Regional alterations in renal haemodynamics and oxygenation: a role in contrast medium-induced nephropathy

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Abstract
Although the nature of renal dysfunction following the use of iodinated radiological contrast agents has long been a matter of dispute, tubular hypoxic injury does play a central role as indicated by both clinical observations and experimental animal models. Indeed, radiocontrast agents induce renal parenchymal hypoxic stress resulting from a critically low ambient pO₂ that develops particularly in the renal medulla. This medullary oxygen insufficiency is a reflection of both increased oxygen consumption for solute reabsorption and a reduction of regional inner medullary blood flow. Cellular adaptation to hypoxia is mediated by hypoxia-induced transcription factors (HIFs), which are regulated by oxygen-dependent proteolysis. HIF action confers cell protection through a wide array of target genes, thus restricting tubular epithelial damage. Most clinical risk factors for contrast nephropathy are characterized by predisposition to medullary oxygen insufficiency (such as altered nitric oxide or prostaglandin synthesis, both vital in maintaining medullary oxygenation), by co-existing vasoconstrictive stimuli, by enhanced transport workload or by structurally altered microcirculation. Under such predisposing conditions, regional hypoxic stress may intensify and surpass the capacity for the generation of adaptive responses, evolving into apoptotic or necrotic tubular cell death, associated with renal dysfunction. Amelioration of medullary hypoxic stress should be taken into account when designing strategies to prevent or attenuate contrast media-induced nephropathy.

Keywords: haemodynamics

Introduction
Imaging procedures with iodinated radiological contrast agents remain an important cause of acute renal failure, despite the adherence to adequate precautions, such as patient selection, proper hydration and the introduction of the least nephrotoxic agents. This reflects the continuously expanding use of imaging techniques, and the fact that older and sicker patients nowadays undergo more extensive imaging and interventional procedures such as angioplasties, that require large volumes of contrast media (CM).

The nature of renal dysfunction following the use of radiocontrast agents is controversial. Primarily altered renal haemodynamics without tubular damage has been suggested, manifested by a decline in glomerular filtration with preserved tubular sodium reabsorption. Direct tubular toxicity has also been proposed [1], with proximal tubular vacuolar changes and simplification of brush border considered as a characteristic CM-induced tubular injury pattern [2]. Nevertheless, these findings seem to represent signs of CM exposure, rather than true indicators of contrast medium-induced nephropathy (CIN), lacking any correlation with kidney dysfunction [3]. Moreover, electron microscopy, at least in animal models, revealed that the ‘vacuolar’ changes in fact reflect basolateral membrane out-pouchings, with otherwise intact cellular structures [4]. Furthermore, kidney ischaemia molecule-1 (KIM-1), an indicator of proximal tubular necrosis, has not been detected in urine of patients with clinical CIN [5].

A more likely pathogenic mechanism for CIN is hypoxic renal medullary injury. As reviewed elsewhere in depth [6], the mammalian renal medulla functions normally at ambient pO₂ as low as 30 mmHg, reflecting limited regional blood supply, oxygen diffusion from descending to ascending vasa recta, a reduced haematocrit due to a skimming phenomena, and high local
oxygen consumption for tubular reabsorption. Highly effective mechanisms, including prostaglandins, nitric oxide (NO) and adenosine, continuously adjust medullary transport activity to the limited available oxygen supply, and acute tubular necrosis (ATN) often reflects their failure to maintain regional oxygen sufficiency [6].

In this review, we examine such CM-induced alterations in renal oxygenation, suggesting potential mechanisms involved and the means by which known risk factors for CIN might predispose to renal hypoxic stress. Strategies for the prevention and treatment of CIN will be reviewed from this perspective.

Contrast media-induced changes in renal parenchymal oxygenation

Using Clark-type oxygen microelectrodes, Brezis was the first to find that CM injection markedly affects renal parenchymal oxygenation [3]. Following the administration of the high-osmolar ionic agent sodium iothalamate, cortical pO2 declined from 40 to 25 mmHg. More impressive was the change observed in outer medullary pO2 which fell from 26 mmHg at baseline to mean levels as low as 9 mmHg. Comparable studies with oxygen microelectrodes were repeated by Liss and colleagues, showing a fall in medullary oxygenation from ~30 to 15 mmHg following the administration of ionic, as well as non-ionic and low osmolar radiological CM [7]. CM-induced intensification of medullary hypoxaemia has also been suggested by non-invasive blood oxygenation level-dependent magnetic resonance imaging (BOLD MRI) [8], which detects increased unsaturated haemoglobin concentration within the renal medulla.

Systemic effects of the dye that may contribute to the decline in renal tissue oxygenation include the induction of pulmonary ventilation–perfusion mismatch [9], reduced cardiac output and renal perfusion pressure [10], rheological alterations of the blood [11,12] and a leftward shift of the oxygen–haemoglobin dissociation curve [13]. However, the greater part of the decline in renal parenchymal oxygenation is attributed to altered intra-renal balance of oxygen supply and demand.

Radiocontrast-induced change in oxygen demand

CM administration is associated with an abrupt transient increase in glomerular filtration and urinary output [14]. This response, comparable with the effect of mannitol, is mediated in part by an increase in plasma volume and the release of natriuretic peptides [15,16]. Natriuresis and diuresis may also be related to an endothelin-B (ET-B)-mediated effect [17], released in response to CM injection [15]. All these factors, in addition to the substantial osmotic load provided by many CM, lead to enhanced solute delivery to the distal nephron, with the pursuant increased oxygen consumption for tubular reabsorption. The decline in outer medullary pO2 despite enhanced regional blood flow (see below) only emphasizes the important role of increased reabsorptive activity in the ensuing regional hypoxia. Indeed, the inhibition of transport activity with the loop diuretic furosemide abruptly reverses CM-induced medullary hypoxaemia [3,18]. Furosemide-related improvement of medullary hypoxaemia takes place even though it induces profound regional vasoconstriction [19], again under-scoring the central role taken by regulated tubular transport activity in the maintenance of medullary oxygen balance.

Radiocontrast-induced intra-renal changes in oxygen supply

The decline in renal parenchymal oxygenation may also reflect CM-induced altered renal microcirculation. Indeed, >30 years have passed since the first observations that renal blood flow briefly and transiently increases following CM injection, with a prolonged subsequent decline to some 10–25% below baseline [20]. The fall in medullary oxygenation cannot be attributed to the modest decline in total renal blood flow per se, since the latter predominantly reflects changes in cortical flow, whereas medullary flow represents only 10% of total renal blood flow [6]. Moreover, medullary flow is usually preserved during a moderate decline in renal blood flow (within the ‘autoregulatory’ range), despite a remarkable fall in cortical blood flow [21], a phenomenon known as ‘cortico-medullary redistribution of renal blood flow’. Furthermore, a fall in cortical blood flow alone is expected to increase medullary oxygenation, the outcome of diminished glomerular filtration rate (GFR) and solute delivery for reabsorption by the distal nephron [21].

The possibility that CM-related medullary hypoxia reflects altered medullary microvasculature has therefore been explored by direct determination of the local microcirculation. Nygren [22] and subsequently Liss and colleagues [23] recorded papillary blood flow with laser-Doppler probes after the exposure of the papilla by the dissection of the renal pelvis. Indeed, they found that ionic high osmolar, as well as non-ionic and low osmolar radiological CM, markedly reduced papillary blood flow. Using video microscopy of trans-illuminated papillary vasa recta and the dual-window cross-correlation technique, they also documented near cessation of red blood cell movement in papillary blood vessels, associated with red cell aggregation [23].

At the outer medulla, however, the microcirculatory response to radiocontrast was found to be quite different. Using needle laser-Doppler probes inserted through the cortex following partial renal decapsulation, Agmon et al. found that the outer medullary regional microcirculation markedly increases with CM injection, as long as NO or prostaglandin synthesis
is intact [24]. Heyman et al. noted a more modest enhancement of outer medullary flow [25], while Liss et al. found a dose-related response, with a decline in regional flow at low and intermediate volumes of contrast, but enhancement at high volumes [26].

Altogether, these findings indicate that CM-induced accentuation of inner medullary hypoxia is mediated to large extent by a decline in regional blood flow and oxygen supply. In contrast, intensification of outer medullary hypoxia predominantly represents enhanced oxygen consumption, not fully compensated by increased regional oxygen delivery. The cause of the disparate papillary and outer medullary microcirculatory response to CM is unknown, but it may reflect structural and functional differences in regional pericytes [27], or diverse distribution of vasoactive mediators or their receptors. An additional artificial effect related to the technical procedures (i.e. papillary exposure and renal decapsulation, respectively) cannot be excluded with certainty.

Numerous mediators are involved in the changes in the renal microcirculation associated with CM injection. Plasma levels of atrial natriuretic peptide [15] and presumably of other related molecules rapidly rise within 5 min after the injection of the contrast material, in parallel with the abrupt transient rise in renal blood flow and diuresis. Intrarenal nitric oxide synthase activity and NO concentration are modified following contrast administration [25], and plasma endothelin increases [15]. Other prominent mediators known to participate in the renal haemodynamic response to CM are adenosine [14,28], prostaglandins [29] and vasopressin [30]. Potential additional participants are serotonin, bradykinin, leukotrienes, histamine, catecholamines and the sympathetic nervous system.

Mechanical factors may also adversely affect the renal microcirculation following radiocontrast. Blood viscosity may be substantially influenced by the CM [31]. Additionally, the early enhanced diuresis is associated with swelling of the renal parenchyma, presumably due to tubular luminal expansion and increased interstitial volume [32]. It is conceivable that this might increase renal interstitial pressure, leading to compression of the vasa recta and peritubular capillaries, with subsequent compromised regional oxygenation.

A link between hypoxic and toxic CM-induced tubular injury

Evidence for independent direct tubular damage as a single mechanism of CM nephrotoxicity depends mainly on studies in cell culture and isolated tubular segments, providing biochemical evidence for tubular membrane oxidative damage [33]. Perhaps more importantly, CM-induced critical medullary hypoxia may lead to the formation of reactive oxygen species with subsequent membranal injury and DNA damage, activating high energy-consuming reparative processes such as poly(ADP-ribose) polymerase (PARP). The activation of PARP induces a vicious circle of additional intracellular energy store depletion and subsequent endothelial dysfunction, further intensifying regional hypoxic injury [34].

Risk factors for CIN: predisposition to medullary oxygen insufficiency

The incidence of CIN among patients without known risk factors is considered negligible, underscoring the value of the multiple mechanisms designed to maintain medullary oxygen sufficiency, adjusting local transport activity to the limited available oxygen supply [6,35]. The prostaglandins PGE2 and PGI2, NO and adenosine are key actors in these protective mechanisms, enhancing outer medullary blood flow and downregulating tubular reabsorptive activity. Reduction of GFR through the activation of the tubulo-glomerular feedback mechanism can also restore medullary oxygen sufficiency.

In rats, the inhibition of prostaglandin or NO synthesis was found to reverse the increase in outer medullary blood flow induced by radiocontrast, and to aggravate regional hypoxia [3,24,36]. Altered protective mechanisms also bring about the susceptibility to develop CIN in high-risk patients [37]. Indeed, predisposing risk factors, such as pre-existing renal dysfunction, diabetes or congestive heart failure, are all characterized by compromised medullary oxygen sufficiency, related to defective nitrovasodilation or prostaglandin synthesis, by increased reabsorptive workload, by enhanced systemic vasoconstrictive stimuli or by structural changes of the renal microcirculation.

For example, diabetes leads to enhanced distal tubular reabsorption due to increased GFR, osmotic diuresis and increased tubular ion pump mass. At the same time, nitrovasodilation is characteristically altered. Not surprisingly, basal outer medullary pO2 is significantly reduced in diabetic animals [38], and medullary post-transcriptional expression of hypoxia-inducible factors (HIFs) is detected shortly after the induction of experimental diabetes ([39], and C. Rosenberger, unpublished data). Altered nitrovasodilation is also prevalent in the aged, among hypertensives and in patients with hypercholesterolaemia or atherosclerosis. The administration of non-steroidal anti-inflammatory drugs which blocks prostaglandin synthesis may also predispose to CIN. Pre-existing renal disease is associated with hypertrophy of remnant nephrons and with structurally altered medullary microcirculation. Heart failure, cirrhosis, nephrotic syndrome or dehydration are predisposing risk factors characterized by effective volume depletion and increased neuro-humoral vasoconstrictive stimuli that might compromise medullary oxygenation [40].
Experimental models of CIN: the concept of medullary hypoxic damage

In rat kidneys, perfused ex vivo with cell-free oxygenated medium, contrast agents hasten the decline in kidney function and extend hypoxic tubular damage, which selectively involves medullary thick ascending limbs (mTALs) and S3 segments in the outer medulla [4]. In vivo, resembling humans, intact animals subjected to CM do not develop CIN. In rats, the CM-associated decline in medullary pO2 invokes an adaptive cellular hypoxic stress response, initiated by post-transcriptional medullary accumulation of HIF, with preservation of renal integrity and function [41]. However, the induction of other insults that mimic predisposing clinical conditions leads to tubular damage in experimental models of CIN [42,43]. Resembling CM in clinical practice, these conditions found to predispose to experimental CIN are characterized by systemic vasoconstrictive stimuli (volume depletion, heart failure or infusion of angiotensin II), by enhanced oxygen requirements (renal hypertrophy or enhanced glomerular filtration), by altered protective mechanisms (direct inhibition of prostaglandin or NO synthesis), by the presence of endothelial dysfunction (hypercholesterolaemia or short-term ischaemia) or by enhancement of interstitial hydraulic pressure (ureteral obstruction) [42,43]. With CM administration under such pre-conditions, apoptotic and necrotic damage rapidly develops [3,4,24,36,43–45], predominantly affecting mTALs and to a lesser extent S3 segments in the outer medulla and medullary rays. Papillary tip necrosis may also develop [44].

As found in such experimental models, uncontrolled activation of energy-consuming reparative systems, such as PARP [34], or the formation of reactive oxygen species [46] may lead to endothelial dysfunction, which may further aggravate regional oxygen insufficiency. The severity of renal dysfunction is proportional to the number of the applied co-perturbations, resembling Rich’s observations in humans [47]. Renal dysfunction correlates with structural damage in the more severe protocols, but not with the more moderate models that cause limited tubular damage, underscoring a potential role for ensuing altered glomerular haemodynamics as the basis for the decline in kidney function [43].

Therapeutic implications

CIN seems an ideal set-up to study protective strategies against ATN, given the ability to intervene before, during and after the exposure to CM. Yet, the only well established strategies to prevent CM-induced kidney dysfunction are to avoid unnecessary contrast studies in high-risk patients and, if unequivocally essential in high-risk patients, to implement proper hydration and to provide the smallest volume of CM possible, preferably using safer low osmolar non-ionic agents [37].

While modern technologies provide advanced non-invasive measures to assess myocardial hypoxic threat, real-time clinical tools to assess renal parenchymal distress currently are unavailable. We depend predominantly upon changes in GFR as a marker of CM nephropathy, while in fact it might reflect activation of protective mechanisms designed to prevent medullary hypoxic injury. This has led to what might be considered conceptually illogical therapeutic interventions, from the perspective of the outer medulla, designed primarily to enhance GFR. Indeed, dopamine and ANP prophylaxis have both failed to prevent CIN, and in patients with diabetes might have increased the risk for renal dysfunction [48,49]. This probably reflects augmented medullary oxygen debt by the increase in GFR and consequent tubular reabsorptive workload [37]. Mannitol prophylaxis has also failed [50], conceivably since it augments GFR (mediated by endogenous ANP) and increases solute delivery for distal tubular reabsorption, hence intensifying medullary oxygen insufficiency [18,19]. The potential adverse effects of theophylline, fenoldopam and other new strategies used to augment GFR following radiocontrast administration upon medullary oxygen balance and tubular integrity are yet to be defined.

Blocking CM-induced activated vasoconstrictive stimuli, such as endothelin, is another plausible therapeutic approach. However, the administration of a non-selective inhibitor of endothelin receptors adversely affected the clinical outcome [51]. The recognition of the important role of endothelin ET-B receptors in maintaining medullary blood flow [52] leads to perhaps a more promising strategy of selective ET-A receptor antagonism [53].

Improving GFR by the non-selective inhibition of adenosine receptors with theophylline might also adversely affect medullary oxygenation, by both increasing the GFR (an effect related to the blocking of A-1 adenosine receptors which induce cortical vasoconstriction), and reducing medullary blood flow (which depends on A-2 adenosine receptors) [54].

Amelioration of altered medullary nitrovasodilation is another potential strategy in the prevention of CIN. Indeed, L-arginine improves radiocontrast-induced altered renal haemodynamics and renal dysfunction in hypercholesterolaemic rats [55]. Recent experimental data also suggest that the renal protective effect of acetylcysteine may be related to improved nitrovasodilation and medullary oxygenation [56], in addition to the effect of scavenging free radicals. Inhibition of PARP activation in response to hypoxic stress may also improve cellular energy depletion, attenuate endothelial dysfunction and protect against medullary hypoxic injury [34]. In the same fashion, inhibition of the generation of reactive oxygen species or their scavenging might improve medullary oxygenation [38] and may be beneficial in the attenuation of CM nephropathy [57].

The loop diuretic furosemide was found to reverse medullary hypoxia induced by CM [3], reflecting the inhibition of reabsorptive activity [19], and to prevent...
hypoxic outer medullary damage in a rat model of experimental CIN [58]. Liss et al. reported that pre-treatment with furosemide did not prevent the CM-induced decline in medullary pO2 but, since baseline oxygen tension was higher, the decline in ambient pO2 did not reach the critically low levels noted without furosemide [59]. In clinical practice, however, results with the loop diuretic were disappointing; while kidney function was maintained with a fluid regimen in patients with pre-existing renal dysfunction undergoing contrast studies, it significantly deteriorated with furosemide treatment [50]. Assessment of the changes in body weight indicates that this unexpected observation may be related, at least in part, to ensuing negative fluid balance and pre-renal azotaemia [60]. It is suggested that such a study should be repeated with a more adequate fluid replacement to compensate for the effect of the diuretic.

Since increased reabsorptive workload and interstitial hydraulic pressure possibly contribute to CM-induced altered medullary microcirculation and oxygenation, we believe that vascular modulation by a selective medullary vasodilator, for instance an ET-B agonist, may not suffice to prevent radiocontrast nephropathy. Therefore, a more comprehensive strategy may be tried, combining the inhibition of tubular transport together with fluid replacement and measures to restore medullary microcirculation.

Conclusions and unanswered questions

Medullary hypoxia plays a central role in CIN, resulting from altered renal microcirculation and enhanced oxygen consumption for tubular reabsorption. The importance of intact homeostatic mechanisms in maintaining medullary oxygen balance and tubular integrity is illustrated in experimental models of CIN, mimicking the clinical setup of predisposing risk factors. We critically need technologies that non-invasively may detect in real time ensuing critical renal parenchymal hypoxia and evolving tubular damage. In their absence, we truly remain ignorant regarding preventive or therapeutic strategies. Attempts to enhance GFR during CM-induced ATN may decrease the intraluminal concentration of the CM and wash out casts, but might exacerbate medullary tubular injury. We frankly have no idea what is clinically more important: a pharmacologically augmented GFR or the amelioration of medullary oxygen balance to minimize progression of tubular hypoxic injury, at the price of diminished GFR.

Currently, the only proven strategies in the prevention of CIN include patient selection, hydration and the use of the smallest volumes required of low osmolar non-ionic agents. Until the above debate is settled, a logical additional preventive experimental approach in high-risk patients might be a combination of a loop diuretic and appropriate hydration, together with renal vasodilators and measures that restore endothelial dysfunction.

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References
