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Risks and Complications of Coronary Angiography: Contrast Related Complications

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1. Introduction

Since Wilhelm Röntgen reported his novel discovery of the X- Ray in 1895(Röntgen, 1898 as cited in Weinmann etal., 2005), the Diagnostic imaging has been an integral part of medicine. He was decorated by the second class of Prussian crown medal and he was also awarded the first physic Nobel Prize at 1901. Levy- Dorn was another pioneer in radiology who understood the potential importance of X-ray in medicine and opened a daily private office for medical examination with X-ray in 1896 just one year after innovation of X-ray by Röntgen. He pointed to the danger of this method to the living organism very early (Hierholzer K & Hierholzer J 1997; Nitze, 1895; as cited in Hierholzer K & Hierholzer J, 2002) Since X-rays are not sufficiently absorbed by soft tissue, contrast media (CM) is used to highlight organs or pathologies. Osborne etal reported that inorganic Iodine enhanced the urinary tracts X-ray images (Osborn etal., 1923). But the most important contributor to the field of urological imaging came from the field of agriculture when A Binz and C Räth, two scientists from the Berlin agricultural college synthesized a new organic iodinated molecule "Selectan"(Binz & Räth 1928 as cited in Hierholzer K & Hierholzer J, 2002), and a research fellow used this agent in clinical investigations. (Swick 1929a, 1929b as cited in Hierholzer K & Hierholzer J, 2002; Weinmann etal., 2005).

In 1928 an urologist, Forssmann, used one of these agents in his own coronary arteries (Hricak & Barbarive 1984).This was an unexpected methodological contribution of urological research to cardiology.

From 1929 on, serial production of Uroselectan was established. This agent was a big step forward in safety, because ionic iodide (Sodium Iodide and Lithium Iodide) cannot be used in a clinical setting. In the early 1950s, a new generation of iodinated agents was launched, which were derivatives of triiodinated benzoic acid, e.g. diatrizoate (Urografin etc.). These agents became standard in diagnostic imaging for the next 30 years and are still widely used in many countries. Almen suggested that non-ionic molecules could reduce osmolality (Almen, 1969, as cited in Weinmann etal., 2005), an idea that was the basis of safer compounds that entered routine clinical use in the 1980s. Water-soluble, non-ionic iodinated contrast agents are now the workhorses in contrast based imagings. More than 90% of contrasts media are used in western countries are non-ionic CM.

There are two main complications of contrast media. The aim of this chapter is to discuss these two major side effects of CM. the most important of these two complication is contrast induced nephropathy (CIN) which will be described in details and the other is anaphylaxis reactions to the CM which will be mentioned briefly at the end of the chapter.

2. Contrast induced nephropathy

According to the report of American Heart Association statistics committee and stroke statistics subcommittee updated at 2007, from 1979 to 2004 the number of cardiac catheterization has been increased 334%. Meanwhile from 1987 to 2004 the number of percutaneous coronary intervention (PCI) has also increased 326%.IN 2004 more than 1,297.000 cardiac catheterization and in 2006 at least 1,313,000 PCI were performed in U.S (American Heart Association statistics committee and stroke subcommittee, 2007). In 2003, about 80 million doses of CM were used worldwide (Persson, 2005). Now in U.S more tha 10 millions radiological examinations with CM are performed annually which 4 millions of these procedures are cardiac catheterizations. In western countries 6000 diagnostic cardiac catheterization and 2000 therapeutical procedure are done per 1million habitants (Costa, 2004; Ultramari etal., 2006). On the other hand the physicians are dealing with a significant increase in the prevalence and incidence of cardiovascular diseases, chronic kidney diseases and diabetes which are considered as risk factors of CIN development. All these patients are in increased need to such a diagnostic and the therapeutical maneuver.

CIN is a very interesting Issue for researchers. It is a type of acute kidney injury (AKI) which in contrast to all other causes of AKI, the exact time of injurious insult is known. Accordingly, it may help the investigators to find a more preciously diagnostic tool beside to develop more effective prophylactic and therapeutical interventions.

CIN is a matter of health conflicts. It is an important causes of increased resource utilization, prolonged hospital stay, increased in hospital and long term mortality and provoke the progression of CKD (Bartholomew etal., 2004; Goldenberg etal., 2009; Gruberg etal., 2000; James etal., 2010; McCullough etal., 1997; Solomon etal., 2009; Subramanian etal., 2007).

2.1 Physicochemical properties and classification of Contrast Media (table1)

CM is derivatives of tri-Iodinated benzene and is classified according to their Ionization, osmolality and structural properties. The ionized media are dissociated in water, while the nonionic agents are not dissociated although they are soluble in water. The ratio of iodine to dissolved particles, describes an important relationship between opacification and osmotoxicity of a contrast agent, higher this ratio, more desirable. In high osmolal CM this ratio is 1.5, which in low-osmolal and iso-osmolal CM this ratio is 3 and 6 respectively. With lowering the osmolality, the viscosity will increase. Viscosity has some deleterious effect on renal blood flow and urinary flow in tubules. Contrast agents are completely filtered. With reabsorption of water in tubules the concentration of CM reaches 50-100 times of plasma concentration.

The first generation CM was Ionic. They had 3 atoms of Iodine, one atom of sodium and 2 active osmotic particles in each molecule,therefore their osmolality was very high (1200-1800 mosm/kgH2o), so they called hyper-osmolal contrast media (HOCM). From late 80s, the next generation of these agents has been marketed. They are non-Ionic. They have only one somatically active particle. They have been known as Low-osmolal Contrast Media (LOCM) because their osmolality is lower than first generation but yet significantly higher than plasma osmolality (600—900 mosm/kgH2o). The third generation of CM is Iso-osmolal Contrast Media (IOCM) (≈300 mosm/kgH2o). They are non-ionic dimers. They have two benzene rings rather than one ring of previous generations. This structure allows 6 Iodine atoms to attach to the one cosmetically active particle.

Type	Name	osmolality (*mosm/kg water*)	ionicity	mono/dimer	amount of iodine *mg/mL*	iodine ratio	viscosity *mPa.sec at 37^{0c}*
HOCM	Iothalamat	1695	Ionic	monomer	400	3:2	2.8
LOCM	Iomeprol	720	nonionic	monomer	350	3:1	4.8
LOCM	Iopentol	683	nonionic	monomer	310	3:1	6.5
LOCM	Iopromide	586	nonionic	monomer	350	3:1	4.7
LOCM	Iopamidol	653	nonionic	monomer	300	3:1	4.6
LOCM	Ioversol	719	nonionic	monomer	320	3:1	6
LOCM	Iohexol	667	nonionic	monomer	300	3:1	5.7
LOCM	Ioxaglate	584	ionic	dimer	320	3:2	7.8
IOCM	Iodixanol	290	nonionic	dimer	320	6:1	11.4

Table 1. Types of contrast media and their physicochemical properties

2.2 Definition & diagnosis

Definition of CIN is a matter of controversy and there is no a unique accepted definition. CIN is a rapid decline in renal function after CM administration while there is obviously no other causes of acute kidney injury (AKI).

Serum creatinine is the standard marker for detecting CIN. Small changes in serum creatinine after CM exposure are seen but it is not considered clinically relevant.

In last two decade, different criteria of renal function deterioration were defined in clinical trials. But the two most popular are: 1- A 25% relative increase of serum creatinine from baseline and 2- An absolute increase of 0.5 mg/dl of serum creatinine from the base. It will happen within 2 days to one week after contrast exposure. None of these two criteria are accurate. The most common method for the assessment of kidney function consists of using the Glomerular Filtration Rate (GFR) which usually measured by creatinine clearance. But serum creatinine is not a real-time marker of change in kidney function. It is neither a specific nor a sensitive marker of GFR evaluation. In the case of rapid changes in kidney function serum creatinine has a 48-72 hours delay related to GFR changes. It cannot show the small changes of GFR too, and other factors rather than GFR may affect the blood level of serum creatinine. Even in patients with stable serum creatinine the GFR may significantly be declined. So many investigators are trying to redefine the cutoff point level of serum creatinine increment. For instance the recent definition of AKI, considers a 0.3 mg/dl increase of serum creatinine as an evidence of AKI development rather than a 0.5 mg/dl increase (Shah & Mehta, 2006). Weisbord etal showed that only a 0.25-0.3 mg/dl increase in serum creatinine after coronary angiography was accompanied with significant increase of mortality within 30 days of procedure (Weisbord etal., 2006). In another study only a 5% increases of serum creatinine within 12 hours after the contrast exposure had 75% sensitivity and 72% specificity for detecting CIN. It also had a strong correlation with the development of renal failure during next 30 days (Ribichini etal., 2010).

Recently more sensitive markers of GFR have been developed and validated. The most promising markers are Cystatin-C and Neutrophilic Gelatinase Associated Lipocaline (NGAL). Cystatin-C may be more accurate than serum creatinine in predicting renal function. In patients with GFR lower than 60ml/min, Cystatin-C may be a better marker of both early detection of CIN and prediction of major side effects like death and chronic

dialysis. But it is not known whether the increased level of Cystatin-C is due to the decreased GFR or it is released from atherosclerotic plaques during angiography .If Cystatin-C increases by more than 10% within 24 hours, then it is a good marker of CIN occurrence and further events. But an increase of less than 10% from baseline will rule out the diagnosis of CIN and the patient can be discharged without any caution (Briguori etal., 2010).There is no study to evaluate the validity of Cystatin-C in earlier time. Cystatin-C has to be better validated in different situations.

NGAL is also an early diagnostic biomarker of acute kidney injury, but studies for validating this biomarker in CIN are limited. It's specificity and sensitivity in diagnosis of CIN in children has been identified (Hirsch etal., 2007).

The most accurate method for measuring GFR is radionuclide techniques which are expensive and labor-intensive. The Cockcroft-Gault or MDRD equations are useful for the calculation of GFR in clinic.

The problem with Studies, regarding CIN is that nearly in all these studies contrast nephropathy is defined by serum creatinine increment which is a soft outcomes value. If hard outcomes like the need for dialysis, readmission, other clinical complications and death are considered, it may cause better understanding the nature of AKI including CIN and therefore its better management. It may also be more useful if RIFLE classification is taken into account rather than Acute Kidney Injury Network criteria for better definition of CIN. Further studies should be done to validate this classification for CIN diagnosis.

The differential diagnosis of CIN is cholesterol atheroemboli, volume depletion and interstitial nephritis.

2.3 Incidence

CIN is the third cause of AKI in hospitalized patients. The cumulative incidence of CIN is 10% of all AKI (Tepel etal., 2006). The incidence of CIN in patients without any risk factor is 0.6-2.3%, but in high risk patients it will be raised up to 90% (McCullough etal., 2006A ; Toprak & Cirit 2002). In two studies in 1979 and 2002, CIN was the third cause of in-hospital AKI (Nash etal., 2002). These studies showed no change in the incidence of CIN in this period (12% in 1979 and 11% in 2002).

Three factors increase the incidence of CIN in future: 1) increase in burden of CKD, 2) Increase in incidence of diabetes, and 3) increase in diagnostic and therapeutically measures requiring CM.

The incidence of CIN is dependent on the renal function. With serum creatinine more than 1.3mg/dl and more than 1 mg/dl in men and women respectively the risk of CIN will significantly increase (Lamiere etal., 2006). It has been shown that by increasing serum creatinine from 1.2 to 2.9mg/dl the risk of CIN increases from 4% to 20% (Barrett etal., 1992;). The incidence of CIN in patients with serum creatinine of 3 mg/dl with or without diabetes is more than 30%.In another study the risk of CIN in patients with serum creatinine equal to1.5mg/dl was 8%, but with serum creatinine of 6.8mg/dl the risk of CIN has been increased to 92% (McCullough etal.,1997). In patients with normal renal function, even in the presence of diabetes or other risk factors the incidence of CIN is less than 2% (Lamiere etal., 2006). The incidence of CIN in diabetic patients with normal serum creatinine is 3.7% (Rihal etal., 2002).In patient with severe renal failure and diabetes the need to dialysis will be increase to 12% if CIN develops after CM exposure (Manske etal.,1990).

With regards to coronary angiography the incidence of CIN after this procedure has been reported to be 3-14%. Only 2% of patients without diabetes and with serum creatinine of 1.1 mg/dl will develop CIN after coronary angiography (McCullough etal.,1997; Rihal etal., 2002).

2.4 Natural course

The natural history of CIN includes an increase of serum creatinine mostly after 24 hours of CM exposure, which picks in 3-7 days and return to normal within 2 weeks. Most patients are non-oliguric but the urine output is usually declined (Rudnick etal., 1995).

CIN is generally and potentially a reversible acute renal failure, but it should not be considered as a benign disorder, because in 30% of patients, renal function would not be fully recovered (Maydoon etal., 2001). The patients with CIN rarely need dialysis. According to a study among 0.8% of patients who needed dialysis after PCI, 13% remained on dialysis for lifetime (McCullough etal., 1997). Another study reported that 13-50% of CIN patients who had needed renal replacement therapy, they may remain on dialysis for the rest of life (Toprak, 2007). If even CIN recovered completely, it will cause more morbidities including bleeding, infection, prolonged hospital stay, increased resource utilization, increase in the risk of CKD and increased in-hospital and long term mortality rate (Gruberg etal., 2000; Perazella, 2009; Rihal etal., 2002). CIN also causes increase in cardiovascular morbidities. The rate of both in-hospital and long term mortality will also significantly be increased due to CIN (Gruberg etal., 2000; Liss etal., 2006; Marenzi etal., 2004; McCullough etal., 1997; Rihal etal., 2002, Weisbord etal., 2006). The overall mortality rate of patients with CIN is 1.1-34%, but it is not obvious that CIN perse is the cause of mortality or CIN is more prevalent in patients who are sicker and their co-morbidities are more than control patients (McCullough etal., 1997 Rudnick & Feldman, 2008).

The in-hospital mortality rate of CIN is estimated to be 22-25%. Meanwhile the rate of death within 5 years is significantly higher in this group of patients in comparison with control group (McCullough etal., 1997; Rihal etal., 2002). Odds of in-hospital death are related to rate of serum creatinine increment (Weisbord etal., 2006). CIN is a cause of CKD in the coming months (Liss etal., 2006). Although it is not known that whether the direct nephrotoxic effect of contrast agents is the cause of CKD or the background renal disease will be unmasked by CIN.

2.5 Risk factors

The risk factors of CIN are shown in table 2. Previous chronic kidney disease (CKD) is the leading and the single most important risk factor of CIN (McCullough etal., 2006B; Rihal etal., 2002; Rudnick etal., 1995). The most important cause of delaying or cancelling angiography is renal failure. In a recent cohort, the Glomerular Filtration Rate (GFR) of 60 ml/min considered as a cutoff point (Bartholomew etal., 2004; Mehran etal., 2004). Diabetes is the second most important risk factor of CIN (McCullough etal., 1997,2006; Rudnick etal., 2006; Weisberg etal., 1994). It remains unclear whether diabetes is a risk factor of CIN perse or it makes the patient prone to this complication because nearly all diabetic patient have overt or covert renal disease (Manske etal., 1990). So the diabetic patients with CKD are the highest risk group (McCullough etal., 2006aTepel etal., 2006; Toprak & Cirit, 2006).

Class IV heart failure is another risk factor of CIN (McCullough etal., 2006B). Many of these patients also have several other risk factors like renal disease (atherosclerotic renal disease) or decreased effective circulating volume and low GFR. Acute myocardial infarction (AMI) is another independent risk factor of CIN if the CM is given within 24hours after the AMI (Rihal etal., 2002; Marenzi etal., 2006a). S-T elevation myocardial infarction (STEMI) also increases the risk of CIN in the time of PCI. The mortality rate of these patients is high too. There is a positive correlation between the mortality rate of these patients and the volume of

contrast that is being used for coronary angiography (Marenzi etal., 2006b). Old age (Iokavou etal., 2003), hypovolemia (McCullough etal., 2006B) and hypotension are other risk factors of CIN. Hypovolemia is among few risk factors which are preventable and should be corrected promptly before starting the procedure. The medications that cause extra-cellular contraction like diuretics or cause vascular tonicity changes like non-steroidal anti-inflammatory drugs (NSAIDS) may be involved in development of CIN or at least may increase the severity of the disease. The use of angiotensin converting enzyme inhibitors (ACIs) or angiotensin receptor blockers (ARBs), while the blood pressure is in normal range are not considered contraindicated and could be continued.

Patient related factors	**Procedure related factors**
CKD	*hyper-osmolal CM*
Diabetes mellitus	*high volume of CM*
Age	*repeated exposure to CM within 24 hours*
Hypovolemia	*intra-arterial injection of CM*
Hypotension	
Low ejection fraction	
Class IV CHF	
Concomitant use of other nephrotoxics	
Hypoalbumenimeia (<3.5g/dL)	
Renal transplantation	
Recent AMI (24 hours before angiography)	
Anemia	

Table 2. Risk factors for CIN

Low hematocrite is associated with increased risk of CIN (Nikolsky etal., 2005), but there is no study to show that correction of anemia will decrease the incidence of CIN.
There are few retrospective studies showing high incidence of CIN in renal transplanted patients (up to 21%), but these patients had other risk factors like diabetes, renal failure, concomitant use of nephrotoxic agents and volume depletion (Ahuja etal., 2000). The coronary artery bypass graft (CABG) at the day of angiography will also increase the risk of CIN (Ranucci etal., 2008). Nowadays in contrast to what is mentioned in the literature multiple myeloma is not considered as a risk factor for CIN.

2.6 Type of CM

The safety of a contrast agent depends in large part on the amount of CM that must be administered. The body's ability to tolerate any substance depends on the amount given. Even isotonic saline is toxic at very large doses. High dosages that disturb the ionic and osmotic balance in the body will elicit adverse reactions without exhibiting a direct interaction with other molecules (chemotoxicity). This kind of toxicity is based on the osmotic activity of the agent or, more precisely, on the osmotic load (mosmol/kg body weight). The important properties of a CM that determine its nephrotoxicity are: osmolality, volume, and repeated use, route of use, viscosity and Ionicity.
Here we briefly review the role of each of the properties of a CM in the development of CIN.

2.7 Osmolality / viscosity (Table2)

Now the HOCM is completely replaced by LOCM or IOCM. There is no doubt that osmolality is a main factor in nephrotoxicity of a CM (Barrett & Carlisle, 1993; Rudnick & Goldfarb, 2003). Although in patients with normal renal function this factor is not important (Barrett & Carlisle, 1993). But in chronic renal failure patients, particularly in diabetic patients, use of HOCM is contraindicated (Solomon, 2005, Solomon & Dumouchel, 2006).The incidence of CIN with HOCM in patients with risk factors is two times in comparison with LOCM (Barrett & Carlisle, 1993).

All studies showed that nephrotoxicity of low osmolal media is lower than hyperosmolal one (Barrett & Carlisle, 1993; Rudnick etal., 1995), but there are many controversies about the difference of LOCM and IOCM in terms of CIN (Aspelin etal., 2003; Barrett etal., 2006; Carraro etal., 1998; Liss etal., 2006; McCullough etal., 2006C; Rudnick etal.,2006; Solomon etal.,2007; Thomsen etal., 2008).The viscosity of IOCM is higher than LOCM and this property of IOCM may offset the benefit of lower osmolality of newer developed agents (Aspelin etal., 2003; Barrett & Carlisle, 1993; Rudnick & Goldfarb, 2003, Seeliger etal., 2007). Systematic reviews were not also able to solve the contradictory results concerning the difference between low and iso-osmolal CM (Heinrich etal., 2009, Reed etal., 2009,McCullough etal., 2006C., Solomon & Dumouchel, 2006). NEPHRIC study showed that with IOCM the risk of CIN in high risk diabetic patients is significantly lower than LOCM (Aspelin etal., 2003). This study is criticized by few numbers of patients. In a meta-analysis it was also shown that IOCM are less nephrotoxic than LOCM (McCullough etal,. 2006C), but in another larger meta-analysis there was no significant difference between LOCM and ICOM in term of nephrotoxicity (Heinrich etal., 2009). In a retrospective study, LOCM was less nephrotoxic than IOCM (Liss etal., 2006). This study showed that the risk of renal failure in future is increased by IOCM whether they had CIN or not.

According to the published studies, the American college of cardiology/American Heart association (ACC/AHA) recommended that there is no difference between low and iso-osmolal agents in CKD patients. The exception is Iohexol and Ioxaglate. The IOCM has lower probability of CIN than these two LOCM (Kushner etal., 2009).

The exact role of Ionicity in development of CIN is not known. The only meta-analysis in this regard showed that Ionic IOCM is similar to nonionic LOCM (Barrett & Carlisle, 1993).

2.8 Contrast Media volume

There is a direct relation between dose of CM and CIN development (Manske etal., 1990; McCullough etal., 1997; Rudnick et al., 1995). The probability of CIN is increased with higher volume of CM. On average, in coronary angiography, PCI and CT scan 130cc, 190cc and 100 to150cc CM is used. Although it has been shown that no patient with less than 100cc CM has developed CIN (Gruberg etal., 2001; McCullough etal., 1997), but unfortunately wide range of the volume of CM defined as cut off value (30-200cc). The relation between the dose of CM and CIN is particularly evident in moderate to severe renal failure patients (CKD3-5) which they should be received ultra-low dose of CM. Unfortunately, the need for CM for interventional purposes is much higher than this safe volume (250-300cc). In the study of Rihal etal it has been shown that with each 100cc CM, the risk of CIN will be increased 12% (Rihal etal., 2002). In another study the risk of CIN is serious when the volume of CM exceeds more than 3.7 fold of creatinine clearance (Laskey etal., 2007).Repeated use of CM within 72 hours increases the risk of CIN

3. Pathogenesis

The primary mechanism of CIN is Ischemia and direct tubular toxicity of CM to epithelial tubular cells.In experimental studies, after contrast infusion there is an early brief vasodilatation of renal vasculature, followed by a long term vasoconstriction (Arakawa etal., 1996; Seeliger etal., 2007). This biphasic response has not been evident in human and mostly increase of renal blood flow has been shown (Weisberg etal.,1992). These studies carried out the direct measurement of blood flow by hemodilution techniques. Nevertheless, if renal blood flow is measured directly by an intra-renal artery guide-wire, no difference of blood flow could be detected at the time of ventriculography, while subsequently by further CM infusion, the blood flow is decreased by3.7-39.5% from base (Mockel etal., 2008).Although these studies showed mild to moderate decrease of renal blood flow after exposure to CM, these findings nevertheless cannot describe the longitudinal decrement of GFR in CIN patients.

3.1 Medullary Hypoxemia

To overcome the discrepancy between renal blood flow rate and GFR decrement, medullary Hypoxemia due to regional blood flow changes is in the focus of attention in describing the pathophysiology of CIN. According to this hypothesis, the pathogenetic axel of CIN is medullary hypoxemia (Agmon etal., 1994; Heyman etal, 2008).

Physiologically, blood flow in outer medulla is low and this part of nephron works in relatively hypoxic state. The cause of this condition is the unique structure of vasa recta which is vital for countercurrent solute exchange. Low blood flow of medulla is also important to maintain the gradient in distal nephron. Meanwhile the thick ascending Limb of Henle as a hard worker of nephron needs a high level of oxygen. Due to this contradictory status, this part of nephron is more vulnerable to ischemic injuries. The decrease of blood flow in outer medulla is critical. In normal physiological conditions, the mechanisms responsible for blood flow and tubular transport are tubule-glomerular feedback, autoregulation and glomerulo-tubular balance which operate hand in hand to maintain the integrity of nephron and the system to work properly. The vasodilators (nitric oxide, prostaglandins, adenosin, dopamin, urodilantin) and vasoconstrictors (local endothelin, AngiotensinII, vasopressin) and transport inhibitors (PDF2, Adenosin, dopamine) together balance the supply and demand of oxygen in this part of nephron. Release of vasoconstrictor mediators or blockade of vasodilator mediators may play a role in the pathogenesis of CIN (Heyman etal., 1994). CM makes imbalance of these mediators. They cause decrease of oxygen tension both in cortex and medulla. It may be due to increased work of active transport in medullary tick ascending limb of Henle in response to osmotic diuresis of hyperosmolal agents.

Proximal tubules reabsorb a scant amount of CM. The osmotic property of CM causes less water reabsorption and increased intra-tubular pressure. The distal delivery of salt and water will be increased in this state which in turn activates tubule glomerular feedback and decreased GFR.

Increased pressure of intrestitium is also a factor for decreasing GFR. It also causes medullary hypoxia. CM may decrease renal blood flow by direct vasoconstriction of renal vasculature. This effect may be due to the change of calcium metabolism (Bakris & Burnett, 1985), or local increase of adenosin (Pflueger etal., 2000) and endothelin (Bagnis etal., 1997).

By CM infusion, the oxygen tension in outer medulla is decreased, nevertheless the sodium delivery to thick ascending Limb of Henle is increased due to osmotic diuresis of CM but

the low oxygen pressure in this part of nephron is not related to the osmolality of CM (Liss etal., 1998). Administration of A1 adenosin receptor antagonists could not humiliate the decreased oxygen tension (Liss etal., 2004), but it seems that prostaglandins and nitric oxide could counteract vasoconstrictor effect of CM (Agmon etal., 1994). In animals, nitric oxide depletion has an effective role in vasoconstriction (Agmon etal., 1994; Ribeiro etal., 2004).

3.2 Reactive oxygen species

The role of oxidative stress in pathogenesis of Ischemia/reperfusion injuries is well known. Activation of oxidative stress processes in ischemia produce reactive oxygen species (ROS) which have a known role in AKI. The diseases which are considered as risk factors of CIN (CKD, CHF, and Diabetes) are associated with high oxidative stress state.

Experimental studies demonstrated that therapeutical strategies reduce the production of ROS and/or increase the nitric oxide activity and by these mechanisms halt the renal injuries due to Ischemia in different models of AKI including CIN. The rational use of antioxidants such as acetylcystein or allopurinol in preventing CIN is to lower or inhibit the oxidative stress processes.

3.3 Direct cytotoxicity

It is not known how much physicochemical properties of Iodinated CM are responsible for CIN and whether direct cytotoxicity of CM play any role in pathogenesis of CIN or not. In vitro studies showed that CM particularly HOCM is cytotoxic to mesangial and tubular cells (Itoh etal., 2006; Peer etal., 2003). The mechanism of such cytotoxicity is not known, but possibly cellular energy failure, disintegration of calcium homeostasis, apoptosis mechanisms and oxidative stress play a role (Beeri etal., 1995; Haller & Hizoh, 2004; Humes etal., 1987;). Internalization of non-ionic agents are seen in proximal tubules, (nephrosis osmotic), but these pathologic findings are also seen in patients who take CM without renal function deterioration (Persson & Tepel, 2006).CM may cause vasoconstriction by direct action on smooth muscles of arteries. More studies, should be run to show the relation of these changes with iso-osmolal contrast agents.

3.4 Others

In experimental studies CM can decrease capillary blood flow by decreasing the velocity of erythrocytes and increasing the red blood cells aggregation. HOCM also decreases erythrocyte volume and alters its membrane deformability. Recently hemeoxygenase activator is introduced as a pathomechanism of CIN development. Hemeoxygenase inhibits ROS production, suppresses pro-apoptotic proteins, activate anti-apoptotic proteins and has anti-inflammatory and vasodilatory effects. In future this enzyme may play an important role in CIN prophylaxis in human.

4. Prophylaxis

If CIN happens, the management is supportive, and because the time of insult is known the best measure is prophylaxis. Although in many studies, meta-analysis and systematic reviews have focused on prophylactic measures of CIN, nevertheless there is no an evidence-based guideline for clinical use.

No general consensus is present about the prophylactic measures of CIN other than stopping nephrotoxic agents, hydration and use of the lowest possible volume of CM and not using HOCM**.** Published guidelines are according to limited studies on very heterogenic patients. So they cause more confusion rather than better understanding and enlightment of the issue of CIN to provide the best reliable prophylactic measures. Probably the European Society of Urogenital Radiology (ESUR) guideline is yet valid (Morcos etal.,1999) and further studies within last 13 years have not been demoted its validity.

4.1 Volume expansion

Theoretically, volume expansion suppresses renin-angiotensin system activity, decreases vasoconstrictor hormones like endothelin, increases sodium diuresis, inhibits tubulo-glomerular feedback, prevents tubular obstruction, protects cells against ROS and finally dilutes the CM in tubules. Overall the toxicity of CM is decreased on tubules by hydration.

Large numbers of studies are about the role of volume expansion in preventing CIN. No controversy is present about the effectiveness of volume expansion. Up to now the volume expansion is known as the most effective measure in nephroprotection of CIN (Thomsen, 2006).This benefit has been shown in many randomized controlled trials (Bader etal.,2004; Dussol etal., 2006; Merten etal., 2004; Mueller etal., 2002; Taylor etal, 1998; Trivedi etal., 2003). But it is difficult to show that which type of fluid in how much dose and at which time is more suitable (McCullough & Soman, 2005). This obscurant is due to the heterogeneity of the studies and different definitions for CIN are used. Unfortunately these studies rarely reported the hard clinical endpoints.

Solomon et al has done the first randomized controlled trials (RCT) in this regard (Solomon etal., 1994). They showed that forced diuresis with diuretic or manitol is worse than hydration with isotonic salin or 0.45% salin. This Study did also very clearly show that volume expansion is highly effective in prevention of CIN in high risk patients and since then this prophylactic measure is the key stone of CIN prevention. Intravenous fluid therapy is also superior to oral hydration (Weisbord & Pavelsky, 2008) as it was shown in the study of Solomon etal .They reported that the control group had had 10 times more CIN than case controls. Because of such significant difference, this study was stopped early. Mueller etal also showed superiority of isotonic saline to 0.45% salin in patients with normal renal function, but if renal failure is present, there is no difference between two types of fluids (Mueller etal., 2002). The study of Merten etal compared sodium bicarbonate with isotonic saline in preventing CIN. Although this study showed better results with bicarbonate, but the study is criticized in different aspects (Merten etal., 2004).

In some studies intravenous bolus of isotonic saline just before procedure, or oral hydration from the night before the procedure, or use of NaCl tablets from 2 days before contrast exposure were examined with different results. (Bader etal.,2004; Dussol etal., 2006; Taylor etal, 1998; Trivedi etal., 2003) Volume expansion with isotonic saline is safe, simple and cheap, but not all patients taking CM will unfortunately suffer it. We showed that in patients that use of isotonic salin may be associated with the hazard of overload, use of 0.45% salin may be as effective as isotonic salin (Vasheghani-Farahani etal., 2010). It has been demonstrated that 26% of high risk patients have not been received any kind of intravenous fluid, and there was no standard about the volume and the type of fluid that were being used in the remaining patients. Urine volume more than 150^{cc} / hour is shown to be a good sign of decreased risk of CIN (Stevens etal., 1999). Cardiologists are the main target group who should know and use the strategies of volume expansion.

4.2 Sodium bicarbonate

The mechanism of sodium bicarbonate in preventing CIN is not clearly understood. Theoretically Sodium bicarbonate can expand the extracellular volume.

Alternatively it has been suggested that sodium bicarbonate will decreased the amount of ROS by increasing the PH of medulla. So the kidney will be protected from oxidant injuries (Atkins, 1986; Bakris etal., 1990; Merten etal., 2004; Morcos etal., 2005; Weisbord etal., 2008). Through this line of explanation, the main protective effect of sodium bicarbonate is not through volume expansion.

There are many concerns about the role of bicarbonate in prevention of CIN (Briguori etal., 2007; From etal., 2008; Masuda etal., 2007; Ozcan etal., 2007, Recio-Mayoral etal., 2007).Most studies compared isotonic saline and sodium bicarbonate have reported contradictory results. Masuda etal., showed Bicarbonate is more effective than saline in prevention of CIN (1.7% Vs 13%) (Masuda etal.,2007). In a meta-analysis, comparing saline and bicarbonate, it was shown that rise of serum creatinine in bicarbonate group is less than salin group, but in term of need to dialysis and death there was no difference between the two groups(Hogan etal., 2008).In the largest RCT comparing salin and bicarbonate, No differences between two groups was shown (Maioli etal., 2008). In another retrospective study including 7977 patients it was shown that the risk of CIN in sodium bicarbonate is significantly higher than salin group (From etal., 2008).We showed that addition of sodium bicarbonate to isotonic salin added no benefit to isotonic salin alone in preventing CIN (Vasheghani-Farahani etal., 2009).These controversial results and heterogeneity of studies make it difficult to be able to extract a conclusion that bicarbonate is even equal to salin in preventing CIN.

4.3 N-Acetyl Cysteine (NAC)

The main mechanism of NAC may be due to its known antioxidant peculiarity. It may diminish the oxidative stress markers ((Drager etal., 2004; Efrati etal., 2003) and / or its vasodilatory effect (Fishbane etal., 2004; Stenstorm etal., 2008).CM decrease urinary nitric oxide and NAC may inhibit this effect of CM. But it has been shown that NAC has no effect on F2- isoprostane a known marker of oxidative stress (Efrati etal., 2003).

NAC has wide first-pass metabolism, so its bioavailability will be very low if it is administered orally. Meanwhile many centers use oral NAC without any evidence-based guidelines (Marenzi etal., 2006b). The drug has also wide intra-patient variation. Its half-life after intravenous injection is 40 minutes. It has wide plasma and tissue protein binding. After oral or intravenous administration of NAC the drug cannot be detected in systemic circulation. So its effectiveness may be due to secondary effects like induction of glutathione synthesis rather than its direct effect. Because there are no tool to measure these secondary effects, no optimal dose of NAC can be defined and the dose of drug for prevention of CIN is empirical.

Clinically the use of NAC was controversial from the early time. Positive and negative results about NAC have created confusions about the role of this agent in CIN prophylaxis protocols. When the first report of NAC was published by Tepel and his coworkers (Tepel etal., 2000), it caused a universal trend to use NAC in all patients have been taking CM. They showed significant decrease in the rate of CIN in patients on NAC (2% Vs 12%). Since then many studies have been conducted with contradictory results. Now After 12 years of use of NAC in prevention of CIN, there is no general consensus about this pharmacological agent. In last decade many RCTs, non-randomized studies and meta-analyses were performed with NAC (Alonso etal., 2004; Bagshaw etal., 2006, Bagshaw & Ghali, 2004; Birck

etal., 2003; Duong etal., 2005; Dzgoeva etal., 1995, Isenbarger etal., 2003; Kshirsagar etal., 2004; Liu etal., 2005; Nallamothu etal., 2004; Onbasili etal., 2007; Pannu etal., 2004; Spargias et al., 2004; Zagler etal., 2006). Some of these studies showed that there is no positive effect for NAC in prevention of CIN (Onbasili etal., 2007; Spargias et al., 2004). On the other hand some meta-analyses showed effectiveness of NAC but the most of these meta- analyses had inconclusive results (Bagshaw etal., 2006; Nallamothu, 2004). In conclusion although huge data is available, the role of NAC in preventing CIN is moot yet. This discrepancy may be due to bias in the publishing of studies with positive results, so these studies should be considered with skepticism (Fishbane etal., 2008).

In a study on patients with myocardial infarction high dose intravenous NAC (1200mg) was effective in prevention of CIN (Marenzi etal., 2006b). Surprisingly no patient in this study had received fluid for volume expansion. An interesting but confusing issue in studies about NAC is the decrement of serum creatinine after CM exposure (Baker etal., 2003; Drager etal., 2004; Kay etal., 2003; Marenzi etal., 2006b). Probably NAC can decrease serum creatinine directly without affecting renal function (Drager etal., 2004). In this study the GFR of patients who were taken NAC four days before CM exposure was significantly higher than those patients were taken NAC only for two days. Interestingly this study and study of Hoffmann and coworkers showed that NAC may decrease serum creatinine in patients that had not received CM (Hoffmann etal., 2004). There are concerns that NAC with increasing tubular secretion of creatinine decreases the serum creatinine without any change in GFR. A recent meta-analysis found that NAC was more protective than saline infusion and the authors recommended the use of NAC because of its low cost, availability and paucity of side effects (Cigarroa etal., 1989). In contrast to this recommendation which is based on safety of the NAC, there is a report of anaphylactic reaction in 3-6% of patients receiving intra-venous NAC (Kanter, 2006).

Briefly, NAC may increase GFR in normal patients and restore GFR in high risk patients for CIN. But it is not known whether these effects are due to direct protective effect of NAC on kidney or it is due to alteration in creatinine metabolism. Some studies reported good effect of NAC while others did not find such positive effects.

In conclusion, there is no agreement about the NAC. Otherwise there is no guideline about the route of administration of NAC or the dose or the time of its administration. There is an important question whether its effect on serum creatinine is real or spurious. It is obvious that we need more good designed RCTs to solve these controversies.

4.4 Type and dose of Contrast Media

It is obvious that HOCM is associated with higher risk of CIN. So for prophylactic purposes it is recommended not to use this type of CM in any patients particularly in the patients with moderate or high risk of CIN. In analysis of present studies about the type of contrast, it is possible that different monomer CM have different toxic effects (Bettmann, 2005; Solomon etal., 2005). Up to now there is no evidence that CIN is more prevalent with LOCM than IOCM. There is a trend to use Iodixanol which is a dimeric IOCM (Barrett & Carlisle, 1993). But different studies showed no superiority of this agent over the other IOCM or LOCM (Baker etal., 2003; Boccolandro etal., 2003; Briguori etal., 2005). Over all, it seems that there is no difference between LOCM and IOCM in regard of CIN.

The other issue in preventing measures for CIN in the term of CM is the dose of the agent. So it is advised that the lowest possible dose of the CM should be administered in patients at risk of CIN. It is obvious that the higher the volume of the CM is associated with the higher

incidence of CIN (Cigarroa etal., 1989; Manske etal., 1990), but there is no magical dose of contrast to believe that below that dose, the CIN will not occur. The renal function is an important limiting factor for dose of CM. In study of Laskey etal. it was reported that if the volume of CM exceeded 3.7 times of creatinine clearance, the risk of CIN will be higher (Laskey eal., 2002). So the absolute value of contrast volume may be too low. There are 2 formulas for calculating relatively the safe volume of CM according to renal function.

$$\text{dose of CM} = \frac{5\ \frac{ml}{kg}\ contrast\,media}{serum\,creatinine\ (\frac{mg}{dl})} \quad (1)$$

Or,

$$= \frac{300\,ml\,contrast\,media}{serum\,creatinine} \quad (2)$$

In any case the dose of contrast should not be exceeded by 300 ml. For IOCM and LOCM the dose may increase by 1.5 times.

4.5 Other preventive strategies

Several studies examined different pharmacologic agents to prevent CIN. Studies about fenoldopam, dopamin, calcium channel blockers, atrial natriuretic peptide, L-arginine and statines are inconclusive. Use of ATP-MgCl2 also failed to show beneficial effect. Mesna is another pharmacologic agent that can inhibit ROS related renal injury.

4.5.1 Theophylin

High level of adenosin is a possible mechanism for occurrence of CIN. It causes afferent arteriole vasoconstriction (Haller etal., 2004; Pflueger etal., 2000). Theophylin is a non specific antagonist of adenosin receptor, so it may theoretically be beneficial. Studies about the theophylin like studies of NAC are not conclusive. Few studies showed effectiveness of theophylin or aminophylin in prevention of CIN , but in a meta-analysis no positive effect of this drug was shown (Bagshaw & Ghali, 2005). So the routine use of theophylin is not recommended. In a study on patients in ICU, infusion of 200mg theophylin half an hour before contrast exposure was superior to NAC (Huber etal., 2006) but arythmogenesity of theophylin is a problem in coronary artery disease. It is possible that in the future, theophylin is replaced by a selective adenosin receptor antagonist with less toxicity and more effectiveness than theophylin in CIN prophylaxis protocols (Pflueger etal., 2000).

4.5.2 Prostaglandin analogues

Prostaglandin I1 and E1 may have some protective effects , but it is associated with severe hypotension. So their routine use is not suggested. Prostacyclin may also have such a role.

4.5.3 Ascorbic acid

Studies about the ascorbic acid are inconclusive (Briguori etal., Spargias etal., 2004). 3 grams of ascorbic acid 2 hours before contrast exposure and 2 grams at night and in the morning after procedure may decrease the risk of CIN (Spargias etal., 2004).

4.5.4 Trimetazidine

This novel pharmacologic agent interferes with different metabolic pathways. It can prevent Ischemia-reperfusion injuries. In a RCT it was effective in preventing CIN (Onbasili etal., 2007).

4.5.5 Erythropoietin

Erythropoietin may have some role in CIN prophylaxis. Its effect has been shown in some studies (Yokomaku etal., 2008).

4.6 Renal replacement therapy

The rationality for use of renal replacement therapy after contrast exposure is to remove the CM rapidly to prevent CIN (Frank etal., 2003; Marenzi etal 2003,2006b; Vogt, 2001).Each session of dialysis can remove 60-90% of administered CM (Deray etal., 2006). CM are totally eliminated by the kidneys. They are handled by the kidneys like Inulin. Different extracorporeal techniques can efficiently remove CM. So it is rational to use these techniques just after contrast exposure to prevent or reduce the risk of CIN. Recent study on severe CKD patients not on dialysis(GFR less than 15ml/min) comparing isotonic salin and prophylactic hemodialysis showed that patients on hemodialysis were discharged from the hospital while 5% of them need hemodialysis. Meanwhile, the rate of chronic dialysis at the time of discharge in salin group was 45% (Solomon etal., 2004). Nevertheless, other studies demonstrated that hemodialysis in patients with previous history of renal failure was not beneficial and the incidence of CIN will not be changed by this modality (Deray, 2006; Vogt, 2001).One meta-analysis has supported this result (Cruz etal., 2006). Patients on dialysis do not also need dialysis after contrast exposure (Hamani etal., 1998; Morcos etal., 2002).

Only few study reported the prophylactic usefulness of hemodialysis (Lee etal., 2007; McCullough & Soman, 2005). But repeatedly it has been shown that hemodialysis has no role in preventing CIN (Cruz etal., 2006; deray, 2006; Marenzi etal., 2006b). In contrast to positive studies one RCT showed that prophylactic dialysis caused more reduction of renal function and these patients need more dialysis after exposure to contrast (Vogt etal., 2001). In one meta-analysis (Cruz etal., 2008), the beneficial effect of pre-procedural extracorporeal blood purification was obscure.

It has been shown that serum creatinine four days after contrast exposure is less in dialysis group, but this difference was not significant.

CRRT, hemodiafiltration (CVVHD) and hemofiltration are also evaluated in this regard (Gabutti etal., 2003, Marenzi etal., 2003). The only technique with enthusiasm was CVVH. But this procedure is very complex and expensive and even if further studies prove its efficacy in large clinical trials, it cannot be ordinarily used in clinic (Klarenbach etal., 2006).

Overall, given the cost and logistic necessity of extra corporeal modalities, it is difficult to suggest routine use of these techniques in prophylactic protocols of CIN and further studies may show its advantage or disadvantage.

4.7 Drugs which should be stopped before procedure

At the time of planning for procedures with CM, all drugs which are taken by patients should carefully be reviewed. There is no RCT about the harmfulness of drugs, but generally speaking the following drugs may be associated with increased risk of CIN.

4.7.1 Non-Steroid Anti-Inflammatory Drugs (NSAIDs)

Case reports and clinical experiences have shown that NSAIDs may increase the incidence of CIN. There is no difference between selective or non selective cycloxygenase inhibitors. They should be stopped several days before procedure.

4.7.2 Antihypertensive agents

No antihypertensive drug is contraindicated for patients that undergo for imaging with CM. But if they cause hypotension, the risk of CIN may be increased. The use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should not be stopped (Erley, 2006). Although In patients with serum creatinine 2 mg/dl or higher it may increase the rate of CIN. Cirit etal. have reported an increased risk of CIN with ACEIs (Cirit etal., 2006), nonetheless another study showed its preventive effect (Dangas etal., 2005).There is also a report that Captopril may cause decrease in incidence of CIN in diabetic patients(Gupta etal., 1999).
There is no study about ARBs.

4.7.3 Metformin

Metformin causes lactic acidosis in patients with renal failure. Otherwise uncontrolled diabetes is a risk factor of CIN. There is no RCT about metformin and CIN. It is recommended to continue the use of the drug until the night before the procedure (Bailey etal., 1996). Others have suggested the continuation of metformin in patients with normal renal function. If metformin is stopped, it is better to start it again when the physician is sure that CIN has not been happened.

4.7.4 Diuretics

Use of furosemide, manitol and endothelial receptor antagonists were associated with increased risk of CIN (Anto etal., 1981; Solomon etal., 1994; Weisberg etal., 1994).Forced diuresis increases the risk of CIN. Although there is no RCT about diuretics, nevertheless it is not theoretically rational to expand the volume from one hand and to contract it from the other hand. So it is recommended to discontinue diuretics 12 hours before the procedure and to restart it 24 hours after that.

4.7.5 Manitol

Like diuretics it may increase the risk of CIN in patients with forced diuresis (Solomon etal., 1994). The problem is raised in neurosurgical patients on manitol. It is suggested to stop the drugs several hours before CM administration and to monitor the hydration status of the patients very carefully (Erley, 2006)

5. Tools for assessment of patients at risk of CIN

In published study there is no controversy about the risk factors of CIN. But nearly all patients undergoing imaging with CM have more than one risk factor, so the investigators are looking for an innovative risk stratification model to detect the patients who are at a higher risk of CIN. There are different scoring tools that could detect the patients at risk of CIN before the procedure and accordingly the physicians can provide and modify the different preventive measures for these patients to decrease the risk of CIN.

Up to the present time there are two popular scoring models. Both of which have been introduced at 2004 and provide good tools for estimating the odds of the CIN. They are more or less similar with few differences in the terms of risk factors and scoring. According to the data of 8357 PCI patients, Mehran et al. determined the independent predictive factors of CIN and provided a scoring model for estimating potential risk of patients (Mehran etal., 2004). Bartholomew et al. also suggested another risk stratification model at the same year (Bartholomew etal., 2004). They evaluated the data of 2047 patients and determined the risk factors and their risk scoring. Table 3 shows these two models comparatively.

According to Mehran's model the risk score of less than 5 is associated with 7.2% risk of CIN and nearly no patients need dialysis (0.04%) but risk score more than 16 will increase the risk of CIN up to 57.7% and need to dialysis to 12.6%.

Bartholomew et al. reported no patients with risk score of less than 1 developed CIN and CIN had occurred in 25% of patients with risk score more than 9.

In regards to risk stratification models, some factors are not predictable before the procedure (like need to balloon pump or volume of contrast), so according to these models it is impossible to estimate the exact reliable and accurate risk of CIN in every patient.

Mehran model		*Bartholomew model*	
Risk factor	*Point*	*Risk factor*	*point*
Hypotension(BP<80 mmHg)	*5*	*Hypotension*	*1*
CHF	*4*	*CHF*	*1*
Intra-aorta balloon pump	*5*	*Intra-aorta balloon pump*	*2*
Diabetes	*3*	*Diabetes*	*1*
Volume of contrast	*1(/ each100cc)*	*Volume of contrast(>260cc/)*	*1*
Previous CKD: *Serum Creatinine> 132 mmol/L* *Or:* *GFR 40-60 ml/min* *GFR 20-40 ml/min* *GFR <20 ml/min*	 *4* *2* *4* *6*	*Creatinine clearance<60ml/min*	*2*
Anemia	*3*	*Peripheral vascular disease*	*1*
Age > 75 years	*4*	*Emergent PCI*	*2*

Table 3. Two most popular risk starfication models of cin

6. Recommendations

Until more accurate and universally accepted guidelines are developed, following recommendations which are based on different studies are useful in preventing CIN.The important issue is how to find the patients at risk before imaging procedures. There are some recommendations in this regard.

The American Radiology College (ARC) has suggested the measurement of serum creatinine in all patients who are suspected of having renal disease or those at risk of nephrotoxicity before the procedure (The committee on drugs and contrast media of the American College of Radiology, 2010). The patients at risk are those with a positive answer to any of the following statements: history of renal disease (including tumor or transplantation), familial history of renal disease, on diabetes therapy, having paraproteinemia disorders, having

collagen vascular disease, taking specific drugs such as metformin or NSAIDs or Nephrotoxic antibiotics. The ESUR has also recommended to measure serum creatinine in some specific patients (Thomsen & Morcos, 2005). Accordingly, the patients with a history of renal disease, renal surgery, proteinuria, hypertension, diabetes, gout, recent use of nephrotoxic drugs are considered high risk patients. The Urogenital Radiology Association also suggests that serum creatinine should be measured in all patients with history of chronic renal failure or those who are candidates for intra-arterial angiography or patients with at least one positive answer to the questioner (Thomsen & Morcos, 2006). 99% of patients with negative answers to all questions had serum creatinine less than 1.7 mg/dl (Thomsen, 2005).A good alternative surrogate marker to the serum creatinine is to measure GFR according to one of the MDRD formulas in all patients with any risk factors of CIN, because the serum creatinine has limitation to find CKD patients.
After finding the high risk patients there are some different preventive measures for people at different risks. But some general recommendations should be taken into account for all patients whether they have risk factor(s) or not.

6.1 General recommendations for all patients taking CM

1. Evaluation of risks in all patients planned to take CM.
2. Measurement of serum creatinine in all high risk patients before and after procedure.
3. List the risk factors according to present risk score models.
4. Encouraging all patients to drink water before procedure.
5. All patients should be taken LOCM or IOCM.
6. The dose of CM should be as low as possible.
7. Continuing use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers is not contraindicated
8. NSAIDS should be stopped several days before procedure.
9. Use of furosemide and manitol should be stopped 12-24 hours before CM administration.
10. Stop metformin the night before procedure until ensure of not happening CIN.
11. No repetition of procedure until to be sure that CIN has not been developed.

6.2 Recommendations for low risk patients

(Normal renal function and risk score≤5 according to Mehran's score)

1. All recommendations for no risk patients
2. Oral hydration (at least 500cc pre-procedure and 2500cc within 24 hours post procedure)
3. Intravenous isotonic salin in patients who are not taking oral intake at rate of 1 ml/kg/hour starting 4 hours before procedure and continuing at least for 6 hours post procedure . It is best to continue the hydration for 24 hours after procedure.
4. No repetition of procedure until serum creatinine returns to base value.

6.3 Recommendation for moderate risk patients

(Patients with CKD1-3 and/or risk score 5-15 according to Mehran's score)

1. All recommendations for low risk patients

2. Delaying the procedure in volume depleted patients or those who have blood circulation collapse or patients with CHF until stability of hemodynamic is achieved.
3. Infusion of 0.45% salin in patients at risk of volume overload.
4. If the time to procedure is less than 6 hours (in emergent angiography) a simultaneous administration of oral and IV Fluid with the dose of 3 ml/kg/hour and maximum 300cc fluid/hour is recommended. The fluid administration should be started one hour before procedure. After procedure the fluid is continued with the rate of 1 ml/kg/hr for 12 hours.
5. Use of NAC 1200mg twice daily in the day and day after the procedure. In emergency situations use of 1200mg intravenous bolus of NAC instead of first oral dose is appropriate.
6. Measurement of serum creatinine 24-48 hours after procedure in patients with moderate and severe risk factors

6.4 Recommendations for high risk patients

(CKD4-5 and/or risk score >15 according to Mehran's score)

1. All recommendations in moderate risk patients
2. Nephrology consultation
3. Use of hydration should be individualized according to volume status of each patient with considering overload hazards.
4. In ICU patients use of 200mg theophylin 30minutes before procedure, particularly if hydration protocol could not completely be follow. But remember the side effects of this drug.

7. Anaphylactic reactions

Anaphylactic reactions to CM are well known from the early use of these agents. These reactions are dermal allergic type reactions, edema, pulmonary edema, angina pectoris, arrhythmia and hypertension crisis. Mostly these side effects are mild and there is no need to treatment. The occurrence of the serious side-effects is within 20 minutes of CM administration. They are exhibited by nausea and vomiting, urticaria, pulmonary edema, bronchospasm, laryngospasm, hypotension, tachycardia, vaso-vagal responses and seizure.

In last decade the reactions to CM have significantly decreased from 5-12% to 0.2-0.7% (Sayol & Bush, 2011). It may be due to shift from HOCM to LOCM and IOCM. Anaphylactic reaction to HOCM is more than LOCM. Ionicity is also a cause of reaction to these agents and nonionic monomers are less anaphylactic. These reactions are either chemotoxic or Anaphylactic (Idio or nonidiosynchratic).The chemotoxic reaction is related to physicochemical property of CM and its severity is dependent on the dose and concentration of the agent.

The mechanisms of anaphylactic reaction are not well understood. Histamine, Leukotriens, Basophiles and prostaglandins may be mediators of this type reaction. It is unlike that antigen- antibody interaction plays any role.

Aging, history of allergy and asthma and previous history of reaction to CM, are the risk factors of anaphylactic reactions. The patients with CKD, cardiovascular disease and epilepsy are also at increased risk. Beta blockers may increase the threshold and severity of anaphylactic reactions (Kadivar & McClennan, 2010).

Treatment of anaphylactic reactions is mostly supportive. In mild reactions anti histaminic drugs are effective, but in more severe cases use of short acting steroids is mandatory and even some critical care facilities may be necessary.

8. Alternatives to Contrast Media

Very high risk patients may be in need for other imaging techniques rather than using contras media. One of these agents is Carbone dioxide which may be a good alternative to iodinated CM. It may be used solely or in conjunction with low dose of iodinated CM. The procedure is simple and the quality of images is good. With using modern technologies such as digital subtract angiography the nephrotoxicity of this method is neglectable (Kessel etal., 2002; Liss etal., 2005; Shaw & Kessel, 2006).

The other alternative is magnetic resonance angiography (MRA). Its main complication in renal failure is nephrogenic systemic fibrosis (NSF). SO in patients with moderate to severe renal failure it is contraindicated and in patients with mild renal failure its use is cautiously recommended.

9. Conclusion

Contrast agents are associated with many complications. There are two more prevalent and important complications related to contrast media: allergic reactions and CIN. The allergic reactions are preventable by knowing the high risk patients and premedication with steroids and antihistamines.

The most important complication of contrast agents is CIN, which is usually a mild to moderate AKI that is rapidly recovered. But it could be associated with increased significant morbidity and mortality. There is no treatment for developed CIN, so it should be prevented by some measures. The proved modalities for prevention of CIN are saline administration, the lowest possible dose of CM, and use of IOCM or LOCM.

All patients at risk should be evaluated carefully before the procedures with CM and the risk factors should be stratified according to available risk stratification models.

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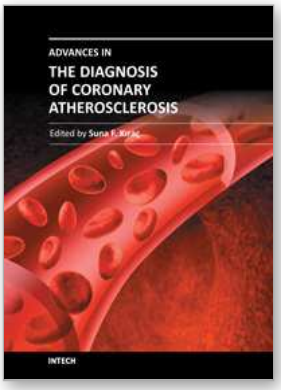

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Coronary artery disease (CAD) and its consequences are most important morbidity and mortality reasons in the developed and developing countries. To prevent hard end-points, early definitive diagnosis and optimum therapy play significant role. Novel advanced diagnostic tests which are biomarkers of inflammation, cell adhesion, cell activation and imaging techniques provide to get the best result in the detection and characterization of calcified or uncalcified atherosclerotic plaques. In spite of last developments in the imaging methods, coronary catheterization is still frequently performed. Following the first cardiac catheterization performed in 1844, date by date historical developments and the mechanics of cardiac catheterization techniques, risks associated with coronary angiography, and also, preventions and treatments of possible complications have been presented in this book. Other important issue is radiation exposure of patients and staff during coronary angiography and scintigraphy. Radiation dose reduction techniques, general radiation protection principles have been discussed in related chapters.

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