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Contrast Medium-Induced Nephropathy (CIN) Gram-Iodine/GFR Ratio to Predict CIN and Strategies to Reduce Contrast Medium Doses

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1. Introduction

Radiographic iodine contrast media (I-CM) has been recognized as the third leading cause of hospital-acquired renal insufficiency or the most common cause among pharmaceutical agents (Nash et al., 2002) with an overall incidence of contrast medium-induced nephropathy (CIN) of 1-2% following percutaneous coronary angiography (PCA) and interventions (PCI) (Mehran & Nikolsky, 2006). The presence of multiple CIN risk factors or high-risk clinical scenarios may create a substantial risk of CIN (≈50%), acute renal failure (≈15%) requiring dialysis and an increased morbidity and mortality (Marenzi et al., 2004; McCullough et al., 2006a, 2006b). At the same time it has been argued that the risk of CIN is lower following IV administration of CM in connection with computed tomography (CT) than after IA injections during cardiac procedures (Davidson et al., 2006; Katzberg & Barrett, 2007; Katzberg & Newhouse, 2010), though there exist no comparative studies based on matched risk factors and CM doses.

Reliable prediction of pre-procedural renal function, identification of CIN risk factors, institution of adequate prophylactic regimens and to modify examination technique to reduce CM-dose are crucial to reduce patient suffering and cost since curative treatment is not available. A wide spectrum of CIN risk factors including high age, diabetes mellitus, poor cardiac function, and hemodynamic instability has been thoroughly outlined in recent reviews (McCullough et al., 2006b; Mehran & Nikolsky, 2006).

A number of prophylactic regimen studies has been performed and meta-analyzed (Kelly et al., 2008). So far no adjunctive medical pharmacological treatment has convincingly been proved to be efficacious in reducing the risk of CIN (Stacul et al., 2006) including acetylcysteine (Biondi-Zoccai et al., 2006) and hydration with sodium bicarbonate instead of saline (Zoungas et al., 2009). Haemodialysis is ineffective and hemofiltration is impractical in routine clinical practice (Stacul et al., 2006).

Thus, treating modifiable risk factors (Mehran & Nikolsky, 2006), instituting adequate intravenous volume expansion with isotonic crystalloid (Stacul et al., 2006) and withdrawal of nephrotoxic drugs, mannitol and loop diuretics are three of the four corner stones to reduce the risk of CIN (Thomsen et al., 2008a). The fourth one is to minimize the dose of the

offending agent itself, i.e. the contrast medium (Davidson et al., 2006; Kane et al., 2008; Sterner et al., 2001). Though low- and iso-osmolal CM should be substituted for high-osmolal CM (Barrett & Carlisle, 1993; Rudnick et al., 1995), the benefit of iso- over low-osmolal CM is only suggestive but not statistically significant according to a recent meta-analysis (From et al., 2010).

The present chapter will focus on:

- The risk of CIN in IV versus IA CM administration.
- Using estimated glomerular filtration rate (eGFR) in absolute terms to evaluate renal function.
- Using gram iodine (g-I) to express CM-dose instead of simply volumes and promoting g-I/eGFR ratio to maximize CM doses as a predictor of CIN instead of the Cigarroa formula (Cigarroa et al., 1989).
- Potential means to reduce CM dose for CT coronary angiography (CTCA) in patients at risk of CIN.
- The potential of using iodine concentrations and doses iso-attenuating with gadolinium (Gd) CM and other means to decrease CM-doses in patients at risk of CIN.

2. IV versus IA CM administration and CIN

The alleged lower risk of CIN following CM-enhanced CT compared with PCA/PCI has lead to conclusions such as

- "In clinical settings such as CM-enhanced multidetector CT makes it defensible to consider using CM even in patients with greater levels of background risk factors (e.g. greater degree of preexisting chronic renal insufficiency) than one would be comfortable with in the IA setting" (Katzberg & Barrett, 2007) and
- "International radiologic professional organizations should revisit the basis of their practice guidelines to reduce their implications about the danger of CIN with CM-enhanced CT"s (Katzberg & Newhouse, 2010).

Such statements and conclusions may jeopardize patient safety, since they were not based on any studies comparing the risk of CIN following CM-enhanced CT and coronary interventions in patients with matched risk factors and CM-doses. In addition, a recent study showed no difference in the incidence of CIN between CT-angiography and digital subtraction angiography (DSA) of the aortofemoral arteries in the same patients. The lack of difference occurred despite that the DSA-results may have been affected by the CM load from the CT performed 3-14 days prior to the DSA (Karlsberg et al., 2011).

It seems inexplicable that the same type of CM molecules passing through the coronary arteries via the coronary sinus to the right atrium should be more nephrotoxic than if the same molecules pass via the arm veins to the right atrium and then through the pulmonary circulation to finally reach the kidneys via the aorta. As a matter of fact in the vast majority of IA injections, the CM has to pass through the venous system before reaching the kidneys (IV relative to the kidneys), i.e. carotid, subclavian, celiac, mesenteric, distal aortic and iliaco-femoral. Left ventriculography or aortography in connection with PCA/PCI is an exception. However, in this case only a minor part will reach the kidneys directly through the aortic route, i.e. about 20% of cardiac output or e.g. 2-3 grams of iodine following a left

ventriculography (6-8 mL of an injected volume of 30-40 mL of 320 to 370 mg I/mL) of a total mean dose commonly ranging between 50 to 100 grams of iodine during a coronary procedures. Spill-over into the aorta also occurs during selective coronary artery injections and through side-holes of guiding catheters during PCI. However, the amount during each injection is so small that it will hardly affect plasma osmolality to cause any hypertonic renal effects and will therefore only affect the kidneys with the same pathophysiological mechanisms as an IV injection will do.

In the relatively few published reports of CIN following CM-enhanced CT the incidence may vary between 0 and 42% depending on definitions, degree of renal impairment and number and degree of risk factors (Katzberg & Newhouse, 2010; Nguyen et al., 2008; Polena et al., 2005; Tepel et al., 2000; Thomsen et al., 2008b). In a recent prospective study of unselected emergency patients 11% (n=70/633) increased their serum creatinine ≥44 μmol/L or ≥25% of whom 9% (n=6) developed CM-induced severe renal failure, which contributed to death in 4 of the 6 patients (Mitchell et al., 2010). Another CIN study showed that IV CM injections were actually associated with a higher mortality risk than IA administration (From et al., 2008). One explanation may be that the entire CM dose in CT is injected within one minute and thus may strike the kidneys at a considerable higher dose rate compared with a coronary arterial procedure that may last for 15-30-60 minutes or even longer.

It should also be noted that in randomized studies comparing renal effects of various CM, high-risk patients (e.g. unstable renal function, heart failure, uncontrolled diabetes, recent CM examinations, etc.) are often excluded (Barrett et al., 2006; Kuhn et al., 2008; Nguyen et al., 2008; Thomsen et al., 2008b). This bias in patient selection compared with coronary studies, where high-risk patients can not be excluded from life-saving procedures, may in part explain the illusive opinion that an IV CM injection implies a lesser risk of CIN than an IA. Thus, it may seem premature to consider the risk of CIN less following IV injections than after IA administration.

3. Evaluation of renal function

It is well recognized that serum creatinine is a poor predictor of renal function (Perrone et al., 1992), especially in elderly patients with decreasing muscle mass, the major source of creatinine. In one study 50% of patients ≥70 years with a normal serum creatinine had a GFR ≤50 mL/min (Duncan et al., 2001).

Measurement of GFR based on exogenous markers such as inulin and I-CM is regarded the best indices of the level of renal function in health and disease (Stevens et al., 2006), but is work-intensive, relatively expensive, time-consuming and therefore unsuitable in clinical practice prior to CM administration. Instead, GFR should be estimated (eGFR) taking into account not only serum creatinine but also anthropometric (weight and height) and/or demographic (gender and age) data as a measure of muscle mass by using dedicated GFR prediction equations (Stevens et al., 2006) such as the MDRD (Modification of Diet in Renal Disease) (Levey et al., 2007), CKD-EPI (Levey et al., 2009) and Lund-Malmö equations (Nyman et al., 2006). Consequently, newly developed CIN risk scores include eGFR using prediction equations (Bartholomew et al., 2004; Mehran et al., 2004). Before adapting a GFR prediction equation the following should be considered:

- The creatinine assay in the local laboratory must be calibrated according to the specific method used when the equation was developed, in practice isotope dilution mass spectrometry (IDMS) with modern equations (Myers et al., 2006).
- Dosing of drugs excreted by glomerular filtration should be based on GFR not adjusted for body surface area, i.e. absolute GFR in mL/min (Stevens et al., 2009). GFR adjusted to body surface area, i.e. relative GFR in mL/min/1.73 m^2, will overestimate actual GFR in small subjects, especially children, and underestimate it in large individuals. The MDRD and CKD-EPI equations primarily gives relative GFR, which can be converted to absolute GFR using a body surface area equation such as the commonly used Dubois formula (Dubois & Dubois, 1916 (DuBois & DuBois, 1916):

$$\text{Body surface area } (m^2) = \text{weight}^{0.425} \times (\text{height}^{0.725}) \times 0.007184$$

  with weight expressed in kg and height in cm.
- Estimated GFR is only within 30% of measured GFR in 80-85% of the patients (Levey et al., 2009; Nyman et al., 2006). Thus, a patient with eGFR of 50 mL/min may actually only have a real GFR of 35 mL/min.

4. Systemic drug exposure, gram-iodine/eGFR ratio and CIN

4.1 Area under the plasma concentration-time curve (AUC)

Following injection of CM, blood samples may be used to calculate AUC. It is directly proportional to CM dose and inversely correlated with GFR (Frennby & Sterner, 2002). AUC is a fundamental pharmacokinetic parameter used to estimate *systemic exposure* of drugs that are distributed and eliminated according to linear kinetics, like contrast media (Chen et al., 2001; Sherwin et al., 2005). The systemic exposure of such a drug is often well correlated with its *toxicity* and hence is generally held as an index for dose optimization (Chen et al., 2001). The clinical value of AUC as a predictor of nephrotoxicity has been shown for a variety of drugs and CM dose/GFR ratio was first proposed as a potential indicator for the risk of CIN in 1997 (Altmann et al., 1997) and later in 2005 (Nyman et al., 2005; Sherwin et al., 2005).

4.2 Gram-iodine/eGFR ratio

CM doses in CIN risk scores and recommendations to minimize the risk of CIN have for obscure reasons often been based only on volumes (Bartholomew et al., 2004; Davidson et al., 2006; Mehran et al., 2004). It should rather be expressed in terms of gram iodine (g-I) since concentrations of commercially available CM varies from 140-400 mg I/mL and it will also reflect the attenuating capacity. This also makes it easier to compare CM doses and expand the experience of CIN made from one examination or department to another if different concentrations are used. Furthermore, common g-I doses for radiography-based procedures, i.e. 10-120 g-I, are in the same numerical range as patients' GFR, i.e. 10-120 mL/min. Thus, forming a g-I/eGFR ratio combines CM volume and concentration, serum creatinine, age and body size into a single continuous risk variable, and provides the examiner with a simple numerical relationship and an expedient way to predict the risk of CIN. This implies also a more sophisticated relationship between CM dose and renal function than the Cigarroa formula (Cigarroa et al., 1989) that lacks CM concentration and

uses serum creatinine instead of GFR; i.e. maximum CM volume = 5 mL × body weight/serum creatinine (mg/dL). From a female perspective, with a possible increased CIN-risk compared with males (Brown et al., 2008), the g-I/eGFR ratio is preferable since creatinine-based GFR prediction equation also contains coefficients for female gender, which is lacking in the Cigarroa formula.

Mounting evidence from coronary interventions indicate that a g-I/eGFR ratio roughly >1.0 represent a significant and independent predictor of CIN (Table 1). At a g-I/GFR ratio <1.0 the reported CIN frequency was <3% (Gurm et al, 2011; Laskey et al, 2007; Nyman et al, 2008).

First author, year	Number	Indication	Volume/ eGFR ratio	Iodine Concentration (mg I/mL)	g-I/eGFR ratio
Laskey, 2007	3179	Unselected population	3.7	350[2]	1.30[5]
Nyman, 2008	391	STEMI	2.9[1]	350	1.00
Nozue, 2009	60	Stable angina	5.1	370	1.89[5]
Worasuwannarak, 2010	248	Elective diabetics	2.60	370[3]	0.98
Mager, 2010	871	STEMI	3.7	370	1.37[5]
Liu et al, 2011	277	STEMI	2.39	370[4]	0.88[5]
Total	5026				
Weighted mean value			3.50		1.24

Table 1. Gram-iodine/eGFR ratio and CIN in coronary interventions. Studies defining CM-volume/eGFR ratio or gram-iodine/eGFR ratio as a significant and independent predictor of CIN (serum creatinine rise ≥25% or ≥44 μmol/L above baseline). Weighted mean value with individual study sizes as weights were finally calculated based on log-transformation of volume/eGFR and g-I/eGFR ratio. Absolute GFR was estimated in 3 reports (Laskey et al., 2007; Nyman et al., 2008; Worasuwannarak & Pornratanarangsi, 2010) and relative GFR in the remaining.
1. Calculated from the g-I/eGFR ratio and iodine concentration.
2. Anticipated mean concentration.
3. 96% 370 mg I/mL and 4% 320 mg I/mL (e-mail communication with the authors).
4. 271 patients 370 mg I/mL and 6 patients 320 mg I/mL (e-mail communication with the authors).
5. Calculated from the volume/eGFR ratio and iodine concentration.

A most recently published registry study involving about 50,000 patients recommended a planned gram-iodine dose restricted to 0.7 x eGFR value and not to exceed 1.0 x eGFR if a CM concentration of 350 mg I/mL for PCI is anticipated (Gurm et al., 2011).

Using a g-I/eGFR <1.0 implies a safer maximum dose compared with the Cigarroa formula. A 60-year old female with a height of 160 cm, weight 70 kg and serum creatinine of 150

μmol/mL (1.7 mg/dL) results in an eGFR of 31 mL/min if the IDMS-traceable MDRD equation is used (Levey et al., 2007). At a CM concentration of 350 mg I/mL, 31 grams of iodine will give a maximum CM volume of 88 mL (31,000/350). The corresponding figures in a male will be 41 grams of iodine and 118 mL. According to the Cigarroa formula the maximum volume will be 206 mL (5 × 70/1.7) for both females and males.

Individual patient data from CT studies are lacking, but weighted mean data from CT-studies shows an 8% incidence of CIN at a g-I/eGFR ratio of 0.9 (Table 2), indicating that the ratio should also be kept <1.0 also at CT.

First author, year	Type of CM	N	CM dose (gram iodine)	eGFR (^{A}mL/min or ^{R}mL/min/1.73 m^2)	g-I/eGFR ratio	CIN (%)
Tepel, 2000[1]	LOCM	42	23	^{A}34	0.7	21
Lufft, 2002	LOCM	33	49	^{A}63	0.8	9.1
Kolehemainen, 2003	LOCM/IOCM	50	35	$^{?}$29	1.2	16
Garcia-Ruiz, 2004	LOCM	50	48	^{A}30	1.6	4.0
Becker, 2005	LOCM	100	27	^{R}41	0.7	9.0
Barrett, 2006	LOCM/IOCM	150	40	^{A}45	1.0[2]	3.9
Thomsen, 2008b[3]	LOCM/IOCM	148	40	^{A}42	1.0	6.1
Nguyen, 2008	LOCM	56	37	^{A}53	0.7	28
Kuhn, 2008	LOCM/IOCM	248	36	^{R}49	0.7	5.2
Weisbord, 2008	LOCM	421	48	^{R}53	0.9	6.5
Total		1301				
Weighted mean data			40	47	0.9	7.8

Table 2. Gram-iodine/eGFR ratio and CIN in CT studies. Literature review of non-randomized and randomized CT-studies reporting mean gram-iodine dose (or volume and concentration), mean eGFR (A = absolute GFR, R = relative GFR), g-I/eGFR ratio (calculated by the author) and incidence of CIN (serum creatinine rise ≥25% or ≥44 μmol/L above baseline). Only results for low-osmolal contrast media (LOCM) included unless there was no significant difference between LOCM and IOCM (iso-osmolal contrast media). Weighted mean value with individual study sizes as weights were finally calculated. The weighted mean of the g-I/eGFR ratio was based on log-transformation.
1. Only control group not receiving acetylcysteine included
2. Based on individual data in the report
3. Based on the CIN definition ≥25% serum creatinine increase

Note that if GFR adjusted to body surface area is used to form the g-I/GFR ratio, a higher maximum dose may be permitted in small individuals while large individuals may tolerate a larger dose certain ratio would indicate. In addition analyzing g-I/GFR ratio as a

significant independent predictor of CIN may give erroneous results. Half of the reports in Table 1 used relative eGFR (Liu et al., 2011; Mager et al., 2010; Nozue et al., 2009) and three of the ten studies in Table 2.

If a CM-based examination is deemed necessary in high risk patients, the author's strategy is to keep the g-I/GFR ratio as low as reasonably achievable, preferably below 0.5. Features classifying a patient at high risk of CIN (Kakkar et al., 2008; Mehran et al., 2004) may include:

- GFR <40 mL/min OR
- CIN risk score ≥16 (Table 3) or ≥three risk factors OR
- Congestive heart failure (NYHA III/IV) OR
- Multiple CM exposures within 72 hours

Risk factors	Integer score
Hypotension (<80 mm Hg for at least 1 h requiring inotropic support or intra-aortic balloon pump within 24 h periprocedurally)	5
Intra-aortic balloon pump	5
Congestive heart failure (New York Heart Association III/IV)	5
Age >75 years	4
Anemia (hematocrit value <39% for men and <36% for women)	3
Diabetes mellitus	3
Contrast medium volume	1 for each 100 mL
Serum creatinine >133 μmol/L (1.5 mg/dL)	4
GFR <60 mL/min/1.73 m² 40-60 20-40 <20	2 4 6

Table 3. Mehran CIN risk score (Mehran et al., 2004).

5. Reducing CM doses in CT-angiography of azotemic patients

During the past decade, CTCA has become a clinical reality as a consequence of major advances in CT technology. Vascular enhancement in CT-angiography is dependent on a number of factors such as CM dose, injection rate, plasma volume, cardiac output (CO) and x-ray tube potential (Bae & Heiken, 2005; Fleischmann, 2003; Kormano et al., 1983; Kristiansson et al., 2010).

5.1 CM distribution volume and injected dose rate

The distribution volume of CM includes the plasma volume and the extravascular extracellular space, both related to body weight. By dosing CM in relation to body weight

and using a fixed injection duration adapted to scan time, a fixed injected dose rate (mg I/kg/s) is obtained and vascular enhancement becomes essentially unrelated to body size (Awai et al., 2004a). When these principles are used, the choice of CM concentration is of no concern regarding CM enhancement (Awai et al., 2004b; Suzuki et al., 2004).

It may be anticipated that fixed CM doses irrespective of body weight have been adjusted to provide a proper enhancement in larger patients. Thus, dosing per kg implies that the risk of CIN may at least be reduced for low weight patients for the same enhancement as in a larger patient. In fact CM doses regarded sufficient for 80-100 kg patients could be halved for 40-50 kg patients to obtain the same degree of enhancement. A maximum dosing weight of 80-90 kg may be chosen, assuming that higher weights in most patients correspond to adipose tissue with minimal contribution to the distribution volume of CM.

Calculation of individual CM volumes and injection rates based on CM dose in milligram iodine/kg, concentration and injection duration can be easily done with a Microsoft Excel spreadsheet or using a dedicated computer program developed to calculate both eGFR and CM injection parameters from predefined CT protocols (OmniVis, GE Healthcare, Stockholm, Sweden).

5.2 Cardiac output and vascular CM enhancement

Arterial enhancement increases with decreasing CO (Bae et al., 1998) due to less dispersion and dilution of the CM bolus and at the same time poor cardiac function is an independent risk factor of CIN. Renal impairment may induce cardiac dysfunction and vice versa, the so called cardiorenal syndrome (Ronco et al., 2008). Since increasing age also predispose to decreasing renal function and cardiac diseases, many azotemic patients will have a reduced CO. Thus, it would be possible to decrease CM dose in most azotemic patients for the same vascular CM-enhancement as that obtained in patients with normal cardiac function. On the other hand a patient with no CIN risk factors and hyperkinetic circulation may need and tolerate a higher CM dose than normal to achieve diagnostic quality without jeopardizing renal function.

Since cardiac function may play a major role for CM-enhancement in CTCA and echocardiography results may be readily available in coronary patients, information of cardiac function should be used when tailoring the CM protocol. Another option is to use electrical velocimetry to measure CO, readily performed in the CT suite (Flinck et al., 2010). This has the advantage that measured CO will reflect cardiac function at the time of the CM injection. CO measured by echocardiography hours to days prior to CTCA may result in inadequate CM injection parameters, since CO is highly dependent on pulse rate and may vary considerably for number a of reasons.

5.3 X-ray tube potential and iodine attenuation

Attenuation of photons by iodine is highly dependent on the x-ray spectra used. As an example decreasing the x-ray tube peak kilovoltage (kVp) from commonly used 120 kVp for CT to 80 kVp brings the x-ray spectra closer to the k-edge of iodine (33.2 keV) and increases iodine attenuation by a factor 1.6 (Prokop, 2003). Thus, the CM dose may be reduced by a factor 1.6 while maintaining the attenuation at the same level as that obtained at 120 kVp.

However, the effective x-ray tube loading in terms of milliampere seconds (mAs) has to be increased by a factor four to keep image noise constant and results in 50% increase in radiation dose for the same reference object (Holmquist et al., 2009; Kristiansson et al., 2010). Thus, the diagnostic quality in terms of contrast-to-noise ratio (CNR) may be preserved. The increased radiation dose and risk of cancer induction may be of less concern in elderly azotemic patients with coronary artery disease and a limited survival time than the risk of CIN.

5.4 Halved CM doses at CT-angiography in azotemic patients

By combining CM dose tailored to body weight, a fixed injection time adapted to scan time, automatic bolus tracking, saline chaser, x-ray tube potential of 80 kVp and anticipating a decreased cardiac output in azotemic patients, it has been possible to halve the CM dose from 300 mg I/kg at 120 kVp and to 150 mg I/kg at 80 kVp when performing 16-row detector pulmonary CT-angiography in patients with eGFR <50 mL/min (Kristiansson et al., 2010). The median g-I/eGFR ratio was 0.3 and no CIN episodes were recorded. A total median dose of 10 grams of iodine was used, which is only 20-40% of non-body size related CM doses reported by those using 16-row detector for pulmonary CT-angiography at 120-140 kVp (Bae et al., 2005; Holmquist et al., 2009; Holmquist & Nyman, 2006; Johnson et al., 2007).

These principles should also be possible to adopt when performing CTCA in patients at high risk of CIN, especially with today's CT-equipments with many more detector rows, more potent x-ray tubes and dual energy options.

6. Percutaneous coronary angiography and interventions

The risk of CIN is related to the CM dose (Davidson et al., 2006; Freeman et al., 2002; Marenzi et al., 2009). Though there are numerous prophylactic studies on pharmacological agents, with hardly any unequivocally positive prophylactic effects so far (Stacul et al., 2006), studies on technical aspects of how to minimize the CM dose in coronary procedures are conspicuous by their almost total absence.

The average CM dose at PCA and/or PCI may range from 40 to 110 grams of iodine (Aspelin et al., 2003; Davidson et al., 2000; Laskey et al., 2007; Marenzi et al., 2009; Nyman et al., 2008; Rudnick et al., 1995; Worasuwannarak & Pornratanarangsi, 2010), while individual doses may range from 10 to inconceivable 500 grams of iodine (Marenzi et al., 2009).

In a Letter to the Editor Kane et al. (2008) reported on utilizing biplane angiography for PCA resulting in a mean CM dose of only 8 grams of iodine (25 mL 320 mg I/mL), half the dose used for monoplane. Despite a higher CIN risk profile among patients examined with biplane, the incidence of CIN was significantly lower compared with those studied with monoplane. Freeman et al. (2002) proposed guidelines for high-risk patients including determination of the "maximum allowed radiocontrast dose", limit necessary images (i.e. left ventriculogram or other images) and excessive "puffs", and whenever possible consider staged diagnostic and therapeutic procedures with several days in between. Another option to reduce CM dose is to use a lower concentration than the perfunctory 320 to 370 mg I/mL as discussed below.

6.1 Iodine concentration iso-attenuating with gadolinium CM

Attenuation increases with the atomic number (Z) of the atom (iodine, Z = 53; gadolinium, Z = 64). At photon energies between the k-edge of iodine (33.2 keV) and that of gadolinium (50.2 keV), iodine attenuates roughly twice as many photons as does gadolinium (Nyman et al., 2002). At all other photon energies the opposite prevail. Thus, a gadolinium (Gd) CM may be used as an x-ray CM. Before the advent of nephrogenic systemic fibrosis (NSF) (Thomsen, 2009), some investigators reported on the use of Gd-CM in a variety of diagnostic angiographic and interventional procedures (Spinosa et al., 2002; Strunk & Schild, 2004) including PCA (Barcin et al., 2006; Briguori et al., 2006; Gupta & Uretsky, 2005; Sarkis et al., 2003; Voss et al., 2004) in patients at risk of CIN due to its perceived non-nephrotoxicity (Prince et al., 1996). However, the non-nephrotoxicity of Gd-CM has been proved wrong (Buhaescu & Izzedine, 2008; Ergun et al., 2006; Sam et al., 2003). In fact, Gd-CM may have a higher, both general and renal, toxicity than I-CM in concentrations and volumes causing the same attenuation as Gd-CM (Elmståhl et al., 2004; Elmståhl et al., 2008; Nyman et al., 2002).

Moreover, the maximum dose of Gd-CM according to the manufacturers' recommendations is only 0.2-0.3 mmol/kg, though average doses used for x-ray angiographic procedures have ranged from 0.2-0.8 mmol/kg. However, average clinical I-CM doses of 40-100 grams of iodine, results in about 4-10 mmol/kg in a 75 kg individual. Thus, the use of Gd-CM is limited in terms of volume and radiodensity (Nyman et al., 2011). Despite this, diagnostic satisfactory PCA has been achieved with 1.0M Gd-CM (Briguori et al., 2006; Voss et al., 2004) or 2:1 (Barcin et al., 2006; Sarkis et al., 2003) and 1:1 mixtures (Gupta & Uretsky, 2005) of 0.5M Gd-CM and I-CM.

Angiographic experiments with a 30 cm thick water-equivalent phantom at 70 and 95 kVp indicate that iodine concentrations at 60 and 80 mg/mL, respectively, are iso-attenuating with 0.5M Gd-CM (Nyman et al., 2011). The attenuation of the 1.0M Gd-CM and the mixtures between 0.5M Gd-CM and I-CM at 320 or 350 mg I/mL would correspond to about 140-200 mg I/mL of a pure I-CM at 70-95 kVp, concentrations that are commercially available. Thus, it seems possible to perform coronary procedures with half or even one third of the standard concentrations, not at least in thinner patients patients in whom automatic or manual down-regulation of the x-ray tube potential will increase attenuation by iodine.

Precautions and techniques to save contrast media during PCA/PCI in azotemic patients are summarized as follows:

- If possible, delay examination, treat risk factors and institute hydration.
- Substitute echocardiography for left ventriculography.
- Use biplane technique if available.
- Consider to use commercially available concentrations in the range of 140-200 mg I/mL, especially in thinner patients.
- Avoid excessive "puffs" and scrutinize each series before the next one to avoid unnecessary standard projections.
- Substitute measurements with pressure wires of indeterminate stenotic lesions for multiple projections.

- Whenever possible consider staged diagnostic and therapeutic procedures with several days in between.

7. Conclusion

- Scientific evidence is lacking regarding the opinion that IV administration of CM should be less nephrotoxic than IA administration.
- Renal function should be estimated taking into account not only serum creatinine but also anthropometric (weight and height) and/or demographic (gender and age) by using dedicated GFR prediction equations.
- CM dose should be expressed in grams of iodine instead of simply volumes since it also takes into account concentration and serves as an index of diagnostic capacity.
- A g-I/eGFR ratio ≥1.0 appears to a significant and independent predictor of CIN in coronary interventions but it may also be valid for CT-angiography.
- If a CM examination is deemed necessary in patients at high risk of CIN, the author's goal is to keep the dose as low as reasonably achievable, preferably below a g-I/eGFR ratio of 0.5, which may be possible by applying a meticulous examination technique and the following CM doses and concentrations:
  - CT-angiography: 100-150 mg I/kg by using 80 kVp, mAs-compensation for constant CNR, fixed injection duration adapted to scan time, automatic bolus tracking and a saline chaser.
  - Coronary arteriography and interventions: 140-200 mg I/mL, especially in thinner patients in whom automatic or manual down-regulation of the x-ray tube potential will increase iodine attenuation.

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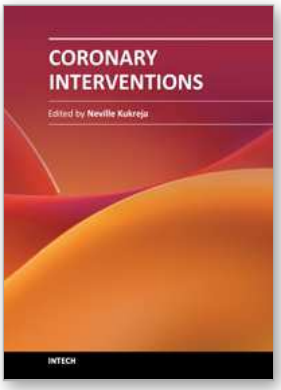

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