Epithelial transport during septic acute kidney injury

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ABSTRACT

A goal for scientists studying septic acute kidney injury (AKI) should be to formulate a conceptual model of disease that is able to coherently reconcile the molecular and inflammatory consequences of sepsis with impaired epithelial tubular function, diminished glomerular filtration rate (GFR) and ultimately kidney failure. Recent evidence has shed light on how sepsis modulates the tubular regulation of ion, glucose, urea and water transport and acid–base homeostasis in the kidney. The present review summarizes recent discoveries on changes in epithelial transport under septic and endotoxemic conditions as well as the mechanisms that link inflammation with impaired tubular membrane transport. This paper also proposes that the tubular dysfunction that is mediated by inflammation in sepsis ultimately leads to increased sodium and chloride delivery to the distal tubule and macula densa, contributing to tubuloglomerular feedback and impaired GFR. We feel that this conceptual model resolves many of the physiologic and clinical paradoxes that septic AKI presents to practicing researchers and clinicians.

Keywords: AKI, ion transport, sepsis, toll-like receptor, tubuloglomerular feedback

INTRODUCTION

Acute kidney injury (AKI) is a very common and especially formidable clinical problem facing acute care physicians. The most common cause of AKI in hospitalized patients is sepsis [1], and AKI is not uncommon even in non-severe sepsis where hemodynamic changes are not readily apparent [2]. Despite its ubiquity in the hospital, historically little is known about how the basic epithelial transport mechanisms that modulate solute, volume and urea clearance are affected by sepsis-induced AKI. A goal for scientists studying septic AKI, and for this review, is to formulate a conceptual model of disease that is able to coherently reconcile the molecular and inflammatory consequences of sepsis with impaired tubular function, diminished glomerular filtration rate (GFR) and ultimately kidney failure.

Experiments performed over the past 20 years that we will review have started to shed light on how sepsis modulates tubular transport function. Here we propose a model that links septic inflammation and tubular transport dysfunction with impaired GFR and kidney failure. For example, there has been a renewed interest over the past 5 years in the role of chloride in septic AKI [3]. Recent large clinical trials have shown that an increased serum chloride concentration may have a deleterious effect on overall kidney function, especially in septic patients [4, 5]. Tubular transport would be directly involved in these deleterious effects as septic AKI is mediated in part by tubular processes that increase chloride delivery to the distal tubule, and we suggest that this phenomenon may play a key role in overall organ dysfunction.
system [7]. Through this macula densa-mediated mechanism, decreased kidney perfusion leads to increased efferent and decreased afferent arteriolar vasoconstriction that increases GFR [7]. When there are increased levels of chloride sensed by the macula densa, the opposite phenomenon occurs, leading to decreased GFR [6]. Subsequent studies have confirmed that high solute concentrations and flow rates of chloride distal to the proximal tubules lead to manipulation of tubuloglomerular feedback, ultimately diminishing GFR (Figure 1) [8–10].

The potentially deleterious effects of increased distal chloride delivery do not seem limited to kidney hemodynamics [3]. In cell culture models, chloride-rich microenvironments have been shown to be pro-inflammatory, leading to increased nitric oxide (NO) release, interleukin-6-interleukin-10 (IL-6: IL-10) ratios and NF-κB DNA binding [13]. In vivo models of sepsis involving rats have also demonstrated that resuscitation with high chloride-containing solutions promote a pro-inflammatory state with increased levels of IL-6, IL-10 and tumor necrosis factor-alpha (TNF-α), even in normotensive rats [14]. Chloride infusion upregulates thromboxane- and cyclooxygenase-mediated renal arterial vasoconstriction [15]. Finally, in isolated perfused rat kidneys, higher concentrations of chloride have been shown to significantly potentiate the vasoconstrictive effects of angiotensin II [16]. It is likely that processes in sepsis—dependent of systemic chloride levels—that increase distal tubular chloride exposure lead to impaired renal function via both hemodynamic and inflammatory processes (Figure 1).

**Tubular Sodium, Potassium and Chloride Transport Regulation in Septic AKI**

Inflammation, one of the hallmark physiologic mediators of sepsis, can severely impair the intricate tubular mechanisms responsible for sodium, potassium and chloride regulation, even in the setting of normal cellular perfusion. The impairments can all lead to increased distal chloride delivery, impairing GFR and overall renal function. Schmidt et al. [11, 12] have shown significant downregulation of Na⁺/H⁺ exchanger 3 (NHE3), Na⁺/K⁺-ATPase, renal outer medullary K⁺ channel (ROMK), epithelial Na⁺ channel (ENaC), Na⁺−K⁺−Cl⁻cotransporter 2 (NKCC2), Na⁺−Cl⁻ cotransporter (NCC), kidney specific chloride channel -1 and -2 (CLK-1 and -2) and Barttin expression in an in vivo model of rat sepsis induced by intraperitoneal injection of liposaccharide (LPS). This finding has been reproduced independently with comparable models showing downregulation of NKCC2 and NHE3 [17, 18]; however, in one of the studies, the α-subunit of ENaC showed increased expression in response to LPS in the inner stripe of the outer medulla (ISOM) (β-ENaC was downregulated) [18]. The upregulation of the α-subunit of ENaC in the later study might be explained by the fact that measurements were taken at 6 h (as compared with at 6, 12 and 24 h in the Schmidt study), when increased levels of aldosterone might still be able to overwhelm only partially impaired transporters [12, 18]. A similar pattern of near ubiquitous downregulation of all tubular sodium transporters has been seen in multiple ischemia–reperfusion models of AKI as well [19–21]. In Schmidt’s model there was preserved arterial blood pressure with a lower dose of LPS, yet the downregulation of transporters was still observed [11, 12].

The decrease in sodium, potassium and chloride transport proteins in response to LPS corresponds with a markedly increased fractional excretion of sodium and chloride [11, 12]. The increased distal chloride delivery may also be due in part to a reduction in paracellular chloride reabsorption as well as significantly elevated levels of IL-1β, TNF-α and interferon-gamma (IFN-γ) (see Figures 1 and 2).

Interestingly, knockout mice that are deficient in TNF-α, IL-1 or IFN-γ do not show any resistance to downregulation of the sodium, potassium or chloride transport proteins in response to LPS, indicating that perhaps multiple overlapping processes are involved (such as the TLR-4-mediated pathways) [11, 12]. In these same experiments, however, glucocorticoid treatment leads to inhibition of all three cytokines after exposure to LPS, with subsequent attenuation of all sodium, potassium and chloride transport protein dysfunction [11, 12]. Glucocorticoids are known to stimulate ENaC and ROMK through serum- and glucocorticoid-inducible kinase (SGK-1) [39] and so this may have counteracted any potential LPS-mediated downregulatory process (Figure 2).

There have been a number of proposed mediators that could link systemic inflammatory mediators such as TNF-α, IL-1 and LPS with impaired epithelial transport function, but much evidence points to a direct role for cyclooxygenase and prostaglandins, especially as mediators of distal sodium and chloride delivery. Rats exposed to exogenous IL-1 exhibit marked natriuresis and diuresis [40–46], and this physiologic phenomenon is largely due to sodium wasting in the cortical collecting duct [44, 45]. This change is accompanied by a corresponding increase in urinary prostaglandin E (PGE2) excretion and is inhibited by pre-treatment with a cyclooxygenase inhibitor, suggesting a possible role for PGE2 in the mechanisms connecting IL-1 with impaired sodium transport in the distal tubule (Figure 2) [40]. While various experiments have demonstrated a similar role for PGE2 on sodium handing in the thick ascending limb of Henle’s loop [42, 44, 46] and cortical collecting ducts [44], other experiments have failed to show a concomitant increase in prostaglandin synthesis in response to IL-1 administration [41]. In most of these experiments (but not all [43]), treatment with cyclooxygenase inhibitors such as indomethacin mitigated salt wasting in hyperinflammatory models of kidney injury [40–42, 46]. Chloride-mediated changes in renal hemodynamics also seem to be directly regulated by products of cyclooxygenase and thromboxane synthetase [15]. In this work using a rodent model, Bulivant et al. [15] demonstrated that hyperchloremia reduced GFR by over 30%, and this effect could be prevented by pretreatment with either indomethacin or thromboxane antagonists.

The mechanistic consequences of implicating PGE2 and other prostaglandins in septic AKI are profound because there are so many potential targets for intervention associated with these mediators. For instance, in the proximal tubule, cyclic
**FIGURE 1:** Proposed mechanism for linking impaired solute transport with decreased GFR. Pro-inflammatory cytokines cause a downregulation of renal chloride entry transport proteins—specifically CLCK-1, CLCK-2, and Barttin—during sepsis [11], increasing distal delivery of chloride. Tubular dysfunction of sodium transport proteins, especially the downregulation of NHE3, Na⁺/K⁺-ATPase, ROMK, NKCC2 and NCC, also generates an increase in the lumen sodium concentration, and thus overall increases lumen positive potential [12]. This causes a decrease in paracellular chloride reabsorption, which ultimately leads to further increased chloride delivery to the thick ascending limb. The net effect is tubuloglomerular feedback and reduced GFR in that nephron.

**FIGURE 2:** Proposed overview of ion channel regulation during septic AKI. Inflammatory mediators such as LPS, IL-1 and TNF-α activate various prostaglandin pathways (COX), leading to increased levels of PGE2. Increased PGE2 levels can modulate intracellular calcium stores as well as stimulate multiple downstream mediators including cAMP. In the proximal tubule, cAMP has been shown to indirectly inhibit NHE3 via PKA phosphorylation of the NHE regulatory factor NHERF-1 [22], which could lead to natriuresis secondary to PGE2-mediated stimulation of cAMP generation from cytokines [23]. More distally, increased intracellular calcium levels may decrease NHE3, NKCC2, ENaC and NCC activity, all via PKC-mediated processes [24–28]. In the distal convoluted tubule and cortical collecting duct, vasopressin, aldosterone and AMPK regulate ENaC [29–31] and aldosterone regulates NCC [32, 33]. These effects are mediated at least in part by Nedd4-2 [29–34], and these processes directly involve cAMP/PKA for vasopressin [35, 36] and SGK-1 for aldosterone [32, 37]. IKKβ has been shown to stimulate ENaC via Nedd4-2 phosphorylation [38], bringing forth a potential link between sepsis-mediated TLR-4 and sodium transport. The net effect of global ion channel downregulation is an increase in luminal sodium concentration, a decrease in lumen negative potential, less paracellular chloride reabsorption and increased distal chloride delivery.
adrenosine monophosphate (cAMP) has been shown to indirectly inhibit NHE3 via protein kinase A (PKA) phosphorylation of the NHE regulatory factor NHERF-1 [22], which could lead to natriuresis secondary to PGE2-mediated stimulation of cAMP generation from cytokines (Figure 2) [23]. PGE2 has also been shown to inhibit sodium reabsorption by increasing intracellular calcium levels, which may have direct inhibitory effects on the Na+/K+-ATPase and apical sodium transport proteins or indirect effects on sodium transport via protein kinase C (PKC)-mediated processes in the collecting duct [24–27]. This modulation of sodium transport via PGE2 and calcium sensing has also been demonstrated in the thick ascending limb involving the NKKC2 cotransporter [28]. In rabbit cortical collecting tubules, PGE2 administered in isolation has been shown to increase cAMP levels [47]. However, when co-administered with vasopressin, PGE2 decreases cAMP levels, leading to sodium wasting [47–49], as cAMP causes an increase in apical membrane sodium transport [50]. Other mechanisms have been proposed connecting cAMP to ENaC activation [49, 51, 52] as well as apoptosis in distal convoluted tubules via regulation of potassium channels [53].

The link between septic AKI and apical sodium handling in the distal convoluted tubule and cortical collecting duct likely also involves the E3 ubiquitin ligase Nedd4-2 (Figure 2). The influences of both vasopressin, aldosterone and AMP-activated kinase (AMPK) on ENaC [29–31] and aldosterone on NCC [32, 33] are mediated at least in part by Nedd4-2 [29–34]. These processes directly involve cAMP/PKA for vasopressin [35, 36] and serum glucocorticoid regulated kinase-1 (SGK-1) for aldosterone [32, 37], which could also be related to PGE2 regulation as discussed above [54–56]. There is some recent evidence likewise suggesting cross-talk between the Nedd4-2 pathway of sodium regulation and NF κ B, 1κ B-kinase-β (IKKβ) has been shown to stimulate ENaC via Nedd4-2 phosphorylation [38], certainly bringing forth a potential link between sepsis-mediated toll-like receptor-4 (TLR-4) and sodium transport. In mouse CCD cells, LPS and TNF-α acutely promote basolateral Na+/K+-ATPase activation via cAMP-independent PKA activation, which ultimately increases sodium transport [57]. However, after 12–24 h it has been shown that activation of the NF-κB pathway transcriptionally downregulates SGK-1 expression, leading to a more chronic impaired ENaC function and the ultimate sodium wasting that is seen in septic AKI [58]. Aldosterone and endotoxin have been shown to independently activate NF-κB, thereby regulating SGK-1 in the collecting duct [58, 59]. It is clear that PGE2, cAMP and the other mediators mentioned above could play a role that interferes with those processes in septic AKI, leading to profound alterations in sodium and chloride handling.

The role for inflammation leading to downregulation of sodium transport proteins has been reinforced by a recent study by Cantaluppi et al. [60]. In primary human proximal tubule epithelial cells exposed to human septic plasma, NHE3, the tight junction protein-1 zonula occludens-1 (ZO-1) and the diffusive glucose transporter (GLUT-2) levels were decreased [60]. However, decreased expression of these transporters was abrogated when a number of inflammatory mediators—including TNF-α, CD154 and Fas-L—were effectively filtered from the plasma by Amberchrom resin adsorption [60].

The idea that tubular impairment in solute handling can be ameliorated by broad manipulation (or impairment) of the inflammatory milieu is not new. After multiple clinical trials failed to show any benefit from single anti-cytokine treatment [61–63], there was a renewed interest in using steroids to treat sepsis. However, high-dose methylprednisolone does not improve survival, and may actually worsen outcomes by increasing susceptibility to secondary infections [64]. While controversial, there are some studies that suggest lower dose steroids may be beneficial in sepsis [65], as well as in patients with functional adrenal insufficiency [66]. In rat models of septic AKI, low-dose steroids have been shown to limit renal dysfunction [67]. While the exact mechanisms for impaired solute handling in sepsis and endotoxemia are not fully elucidated, it does appear that inflammatory cytokines play a large role in the process. Further research is needed to identify what inflammatory ‘milieu’ would be the most favorable one to counteract the detrimental effects of sepsis on kidney function.

Finally, while it has been established in experiments utilizing endotoxemia that inhibiting inducible nitric oxide synthase (iNOS) can have a dramatic effect on GFR [68], endogenous NO has also been implicated as a mediator of epithelial sodium and chloride transport independent of its effects on vascular function [69]. It has long been known that NO has natriuretic and diuretic effects on animals, presumably through its impact on vasoregulation [69–71]. In non-septic studies, NO has been shown to inhibit NKKC2 [72] and apical sodium transport proteins in the cortical collecting duct [73]. More recently, septic models of AKI have linked endotoxemia with increased iNOS expression and downregulation of the NHE3 and NKKC2 transporters [18]. Regardless of the specific roles that inflammatory cytokines, PGE2, cAMP, Nedd4-2, or iNOS play in septic AKI, the overarching consequence of sepsis on these mediators seems to be increased delivery of sodium and chloride to the macula densa. We propose that this putative effect of septic inflammation—the increased delivery of sodium and chloride to the distal tubules and the macula densa—plays a critical role in the overall reduction in GFR and renal function.

**ACID–BASE REGULATION**

During sepsis, especially severe sepsis where multiple organ failure is common, metabolic acidosis becomes a formidable clinical problem [74, 75]. The role that impaired renal excretion of acid plays in contributing to the mortality and morbidity from sepsis is unknown. However, studies have suggested that survivors of sepsis are better able to regulate their acid levels than non-survivors via clearance of lactate and unmeasured anions by the kidney [74].

The workhorses of acid–base regulation in the kidney are the NHE transporters [7]. They have been shown to be significantly downregulated in vivo models of sepsis in mice exposed to intraperitoneal LPS injection [12]. It is unclear how this downregulation is mediated, but in non-septic...
Chinese hamster ovary cells, PKA and cAMP inhibit NHE activity [76], raising the question of whether these mediators influence acid handling in septic AKI (Figure 2). New evidence has also pointed to a possible role for SGK-2 and its stimulatory impact on NHE3 function in rat kidney proximal tubule cells [77]. The regulation of NHE3 by phosphorylation, trafficking and expression in non-septic models has been reviewed [78].

A direct role for TLR-4 receptor-mediated regulation of NHE transporter proteins has been recently proposed and supported by various experiments using highly selective inhibitors [79]. Good et al. [79] demonstrated decreased HCO$_3^-$ absorption on both the basolateral and apical sides of isolated rat and mouse medullary thick ascending limbs (MTAL) that were exposed to LPS. Impaired HCO$_3^-$ absorption was eliminated in TLR-4 $\sim$/ $\sim$ knockout mice [79]. Interestingly, they identified two separate mechanisms for basolateral and apical regulation: basolateral LPS inhibited HCO$_3^-$ absorption via the Ras/MEK/ERK pathway, whereas apically administered LPS inhibited HCO$_3^-$ absorption via the PI3K/mTOR/S6K pathway, suggesting that multiple independent TLR-4 pathways are involved in activating NHE1 and NHE3 separately [79, 80]. Further work has shown that ERK directly inhibits NHE3 via the TLR-4/MyD88/MEK/ERK signaling pathway [81], as is seen in aldosterone treatment models [82]. More recently, this same group has also identified a possible role for TLR-2 in impaired HCO$_3^-$ absorption in medullary thick ascending limbs exposed to bacterial lipoprotein that is distinct from TLR-4 pathways, suggesting a role for TLR-2 in MTAL transport dysfunction in gram-positive sepsis [83]. However, they have also demonstrated that TLR-2 is required for LPS-induced TLR-4 signaling to impair NHE3, complicating the overall picture [84].

**GLUCOSE AND UREA TRANSPORT**

Recent evidence has also demonstrated impaired Na$^+$–glucose cotransporter -2 and -3 (SGLT-2 and -3), GLUT-2 and Na$^+$/K$^+$-ATPase expression in mice injected with LPS [85]. The decreased expression of those transporters was associated with an increase in fractional excretion of glucose, decreased plasma glucose concentrations and decreased GFR [85]. However, they also found increased expression of the high affinity glucose transporters SGLT-1 and GLUT-1, which might have been related to the increased glucose exposure to the late proximal tubule (S3 segment) as a result of the dramatic upstream downregulation of SGLT-2 in the early proximal tubule (S1 segment) [85]. Administration of TNF-$\alpha$, IL-1, IL-6 or IFN-$\gamma$ reproduced the alterations in glucose transporter expression seen with LPS administration, although knockout mice for those cytokines were not resistant to the effects of LPS on glucose transporters [85]. As seen in their studies on sodium transporters, these authors were able to ameliorate the effects of LPS on the glucose transporters by large dose glucocorticoid administration [85].

The clinical significance of impaired glucose handling by the kidney during sepsis is unknown. Sepsis is generally considered a hypermetabolic state [86], and is associated with hyperglycemia in over 90% of critically ill patients [87]. In Schmidt’s study [85] above, hypoglycemia and increased fractional excretion of glucose occurred without concomitant hyperinsulinemia, which the authors felt demonstrated an insulin-independent renal glucose deprivation process. Rencircling this finding with clinical observation is not difficult; the overwhelming stress state in the septic patient likely induces a metabolic hyperglycemia that overwhelms any increase in renal wasting of glucose [87]. Nevertheless, their findings are significant in that they point to further distinctions between ischemic AKI and septic AKI. While LPS administration did induce hypotension in the Schmidt study, the effects of LPS on glucose handling were attenuated in the mice that were given steroids, despite no change in hemodynamics [85]. Additionally, in kidney ischemia–reperfusion models of AKI, SGLT-1 has been shown to be downregulated after injury, in contrast to the LPS model [88].

In a similar series of experiments, Schmidt et al. [89] found no change in protein expression using the renal arterial ligation model of ischemic AKI on the urea transporters UT-A1, UT-A2, UT-A3, UT-A4 and UT-B. However, they again demonstrated significant downregulation of all urea transporters after LPS exposure, and this downregulation was attenuated with glucocorticoid treatment [89]. Glucocorticoid attenuation in this model is surprising, given that in other rat experiments, administration of dexamethasone has been shown to independently downregulate UT-A1 and UT-A3 [90]. Knockout mice deficient in TNF-$\alpha$, IL-1$\beta$, IL-6 and IFN-$\gamma$ were not protected from the effects of LPS [89]. Urea is passively reabsorbed in different segments of the tubule to some degree. However, much of its reabsorption is facilitated by the above transporters located throughout the nephron, especially in the medullary collecting duct where it is significantly regulated by vasopressin [7, 91]. Approximately 50% of urea is reabsorbed in the kidney under normal conditions [7], with the rest excreted in the urine. The kidney’s overall ability to concentrate urine is dependent on medullary collecting duct reabsorption of urea, with subsequent increase in medullary osmolality [7]. In the experiments conducted by Schmidt, however, mice injected with LPS suffered a significant decrease in urea concentration in the inner medulla, and this correlated with a significant decrease in the expression of urea transporters [89]. It is unclear whether this impairment of urea reabsorption and overall urine concentrating ability seen in mouse septic AKI models occurs in humans. However, the differing effects seen in LPS-exposed mice compared with ischemia–reperfused mice strongly suggest their pathophysiological mechanisms are fundamentally different.

**WATER TRANSPORT REGULATION**

In the normal human kidney, fluid leaving the proximal tubule is isosmotic to plasma, and then is regulated by countercurrent multiplication in the loop of Henle [50]. Urine osmolality is then tightly regulated within the cortical...
collecting tubule by the neuropeptide vasopressin [92]. It has been shown that the vasopressin response to osmotic stimulation (administration of intraperitoneal hypertonic saline) in the hypothalamus is potentiated by LPS administration in rats [93, 94]. Concomitant with these effects in the hypothalamus, Grinevich et al. [95] demonstrated that LPS administration induced decreases in urine osmolality and downregulation of the V2 vasopressin receptor (V2R) and aquaporin-2 (AQP2) expression in the kidney, perhaps as a compensatory response to the potentiated vasopressin release in the hypothalamus. Interestingly, blood pressure was not impacted in this study, yet LPS injection was associated with a rapid increase in IL-1β and IL-6 expression in the renal medulla, suggesting that local increases in cytokines may play a role in the downregulation of V2R and AQP2 [95]. It is not clear to what extent the TLR-4 pathways play a role in this phenomenon, although the authors do suggest a possible mechanism mediated through NO synthase and cyclooxygenase, as discussed above regarding solute handling in the kidney. Wang et al. showed that aquaporin-1 (AQP-1) plays an important role in endotoxin-induced AKI [17]. AQP-1 knockout mice were predisposed to more severe endotoxemic renal injury and impaired solute and water handling than wild-type mice [17]. They also showed a similar downregulation of AQP-2 (as has Olesen et al.) [18] and AQP-3 in their in vivo model of sepsis.

Supporting a mechanism for impaired V2R function in septic AKI, Chagnon et al. [96] challenged rats with LPS and concomitantly administered arginine vasopressin [96]. They found that vasopressin’s ability to recruit AQP-2 was markedly impaired in septic AKI, which led to impaired water retention. This finding confirmed prior data in LPS-exposed rats showing that increases in endogenous vasopressin were not associated with subsequent elevations in AQP-2 expression, even in the setting of markedly increased free water excretion [97, 98]. Although iNOS has been implicated in some septic models [18], the molecular mechanisms contributing to the vasopressin/AQP-2 expression discordance seen in septic AKI are unknown. The impact of sepsis on other types of aquaporins is currently unknown.

CONCLUSION

Septic AKI is a common and formidable problem for clinicians, especially intensivists and nephrologists. However, research over the past decade has provided new insights into septic AKI pathogenesis. Basic non-hemodynamic factors, such as the generation of inflammatory cytokines and prosta-glandins, play a unique role in epithelium of the kidney tubules. These inflammatory mediators alter the ability of tubular cells to handle solutes, regulate intravascular volume and contribute to maintaining acid-base homeostasis in septic patients. The key theme from these recent studies is that sepsis impairs tubular transport in a manner that increases distal tubular delivery of sodium and chloride. We propose that this supraphysiologic delivery of solutes to the macula densa induces tubuloglomerular feedback and the ultimate reduction of GFR that occurs in septic AKI. Further studies to more directly test this hypothesis and better elucidate the mechanisms involved are warranted and should provide targets for future investigation and therapeutic intervention.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests or conflicts of interest. The work presented in this paper has not been published previously in whole or part.

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FULL REVIEW
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