned, can be

counterproductive by assuming there is leverageable personal agency where little in fact exists.[5]

HSN is a global yet primarily rural phenomenon. This limits researchers' ability to fully characterize its features, extent, and impact (individual, social, and general economic). Unfortunately, chronic kidney disease (CKD) and end-stage renal disease (ESRD) show an increasing but likely underreported incidence globally as a direct consequence of climate change intensification. In many cases, preexisting conditions such as diabetes and hypertension augment one's susceptibility to the harmful effects of excessive heat exposure and dehydration.[3,5] Workers' limited autonomy and other social factors appear to contribute substantially.[5]

Despite HSN's occurrence in diverse and often remote geographic areas, the condition's multiple synergistic causes and resulting renal damage have already been reasonably well described. It has long been known that acute kidney injury (AKI) can occur secondary to heat stroke.[6] More recently, an upsurge in CKD cases of an apparently distinct etiology has been noted among workers in some of the world's hottest locations, including California's Central Valley, Central America, southern Mexico, northern Africa, the Middle East, and South Asia (particularly India, Sri Lanka, and Thailand).[3]

Prior to accumulation of stronger evidence supporting heat exposure as the principal causative factor, terms such as *Mesoamerican nephropathy* and *Sri Lanka nephropathy* were coined. Exposure to toxins such as heavy metals and/or agrochemicals had initially been considered the primary cause AKI and CKD in those settings. High environmental temperatures and dehydration were acknowledged as possibly exacerbating a toxic insult, even as their precise roles remained uncertain. However, lack of increased renal failure incidence in milder climes despite laborers' contending with similar ambient pesticide and toxic metal levels suggests a lesser (though possibly still contributory) etiologic role for toxins.[3]

A common thread in the rising global occurrence of nephropathy now appears to be extreme work intensity combined with repetitive and/or acute exposure to excessive heat; thus the term *heat stress* nephropathy. Mesoamerican nephropathy may have emerged nearly a half-century ago, but the Central American renal failure incidence has increased in close association with an increasing annual number of extremely hot days and heatwave durations. When environmental temperatures exceed 35ºC (95ºF), humans lose their ability to maintain body temperature within a few hours or less of vigorous work. In recent years, field temperatures in many world regions have commonly far exceeded that, and for lengthening time periods.[3-5]

Convergence of extremely hot surroundings, prolonged physical exertion, and grossly inadequate intake of condition appropriate fluids sets the stage, at minimum, for profound dehydration and renal malperfusion. Previously, AKI from this mechanism was considered a mainly pre-renal insult and, absent severe heat stroke, believed fully reversible in most cases through sufficient rehydration.[3] However, clinical studies of workers from Central America, India, and elsewhere provide details as to a more complex situation expressed as HSN. Repetitive severe heat exposures and chronically inadequate hydration together appear to produce CKD in many instances, often with progression to ESRD.[3-5]

Heat stress-related dehydration acutely produces a hyperosmolar state leading to hypotension, confusion, and renal ischemia. Limited access to water and/or laborers' circumspection over accessible water's safety adds insult to injury. Consumption of soft drinks, fruit juices, and energy beverages, if available, often only worsens serum hyperosmolarity. Preexisting chronic illnesses such as diabetes mellitus (DM) and hypertension (HTN), when present, augment an individual's susceptibility to AKI and/or development of CKD. Medications such as certain antihypertensives, and indiscriminate use of nonsteroidal anti-inflammatory agents (NSAIDs), likely contribute in some cases. Further, marked

heat stress can provoke rhabdomyolysis and systemic myoglobin release, which can amplify the renal insult.[3-5]

Predictably, dehydration-related hypovolemia activates the renin-angiotensin-aldosterone system, altering renal perfusion and promoting sodium reabsorption at the expense of potassium and hydrogen ions. Compensatory sympathetic nervous system activation occurs in response to significantly decreased circulating blood volume. With progression to AKI, laboratory evaluation demonstrates serum creatinine (SCr) elevation and abnormal expression of numerous biomarkers reflecting renal damage. Commonly present as well are hyperuricemia, hypokalemia, and/or mild anemia; urinalysis shows absent or low-grade proteinuria, uricosuria, and (sometimes) microscopic hematuria. Accrued renal biopsy results from affected populations reveal marked tubular atrophy, interstitial fibrosis, glomerulosclerosis, but only mild inflammation.[3-5]

The renal damage appears to be more prominent at the tubular than glomerular level, consistent with dehydration as a major cause.[5] Similar pathological patterns are present in kidneys obtained from experimental animals under conditions modeling HSN.[7] One proposed underlying mechanism relates to dehydration-linked serum hyperosmolarity and aldose reductase/fructokinase pathway activation. Fructokinase-catalyzed transformation of glucose into fructose in the proximal tubule is thought to cause tubular injury through release of oxidants. Together with varying degrees of circulating vasopressin elevation, hypokalemia, and rhabdomyolysis, dehydration-related changes are postulated to provoke the AKI and CKD correlated with HSN, particularly when superimposed on a background of cardiovascular disease (previously diagnosed or unrecognized).[8]

To put HSN in context, it is useful to consider the full range and expression of acute and chronic renal dysfunction. While review of the broader topic of renal failure is beyond the scope of this article, a number of recent comprehensive AKI update reviews have appeared in the literature.[9,10] The time-honored distinction between of pre-renal, renal, and post-renal causes has retained its usefulness. While further differentiation of renal disease causes varies from one source to another, a common construct is to separate etiologies into four categories: 1) decreased renal perfusion, 2) urinary tract obstruction 3) parenchymal kidney disease other than acute tubular necrosis (ATN), and 4) ATN.

HSN has elements of the first and last categories, whereas it really does not involve the obstructive or severe inflammatory features represented by the second and third categories, respectively.[3] Though increasingly recognized as a distinct renal disease form, HSN does not yet appear on lists of AKI-associated conditions appearing in most contemporary review articles.[9,10] Irrespective of its cause, AKI is characterized by a decrease in glomerular filtration rate (GFR) of rapid onset, the consequences of which being expressed to varying degrees as intravascular volume overload, serious electrolyte disturbances, impaired drug and toxin elimination, and uremic complications.[9,10] Some elements of sepsis-related nephropathy are similar to those of HSN, but the profoundly intense inflammatory milieu associated with the former suggests that the two conditions share fewer aspects than those separating them[3,11].

Table 1 summarizes the factors contributing to HSN.

Of all the AKI and CKD causes, it could be argued that renal dysfunction as a complication of cardiovascular surgery (CVS) most closely resembles that of HSN in pathophysiologic terms. For decades, AKI has been a dreaded and all too frequent outcome after cardiac, aortic, and peripheral vascular surgery. Some degree of renal dysfunction is noted in as many as 30% of patients following heart surgery.[12] CVS-related AKI (CVS-AKI) has consequently been the subject of considerable study over the past several decades.[12-14] With the global reach of CVS constantly expanding, there has been a growing appreciation for the complex influences of social and environmental factors on development and

progression of cardiovascular disorders and many other diseases.[2] Also, when either CVS-AKI or HSN results in CKD and ESRD in developing countries, availability of advanced critical care facilities, renal replacement therapy, and other supportive resources may be quite limited, rendering the renal failure particularly lethal.[2]

Thus for both HSN and CVS-AKI there are often key contributing social forces at play.[2,3,5] While in each category there may be converging chronic diseases that heighten the risk of renal injury after an intense physiologic insult (e.g., excessive heat exposure/dehydration or major cardiovascular operation), an individual's sociopolitical circumstances can be significantly impactful as well. Originating in medical anthropology, the concepts of a *biosocial complex* and a *syndemic model of health* are now embraced by many medically related disciplines.[15] While the term "syndemic" generally refers to clustering of two or more diseases within an at-risk population (e.g., AIDS plus tuberculosis), the model can reasonably be extended to include attempted surgical remediation of cardiovascular disease under sociopolitical constraints, as well as HSN with its particular backdrop as noted.[2,3,5]

Table 1: Contributors to HSN

Extreme and repetitive occupational heat exposure	Complicating effects of certain antihypertensive medications (ACEIs, ARBs)
Acute and/or chronic dehydration	Indiscriminate NSAID use
Altered renal hemodynamics (malperfusion)	Myoglobinemia
Inadequate and/or inappropriate fluid ingestion	Exposure to environmental toxins
Underlying chronic diseases (DM, HTN)	Sociopolitical factors

Globally, millions of patients undergo CVS each year.[2] The well-established risk factors for development of cardiovascular disease, either individually or in combination, are HTN, DM, hyperlipidemia, and tobacco use. With or without recognizable predisposing factors for AKI, CVS in its various forms can impose significant physiological stress on the kidneys.[12-14] The predominant impact results from altered renovascular hemodynamics during both cardiac and major non-cardiac vascular surgery. Cardiopulmonary bypass (CPB), despite maintaining cardiac output, transiently upsets through its characteristic non-pulsatile flow the normal balance between renal cortical and medullary blood flow. A paradox occurs whereby increased cortical perfusion under CPB can drive up medullary oxygen consumption in support of increased solute transport that in the process produces corticomedullary ischemia .[12] Aortic manipulation (e.g., cannula placement, suprarenal cross-clamping) can alter renal blood directly through reducing perfusion pressure or indirectly via liberation of atheroemboli which can occlude small renal blood vessels and incite production of harmful inflammatory mediators[12-14]

Often placing CVS patients at increased risk for AKI and CKD, either independently or in combination, are preexisting diabetes and hypertension, baseline subclinical renal disease, and proximate contrast agent exposure.[12-14] During and immediately following general anesthesia administration and conduct of CVS, sympathetic nervous system activation along with elevated circulating catecholamines further alter renal hemodynamics, as does routine infusion of vasoactive agents. Provision of the latter is commonly necessary to support cardiac function, but also to mitigate a degree of cytokine-induced vasoplegia result from exposure of blood to the internal lining of CPB circuitry.[12,13] So too can blood elements can be traumatized by the pump, oxygenator, filters, and cardiotomy suction catheters. Plasma-free hemoglobin (PFH) derived

from damaged erythrocytes and associated iron liberation can adversely impact renal blood flow through separate mechanisms.[12-14] The contribution of PFH to CVS-AKI is perhaps reminiscent of the circulating pigment (myoglobin) effects appearing at times to intensify HSN. As with HSN, elevated serum osmolality with or without hyperglycemia can occur during CVS and for hours or days thereafter, producing its own negative renal effects.[3]

Though a lot is known about the causes of CVS-AKI, much remains to be determined as to its prevention, diagnosis, and treatment. Contemporary lists of medications to either avoid or use with caution preoperatively and in the initial postoperative period include angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, metformin, and nonsteroidal anti-inflammatory drugs (NSAIDS).[12,13] Relevant clinical studies are conflicting, however, precluding definitive statements on exactly which agents to withhold or limit. Likewise, trials designed to determine efficacy of a particular pharmacological or non-pharmacological approach toward mitigating CVS-AKI have yielded inconsistent results.[12,13] While, for instance, calcium channel blockers and fenoldopam seem through different mechanisms to have theoretical benefits on renal blood flow in the early postoperative period, hypotension associated with their use may cancel out any positive effects.[12]

Similarly, early promise of off-pump coronary artery bypass techniques to, among other potential advantages, eliminate the ill effects of CPB and aortic cross clamping has generally been negated by hypotension and reduced renal blood flow consequent to transiently impaired cardiac output.[12-14] The latter occurs when positioning the heart in hemodynamically disadvantageous positions for performance of distal anastomoses. Even with the advent of trans-catheter aortic valve replacement (TAVR) with avoidance of both CPB and “unnatural” cardiac positioning, renal benefits remain uncertain despite far lesser TAVR-related hemodynamic and inflammatory consequences.[12]

Emerging from the 20th International Consensus Conference of the Acute Disease Quality Initiative (ADQI) Group in 2017 was a comprehensive review of studies on CVS-AKI’s pathophysiology, risk predictors, diagnostic criteria, and potential therapies.[13] A limited number of evidence-based guidelines emerged. General preventive measures with relatively high levels of supporting evidence include: limiting perioperative blood glucose level variability, provision of balanced crystalloid solutions rather than hypertonic ones, judicious transfusion of blood/blood products, preoperative discontinuance of ACE inhibitors and ARBs, use of a postoperative Kidney Disease Improving Global Outcomes (KDIGO) diagnostic bundle, and employment of a low-tidal volume ventilator strategy.

AKI scoring systems, such as of the KDIGO,[16] hinge on urine output and serial serum creatinine (SCr) measurements. AKI is characterized by a rise of SCr from baseline by 0.3 mg/dl (26.5 mol/l) within 48 hours of surgery, a SCr increase from baseline of 50% within one week of surgery, or a decreased urine output to less than 0.5 ml/kg/hour for at least 6 hours. The combination of SCr analysis and urine output together provide is more diagnostically precise than either metric considered alone. Yet even when taken together, the relative lack of sensitivity and specificity of both can compromise the timeliness and accuracy of AKI diagnosis and assessment of therapeutic measures. Serum and urine biomarker levels hold promise in that they more rapidly and specifically reflect the degree of renal injury occurring after an acute insult.[10,12,13]

The two main categories are those proteins released by the injured kidney, and the other being those filtered by the kidney (thereby reflecting changes is glomerular function).[12] More specifically, recently identified AKI-related biomarkers appear allow distinction between glomerular filtration impairment, overall glomerular integrity, tubular stress, tubular damage, and generalized renal inflammation.[10] Markers of parenchymal injury (NGAL, KIM 1, IL-18, NAG, GST, TIMP, and IGFBP, among others) and glomerular

function (cystatin C) rise in both plasma and urine quite soon after AKI, representing a timelier window on the state of affairs as compared to slowly rising (and falling) SCr.[10,12] Validation of biomarkers' clinical usefulness for AKI diagnosis and renal function tracking has been marginal to date, but a diagnostic panel employing markers of growth-phase cell cycle arrest (urinary) tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) has been marketed as Nephrocheck® (Ortho Clinical Diagnostics) and integrated into clinical use, as have kits utilizing cystatin C and NGAL. Indeed, the Acute *Dialysis* Quality Initiative Group has recommended use of urine output, SCr (and ratios utilizing it), and renal damage biomarkers to better more accurately diagnosis and follow AKI.[10]

Once the diagnosis of CVS-AKI has been established, recommended goals are to optimize cardiac function, avoid potentially renal-toxic medications and those unproven to provide renal benefit, and when need for renal replacement therapy (RRT) is established initiate it early rather than later.[12,13] Lastly, nutritional support in CVS-AKI cases is considered essential, as malnourished patients experience increased mortality relative others who develop postoperative renal failure. Recommended is ensuring provision to such patients of 20-30 kcal/kg/day, with increased protein provision if RRT is needed.[13] Other therapies currently being evaluated (e.g., remote ischemic preconditioning and provision of mesenchymal stem cells) may be of benefit in preventing or treating AKI, but verification of their efficacy awaits further clinical testing.[12]

Table 2 summarizes the factors contributing to CVS-AKI:

Table 2: Contributors to CVS-AKI

CPB, aortic cross-clamping, hemodynamically disadvantageous positioning (off-pump)	Complicating effects of certain antihypertensive medications (ACEIs, ARBs)
Altered systemic hemodynamics	Indiscriminate NSAID use
Compromised renal perfusion	Circulating free hemoglobin, cytokines
Transient hyperosmolar state	Proximate intravascular contrast exposure
Underlying chronic diseases (DM, HTN)	Social factors (severe resource limitations in some regions)

Given considerable pathophysiological overlap between CVS-AKI and HSN, it is possible that discoveries found beneficial in prevention and/or treatment of the former may be applicable to the latter. The two entities are obviously not the same. Farmworkers are subjected neither to CPB nor aortic cross-clamping, and cardiovascular surgery patients are *largely* free of the sociopolitical factors contributing to HSN. Nonetheless, it may be reasonable to conclude the following:

1) As in CVS-AKI, it may be prudent for ACE inhibitors and ARBs to be avoided, and NSAID use minimized, in treatment of laborers at predictably at high risk of exposure to acute or chronic dehydration due to typically prolonged exertion at excessively high temperatures.

2) Isotonic replacement fluids, as opposed to hypertonic ones, should be utilized preferentially in both the case of HSN and CVS-AKI.

3) If utility and cost-effectiveness of urine biomarker kits for diagnosis and acute tracking of CVS-AKI become general accepted, their use by physicians caring for HSN-at-risk workers should be seriously considered so as to improve diagnostic capabilities and better gauge intervention efficacy.

4) The value of adequate nutritional support during treatment of CVS-AKI has been reasonably

well established. It is probable that similar provision of high-quality nutrients and sufficient caloric/protein intake would benefit the HSN population as well.

5) Given much greater ease of performing clinical studies in the CVS-AKI group, a practical approach for providers caring for patients with or at risk for HSN would be to monitor progress in prevention, diagnosis, and treatment of CVS-AKI and extrapolate, within reason, lessons learned in that area.

6) Similar to CVS-AKI, a series of marginal advances in combination is more likely to realize substantive benefit than one single approach (e.g., some new pharmacological agent). While medical progress is sought in both areas, it is recognized that improvement on the sociopolitical fronts in various global regions holds tremendous potential to mitigate the growing worldwide burden of HSN. But as climate change continues its march in an ever more threatening direction, the search for *medical* strategies to better diagnose, prevent, and treat HSN remains essential.

Table 3 summarizes a multifaceted approach to both HSN and CVS-AKI:

Table 3: Multifaceted Approach to Both HSN and CVS-AKI

Avoidance of ACEIs and ARBs in populations at risk; judicious NSAID use
Isotonic fluid replacement; minimization of serum hyperosmolarity
Improved nutritional support
Application of urinary biomarker testing for diagnosis and treatment progress monitoring
Potential application of future CVS-AKI research findings to HSN diagnosis and treatment
Attention to aggravating sociopolitical factors

Conclusion:

While clearly representing distinct entities, there are pathophysiological similarities between HSN and CVS-AKI (and CKD). Given that, approaches validated as helpful in the latter case should at least be considered as potentially applicable to the former. Mitigation of HSN through medical means offers some hope, although its prevention through well-conceived, implementable, and enforceable public policy would be preferable. Absent that in many jurisdictions, application of knowledge from the CVS sphere could provide at least some benefit toward prevention and management of HSN.

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