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# Creatinine measurement in the radiology department 2

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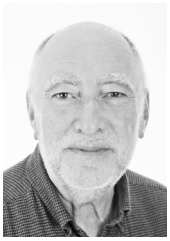

Chris Higgins
Little Acre, Main Road
Shurdington
Nr Cheltenham
Gloucester
GL51 4XF, UK
E-mail: cjhiggins@hotmail.co.uk

Clinical laboratory measurement of serum/plasma creatinine concentration has been used to assess patient kidney function for well over 50 years.

With the incorporation of creatinine analyses to blood gas and other point-of-care platforms the test is now available outside the laboratory, at the bedside and in the clinic. This is the second of two articles that highlight the clinical value of creatinine measurement in the radiology department.

An ever-increasing number of patients submitted for X-ray and other body-imaging examinations such as computed tomography (CT) and magnetic resonance imaging (MRI) scan are given image-enhancing contrast agents that can be associated with adverse effects.

Among these adverse effects are two conditions that are the focus of the two articles: nephrogenic systemic fibrosis (NSF) and contrast-induced nephropathy (CIN). The significance of serum creatinine measurement in NSF was the subject of the first article [1].

Here the focus is CIN and how measurement of serum creatinine is used to both diagnose the condition and help identify those at risk.

The article will include discussion of controversies surrounding the pathogenesis and incidence of CIN and the significance of pre-existing renal disease, but it begins with a brief general consideration of the role of plasma creatinine measurement for the assessment of renal function.

## Creatinine - a blood marker of renal function

Creatinine is an endogenous product of muscle metabolism; specifically it is derived from creatine, a substance that in its phosphorylated state is involved in ATP-mediated energy transfer within muscle cells.


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Daily rate of creatinine production from creatine depends on total muscle mass and so varies greatly between individuals, but it is of the order of 0.5 g for children, 1.5 g for adult females and 2.0 g for adult males [2].

Although there is variability between individuals, for a given individual the daily creatinine production remains pretty well constant so long as total muscle mass is unchanging.

Creatinine has no metabolic function and once released to blood from muscle cells, its fate is elimination from the body. This elimination is exclusively via the kidneys in urine.

The concentration of plasma creatinine thus reflects the balance between the rate of creatinine production by muscle tissue and the rate of elimination by the kidneys.

In healthy adults plasma creatinine concentration is maintained within the approximate reference range of 60-120 µmol/L (0.7-1.4 mg/dL) [3], with females having values at the lower end of this range and males at the higher end, reflecting their differing muscle bulk.

Most meat for consumption is muscle, so diet is a potential source of creatinine, but by comparison with creatinine derived endogenously from muscle metabolism, the amount of exogenous (dietary) creatinine is usually slight and transitory.

Still, diet is a potential source of variability in plasma creatinine concentration [4] that can be eliminated by ensuring a meat-free diet during the 12 hours prior to measurement.

The value of plasma creatinine as a marker of renal function is based on the constancy of endogenous creatinine production. Given this constancy, increase in plasma creatinine concentration can only be due to reduced elimination in urine (if dietary effect is excluded) and therefore reduced renal function.

Irrespective of its cause, reduction in kidney function is associated with increased plasma creatinine concentration, although plasma creatinine concentration is an insensitive marker of early asymptomatic chronic kidney disease.

Loss of up to a half of renal function is required for there to be discernible increase in plasma creatinine concentration. However, above this level of dysfunction plasma creatinine concentration is reliably inversely correlated with renal function.

Among patients with the most advanced end-stage renal disease, when renal replacement therapy (either dialysis or transplantation) is required for survival, plasma creatinine typically exceeds 600 µmol/L (6.8 mg/dL) and may be as high as 1000 µmol/L (11.3 mg/dL).

In the context of rapid loss of function as in acute renal failure, in which progress from normal renal function to end-stage renal disease can occur over a period of days or weeks, the inability of plasma creatinine to detect minimal loss of renal function is not a problem; the loss of function is so rapid that plasma creatinine is always raised to some extent and normal plasma creatinine concentration excludes a diagnosis of acute renal failure.

However, in the context of the much more common chronic kidney disease (CKD), in which disease progresses slowly over months and years, plasma creatinine remains within the reference range in the early asymptomatic stages, implying incorrectly no loss of renal function.

The glomerular filtration rate (GFR) is the parameter that best defines kidney function and it is a more reliable indicator of early CKD than serum creatinine.

It is technically difficult to measure directly, but plasma creatinine concentration can be used to estimate this important parameter [5], and estimated GFR (eGFR) based on plasma creatinine concentration, age, gender and ethnicity has emerged in recent years as the internationally recommended means of assessing renal function and identifying those with CKD [6-8].

The recommended equations for calculating eGFR in adults and children are described in Table I. The way eGFR is used to stage and monitor CKD is detailed in Table II.


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| |
|---|
| **eGFR (mL/min/1.73 m$^2$)** =<br>175 × [plasma creatinine (mg/dL)]$^{-1.154}$ × [age (yrs)] $^{-0.203}$ × 1.212 (if black) and × 0.742 if female<br><br>*This equation should only be used if creatinine method has been recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in conventional units (mg/dL)* |
| **eGFR (mL/min/1.73 m$^2$)** =<br>186 × [plasma creatinine (mg/dL)]$^{-1.154}$ × [age (yrs)] $^{-0.203}$ × 1.212 (if black) and × 0.742 if female<br><br>*This equation should only be used if creatinine method is not recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in conventional units (mg/dl)* |
| **eGFR (mÆ/min/1.73 m$^2$)** =<br>175 × [plasma creatinine (µmol/L) × 0.01132]$^{-1.154}$ × [age (yrs)] $^{-0.203}$ × 1.212 (if black) and × 0.742 if female<br><br>*This equation should only be used if creatinine method has been recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in SI units (µmol/l)* |
| **eGFR (mL/min/1.73 m$^2$)** =<br>186 × [plasma creatinine (µmol/l) × 0.01132]$^{-1.154}$ x× [age (yrs)] $^{-0.203}$ x× 1.212 (if black) and × 0.742 if female<br><br>*This equation should only be used if creatinine method is not recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in SI units (µmol/l)* |

TABLE Ia: Equations for estimating GFR in adults from plasma creatinine concentration

| |
|---|
| **eGFR (mL/min/1.73 m$^2$)** =<br>[k × height in cm] / Serum creatinine (mg/dL)<br><br>Value of k depends on age = 0.33 (premature babies)<br>0.45 (full term babies to 1 yr)<br>0.55 (1 yr to 13 yrs)<br>0.70 (adolescent males)<br>0.55 (adolescent females)<br><br>*This equation should only be used if creatinine method is **not** recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in conventional units (mg/dl)* |
| **eGFR (mL/min/1.73 m$^2$)** =<br>[0.41 × height in cm] / Serum creatinine (mg/dL)<br><br>*This equation should only be used if creatinine method has been recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in conventional units (mg/dl)* |
| **eGFR (mL/min/1.73 m$^2$)** =<br>[k × height in cm] / [Serum creatinine (**µ**mol/L) × 0.01132]<br><br>Value of k as above<br><br>This equation should only be used if creatinine method is ***not*** recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in SI units (mmol/l) |
| **eGFR (mL/min/1.73 m$^2$)** =<br>[0.41 × height in cm] / [Serum creatinine (**µ**mol/l) × 0.01132]<br><br>This equation should only be used if creatinine method has been recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in SI units (**µ**mol/l) |

TABLE Ib: Equations for estimating GFR in children from plasma creatinine concentration


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| STAGE | GFR | DESCRIPTION |
|---|---|---|
| Stage 1 CKD | ≥90 | Normal or increased GFR, with other evidence of renal damage (e.g. proteinuria) |
| Stage 2 CKD | 60-89 | Slight decrease in GFR, with other evidence of renal damage (e.g. proteinuria) |
| Stage 3 CKD | 30-59 | Moderate decrease in GFR with or without other evidence of renal damage |
| Stage 4 CKD | 15-29 | Severe decrease in GFR, with or without other evidence or renal damage |
| Stage 5 CKD | <15 | End-stage renal disease (renal failure) |

TABLE II: How e-GFR is used to stage chronic kidney disease (CKD)

*CKD may be stable or progressive. Progress is defined as decline in eGFR of >5mL/min/1.73 $m^2$ in one year or >10 mL/min/1.73 $m^2$ in 5 years.*

For the following discussion of contrast-induced nephropathy it is important to note that CKD is a common and growing health problem in the developed world, affecting predominantly those over 60 years.

In the US an estimated 19 million individuals (11 % of the adult population) have some degree of CKD and the number progressing to end-stage renal disease increases at an annual rate of 5-8 % in developed countries [9].

It is clinically silent in the early stages, and many individuals (40 % in one study) are quite unaware of their diminished renal function [10].

## Iodinated contrast agents (ICAs) and their nephrotoxicity

Contrast agents administered to enhance X-ray images generated conventionally and during computed tomography scan are of two broad types: negative and positive [11]. Negative contrast agents are all gases (air, oxygen or carbon dioxide) and are radiolucent, i.e. more readily penetrated by X-rays than surrounding tissues.

They appear darker on the X-ray image. Inspiration of air during chest X-ray is an example of the use of negative contrast that has been employed since the inception of diagnostic radiology at the end of the 19th century.

Positive contrast agents, which have been in use since the 1920s, are barium or iodine-containing solutions. They are radiopaque and less readily permeated by X-ray than surrounding tissue.

Application of barium contrast is limited to investigation of the gastrointestinal tract. Of all contrast agents the most commonly used are water-soluble iodine-based solutions (iodinated contrast agents, ICAs).

They can be used anywhere in the body, and although most often administered intravenously they can also be administered intrarterially, intrathecally, and intra-abdominally. It is specifically this class of contrast agents, ICAs, that are responsible for contrast-induced nephropathy (CIN).

All ICAs used since the 1950s have been based on an iodinated benzene ring, in which three of the six carbon atoms are replaced by iodine atoms [11].

Variations in side chains at the other three carbon atoms differentiate ICMs. Another structural difference is that some are monomers (one iodinated benzene ring) and some are dimers (two iodinated benzene rings). ICMs are commonly classified according to their osmolarity and ionicity.

Over the years an improved safety profile has been achieved by evolution of ICMs that were initially all monomeric, ionic and of high osmolarity (1500-2000


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mOsmol/kg) to agents that are for the most part non-ionic and have a much reduced osmolarity (either low osmolarity, 600-700 mOsmol/kg or iso-osmolar with blood plasma (290-300 mOsmol/kg)).

The newest and presumed safest contrast agent, iodixanol, is a non-ionic dimer that is iso-osmolar with blood plasma [12]. There is a significant cost differential between older high-osmolarity products (the least expensive) and newest iso-osmolar products.

As with any administered pharmaceutical product, ICAs are associated with risk of adverse effect. CIN is one of several potential adverse effects that affect a minority of patients given ICA.

The massive increased use of ICA over the past 2 decades (over 80 million ICA doses are administered annually [13]), and the increased prevalence of CIN risk factors, most notably CKD and diabetes, have inevitably raised the profile of CIN in recent years, and one study found CIN to be the third most common cause of acute renal failure occurring after admission to hospital [14].

As its name suggests CIN is a pathology of the kidneys that results from the nephrotoxicity of ICA. The mechanism of this nephrotoxicity is not fully understood, but the central pathology among those with CIN is thought to be medullary hypoxia arising from local reduction in renal blood flow [15-17].

This local reduction in renal blood flow is the presumed net effect of the observed complex vasconstrictive/vasodilatory effects of ICA on the renal vasculature.

The renal medulla is a region of kidney anatomy that is physiologically predisposed to hypoxia, normally having a $pO_2 \approx$ 10-20 mmHg, much lower than that of the renal cortex ($pO_2 \approx$ 50 mmHg) [17].

A fine concentration balance of local agents (nitric oxide, prostaglandin, vasopressin, etc.), which affect renal blood flow, normally preserves this relative hypoxia whilst preventing hypoxia severe enough to cause ischemic damage to tubule cells.

The model supposes that administration of ICA disrupts this fine balance in favor of an increased level of hypoxia and potential ischemic damage that presumably becomes real for CIN-affected patients.

Additional contributory mechanisms of ICA toxicity have been proposed, including free radical-mediated damage, the result of oxidative stress induced by ICM [18], and direct cytotoxic effect of ICA on renal tubule cells.

The oxidative stress mechanism is given credence by studies, which have shown that administration of antioxidant drugs (N-acetylcysteine, ascorbic acid) can protect against CIN [16, 18].

## Diagnosis of CIN depends on serum creatinine measurement

The acute loss of renal function associated with CIN is detectable like any other form of acute renal failure by a rise in serum creatinine concentration.

The definition of CIN that is traditionally used to make the diagnosis is an absolute increase in plasma creatinine concentration from baseline of at least 44 µmol/L (0.5 mg/dL) or a relative increase of at least 25 % within 48 hours of ICM exposure in the absence of any identifiable alternative cause for the increase [12-16].

This arbitrary definition has, however, not been universally applied and a variety of relative thresholds of increase in creatinine from baseline (20 %, 25 % 33 % or 50 %) or absolute thresholds of increase in serum creatinine (ranging from 17-88 µmol/L) have been used to define CIN [19].

Without a uniform definition determining incidence is difficult. One source suggests that incidence in the general population ranges from 0.6 to 2.3 %, depending on the CIN definition used [20]. Incidence is of course much higher (≈50 %) if only those at greatest risk of CIN are studied.

A further difficulty with diagnosing CIN in particular patients is excluding any other cause and attributing


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causality of any observed increase in serum creatinine solely to ICA.

Any number of other factors (reduced blood volume, surgery, atheroembolic disease, other potentially nephrotoxic drugs, etc.) could singly or collectively contribute to renal impairment and increased serum creatinine in particular patients given ICA [21].

An important recent study in this regard looked at serial serum creatinine concentration over a period of 10 days among 32,000 unselected hospital patients who had not received ICA [19].

This revealed that substantial day-to-day variation (both increase and decrease) in plasma creatinine is quite common among hospitalized patients.

Of particular note was the discovery that close to 20 % of this studied population met the criterion for diagnosis of CIN (i.e. 25 % increase in serum creatinine over a period of 48 hours), although none had actually received ICA.

This finding is taken as evidence that the incidence of CIN is probably much lower than previously supposed. Controversies surrounding the definition, incidence and significance of CIN are reflected in a survey of experts conducted in 1999 [22] and recently reviewed by Ellis and Cohan [23].

## Clinical course of CIN and related risk factors

The clinical course of CIN is characterized by a rise in serum creatinine within 24 hours of administering ICA that peaks within 3-7 days and returns to baseline within 14 days [15]. In a small minority (≈1 %), acute loss of renal function is of such magnitude that dialysis is necessary.

Although rapid recovery with or without the need for dialysis is the norm, CIN is associated with increased risk of morbidity and mortality, both in the short and long term. One study revealed that in-hospital mortality rate among those given ICA was just 1.1 % for those who did not develop CIN, but 7.1 % for those with CIN, and 35.7 % for those who developed CIN of such severity that dialysis was needed [24].

In the long term CIN is associated with increased risk of progressive CKD and end-stage renal failure. Two- and five-year mortality rates are increased by CIN. It remains unclear, however, to what extent these adverse associations represent cause and effect [23].

There are a number of risk factors that predispose patients to CIN. Foremost among these is pre-existing renal impairment (CKD or acute renal failure). Current expert opinion is that those with normally functioning kidneys are at "extremely low risk" of CIN [25].

Diabetes is another major risk factor. This likely reflects either overt or covert diabetic renal disease (diabetic nephropathy) rather than diabetes itself [15]. The combination of diabetes and CKD is associated with the highest risk of CIN.

Other conditions that have been found to be associated with a higher than normal risk of CIN include advanced heart failure, myeloma, blood volume depletion and hypotension. All of these conditions can be associated with subclinical renal impairment, if not CKD.

Expansion of blood volume (iv or oral fluid therapy), prior to administration of ICA, is widely used to prevent CIN among those at risk.

The type and volume of ICA used is significant. High-osmolar ICAs are associated with higher risk of CIN than low-osmolar products.

Initial evidence that the newest iso-osmolar products are safer, in terms of CIN risk, than low-osmolar products has, however, not been confirmed by some further study, and this particular issue remains controversial [15].

The nephrotoxicity of ICA is dose-dependent, so that CIN is more likely following procedures (e.g. angiography) that require the highest dose.


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Dose reduction, consistent with a diagnostically useful enhanced X-ray image, is a recommended strategy for prevention of CIN among high-risk patients.

## Identifying those at risk of CIN depends on serum creatinine measurement

Despite the many controversies surrounding the definition, incidence and pathophysiology of CIN, there is a current consensus that kidney function can be damaged by large doses of ICA [23].

It is also accepted that the less renal function a patient has at the time ICA is administered, the greater is the risk of that damage. Furthermore there are strategies available to prevent or reduce the risk of that damage.

These three propositions underpin current radiology policy for CIN prevention, which requires that all patients submitted for radiological investigation or treatment, involving prior administration of ICA, have their renal function assessed in order to determine their risk of CIN [25-27]. This allows targeted preventative strategies for those at high risk.

The recommended method for assessing renal function and therefore risk of CIN is estimated GFR (eGFR), based on plasma creatinine measurement and calculated using the appropriate formula (Table I).

eGFR > 60 mL/min/1.73 m2 indicates no CIN risk; no preventative measures are indicated for patients in this group [25-27].

High risk is indicated by eGFR < 60 mL/min/1.73 m2 and the need for preventative strategies (hydration, NAC administration, iso-osmolar products only, and lowest possible dose).

Highest risk is indicated for those eGFR with < 30 mL/min/1.73 m2; consideration of ICA avoidance and alternative diagnostic strategies might be appropriate for patients in this group, but CIN-preventative measures are required if administration of ICA is necessary.

CIN research has a long history dating back before the concept of eGFR gained wide acceptance as being superior to plasma creatinine concentration for assessment of renal function.

Although most authorities [25-27] now recommend e-GFR for assessing CIN risk, some maintain that plasma creatinine is appropriate [23]. If eGFR is not available, plasma creatinine concentrations of >115 µmol/L (>1.3 mg/dL) for men and >88 µmol/L (>1.0 mg/dL) for women have been proposed as a suitable cutoff to indicate increased risk of CIN, but higher cutoffs >133 µmol/L (>1.5 mg/dL) or >177 µmol/L (>2.0 mg/dL) have also been proposed [27,23].

The disadvantage of relying on plasma creatinine measurement for assessment of CIN risk is highlighted by the results of a recent clinical study that demonstrated many patients (40 % in this study) with an e-GFR < 60 mL/min/1.73 m2 have a plasma creatinine that by some commonly used cutoffs indicate no risk of CIN.

These results imply that patients who are at risk of CIN might be missed if plasma creatinine rather than eGFR is used to assess that risk [28].

Ideally, for maximum safety, all patients requiring ICA would have plasma creatinine measured (and eGFR calculated) in the hours prior to its administration.

Although this may be considered appropriate and practical in some institutions [26], all current guidelines [25-27] acknowledge that such blanket testing is often not logistically possible or financially justifiable.

An alternative recommended approach is to reserve creatinine testing for those whose age and clinical/drug history indicate they have, or might have renal impairment. The patient groups that require creatinine (eGFR) testing prior to ICA administration include the following:

- the elderly (>70 years)
- those with a history of renal or cardiovascular disease


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- those with hypertension/hypotension/hypovolemia
- diabetics
- the acutely/critically ill (e.g. sepsis)
- those prescribed potentially nephrotoxic drugs/or have a history of chemotherapy
- recipients of renal transplant

These "at risk of renal impairment" patients can be identified by a carefully designed patient questionnaire and/or medical case note review.

Although contemporary creatinine measurement is the most reliable assessment of current renal function, most authorities allow that for stable outpatients a plasma creatinine (eGFR) obtained within the 30-day period prior to the scheduled procedure is all that is needed.

For inpatients, whose renal function may well be in a state of flux, a more recent result (within 24 hours of the procedure) is necessary, and in an emergency setting it may be necessary to order "STAT" creatinine.

Point-of-care creatinine testing has a useful and emerging role in CIN prevention, which has been acknowledged in some guidelines [27]. In an emergency situation, the availability of point-of-care testing has obvious advantage.

When scheduled patients arrive for X-ray or CT scan and, for any number of logistical failures, their plasma creatinine (eGFR) result is not available, point-of-care measurement provides an appropriately rapid solution.

It also provides the most convenient solution for those radiology departments who want to implement a policy of assessing renal function of all patients immediately prior to scan.

Recent studies [29, 30] have demonstrated the reliability of point-of-care assays based on enzymic determination of creatinine to provide results comparable with those made in the laboratory. CIN risk can be assessed at the point of care as reliably as it is in the central laboratory, but in a fraction of the time.

## Summary

- CIN is a poorly understood adverse effect of the iodinated contrast agents given to patients prior to X-ray imaging procedures. This adverse effect is acute renal damage, evidenced by a transitory rise in plasma creatinine concentration (fall in eGFR) in the days following administration.

- Although the acute renal damage is usually self-limiting, CIN is associated with significant morbidity and mortality in the short and long term.

- Only those with renal impairment (eGFR < 60 mL/min/ 1.73m2) are at risk of CIN. Those with greatest renal impairment are at highest risk.

- It is important to identify patients at risk of CIN before they are given iodinated contrast agents because there are effective strategies for CIN prevention.

- Estimated GFR (eGFR) based on plasma creatinine measurement is the recommended method for identifying at-risk patients.

- Point-of-care creatinine testing is an acceptable alternative to laboratory testing and has a potential logistic advantage for CIN prevention in some circumstances.


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