REVIEW

Clinical update

Contrast-induced kidney injury: mechanisms, risk factors, and prevention

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In general, iodinated contrast media (CM) are tolerated well, and CM use is steadily increasing. Acute kidney injury is the leading life-threatening side effect of CM. Here, we highlight endpoints used to assess CM-induced acute kidney injury (CIAKI), CM types, risk factors, and CIAKI prevention. Moreover, we put forward a unifying theory as to how CIAKI comes about; the kidney medulla's unique hyperosmolar environment concentrates CM in the tubules and vasculature. Highly concentrated CM in the tubules and vessels increases fluid viscosity. Thus, flow through medullary tubules and vessels decreases. Reducing the flow rate will increase the contact time of cytotoxic CM with the tubular epithelial cells and vascular endothelium, and thereby damage cells and generate oxygen radicals. As a result, medullary vasoconstriction takes place, causing hypoxia. Moreover, the glomerular filtration rate declines due to congestion of highly viscous tubular fluid. Effective prevention aims at reducing the medullary concentration of CM, thereby diminishing fluid viscosity. This is achieved by generous hydration using isotonic electrolyte solutions. Even forced diuresis may prove efficient if accompanied by adequate volume supplementation. Limiting the CM dose is the most effective measure to diminish fluid viscosity and to reduce cytotoxic effects.

Keywords   Iodinated contrast media • Acute kidney injury • Pathophysiology • Prevention

Introduction

Large doses of iodinated contrast media (CM) are often indispensable for percutaneous cardiac interventions. Although available CM are very well tolerated, they can cause acute kidney injury (AKI). As interventional cardiac procedures are steadily increasing, CM-induced AKI (CIAKI) has become the third leading cause for hospital acquired AKI.[1] The consequences of kidney damage can be severe: patients with CIAKI suffer from an increased rate of in-hospital complications including a mortality rate of ~20% and may become predisposed to long-term loss of kidney function.[2–7] Even after adjusting for co-morbidities, in-hospital mortality is about five-fold higher in CIAKI patients than in patients who received CM but did not develop CIAKI, and 1-year and 5-year mortality rates are about four-fold higher.[2,4–6,8]

Several investigations have set out to understand the mechanisms of CIAKI. From these studies, we have learned that CM can cause kidney damage via several routes. Contrast media can induce cell damage and even cell death. Moreover, CM can reduce blood flow through kidney areas that are at risk for hypoxic damage, i.e. the outer medulla. In parallel to reduced blood flow, tubular fluid flow is similarly affected. Many more potentially damaging CM effects have been reported, putting forward a plethora of contributing mechanisms to CIAKI. Here, we set out to shape a uniform scheme from the various findings on how CIAKI comes about.

Confounding factors stand in the way of forming a coherent view on CIAKI. For instance, CM vary with regard to physico-chemical properties, as outlined in the first section of this review. Furthermore, CIAKI is not reliably recognized by the commonly used marker, serum creatinine concentration (SCrea). The drawbacks of SCrea are discussed before presenting the pathophysiology behind CIAKI.

Individual risk factors for the development of CIAKI will be outlined, before effective protection against CIAKI is discussed taking into account clinical trials demonstrating effectiveness and preclinical findings supplying the theoretical background.

Classes of contrast media

X-ray CM for intravascular administration are tri-iodinated benzene derivatives that rely on iodine for their radio-opacity.[9] In order to achieve high attenuation, solutions with high iodine

concentration (usually 250–400 mg I/mL solution) and, therefore, high molar concentrations of benzene derivatives are required. The molar concentration is a major determinant of two important physicochemical properties of CM solutions: osmolality and viscosity. Although both high osmolality and high viscosity have been implicated to contribute to CIAKI, the current labelling of CM classes relies on their distinct osmolalities. This classification according to osmolality has historical reasons. The pioneer generation of CM comprised solutions of ionic monomers (iothalamate, diatrizoate) at high molar concentrations. As a solution's osmolality is linearly related to its molar concentration, but also increases with its ionicity, the osmolalities of first generation CM were exceedingly high (~1000–2500 mosmol/kg H_2O) compared with blood plasma (290 mosmol/kg H_2O).[10] These compounds are termed *high-osmolar* CM (HOCM) and were found to be associated with a considerable risk for CIAKI.[10–12] The development of the second generation CM focussed on lowering solution osmolality. By forming either ionic dimers (ioxaglate) or non-ionic monomers (iopromide, iopamidol, iohexol, ioversol), osmolalities of ~400–800 mosmol/kg H_2O were achieved.[10] These compounds are referred to as *low-osmolar* CM (LOCM) and their use reduced the risk for CIAKI.[10,11] The term *low osmolar* is misleading, as the osmolality of LOCM is actually *higher* than that of plasma.

The final step to take in CM development seemed obvious: *iso-osmolar* CM (IOCM), and this step was taken by creating non-ionic dimeric compounds (iodixanol, iotrolan). Pure IOCM solutions are actually hypo-osmolar, electrolytes are added to the clinically used solution to reach plasma osmolality.[13] The low osmolality achieved with the IOCM came at the price of considerably increased viscosity. At comparable iodine concentration and, thus, comparable X-ray attenuation, non-ionic dimer IOCM have about twice the viscosity of non-ionic monomer LOCM.[10,14] Note that all CM classes have markedly higher viscosities than plasma, ranging from 2.5-fold in HOCM to 11-fold in IOCM.[10]

It is important to keep in mind that the viscosity of a given CM solution increases exponentially with its molar concentration, whereas osmolality increases only linearly with concentration.[15] As will be discussed below, this concentration–viscosity relationship has important consequences for vascular and tubular fluid dynamics, and, thus, for mechanisms of CIAKI. Therefore, the current classification of CM classes according to their osmolalities is unfortunate.

Contrast media-induced acute kidney injury diagnostics: the problem with serum creatinine concentration

A widespread, rather general, definition of CIAKI is an impairment in the glomerular filtration rate (GFR) within 2 to 3 days following the intravascular administration of CM and the absence of an alternative aetiology. Thus, the diagnosis of CIAKI is not based upon a marker of *injury* (as plasma troponin is for acute myocardial injury), but on a marker of *disturbed function*, i.e. of a *decrease in GFR*. Because direct measurement of GFR by clearance methods requires tedious urine collection, in clinical practice CIAKI is diagnosed by an increase in the surrogate marker for GFR, SCrea. Also in clinical trials on CIAKI, with very few exceptions, SCrea is the only outcome measure.[16] Unfortunately, SCrea is a rather poor marker for GFR. SCrea is determined by the interplay of creatinine production, GFR, and the kinetics of creatinine distribution among the body's fluid compartments. Owing to the exponential relationship between SCrea and GFR, SCrea is very insensitive in patients with normal pre-existing renal function.[3,17,18] Moreover, SCrea is notoriously insensitive to rapid GFR changes such as the immediate GFR drop induced by CM: due to distribution kinetics, creatinine accumulation may take days, before SCrea increase fulfils diagnostic criteria.[3,18–21] Reflecting these drawbacks of SCrea, CIAKI is currently diagnosed when a certain absolute (e.g. 44 or 88 μmol/L) or percentage (e.g. 25 or 50%) increase in SCrea is observed within 48 or 72 h post-CM.[3,17,22] The ideal margins of absolute and relative increases are still a matter of debate, which has direct consequences for CIAKI incidence reported from clinical trials.[17,23–26] Likewise, the timing and frequency of post-CM SCrea measurements (e.g. 24 vs. 72 h) directly influences trial outcomes, due to the sluggish increase in SCrea.[16] An obvious case is that of outpatient procedures: as SCrea is seldom assessed at 48 or 72 h, CIAKI will often go undetected.[27]

Taken together, the poor performance of SCrea to reflect changes in GFR, sometimes even worsened by inconsistent margins and timings of measurements, is generally recognized as a major reason behind differences, if not contradictory results, in trial outcomes.[16,17,27–31] Many important questions, e.g. regarding specific prophylactic strategies or comparisons among CM, are not yet answered unequivocally, because the vast majority of clinical trials relied on SCrea as outcome measure. Thus, there is general agreement that trials with robust clinical outcome measures like requirement of dialysis are required.[16,17,27–31] Pre-clinical studies with direct measurements of GFR by clearance methods can help fill in gaps by elucidating pathophysiological mechanisms of CIAKI and by comparing specific prophylactic strategies and CM types.

Contrast media-induced acute kidney injury: outline of the pathophysiology

In spite of the clinical importance of CIAKI, our understanding of the pathophysiology behind CIAKI is still incomplete. Mechanisms underlying CIAKI include direct cytotoxic effects, auto-, and paracrine factors that perturb renal haemodynamics, altered rheological properties that affect renal haemodynamics and tubulodynamics, and regional hypoxia. All these mechanisms may act in concert. However, the mechanisms' importance varies with the CM used, with the kind and degree of pre-existing individual risk factors, and with the patient's hydration status. We will discuss the mechanisms separately to highlight mechanisms shared by all CM, in contrast to mechanisms related to physicochemical properties of CM, which vary with the different classes of CM.

Renal medullary hypoxia is pivotal to the pathophysiology of CIAKI.[11,12,32–34] The outer medulla is especially vulnerable to hypoxia: Oxygen requirements are high due to salt reabsorption

in Henle's thick ascending limbs, while oxygen delivery is sparse. Low oxygen supply to the outer medulla is due to the great distance between descending vasa recta (DVR) that supply the medulla with blood. Moreover, arterio-venous shunt diffusion results in very low oxygen tension (pO$_2$). Contrast media in the medulla affect the fragile balance between oxygen delivery and oxygen consumption by several mechanisms, the main mechanism being reduced blood perfusion (Figure 1).[32,33,35] Medullary hypoperfusion relies on increased resistance to blood flow, due, among others, to DVR vasoconstriction. In both the cortex and the medulla, CM can shift the balance between vasodilatory and vasoconstrictive factors towards vasoconstriction.[9,11,12,33] Because medullary perfusion comprises <10% of total renal blood flow (RBF), the vasoconstrictive response of total RBF to CM observed in several studies reflects cortical rather than medullary effects. The degree of medullary vasoconstriction may markedly differ from the cortex, as may the factors involved.[9,11,12,33]

Cortical vasoconstriction, or more precisely, preglomerular vasoconstriction is one cause behind CM-induced reduction in GFR (Figure 1).[11,12,33] Preglomerular constriction can also reduce medullary flow as DVR emerge from efferent arterioles, yet GFR reduction tends to reduce oxygen demand due to decreased work load of tubular reabsorption.

Because of the central role of medullary hypoxia for CIAKI, the first chapter on CIAKI pathophysiology will focus on new experimental findings that connect DVR constriction with cellular damage induced by cytotoxic properties of CM.

Osmolar and viscous properties of CM can aggravate the cytotoxic and vasoactive effects of CM, in addition, they can trigger pathophysiological mechanisms on their own.[9,12,33] High viscosity reduces GFR and medullary oxygenation and impedes urine flow, thus leading to renal retention of CM (Figure 1). Osmolality is not included in Figure 1, because its effect is ambiguous. This will be discussed in the second chapter on pathophysiology, where new findings on mechanisms related to osmolar and viscous CM properties will be highlighted.

Pathophysiological impact of cytotoxic contrast media properties and vasoconstriction

All types of CM exert cytotoxic effects in vitro: cultured cells of virtually every type including endothelial and renal tubular epithelial cells present signs of severe cell damage or apoptosis when exposed to CM.[9] Currently, there is no CM devoid of cell toxicity signs,[36] and no CM without clinical nephrotoxicity.[37] The cytotoxicity of CM may rely on iodine—iodine has a well-documented toxicity towards human cells and bacteria, being used for decades as an antiseptic agent.[38] Iodine can be released from CM due to photolysis,[39] and very small amounts of free iodine may be highly cytotoxic.[40] Factors influencing CM photolysis are time of storage and exposure to light.[40] Free iodine is thought to be responsible for the bactericidal action of iodine-based antiseptics, possible via cell membrane damage,[41] and signs of cell membrane damage have been reported in cell culture studies with CM.[9]
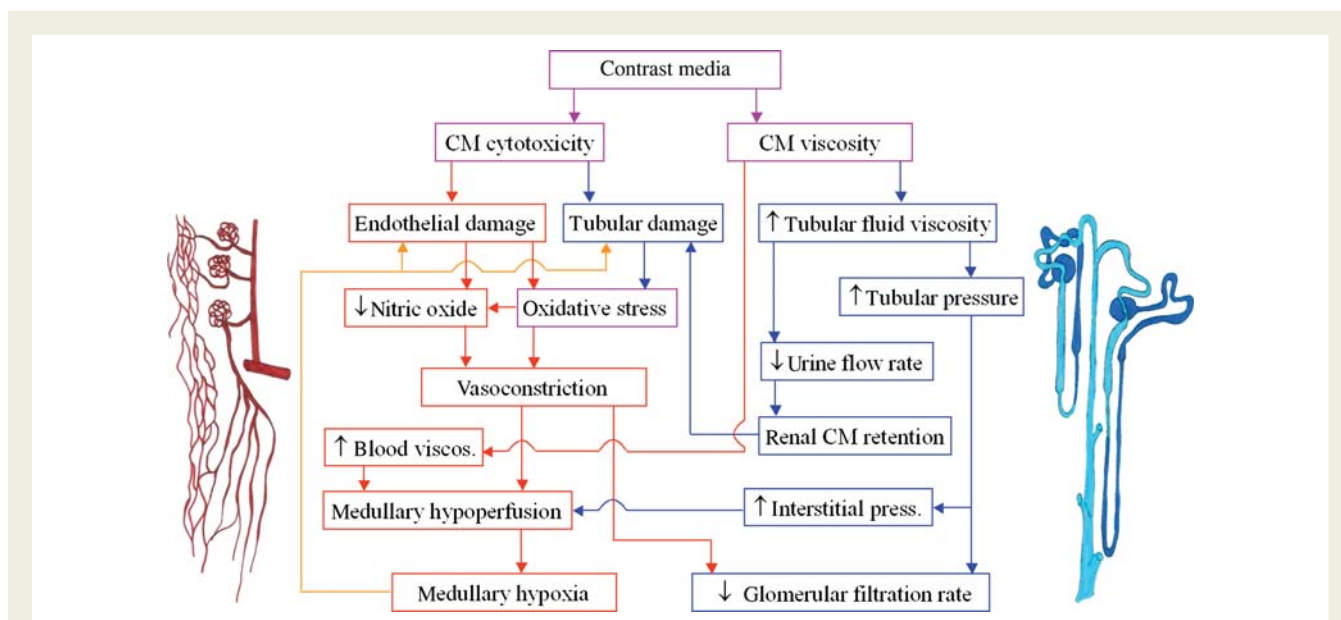

Figure 1 Simplified scheme depicting major mechanisms of contrast media-induced acute kidney injury pathophysiology. Contrast media effects that primarily affect the nephron are depicted in blue (see stylized nephrons with glomeruli, tubules and collecting duct at the far left), effects that primarily affect blood perfusion and tissue oxygenation are depicted in red (see stylized vasculature including afferent and efferent arterioles, tufts of glomerular capillaries, peritubular capillaries and descending vasa recta at the far right), and contrast media properties and effects that affect both in pink. The orange arrows indicate a feedback that may result in a vicious cycle: medullary hypoxia aggravates cellular damage that, by several factors, increases vasoconstriction.

Specific properties of CM solutions such as high osmolality may increase the intrinsic cytotoxicity of CM: the higher the osmolality of a cell culture medium, the higher the toxicity of iodine at a given concentration.[9] Intriguingly, elevated glucose concentration also aggravates CM-caused oxidative stress in mesangial cells,[42] thus providing a further explanation why diabetic patients have a higher risk for CIAKI. With regard to the role of CM ionic strength, the results of *in vitro* studies are equivocal,[9] while clinical trials indicate that ionic CM have a higher clinical nephrotoxicity than non-ionic CM.[43]

Contrast media result in medullary hypoperfusion, mainly by constricting DVR. Descending vasa recta are lined with pericytes, which allow them to actively regulate medullary blood flow.[44] As recently demonstrated in isolated DVR, CM directly constrict DVR.[45] Contrast media shift the balance between vasodilatory, e.g. nitric oxide (NO), and vasoconstrictive factors, e.g. reactive oxygen species (ROS) such as superoxide, towards vasoconstriction (*Figure 1*). Nitric oxide bioavailability in DVR is reduced by CM, superoxide concentration increases.[45] Low NO bioavailability impairs DVR endothelial function,[46] which may explain why clinical conditions associated with impaired endothelial function such as diabetes mellitus and chronic kidney disease have an increased CIAKI risk.[37] All CM types cause similar degrees of DVR constriction.[47]

Contrast media damage aortic endothelial cells *in vivo*.[48,49] It is therefore probable that impaired NO production by DVR is due to a loss of endothelial cell viability, that may be aggravated by oxidative stress.[45] Increased endothelin levels following CM as observed both *in vivo* and *in vitro*,[50] are probably also induced by endothelial damage, and could contribute to CIAKI. A further consequence of low NO production by DVR is their higher sensitivity to angiotensin II,[45] and possibly also to other vasoconstrictors, effects that would additionally aggravate medullary hypoperfusion. Tubular epithelial cells are also damaged by CM *in vitro* and *in vivo*, and CM impair various functions of tubular cells.[36,51,52] Moreover, CM cause oxidative stress, as has been found in cultured tubular cells.[53]

Pathophysiological impact of osmolar and viscous contrast media properties

Clinical trials comparing the pioneer generation HOCM (osmolalities 1000–2500 mosmol/kg H_2O) with the second generation LOCM (osmolalities: 400–800) indicated that lowering the compounds' osmolality reduced the incidence of CIAKI. In fact, a correlation between osmolality and nephrotoxicity was observed for CM with osmolalities >800.[10,12] Because adding a hyper-osmolar solution to normal tissue results in cell shrinkage, which may increase the cytotoxicity of CM,[9] the mechanism behind the deleterious effects of hyper-osmolar CM appears easy to explain. However, matters are more complex, as quantitative aspects of hyper-osmolality have to be taken into consideration.

The renal medulla is unique in that its osmolality is higher than that of all other tissues. In humans, the cells comprising the area at risk for CIAKI, the outer medulla, are constantly exposed to osmolalities of 400–600 mosmol/kg H_2O, and the cells of the inner medulla to osmolalities up to 1200. Contrast media administered intravascularly are considerably diluted before reaching the kidney, which reduces their osmolality. In the kidney, CM are freely filtered in the glomeruli, but cannot be reabsorbed by the tubuli. Because water is reabsorbed along the length of the tubule, CM become increasingly concentrated en route through the tubules, which increases tubular fluid osmolality. Direct hyperosmolar injury of renal tubular cells can occur only if tubular fluid osmolality is in excess of ambient medullary osmolality. It is perfectly possible that HOCM solutions >800 mosmol/kg H_2O are concentrated in tubules to such an extent, although, to our knowledge, this has never been shown in human beings.

A number of additional explanations have been forwarded for the higher CIAKI incidence of HOCM vs. LOCM. Because HOCM and other high-osmolar solutions can cause a distinct histological pattern with vacuolization of proximal tubular cells ('osmotic nephrosis') these alterations were thought to rely on osmotic forces. This explanation proved wrong, because the alterations are caused by pinocytosis, and were also observed following IOCM.[54,55] The CM-induced medullary hypoxia was suggested to result from increased osmotic work load that would increase oxygen consumption.[32] However, furosemide that reduces oxygen-dependent tubular transport could not prevent the CM-induced decrease in medullary pO_2.[56] High-osmolar contrast media influence the shape and rigidity of erythrocytes making it more difficult for them to flow through narrow vessels like the DVR, which probably contributes to medullary hypoperfusion.[57] Finally, it must be noted that several studies indicate that undesirable effects of HOCM may rely on their electric charge rather than their high osmolality.[9]

The realization that HOCM were associated with a higher CIAKI incidence than LOCM had two consequences. First, HOCM are virtually not used any longer in Western Europe. Second, IOCM were introduced, featuring iso-osmolality (in clinically used solutions) but at the price of higher viscosity. The fluid flow rate through a tube increases with the pressure gradient and decreases with the resistance. As Poiseuille's law describes, the resistance increases with fluid viscosity (it also increases with the tube's length and decreases with its radius). Thus, any increase in fluid viscosity will reduce the flow rate at a given pressure gradient. The ensuing congestion, in turn, will increase the upstream pressure. We are all aware of a practical implication of this viscosity effect: in order to allow flow through catheters, we preheat the most viscous CM (as viscosity decreases with increasing temperature). Considering the minute diameter and the relatively great length both of renal tubules and of DVR, it does not surprise that high CM viscosity plays a role in the pathophysiology of CIAKI, as had early been suggested by Ueda[58–60] and Lancelot.[61,62]

Today, the results of several studies add up to a comprehensive view on mechanisms mediating viscosity-induced renal damage (*Figure 1*). First, IOCM were shown to increase urine viscosity significantly more than LOCM in well-hydrated patients,[63] in well-hydrated dogs,[60,62] and rats.[63,64] In absolute terms, these increases in urine viscosity were rather small, which does not surprise, because the subjects were very well hydrated. The degree of tubular water reabsorption and, thus, the degree of CM enrichment

in the tubular fluid, depends on the subjects' hydration status. Owing to the exponential concentration−viscosity relationship, even minor increases in water reabsorption will greatly increase tubular fluid viscosity. Despite the strong recommendation of pre-hydration embodied in all guidelines, in every-day clinical practice, a considerable portion of patients are, for various reasons, not sufficiently hydrated.[30,65] Prospective trials without ample hydration should not be done. Therefore, we studied freely drinking rats that concentrated their urine to an extent comparable with non-hydrated humans.[21] As shown by *Figure 2*, injection of the IOCM, iodixanol led to a massive increase in urine viscosity. Peak urine viscosities were even higher than that of native iodixanol solution, meaning that the tubular concentration process enriched iodixanol to higher levels. In sharp contrast, following the LOCM, iopromide urine viscosity was only slightly elevated and, thus, far below the viscosity of native iopromide solution. Micropuncture studies[64] and functional MRI studies[66] also found tubular fluid viscosity much higher following IOCM than LOCM.

The large difference observed between urine viscosities following iodixanol vs. iopromide cannot be explained by the viscosity of the native solutions, for which the difference is much less (*Figure 2*). It must rely on the tubular concentration process. Water reabsorption in the tubules is driven by osmotic gradients between the tubule's lumen and the interstitium. The osmotic force of non-reabsorbable substances including all CM diminishes the osmotic gradient, thereby inducing osmodiuresis. Iopromide 370 mg I/mL with an osmolality more than twice as high as iodixanol 320 mg I/mL thus generates much more diuresis (*Figure 2*). The higher urine flow induced by iopromide counteracts tubular concentration and, thus, excessive urine viscosity levels.[21] This finding was corroborated for a variety of LOCM and IOCM *in vivo*, and by osmotic-gradient driven enrichment *in vitro*.[13,64] Remarkably, even when urine flow was increased by hydration (infusion of isotonic NaCl), urine flow was still higher and urine viscosity still much less following iopromide than iodixanol.[21,67] Taken together, the higher osmolality of LOCM bears the advantage of preventing excessive urine viscosity levels.

The high viscosity of tubular fluid following IOCM causes various intrarenal disturbances (*Figure 1*): First, the increase in tubular fluid viscosity increases resistance by the same magnitude, which increases tubular pressure[59] and hinders glomerular filtration.[58] This is also evident from *Figure 2*: following iodixanol, but not iopromide, a marked decrease in GFR is observed that parallels the increase in urine viscosity. Second, the increase in resistance markedly slows tubular flow,[63] and the intrarenal retention time of IOCM is much longer than that of LOCM as shown in rats and minipigs (*Figure 3*).[14,68] Thus, highly viscous CM have a prolonged contact time with the tubular epithelial cells, and, accordingly, tubular damage is greater, as indicated by biomarkers.[14] The longer exposure time may, furthermore, promote pinocytotic uptake by tubular cells:[54,55] In the kidneys of renally impared ZSF1 rats, IOCM were detected for weeks.[14] Third, the increase in tubular pressure will distend the tubules and, due to the rather tough renal capsule, increase renal interstitial pressure.[69] This will compress renal vessels, among them the narrow DVR. The ensuing increase in vascular resistance will probably contribute to the reduction in medullary blood flow.
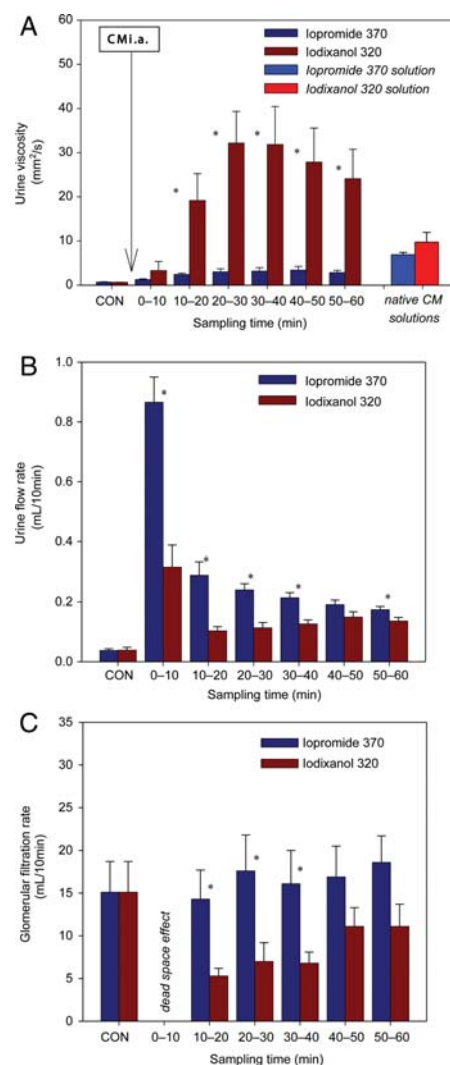

Figure 2 Viscosity of urine samples, urine flow rate, and glomerular filtration rate (measured by creatinine clearance) in rats before (CON) and following contrast media administration (six 10-min sampling periods). Pre-warmed (37°C) iopromide 370 mg I/per mL or iodixanol 320 mg I/mL was injected into the aorta (i.a.) as a bolus of 1.5 mL. Rats had access to drinking water prior to the experiment, but were not hydrated by infusions. For comparison, the viscosity of native contrast media solutions is shown at the far right ($n = 3$ measurements per CM). Viscosity was measured at 37°C. Data are mean $\pm$ SEM, $n = 7$ rats per group. *$P < 0.05$ iopromide vs. iodixanol. In all sample periods after CM, urine viscosities and urine flow rates were significantly higher than in the respective control sample. In rats receiving iodixanol, glomerular filtration rate was significantly lower than control glomerular filtration rate 10−40 min post-iodixanol injection, whereas glomerular filtration rate remained unchanged in rats receiving Iopromide. Glomerular filtration rate values for the first period following CM are not depicted, as high creatinine clearance values obtained for this period do not represent actual increases in glomerular filtration rate, but rely on the dead-space effect. Redrawn from data in Ref.[21]
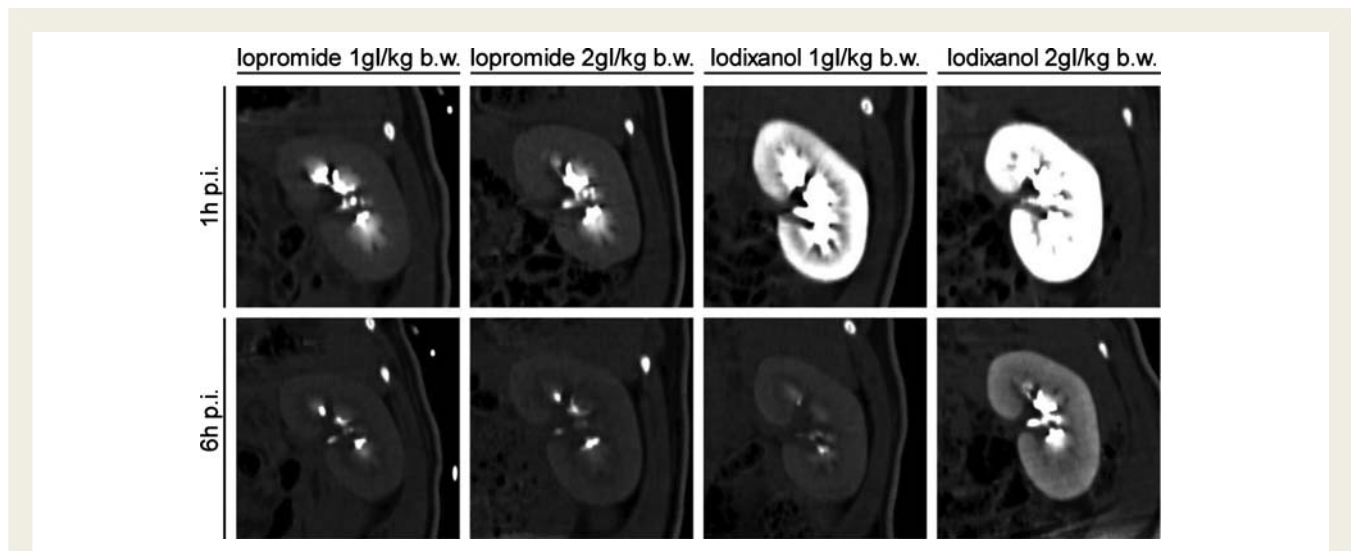
Figure 3 Renal retention of iopromide 300 mg I/mL and iodixanol 320 mg I/mL, respectively, following intravenous administration in minipigs. Representative CT scans (64-slice scanner) 1 h (upper row) and 6 h (lower row) post-injection at dosages of 1 and 2 g iodine/kg BW, respectively. Reprinted with permission from Ref.[68]

Increased viscosity of blood contributes to reduction in medullary blood flow. This was demonstrated by a study in rats that compared the effects of four solutions: iodixanol and iopromide (both at 320 mg I/mL), mannitol solution with equal osmolality as iopromide, and dextran 500 000 solution with equal viscosity as iodixanol.[63] Remarkable differences were observed in medullary perfusion and oxygenation: Only the high viscous solutions (iodixanol and dextran) resulted in long-lasting medullary vasoconstrictions and, thus, in lower medullary pO_2. The high osmolar solutions (iopromide and mannitol) did not affect these parameters. The results are in line with studies that also found medullary perfusion and oxygenation reduced, and markers of renal hypoxia increased following IOCM, but not LOCM.[14,61,62] Because dextran 500 000 is not filtered in the glomeruli, the medullary hypoperfusion induced by this high viscous solution[63] cannot rely on high tubular fluid viscosity. However, events corresponding to the tubular concentration process take place in the DVR: As blood flows through the hypertonic environment of the medulla, a portion of plasma water will leave these vessels towards the hypertonic interstitium. This will enrich CM within the vessels, thus increasing blood viscosity (*Figure 1*).

Taken together, pre-clinical studies clearly indicate that viscosity is a major pathophysiologic factor in CIAKI. It may therefore seem surprising that current meta-analyses of up to 36 prospective randomized controlled clinical trials[70–105] conclude that there is no significant difference in CIAKI incidence between LOCM and IOCM.[106–108] Apart from the heterogeneity of the trials included in the meta-analyses and the poor sensitivity of SCrea (the endpoint used in the vast majority of trials), there is a most likely explanation: Virtually all prospective clinical trials are performed according to protocols with ample pre-hydration. Because of the exponential concentration–viscosity relationship, even minor dilution will greatly reduce tubular fluid viscosity. In well-hydrated humans, we found that urine viscosity increased more when iodixanol was given as compared with iopromide.[63] This difference, although statistically significant, was small, because these well-hydrated patients' kidneys did not produce concentrated urine.[63] The undesirable effects of high tubular fluid viscosity are likely to be seen only in non-hydrated patients.

In contrast to prospective clinical trials, in everyday clinical practice, many patients are not sufficiently hydrated.[65] Such patients are certainly among the patients included in the Swedish general register on cardiac interventions that was used for studying 57 295 patients receiving CM.[109] In this study, patients given the IOCM, iodixanol experienced clinically relevant renal failure including requirement of dialysis two to three times as often as patients receiving LOCM. Likewise, in another registry study in 58 957 patients, CIAKI incidence was significantly higher following iodixanol than LOCM (as assessed by SCrea and by required dialysis, and a higher in-hospital death rate).[110] However, in this latter study, the use of iodixanol was more frequent in older patients with more co-morbidities and worse baseline renal function, and in propensity-matched models, the differences did not reach statistical significance. It is conceivable that patients with higher risk scores received better hydration; unfortunately, the authors were unable to assess for differences in hydration.[110] Taken together, in patients who are not sufficiently hydrated, LOCM probably have an advantage over IOCM.

Predicting the risk of contrast media-induced acute kidney injury

Patients undergoing percutaneous cardiac interventions have varying risks for the development of CIAKI,[1,6,12,26,65] and efforts to risk stratify patients should be performed. In a series of 1826 patients undergoing coronary procedures, the only independent predictors of CIAKI were estimated GFR, diabetes mellitus, and

CM dose.[111] Perhaps the greatest risk factor is baseline renal dysfunction.[26] Dehydration secondary to inadequate fluid intake or diuretic agents potentiates the risk.[26] Thus, adequate hydration and withdrawal of any potentially nephrotoxic medications should be performed prior to the procedure. Diabetes mellitus is a major risk factor and is synergistic with baseline GFR.[12] Proteinuria is an important marker of pre-existing renal damage and a risk factor for CIAKI.[112,113] A quantitative estimate of GFR using one of the validated formulae (e.g. Cockcroft–Gault and MDRD equations) should be made prior to angiography, if a known risk factor is positive (i.e. renal dysfunction, diabetes mellitus, >65 years, nephrotoxic drug consumption, gout, hypertension), or if risk factors are unknown.[26,114] Patients that have an estimated GFR <60 mL/min per 1.73 m^2 are at increased risk for development of AKI.[1,6,12,26,65]

Most challenging, however, are patients that present with acute coronary syndromes or myocardial infarction, particularly if complicated by hypotension or cardiogenic shock. Emergency angiography and treatment are usually required. In these circumstances, operators may be forced to use large CM doses without having sufficient time for adequate patient preparation, and in almost all studies patients with acute myocardial infarction have a high risk of CIAKI.

A number of CIAKI risk scores have been developed, the best known being that of Mehran et al.[115] In this score, a number of clinical variables related to haemodynamic stability, age, diabetes mellitus, and estimated baseline GFR are summated yielding an integer score that is directly related to the risk of CIAKI and haemodialysis.
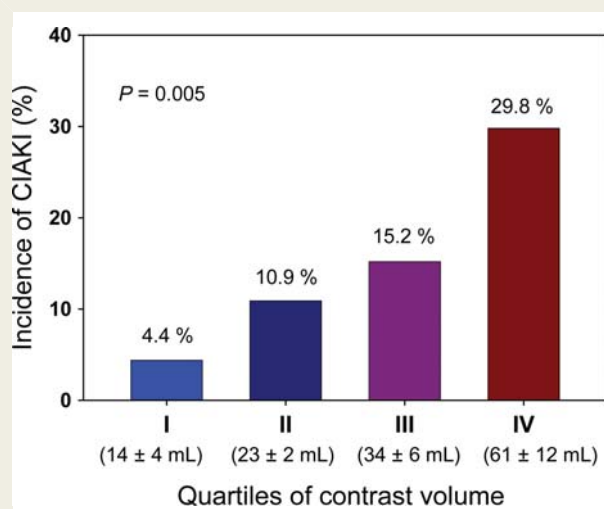

Figure 4 Dose-dependent association of volume of administered contrast media with the incidence of contrast media-induced acute kidney injury in 185 patients. Patients who received the lowest quartile of contrast media volume (mean ± SD in parenthesis below) were seven-fold less likely to develop contrast media-induced acute kidney injury compared with those with the highest quartile of contrast volume; the risk of contrast media-induced acute kidney injury doubles with every 20 mL of contrast administered. Reprinted with permission from Ref.[116]

A score ≤5 is associated with a risk of CIAKI of ≤7.5% and a risk of dialysis of 0.04%. In contrast, a score ≥16 is associated with ≥50% likelihood of CIAKI, and a risk of dialysis of over 12%.[115] All laboratories that employ CM should have adequate protocols for risk prediction, hydration, and prevention of CIAKI.

A specific CIAKI risk factor that has not received adequate attention is CM dose. Regardless of CM type, the amount of CM a patient receives is a powerful predictor of CIAKI.[116,117] In 185 patients with National Kidney Foundation stages 3–5 chronic, non-dialysis-dependent kidney disease, undergoing coronary angiography with iodixanol, the CM dose was strongly associated with the incidence of CIAKI.[116] In multivariate analysis, the only significant factor associated with CIAKI was the CM volume, and the risk doubled with every 20 mL of CM (*Figure 4*). Careful attention to procedural technique can minimize contrast load and operators should be familiar with techniques of 'ultra-low' dose angiography. Where available, biplane angiography should be used that lowers CM dose, thus significantly reducing the CIAKI risk when compared with monoplane angiography.[116]

Contrast media-induced acute kidney injury prevention: focus on hydration and contrast media dose reduction

Strategies for prevention of CIAKI have been addressed in excellent reviews and meta-analyses.[12,26,29,31,34,118–121] Pharmacological means evaluated include calcium antagonists, adenosine antagonists, *N*-acetylcysteine, prostaglandin analogs, L-arginine, statins, atrial natriuretic peptide, endothelin antagonists, dopamine, fenoldopam, hypertonic mannitol, and furosemide. With the possible exception of high-dose *N*-acetylcysteine,[122,123] no treatment has been unequivocally proven efficient in reducing CIAKI risk, while endothelin antagonists may even have detrimental effects.[12,26,29,31,34,118–121] As pointed out by many authors, the problem of the poor endpoint SCrea, the vast heterogeneity of the clinical studies, and, in some instances, publication bias has hitherto precluded a definitive appraisal of the efficacy of many pharmacological prevention strategies. The same applies for comparisons among different hydration regimens.[29,124] Pre-clinical studies using standardized protocols and direct GFR measurement in order to evaluate different hydration regimens constitute the focus of the following chapter.

The beneficial effects of hydration are generally agreed on, hence the strong recommendation included in guidelines.[26] Dehydration is one of the major individual risk factors, and it is one that is readily avoided. The role of the hydration status for CIAKI becomes obvious from the pathophysiology. Hypovolaemia triggers physiological countermeasures aiming at volume preservation, in particular, activation of the renin–angiotensin system (RAS) and of vasopressin.[125–127] Angiotensin II and vasopressin augment tubular fluid resorption, which reduces urine flow rate. In addition, angiotensin II elicits renal vasoconstriction,[45,128] which aggravates CM-induced medullary hypoperfusion. Hydration suppresses RAS and vasopressin, thus resulting in high urine flow rates that flush

the tubules and lower CM concentration in tubular fluid. Because of the exponential concentration–viscosity relationship, dilution greatly reduces tubular fluid viscosity. As shown by *Figure 5*, hydration of rats by isotonic saline at 4 mL/kg BM per hour (a standard regimen comparable with many clinical trials[129,130]), increased urine flow rate when compared with non-hydrated rats, and, to an even larger extent, attenuated the rise in urine viscosity induced by iodixanol.[21] This expedites CM excretion,[21] thus reducing the exposure time of tubular cells to potentially toxic CM. Because the increase in tubular fluid viscosity is smaller, glomerular filtration is less hindered, as seen by the diminished extent of GFR decrease (*Figure 5*).[21]

Whether bicarbonate (NaHCO$_3$) solution is superior to saline is disputed. Meta-analyses of clinical trials suggest less incidence of CIAKI as assessed by SCrea only, but no benefit when hard endpoints such as required dialysis are considered.[26,130–133] As shown by *Figure 5*, NaHCO$_3$ infusion in rats does not significantly alter the effects that iodixanol exerted on the urine flow rate, urine viscosity, and GFR, when compared with saline infusion.[67] NaHCO$_3$ was thought to help preventing against CIAKI by shutting in medullary ROS.[134] However, NaHCO$_3$ is predominantly reabsorbed by the proximal tubules,[135] so medullary NaHCO$_3$ concentrations will be low. The above results indicate that it is primarily isotonic fluid expansion itself that protects against a decline in GFR and excessive urine viscosity.[67]

Osmodiuretics have a stronger diuretic effect than saline, yet previous trials indicate that osmodiuretic mannitol promotes rather than to prevents CIAKI.[136,137] However, these studies utilized hypertonic mannitol solutions that result in rebound volume contraction. Combining the osmodiuretic effects of a non-hypertonic mannitol solution with sustained volume expansion may alleviate adverse renal effects of CM. In a recent proof of principle study,[138] a regimen with 3.2% mannitol 3.2% glucose solution infused at 12 mL/kg/h was compared with a standard regimen of isotonic saline at 4 mL/kg/h in rats (higher infusion rates required for the mannitol-glucose regimen because of the profound diuretic effect of mannitol). As shown by *Figure 5*, the mannitol-glucose regimen resulted in higher urine flow rates than the NaCl regimen, yet maintained a good volume status. By virtue of its stronger diuretic effect, the mannitol-glucose regimen greatly diminished the increase in urine viscosity and completely prevented the decrease in GFR caused by iodixanol (*Figure 5*).[138] Iso-osmolar CM may benefit most by mannitol's diuretic action, since their low osmolality causes only slight diuresis.[138]

Based upon the results of early trials,[136,137] loop diuretics such as furosemide are generally held to promote CIAKI.[26,118,121] By increasing urine output, diuretics contract extracellular volume. However, when volume contraction is counterbalanced by volume supplementation, furosemide may prove effective in preventing CIAKI, as recently demonstrated by two clinical trials.[139,140] Using a novel servocontrol device, the rate of intravenous saline infusion was adjusted to match the urine output, thus providing volume expansion even in the face of furosemide-forced diuresis. This procedure significantly reduced the CIAKI incidence in patients with chronic kidney disease[140] as well as in high-risk patients.[139]
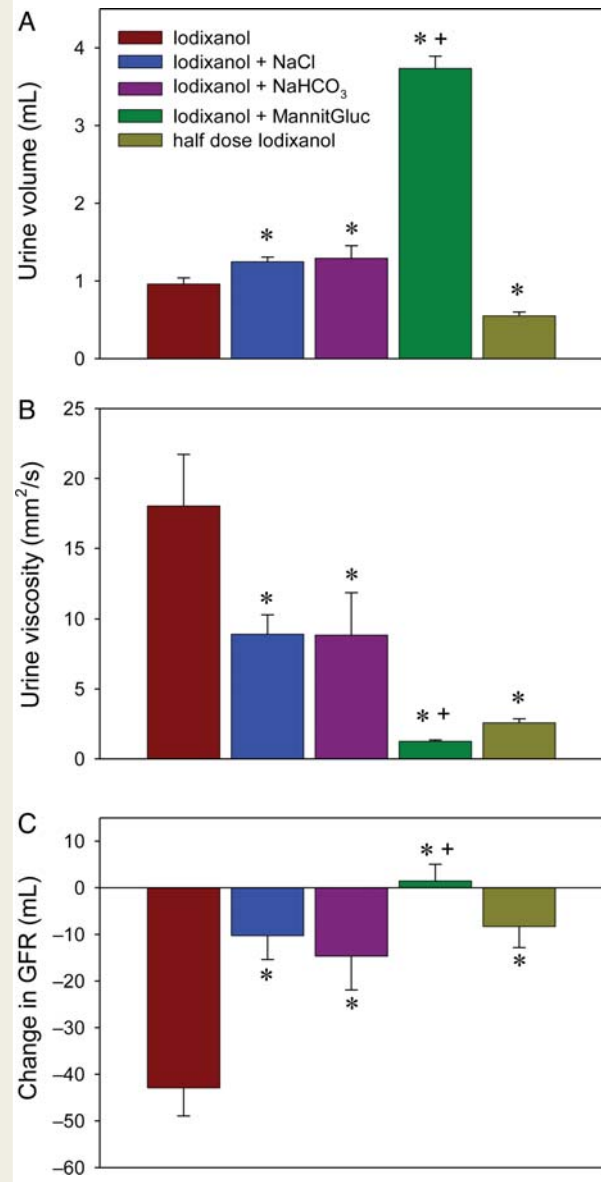

Figure 5 Urine volume, urine viscosity, and change in glomerular filtration rate within 60 min after bolus injection of iodixanol 320 mg I/mL into the thoracic aorta of five groups of rats. Rats in Groups 1–4 received a bolus injection of 1.5 mL iodixanol; rats in Group 1 were not hydrated by infusion (iodixanol), rats in Group 2 were hydrated by continuous intravenous infusion of isotonic saline (iodixanol + NaCl) at a rate of 4 mL/h/kg BM, that in Group 3 by isotonic bicarbonate solution (iodixanol + NaHCO$_3$) at 4 mL/h/kg BM, Group 4 by 3.2% mannitol 3.2% glucose solution (iodixanol + MannitGluc) at 12 mL/h/kg BM. Infusions started 60 min before iodixanol injection and were continued throughout the observation period. Rats in Group 5 received only 0.75 mL of iodixanol and were not hydrated by infusion. Viscosity was measured at 37°C. Data are means ± SEM (7–11 rats per group); *$P < 0.05$ vs. non-hydrated rats receiving the full dose (1.5 mL, iodixanol), +$P < 0.05$ vs. rats hydrated by isotonic saline. Data taken from Refs.[21,67,138]

The effects of reducing the CM dose were studied in rats not hydrated by infusions (*Figure 5*).[21] As could be expected, injections of 0.75 instead of 1.5 mL iodixanol led to a smaller increase in urine volume, at the same time, it blunted the viscosity rise and the decline in GFR. This is in full agreement with the clear-cut association of CM dose with incidence of CIAKI as assessed by SCrea in patients[116,117] and underscores the guidelines' recommendation to use the smallest amount of CM possible.[26]

Conclusions

In an attempt to provide a consistent model for CIAKI, we put forward a concerted action of cytotoxic CM effects and mechanisms related to physicochemical properties. While flowing through the medulla, CM become more concentrated. In consequence, fluid viscosity increases exponentially, thereby decreasing tubular flow and blood flow. The retained CM damages tubular cells and endothelial cells, causing medullary hypoperfusion and hypoxia. The contribution of viscosity to CIAKI varies considerably with the subject's hydration status and with the class of CM used.

Hydration prevents CIAKI by flushing the tubules. Infusing isotonic saline appears equally effective as infusing isotonic NaHCO3. Even forced diuresis by non-hypertonic mannitol solution or by furosemide may prove helpful, but only if volume supplementation is adequate. Decreasing the CM dose diminishes tubular fluid viscosity and cytotoxic effects.

There is an urgent need for a clinical marker of CIAKI more reliable than SCrea, as is a need for clinical trials with robust clinical outcome measures, e.g. requirement of dialysis.

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