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Contrast nephropathy may be partly mediated by autonomic dysfunction: Renal failure considered as a modern maladaptation of the prehistoric trauma response

Anthony J. Yun *, John D. Doux, Patrick Y. Lee

Department of Radiology, Stanford University, 470 University Avenue, Palo Alto, CA 94301, United States

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Summary The mechanism behind iodinated radiocontrast nephropathy remains elusive. Direct oxidative damage is the prevailing hypothesis, but the apparent protective effect of iodine against oxidation contradicts this view. We propose that autonomic dysfunction participates in the pathogenesis of radiocontrast nephropathy and may account for other contrast-associated reactions previously attributed to allergy. Iodine, through its effects on thyroid function and chemoreceptor response to metabolic acidosis, may induce hyperadrenergia and consequently diminish renovascular flow and urine output. The renal response to adrenergia likely served an adaptive function during prehistoric evolution when trauma was a dominant source of hypovolemia and adrenergia, but the response may behave maladaptively today as evolutionarily naïve triggers for adrenergia have emerged. Autonomic dysfunction can further impair renal function by deranging renovascular autoregulation and inducing oxidative reperfusion injury as a secondary phenomenon. Many other causes of acute renal failure such as drug toxicity, surgery, hospitalization, and diabetes may operate through hyperadrenergia, impaired renovascular autoregulation, and oxidative reperfusion injury. Dialysis, a volume reduction therapy for renal failure, can counterintuitively worsen renal dysfunction by exacerbating adrenergia, which may explain its association with accelerated atherosclerosis, inflammation, and cancer. Other examples of vicious cycles that perpetuate renal dysfunction may include renal artery stenosis, carotid stenosis, and atherosclerosis as well as the cardio-renal, hepato-renal, and pulmonary-renal syndromes. The benefits of hydration and bicarbonate in protecting renal function may operate in part through baroreceptor- and chemoreceptor-mediated reduction of sympathovagal ratio, respectively. New treatment paradigms for renal failure including pharmacologic and electro-mechanical therapies are envisioned based on autonomic remodeling, reduced sympathovagal ratio, and neuromodulation of pathways typically associated with trauma such as renin, angiotensin, vasopressin, and aldosterone.

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* Corresponding author. Tel.: +1 650 387 6667; fax: +1 650 325 5028.
E-mail address: ayun@stanford.edu (A.J. Yun).

Hypothesis

Radiocontrast nephropathy (RCN), also known as contrast-induced nephropathy (CIN), is the third leading cause of hospital-acquired acute renal failure [1]. The pathophysiology of this condition remains elusive. It is generally accepted that higher doses of contrast increase the risk of RCN [2–4], and that volume expansion by hydration appears to reduce risk [5–8]. Osmolality has been thought to be a factor [2–4], but data to this end have proven somewhat inconsistent, as osmolality does not appear relevant in cases where renal function was normal at baseline [9]. We propose that RCN and many other causes of renal failure may be partly attributable to the primary and secondary effects of autonomic dysfunction, and as such may be considered as a modern maladaptation of the prehistoric trauma response.

Evidence

Evidence against the direct oxidative damage hypothesis

Direct oxidative damage has been generally considered to be the most likely mechanism for RCN [10–12]. Consequently, prevention has largely focused on the use of reducing agents such as *N*-acetylcysteine [13,14]. Confirmatory trials with such agents have yielded mixed results at best [15–18]. Sodium bicarbonate has shown some promise in a single trial [19] with its effects also attributed to the anti-oxidant properties of the bicarbonate anion.

However, invoking oxidative damage from contrast remains at odds with the observation that iodine, the key component of contrast, itself acts as an antioxidant in multiple settings, particularly since the risk of nephropathy appears to worsen with increasing iodine concentration [2–4]. Species living on the ocean surface, a highly oxidative environment due to the exposure to sunlight and atmospheric elements, are known to concentrate iodine 30,000-fold as a mechanism of self-defense [20]. Iodine exists most commonly as the iodides, potassium and sodium; in these forms iodine can act as an electron donor in the presence of free radicals such as H_2O_2 and peroxidase [21].

Like the ocean, the eye represents a highly oxidative environment affected in no small part by ultraviolet exposure. Cells in the eye also concentrate antioxidants, and failure of antioxidant protection has been suggested in the formation of cataracts [22]. Ocular accumulation of iodine,

and its antioxidant behavior in that context, has been shown in rabbits [23]. The anticataract effect of iodide appears to involve a direct or indirect antioxidant mechanism [24], and the use of antioxidants such as iodide to prevent oxidative stress in the eye has been accordingly proposed [25].

Iodine also protects against causes of oxidative damage other than sunlight. Oxidative stress constitutes one of the mechanisms of thermal and chemical injury. Iodine has shown to be protective in these settings by exerting an antioxidant effect [26]. The protective effects of iodide during acute radiation exposure, which damages host cells in part through oxidation, are generally attributed to displacing effects on the thyroid [27], but a direct antioxidant function may also apply. Indeed, the function of radio-contrast is entirely reliant upon the ability of iodine to absorb ionizing radiation. Dietary iodides protect against lipid peroxidation in rat brains [28], and iodide increases the total antioxidant status in human sera [29].

Many contrast reactions may be due to autonomic dysfunction

The physiologic consequences of radio-contrast administration are varied and poorly understood, particularly with respect to the dispute surrounding the concept of iodine allergy [30]. True allergic reactions are probably rare, responsible epitopes are unknown, and the predictive value of skin tests has been questioned [31]. Anaphylactoid reactions are rarely reproducible, and steroids generally do not ameliorate serious anaphylactoid reactions [32]. Furthermore, the molecular size of iodine may be too small to efficiently incite an antibody reaction [32].

The idiosyncratic nature of contrast reaction – patterns of incidents within an individual can be quite irregular – suggests that these reactions may not be allergic, but represent a physiologic response. Indeed, responses to contrast administration, such as flushing, rash, urticaria, bronchospasm, laryngeal edema, feeling of warmth, nausea, vomiting, cardiac dysfunction, pulmonary dysfunction, vascular collapse, and renal failure, [33] may be often mistakenly classified as an allergic reaction when they may actually represent autonomic dysfunction.

Indeed, these symptoms all occur in the context of autonomic derangement, particularly heightened sympathovagal ratio. Nausea and vomiting are well-known manifestations of autonomic dysfunction [34]. Bronchospasm, laryngeal edema, and pulmonary edema appear to involve

a component of autonomic dysfunction [35–37]. The feeling of warmth, a likely manifestation of thermogenesis, is mediated by the sympathetic system [38]. Urticaria can be autonomic in origin [39], and other cutaneous eruptions can arise from local vasculopathies, perhaps mediated by endothelial dysfunction associated with autonomic dysfunction [40]. Coronary vasospasm attributed to iodine allergy may alternatively represent a sympathetic crisis not unlike those precipitated by sympathomimetics such as amphetamines [41]. The vascular collapse associated with anaphylaxis is partially mediated by the autonomic system [42].

Since the myriad of physiologic consequences associated with contrast reaction appear to be at least partially mediated by a common pathway involving the autonomic system, we are left with the possibility that the renal failure associated with contrast reaction is also a manifestation of autonomic dysfunction and sympathetic excess. Indeed, volume retention through reduction of urine output constitutes one of the hallmarks of sympathetic activity.

Contrast nephropathy may be due to autonomic dysfunction

We propose an alternative hypothesis that RCN is caused by autonomic dysfunction. How iodinated contrast might induce acute autonomic dysfunction remains unclear. The induction of subclinical thyrotoxicosis by an acute iodine load may represent one possibility, which in turn would result in sympathetic bias and autonomic dysfunction [43]. While true thyroid storm represents a rarely reported consequence of contrast administration [44,45], whether subclinical thyrotoxicosis is underreported in many cases remains unknown. The symptoms of thyrotoxicosis do closely resemble those of catecholamine excess, which can be reduced by β -adrenergic receptor antagonists [46,47]. Renal dysfunction also represents one of the consequences of thyrotoxicosis [48]. Thyrotoxicosis may reduce urine output by increasing the release of renin [49,50], one of the mediators involved in the activation of the volume retention pathway also promoted by catecholamines, the renin-angiotensin system, and aldosterone. Amiodarone, another potential cause of thyrotoxicosis involving iodine administration, has also been shown to cause renal failure [51].

Alternatively, iodine-induced subclinical elevation of thyroid function may activate the sympathetic system through another pathway. Excess

thyroid function is known to induce renal tubular acidosis [52,53] which in turn, can promote the sympathetic system through carotid chemoreceptor activation [54], a response designed to normalize acid-base balance. Thus, the benefit of bicarbonate administration in reducing the risk of RCN, which is currently ascribed to the antioxidant effects of bicarbonate, may be independently attributable to the reduction of acidosis-induced sympathetic bias as a cause of renal failure [19].

Underlying renal disease represents the major risk factor for the development of RCN. While renovascular vasoconstriction may have evolved to protect the kidney from naturally occurring toxins, this reaction may prove maladaptive in diseased kidneys. Chronic comorbid diseases, including diabetes mellitus, hypertension, heart failure, and liver failure, reduce the reserve of the kidneys to cope with metabolic insults. Under normal circumstances, renovascular autoregulation acts to preserve blood flow despite variations in systemic blood pressure. With chronic comorbidities producing ongoing stressors, not only would an ongoing sympathetic bias reduce the operating range of any autoregulatory processes, but remodeling of the renal vasculature with smooth muscle proliferation would also occur, further limiting the ability of the kidneys to locally govern blood flow. In this state, the kidneys would be more susceptible to the effects of sympathetic bias, with impairment of their ability to react to nephrotoxic insults and to recover from ischemia.

Hydration may attenuate contrast nephropathy by modulating autonomic balance

The benefit of hydration in RCN may operate in part through reduction of sympathetic activity [55]. The risk of dehydrated patients developing RCN may be a function of increased sympathetic bias in these patients. As an adaptive response, dehydration increases renin, aldosterone, vasopressin, and catecholamines to reduce urine output in order to preserve volume. Notably, prophylactic hemodialysis, which increases sympathetic activity and potentially induces hypovolemia, has shown no benefit in preventing RCN [56,57]. On the other hand, prophylactic hemofiltration, which maintains intravascular volume while removing the contrast agent, can attenuate the risk of RCN [58].

As opposed to the notion of direct oxidative injury, many agents may cause renal oxidative damage secondarily by first inducing renovascular dysfunction. Specifically, initial vasoconstriction

caused by these agents may be followed by reperfusion injury that involves oxygen free radicals, a phenomenon not unlike those seen after stroke or myocardial ischemia. Commonly described nephrotoxic agents such as cisplatin, aminoglycosides, NSAIDs, heavy metals, cyclosporine, and iodine contrast are thought to inflict damage through different mechanisms of cellular injury [59–63]. However these agents are also associated with afferent renal arteriolar vasoconstriction [64]. Thus, nephrotoxic insults may result in a common injury pathway leading to renovascular constriction, perhaps in an effort to limit exposure to the toxin. This vasoconstriction may be amplified by feed-forward induction of sympathetic bias, leading to a decline in glomerular filtration rate. In addition, since the kidney parenchyma is relatively hypoxic at baseline, vasoconstriction can exaggerate this state. Shortly after reperfusion with blood, potentially damaging oxygen free radicals including the superoxide anion ($\cdot\text{O}_2$) and hydroxyl radical ($\cdot\text{OH}$) can be generated [65]. Indeed, areas of the kidney that are more susceptible to injury lie in the areas of relative hypoxia, namely the inner cortical and medullary segments [66,67]. By counteracting sympathetic signals that accelerate and amplify vasoconstriction, hydration may deter these processes and prevent downstream sequelae.

Darwinian perspective

We have previously proposed that traumatic injury likely exerted significant selective pressure during prehistoric evolution [68]. Here, we extend this notion and argue that the response to injury was a critical factor in shaping many components that control homeostasis. The sympathetic nervous system likely represents one of several linked mechanisms that developed to contend with the sequelae of injury. In this case, it likely served to maintain fluid pressure within a circulatory system in the face of significant volume loss due to hemorrhage [68]. The systemic response of our current physiology to trauma reinforces this idea, as trauma activates several neuroendocrine pathways including the synthesis and release of hormones such as renin, angiotensin, aldosterone, vasopressin, and catecholamines. These molecules all serve to promote volume retention by the kidneys through reduction of urine production [69,70].

The ability to survive injury, as might occur during interactions with conspecifics, predators, prey, and the environment, may have represented a significant selective force in shaping physiology during prehistoric evolution [68]. The convergent

pathways of adrenergia, inflammation, and coagulation may have emerged to meet adaptive needs during traumatic injury such as hemostasis, microbial defense, and blood pressure maintenance [68]. Volume retention by the kidneys represents one of the adaptive mechanisms that help to preserve blood pressure. Renal volume retention is mediated by numerous factors such as catecholamines, aldosterone, vasopressin, angiotensin, renin, and natriuretic peptides. Traumatic injury leads to sympathetic activation and release of these factors.

In the setting of traumatic injury, volume retention by the kidneys is presumably highly adaptive. Individuals who survive and subsequently reproduce perpetuate those physiologic pathways that aided in survival. However, modern humans have substantially remodeled their own environment such that trauma may have become a less prevalent activator of adrenergia and the associated physiologic responses that promote volume reservations by shutting down renal function. Instead, new stressors have emerged during modern times that may induce renal dysfunction as part of a maladaptive response of a prehistoric pathway. The renal vasoconstriction that occurs after trauma is not unlike that which occurs after radiocontrast administration [71].

Chronic renal failure is accompanied by increased sympathetic nervous system activity [72,73]. Although operational even in the case of bilateral nephrectomy, the presence of the kidneys increases the magnitude of sympathetic activity. With this coupling of renal failure and autonomic overdrive in mind, we propose that in many cases acute renal failure due to direct injury reflects an invocation of the trauma response. Reinforcement of this response via positive feedback loops then leads to functional and structural compromise of the kidney.

Implications

The reasons for renal failure remain unclear. Whether the kidney does represent an inexact organ, or if what is interpreted as failure constitutes a legitimate mechanism to prevent volume loss, remains unknown [74]. However, framing RCN as a maladaptation of the prehistoric trauma response may shed light on the pathophysiology of other causes of renal failure. In cardiorenal syndrome, inadequate systemic perfusion due to impaired cardiac function leads to synergistic induction of the renin-angiotensin system and the sympathetic nervous system, resulting in decreased urine output. The increased volume load

further impairs cardiac function, leading to iterative damage to both the heart and the kidneys [75,76]. This same process may be responsible for the progressive renal failure and volume retention seen with other sources of insidious trauma, including aging, diabetes, and atherosclerosis, the latter most dramatically as a feed-forward cycle in the case of renal artery stenosis and carotid stenosis [77–81]. It may also explain the increased risk of renal failure in the post-operative setting and during hospitalization [82,83]. The relatively diminished urine production which typically occurs the first few days following a surgical procedure may represent a less egregious manifestation of this response. Indeed, the frequent phenomenon of fluid accumulation in the extravascular space under such circumstances may reflect an attempt by the body to further conserve volume in conjunction with this response.

The invocation of positive feedback in cardiorenal syndrome carries implications beyond this specific clinical entity. Sympathetic induction through volume compromise and renal dysfunction may explain why diseases with increased sympathetic activity, such as accelerated atherosclerosis, inflammation, and cancer, are also associated with dialysis [84–87]. This principle may also serve as the basis for the association of kidney disease with other phenomena that exhibit sympathetic bias, such as sleep apnea, epilepsy, HIV, and malignancy [88–91]. Once chronic renal failure sets in, secondary consequences may include thyroid and parathyroid dysfunctions, both of which can lead to iterative damage of the kidneys.

Hepatorenal syndrome may represent another example of feed-forward dysfunction involving multi-organ failure. Underlying hepatic disease is a potential source of systemic hyperdynamic circulatory dysfunction with reduced arterial blood pressure, owing to preferential splanchnic arterial vasodilatation and loss of oncotic pressure secondary to hypoproteinemia [92]. The resulting activation of the prehistoric “trauma response”, involving the sympathetic nervous and renin-angiotensin-aldosterone systems, induces renal vasoconstriction with renal hypoperfusion, lowers glomerular filtration rate, and promotes sodium-water retention [92]. This response likely amplifies to override local autoregulatory processes in the form of pressure and volume signals within the vasculature that attempt to direct the body to behave otherwise. Unilateral lumbar sympathetic blockade has been shown to reverse the renal failure component of hepatorenal syndrome, suggesting that sympathetic bias is the direct cause of the renal failure in hepatorenal syndrome [93]. In turn, increased

sympathetic activity can worsen underlying hepatic disease in a self-propelling fashion. Sympathetic bias is known to shift immune T helper (Th) balance towards Th2 bias, a state more favorable not only for tumor survival, but also for viral survival including the hepatitis B virus and hepatitis C virus that are involved in chronic liver disease [94]. Indeed, sympathetic bias has been observed in patients with cirrhosis and other forms of chronic liver diseases [95]. Toxins that a diseased liver fails to metabolize may function in similar fashion to toxins in the kidney to promote this process.

Pulmonary-renal syndrome may develop through a similar mechanism. Any source of chronic uncompensated hypoxia, hypercapnia, or respiratory acidosis can activate chronic systemic sympathetic bias through maladaptive carotid chemoreceptor activation [96]. The resulting activation of the prehistoric “trauma response” by the kidney may maladaptively promote the renin-angiotensin-aldosterone systems, renovascular constriction, renal hypoperfusion, sodium-water retention, metabolic acidosis, and reduction of glomerular filtration rate. The chronic metabolic acidosis can in turn further worsen the sympathetic bias through chemoreceptor activation. Chronic systemic autonomic dysfunction can produce derangements of local pulmonary vascular autoregulation and induce local ventilation-perfusion mismatches, which would further exacerbate the underlying hypoxia, hypercapnia, and acidosis in self-propelling fashion.

Other syndromes of multi-organ failure may also operate through previously unrecognized dysfunctions of feed-forward sympathetic bias. Vicious cycles of sympathetic bias may play a contributing role in hepatic dysfunction associated with congestive heart failure, a process generally attributed to passive congestion from right heart failure. Chronic hepatic dysfunction may predispose to pulmonary dysfunction in response to otherwise minor insults if ongoing autonomic dysregulation increases ventilation-perfusion mismatch. Once autonomic dysfunction is invoked by a particular physiologic system, that system may have the opportunity to engage and interfere with other systems in an iterative fashion.

Numerous therapeutic implications are apparent. The primary focus in the management of both acute and chronic renal failure may involve the reduction of sympathovagal ratio as well as the remodeling of the autonomic and neurohormonal axes. The benefits of hydration may operate through reduction of sympathovagal ratio [55]. The renal toxicities of diuretics may arise from the autonomic effects produced by dehydration. Concomitant use of agents capable of adrenergic

or angiotensin blockade [97,98] may yield additional benefits. Preliminary results suggesting the potential benefit of selective dopamine-1 receptor antagonists such as fenoldopam reinforce this notion [99]. Drug delivery using targeted routes of administration may allow for development of more aggressive therapies designed to lower renin, beta-natriuretic peptide, angiotensin, vasopressin, and aldosterone levels, but restricted to the local environment of the kidney to avoid the deleterious effects of systemic distribution. When deployed either within or around the kidney, or at remote sites critical to feedback loop control, devices may function effectively as both acute and chronic interventions for disease, employing electrical, thermal, vibrational, magnetic, acoustic, baropressure, optical, or other sources of energy to modulate autonomic balance.

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