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Review Article

The Renal Problems in X-Ray Based Imaging Techniques Using Iodinated Radiographic Contrast Agents

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Abstract. Iodinated radiographic contrast agents (IRCA) are pharmaceuticals commonly used for improving the visibility of internal organs and structures in X-ray based imaging techniques such as radiography, angiography and contrast-enhanced computed tomography scans, and for performing cardiac catheterizations and percutaneous coronary interventions. Like all other pharmaceuticals, however, these agents are not completely devoid of risk. The main risk is their nephrotoxicity. Following the description of Contrast-Induced Nephropathy (CIN) and its pathogenesis, the conditions favoring the development of CIN are discussed in depth. The main predisposing condition is a pre-existing renal impairment, particularly when associated with diabetes mellitus. Then, measures to prevent CIN are suggested. The important rules in CIN prevention are: monitoring renal function, discontinuation of potentially nephrotoxic drugs, use of either iodixanol or iopamidol at the lowest dosage possible. Above all, the main procedure for prevention of CIN is an adequate hydration of the patient with either isotonic sodium chloride or sodium bicarbonate solutions.

Keywords: Iodinated radiographic contrast agents; Contrast-Induced Nephropathy; Contrast-Induced Acute Kidney Injury; Acute Renal Failure; Radiographic contrast media; Nephrotoxicity; Cell injury; Renal tubular injury

1. Introduction

Iodinated radiographic contrast agents (IRCA) are pharmaceuticals commonly used for improving the visibility of internal organs and structures in X-ray based imaging techniques such as radiography, angiography and contrast-enhanced computed tomography (CT) scans, and for performing cardiac catheterizations and percutaneous coronary interventions. IRCA are required for a large number of X-ray and CT studies to enhance vessels and organs dependent on the blood supply. After intravascular injection, they are diluted in the bloodstream and rapidly distributed throughout the extracellular fluid. The main route of excretion is through the kidneys, related to the poor binding of the agent to serum albumin. Like all other pharmaceuticals, however, these agents are not completely devoid of risk, the main one being nephrotoxicity, as we will describe later.

2. X-ray Based Imaging Techniques for Diagnostics and Intervention

Excretory Urography, also known as intravenous pyelogram, is an X-ray based examination in which anatomic and physiologic abnormalities of the kidneys, renal pelvis, ureters and bladder are detected by obtaining a timed series of images of the abdomen and pelvis after the injection of intravenous (i.v.) iodinated contrast media. It is performed using conventional X-ray. The minimum concentration of contrast medium in the glomerular filtrate necessary to produce an appreciable nephrogram is probably in the region of 70 mg iodine per cent [1]. This technique is still used for pediatric patients and for young adult patients. It has been largely supplanted by cross-sectional imaging techniques, particularly CT urography (CTU), in adults. The remaining major indication for urography is hematuria. Patients with hematuria require evaluation of both the renal parenchyma and the urothelium. But urography is less sensitive than CT in detecting renal masses and does not allow reliable differentiation of solid masses from cysts.

With the recent introduction of multi–detector row helical CT, the uroradiologic evaluation of patients with common and complex diseases is, in fact, changing rapidly. In Contrast Enhanced Computed Tomography (CECT) examinations, contrast agents are used to highlight specific tissues and parts of the body. Sufficient contrast is important in perceiving a difference in the density between areas of a CT image.

Application of multi–detector row CT to evaluate the urinary tract (termed CT urography) allows the evaluation of the renal parenchyma and urothelium. It uses CT images after i.v. injection of iodinated contrast material to obtain images of the urinary tract, to evaluate patients with hematuria, to evaluate patients with acute renal colic, to detect renal/ureteral stones, to follow patients with prior history of cancers of the kidneys or of the urinary tract, to identify abnormalities of the urinary tract either congenital or in patients with recurrent urinary infections, to assess the integrity of the urinary tract following trauma or therapeutic interventions. It can provide valuable information about other abdominal and pelvic structures and diseases that may affect them. The dose of contrast medium instilled will vary with factors, such as the patient's body weight and presence of both kidneys versus a solitary kidney (whether functionally or anatomically solitary).

An i.v. injection of an IRCA improves the visualization of organs like the liver, spleen, pancreas and kidneys and provides information about the blood supply. High resolution CT scans with thin slices and i.v. injection of IRCA provide detailed images of vascular anatomy and the adjacent bony structures.

Contrast agents are used in CT angiography [2] to delineate vessels and to provide dynamic information of blood supply. Common angiography allows visualization of the coronary arteries (Coronary Angiography), of the arteries of the lung (Pulmonary Angiography), the brain (Cerebral Angiography), the neck (Carotid Angiography), the legs or arms (Peripheral Angiography), and of the aorta (Aortography).

Traditional coronary angiography is an X-ray with radio-opaque contrast injected in the coronary arteries that shows the coronary circulation. For doing this, a catheter is inserted into the radial artery or into the inguinal femoral artery up through the blood vessel until it reaches the coronary artery; X-ray imaging is used to guide the catheter up to the coronary artery.

A Computed Tomographic Angiography [2] or computer-ized tomography angiogram is a diagnostic imaging test that combines conventional CT technique with that of traditional angiography to create images of the blood vessels in the body.

Coronary CT angiography (CCTA) is a noninvasive alternative to conventional invasive coronary angiography for detecting coronary artery stenoses and plaques. Unlike a traditional coronary angiogram, CT coronary angiography does not use a catheter inserted in the peripheral vessels up to the heart. In fact, it relies on a powerful X-ray machine to produce images of the heart and heart vessels. Since the IRCA is injected into a vein in the arm rather than into a coronary artery, as in traditional angiography, without using a catheter, CT angiography is considered noninvasive. One of the major concerns with CCTA is the amount of IRCA injected [3]. The amount of IRCA has generally been decided based on body weight, body mass index, or body surface area [4, 5].

Percutaneous coronary intervention (PCI), usually called coronary angioplasty or percutaneous transluminal coronary angioplasty (PTCA), is a non-surgical procedure used to treat the stenotic coronary arteries in coronary heart disease. During PCI, using a guidewire, the cardiologist feeds a deflated balloon on a catheter; the catheter is inserted into the radial artery or into the inguinal femoral artery up through the blood vessel until it reaches the coronary artery; X-ray imaging is used to guide the catheter up to the stenotic coronary artery. The balloon is then inflated to dilate the stenotic artery by compressing the fatty tissue on the artery wall, thereby allowing blood to flow. Coronary stents are today usually utilized in PCI procedures; it is a tiny, expandable metal coil that is inserted into the newly-opened section of the coronary artery to keep the stenotic artery permanently open.

3. The Iodinated Radiographic Contrast Agents (IRCA)

The X-ray IRCA are based on the tri-iodinated benzene ring. Iodine is an important element used in contrast media, possessing high-contrast density.

IRCA have different osmolalities (Table 1). The ionic High-Osmolar Contrast Media (HOCM, e.g., diatrizoate)

have an osmolality ranging between 1500 and 1800 mOsm/kg; thus, they have 5 to 8 times the osmolality of plasma. Nonionic Low-Osmolar Contrast Media (LOCM, e.g., iohexol) have an osmolality ranging between 600 and 850 mOsm/kg and therefore 2–3 times the osmolality of plasma. Finally, the nonionic Iso-Osmolar Contrast Media (IOCM, e.g., iodixanol) have an osmolality of about 290-300 mOsm/kg; they have therefore the same osmolality as plasma [6-8]. This decreasing osmolality in the development of IRCA reflects the attempts to reduce IRCA nephrotoxicity.

At equal iodine concentrations (300 mg I/mL), the HOCM ioxithalamate has been shown to have stronger cytotoxic effects on proximal tubular cells *in vitro* than LOCM or IOCM [9]. The same is true for other HOCM. In order to reduce the incidence of severe nephrotoxicity in patients with pre-existing renal failure, LOCM is preferred to HOCM or IOCM [10-13]. At equal iodine concentrations it has been demonstrated that there is no difference in the cytotoxicity of the LOCM iomeprol and IOCM iodixanol on renal proximal tubular cells *in vitro* [14]. Recent studies of meta-analyses have demonstrated no difference in the incidence of nephrotoxicity between IOCM and LOCM [14-17] with the exception of the LOCM iohexol that is more nephrotoxic [10, 18].

The different IRCA also have different viscosities (Table 1). The lower the osmolality, the higher is the viscosity; at comparable iodine concentrations and x-ray attenuation, the nonionic dimeric IOCM have about twice the viscosity of the nonionic monomeric LOCM [19–21].

4. Contrast-Induced Nephropathy (CIN)

The most important and unwanted side effect of IRCA is their nephrotoxicity that is referred to as Contrast-Induced Nephropathy (CIN) or Contrast-Induced Acute Kidney Injury (CI-AKI), an Acute Renal Failure (ARF) that occurs between 24 and 72 hours after the radiographic procedure using IRCA that cannot be attributed to other causes [22, 23]. Usually it is a nonoliguric ARF with asymptomatic transient decrease of renal function as mirrored by the increase in serum creatinine (SCr) of at least 0.5 mg/dl or by 25% from baseline. The maximum value of SCr is reached on the third to the fifth day, then returning to baseline within 10 to 14 days. The basal value of renal function, i.e., before the IRCA injection, may be obtained with the calculation of the so-called estimated glomerular filtration rate (eGFR), i.e., the creatinine clearance (CrCl) obtained using the MDRD (Modification of Diet in Renal Disease) formula [24] or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [25], or the very simple Cockcroft-Gault formula [26].

As underlined by Bragadottir et al. [27], undoubtedly SCr is not an adequate marker of renal function, because of

fluctuations in creatinine production from muscle creatine. SCr is affected by age, gender, race and weight which affect muscle mass. Thus, daily changes in SCr poorly reflect changes in kidney function in patients with ARF. The measured CrCl method requires a steady state condition that is not always met in critically ill patients, in whom changes in the hemodynamics may result in dramatic changes in renal function over a 24-hour urine collection period; furthermore, timed collection of urine is cumbersome and not accurate. The three equations suggested include corrections by age, sex, and race and body weight, thereby overcoming some of the limitations associated with using serum creatinine alone. These equations are also not ideal in critically ill patients with ARF. But Robert et al. [28] have compared the Cockcroft and Gault formula with inulin clearance in 20 critically ill patients and found a good correlation between inulin clearance and the formula, using the ideal body weight in their calculation. Anyhow, the eGFR obtained before IRCA injection is calculated using the SCr in patients who are usually in a stable condition. The patient may become critically ill only if CIN occurs. Unfortunately, sometimes the patients are in an unstable condition, being critically ill even before CIN.

In some cases, CIN may cause a severe impairment of renal function with oliguria (<400 mL/24 hours), that requires dialysis; for this type of ARF the mortality is high.

The clinical feature and the management of CIN are the same as that for ARF due to other causes [29–32]. In hospitalized patients who exhibit normal renal function prior to the injection of IRCA the incidence of CIN seems to be approximately 5% [33]; it is about 2% [34] or even 1% in outpatients with eGFR >45 ml/min per 1.73 m^2 [35].

CIN is uncommon in patients with normal pre-existing renal function. It is more frequent in patients with reduced basal renal function, especially when associated with diabetes mellitus [36]. Among all procedures utilizing IRCA for either diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary interventions are associated with the highest rates of CIN [37]. This occurs for three reasons. Firstly, because of intra-arterial injection of IRCA. The IRCA, in fact, seem to be more nephrotoxic when given intra-arterially because of the higher acute concentration they reach in the kidneys [38, 39], especially if the arterial injection is suprarenal [40–46]. Secondly, because of the high dosage of the IRCA used for these procedures. Thirdly, because of the type of patients undergoing these procedures, who are usually in advanced age, with one or more comorbid conditions, such as advanced vascular disease, severe long-standing hypertension, diabetes and some renal function impairment [47]. Sometimes, in fact, the patients with coronary artery disease already have an initial renal dysfunction due to advanced age [48].

Bruce et al. [49] have observed that the incidence of CIN in the iohexol group of patients undergoing CT was similar to that of the control group (without iohexol) up to a basal

Table 1: Iodinated Contrast Media Used in Clinical Practice.

Name	Type	Iodine content mg/mL	OSM mOsm/kg	Osmolality type	Viscosity cps at 37°C
Ionic					
Diatrizoate (Hypaque 50, Renografin)	Monomer	300	1,550	HOCM	10.5
Metrizoate (Isopaque 370)	Monomer	370	2,100	HOCM	3.4
Iothalamate (Conray)	Monomer	325	1,843	HOCM	4.0
Ioxaglate (Hexabrix)	Dimer	320	580	LOCM	7.5
Nonionic					
Iopamidol (Isovue-370)	Monomer	370	796	LOCM	9.4
Iohexol (Omnipaque 350)	Monomer	350	884	LOCM	10.4
Iodixanol (Visipaque 320)	Dimer	320	290	IOCM	11.8
Iotrolan (Isovist)	Dimer	300	320	IOCM	8.1
Ioxaglate (Hexabrix)	Dimer	320	600	LOCM	7.5
Ioxilan (Oxilan 350)	Monomer	350	695	LOCM	8.1
Iopromide (Ultravist 370)	Monomer	370	774	LOCM	10.0
Ioversol (Optiray 300)	Monomer	300	651	LOCM	5,5
Iomeprol (Iomeron 350)	Monomer	350	618	LOCM	7.5

Ionic and nonionic contrast media may be monomeric or dimeric; 3 iodine atoms are delivered with each benzene ring of a contrast medium: if a contrast molecule contains only 1 benzene ring, it is called a Monomer, if it contains 2 benzene rings, it is called a Dimer. In a solution, ionic contrast media break up into their anion and cation components, thereby increasing osmolality; while nonionic contrast media do not break up in solution. Nonionic dimers are the ideal contrast media as they deliver the most iodine with the least effect on osmolality.

The osmolality of contrast media is compared with the osmolality of plasma. HOCM = High-Osmolar Contrast Media have the highest osmolality, i.e., 5–8 times the osmolality of plasma. LOCM = Low-Osmolar Contrast Media have an osmolality still higher than plasma, i.e., 2–3 times the osmolality of plasma. IOCM = Iso-Osmolar Contrast Media have the same osmolality as plasma. Cps: Viscosity in Centipoise Data of viscosity from [188].

(Reproduced and modified from [6], with permission).

(Reproduced and modified from [57], with permission).

value of SCr of 1.8 mg/dL; but when baseline SCr was above 1.8 mg/dL the incidence of CIN was higher in the iohexol group.

On the basis of their retrospective study, Davenport et al. [50] concluded that i.v. IRCA is a nephrotoxic risk factor, but not in patients with a stable SCr <1.5 mg/dL or eGFR >45 mL/min/1.73 m^2.

5. Pathogenesis of CIN

The pathogenesis of CIN has not been fully elucidated. Many mechanisms are known to be involved [51]. Immediately after intravascular injection, the IRCA cause hemodynamic changes: transient renal vasodilatation with increase in renal blood flow (RBF), followed by a prolonged renal vasoconstriction (including the constriction of medullary *vasa recta* [52]) with an increase in intrarenal vascular resistances and a reduction in RBF [53] (see Figure 1), that is associated with a decrease in the vascular peripheral resistances in extrarenal vessels [54, 55]. Then IRCA are freely eliminated by the kidneys by glomerular filtration because of their poor binding to serum albumin.

The consequent renal ischemia will be particularly marked in the outer renal medulla due to its distance from the *vasa recta* [54, 55]. This poor blood supply is responsible for the poor oxygen (O_2) delivery to the outer renal medulla even under physiological condition, despite the need for O_2 because of the high local O_2 consumption due to the important active tubular reabsorption in the medullary thick ascending limb of Henle's loops that are here located. Any condition that increases tubular fluid reabsorption in these tubular segments will increase outer medulla hypoxia. Since the IRCA cause an osmotic diuresis, the consequent increase of tubular fluid delivery to the medullary thick ascending limb of Henle's loops and the resulting increase in its tubular reabsorption (that implies an increase in O_2 consumption) will be responsible for a more severe hypoxia [6, 56, 57].

Medullary hypoxia is a crucial point in the pathogenesis of CIN (see Figure 1). It causes the formation of reactive oxygen species (ROS) [58, 59] which (a) exert direct tubular and vascular endothelial injury, (b) intensify renal parenchymal hypoxia by virtue of endothelial dysfunction and dysregulation of tubular transport [60, 61], (c) decrease of nitric oxide (NO) synthesis that is in part believed to be due to its reaction with ROS, in particular superoxide anions (O_2^-) [62, 63], leading to the formation of the more detrimental powerful oxidant peroxynitrite anion ($ONOO^-$) [64] (Figure 1).
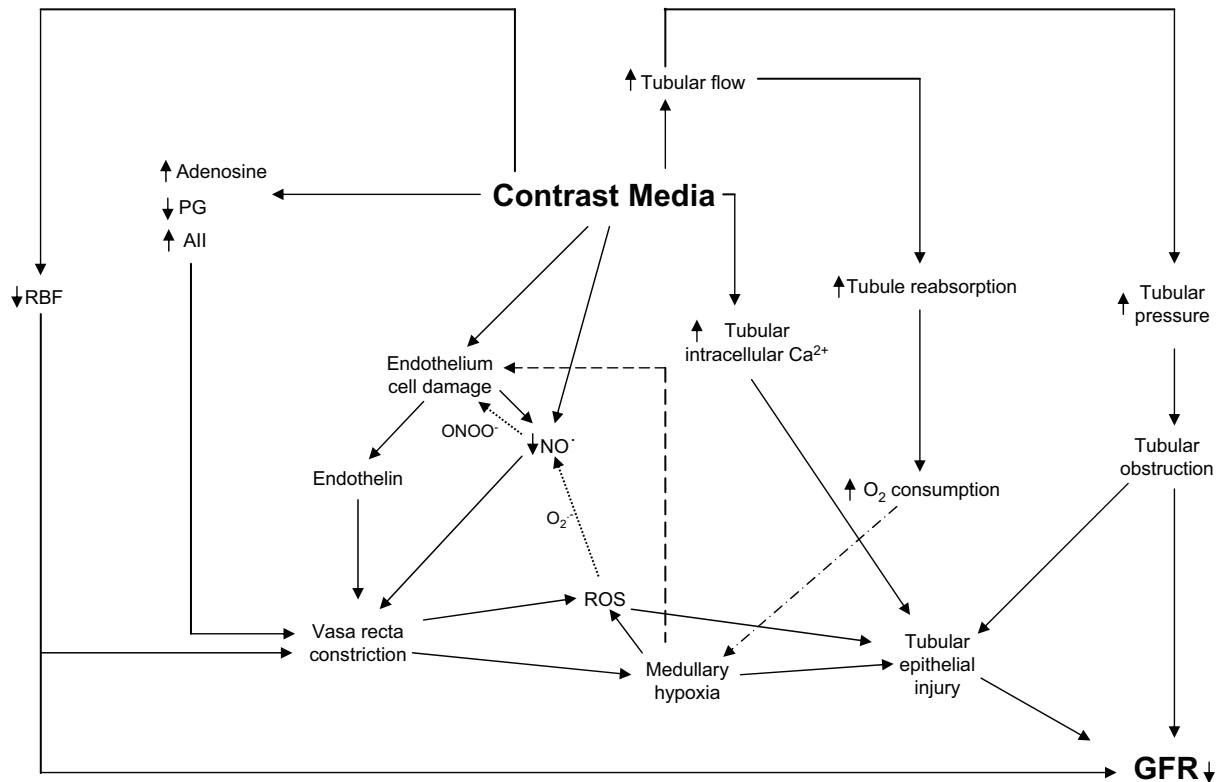
Figure 1: The complex mechanisms that lead to radiocontrast-associated decline of GFR. The dotted arrows indicate the reaction of the reactive oxygen species (ROS) (superoxide anions: O_2^-) with nitric oxide (NO$^{.}$) that not only causes a reduction in NO levels, but also leads to the formation of peroxynitrite anion (ONOO$^-$), a potent oxidant that causes cell injury.

It has been recently demonstrated that a recombinant manganese superoxide dismutase, administered *in vivo* to rats undergoing diatrizoate treatment, was able to reduce renal oxidative stress, thereby preventing the reduction of GFR and the renal histologic damage that follows IRCA administration [65].

The IRCA have also a cytotoxic effect causing apoptosis and cell death of both endothelial and epithelial tubular cells [62]. The damaged and the apoptotic endothelial cells may contribute to the decrease in NO production in descending *vasa recta* [62] and may also release endothelin that contributes to renal vasoconstriction [56, 66].

Once the IRCA have been filtered by glomeruli, they are concentrated inside the renal tubules because of water reabsorption (IRCA are not reabsorbed by renal tubules), exposing the renal tubular cells to their severe direct damage [67].

Many investigators have studied the possible molecular mechanisms of IRCA cytotoxicity highlighting signaling pathways that may be affected by IRCA [68–77]. It has been demonstrated that all IRCA cause a dramatic decrease in the phosphorylation (activation) of the Akt kinase [69, 71]. This kinase has an important role in cell survival and proliferation [78–80]. Therefore, this may explain in part the cytotoxic

effects of IRCA. The decrease in cell viability due to IRCA exposure of human renal tubular cells transfected with a plasmid encoding constitutively active Akt was lessened [69]. Yano et al. [81] have suggested that Akt plays a role in reversing the up-regulation of pro-apoptotic molecules by IRCA in porcine renal tubular cells.

As well as the observed reduction in the phosphorylation (activation) of Akt, IRCA also caused the dephosphorylation (inactivation) of the ERK1/2 kinases that are believed to play a pivotal role in cell survival/proliferation, concomitant with a decrease in cell viability [69]. Our group also demonstrated, in HK-2 cells, that IRCA affect the activation/deactivation of transcription factors, like FoxO3a and STAT3, which control the genes involved in apoptosis and cell proliferation as well as the phosphorylation of the p38 and JNK MAP kinases that are known to play a role in apoptosis [70, 71].

Contrast-induced apoptosis may also be due to the activation of shock proteins and the concurrent inhibition of cytoprotective enzymes and prostaglandins [82, 83].

Under physiological conditions, the Na^+/Ca^{2+} exchanger (NCX) pumps the Ca^{2+} outside the renal tubular epithelial cells using the Na+ concentration gradient across the cell membrane to keep a low intracellular Ca^{2+} level. After IRCA injection, NCX may reversely extrude Na^+ for Ca^{2+} influx

and result in intracellular Ca^{2+} overload that is considered to be an important factor in the pathogenesis of CIN [84, 85] (see Figure 1).

As mentioned above, the concentration of the IRCA within the tubular lumen increases considerably because of tubular fluid reabsorption. The result will be a progressive increase in tubular fluid osmolality and an overproportional increase in tubular fluid viscosity because of the exponential concentration-viscosity relationship [21, 51]. But the fluid flow rate through a tube increases with the pressure gradient and decreases with the flow resistance; thus, the resistance increases proportionally to fluid viscosity; consequently, the increased viscosity caused by IRCA increases the intratubular pressure [21], thereby creating a condition of tubular obstruction that contributes to the tubular epithelial damage and to the fall of GFR [57] (see Figure 1).

Thus, in summary, the IRCA cause a fall in GFR (a) by renal vasoconstriction with decrease of RBF, (b) by renal tubular epithelial injury and (c) by osmotic diuresis (see Figure 1), with crucial points being renal medullary hypoxia and oxidative stress [51].

6. Conditions Predisposing to CIN

Renal insufficiency represents the most important condition predisposing to CIN whatever its cause.

The lower the eGFR, the greater is the risk of CIN following the administration of IRCA. An eGFR of 60 ml/min/1.73 m^2 has been suggested as a reliable cut-off point for identifying patients at high risk for CIN [37].

Despite the recent observation by Neyra et al. [86] in a retrospective observational in-hospital study that CIN occurred with similar frequency, following coronary angiography, in 1160 patients with (eGFR < 60 mL/min/1.73 m^2) or without (eGFR ≥ 60 mL/min/1.73 m^2) renal insufficiency, the incidence of CIN in patients with CRF ranges from 14.8 to 55%.

Patients with CRF have defective antioxidant systems [87] and increased oxidative stress associated with inflammation and endothelial dysfunction [88]. This may explain why pre-existing CRF represents the most common condition predisposing to CIN.

Another important condition favoring the development of CIN is Diabetes mellitus, particularly when associated with renal insufficiency [89].

Since patients with diabetes mellitus have a high sensitivity of their renal vasculature to the vasoconstrictive agent adenosine and the IRCA from one side increase the release of renal adenosine and from another side stimulate renal adenosine receptors, all of these conditions may explain the particular susceptibility of diabetic patients to IRCA [90]. Diabetics also have an increased circulating and renal levels of endothelin, and IRCA further increase the production of endothelins [91]. This also may contribute to the particular susceptibility of diabetic patients to IRCA.

In a double-blind randomized study using iopamidol-370 or iodixanol-320 for coronary angiography in 122 diabetic patients with a SCr of ≤2 mg/dL, 17 patients (10 iopamidol vs 7 iodixanol; p = NS) had an increase in SCr ≥25% over baseline; the Authors concluded that diabetic patients with normal or mild renal dysfunction are at risk for CIN [92].

In a recent prospective observational study on 585 unselected patients who underwent elective or emergency coronary angiography or PCI, a 5.1% incidence of CIN was observed in diabetic patients with preserved renal function, an incidence comparable to that of a non-diabetic population [93]. On the other hand, in 421 patients with CRF undergoing coronary angiography 137 with diabetes mellitus had a 20% incidence of CIN against 11% in 140 with pre-diabetes and 5.5% in 144 with a normal fasting glucose [94].

The incidence of CIN in diabetic patients seems to vary from 5.7 to 29.4%; at any given degree of baseline GFR, diabetes doubles the risk of developing CIN compared with non-diabetic patients [37].

Thus, most Authors do not regard the presence of diabetes mellitus in the absence of renal failure as a risk factor for CI-AKI [95].

Predisposing factor may be dehydration, used to indicate salt depletion, as it may occur after salt losses (following abnormal gastrointestinal, renal or dermal fluid losses) that are not adequately replaced by salt intake. The term *dehydration* indicates deficit of water, as it may occur in old patients who do not ingest adequate amount of water during the day because of their impaired sensation of thirst due to their advanced age [96]. Sometimes, however, dehydration is used to indicate salt depletion, as may occur after salt loss (following abnormal gastrointestinal, renal or dermal fluid losses) that are not adequately replaced by salt intake. When we perform intravascular injection of IRCA in patients who are dehydrated and/or hypovolaemic, angiotensin II and vasopressin augment tubular fluid reabsorption in the kidney, which further increases the tubular concentration of the IRCA, and, due to the concentration-viscosity relationship, overproportionally increases tubular fluid viscosity. This will lead to a fall in the GFR and to an increase of the direct cytotoxicity of IRCA on renal tubular epithelium. This is why dehydration and/or volume contraction and reduction of 'effective' circulating blood volume are major risk factors for CIN.

Other predisposing factors include: (a) concomitant use of nephrotoxic drugs such as aminoglycosides, cyclosporin A, amphotericin, cisplatin and nonsteroidal anti-inflammatory drugs [97, 98]; (b) hypercholesterolemia [99]; the use of renin-angiotensin-aldosterone system blocking agents such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) (whose role in the pathophysiology of CIN remains controversial [89]) (d) prolonged hypotension; (e) reduction of the 'effective'

intravascular volume due to congestive heart failure, liver cirrhosis, nephrotic syndrome [29]; (f) use of large doses of IRCA and/or their multiple injections within 72 hrs; (g) route of administration (intravenous of IRCA are less risky than intra-arterial injection); (h) high osmolality and viscosity of contrast media; (i) advance age (>65 years); (j) anemia; (k) sepsis and (l) renal transplantation [6, 57, 100, 101].

7. Measures for Prevention of CIN

The most important and crucial preventive measure of CIN is an adequate hydration of the patient [101–104]. In the past, physicians, in preparing the patient for a radiographic procedure using IRCA, were suggesting to avoid any oral intake starting the day before contrast administration. This measure was decided with the purpose to prevent vomiting and nausea (common symptoms with the use of high-osmolality IRCA) and to allow for tracheal intubation in case of any emergency. The strategy to keep the patient in a fasting state was correct, indeed, at that time; but many patients and physicians erroneously considered a restriction of fluids in parallel with the restriction of food [102]. This misconception caused patient dehydration before using IRCA.

Thus, we have not only to avoid the erroneous measure of ceasing liquids to the patients, but contrarily we have to give the patient a volume supplementation, e.g., 500 mL of water orally before and 2,500 mL for 24 hours after IRCA administration to secure a urine output of at least 1 mL/min [105]. In high-risk patients the oral water load may be replaced by i.v. infusion of 0.9% saline at a rate of approximately 1 mL/kg b.w. per hour, beginning 6–12 hours before and continuing for up to 12–24 hours after the radiographic examination (if urine output is appropriate and cardiovascular conditions allow it) [38, 102]. The purpose is to cause expansion of the intravascular volume, to suppress the renin-angiotensin cascade and consequently to reduce renal vasoconstriction and hypoperfusion. Furthermore, the resulting increase in urine output will limit the duration of IRCA contact with renal tubules and consequently its toxicity on the renal tubular epithelium [106, 107].

Some Authors suggest using sodium bicarbonate hydration that has been shown to be superior to sodium chloride in clinical studies and meta-analysis [108–118]. For coronary angiography or intervention 154-mEq/L infusion of sodium bicarbonate as a bolus of 3 mL/kg b.w./hour for 1 hour before the administration of IRCA, followed by 1 mL/kg/hour for 6 hours during and after the procedure have been used [109]. The reason for using bicarbonate is that alkalinization of tubular fluid by bicarbonate will reduce the production and increase the neutralization of oxygen free radicals, thereby protecting the kidney from injury by IRCA [111, 112, 119, 120].

However, other studies have not found any benefit with sodium bicarbonate hydration versus sodium chloride [121–124] or have observed even an increased incidence of CIN [125].

The Committee of the European Renal Best Practice "recommends volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no volume expansion, in patients at increased risk for CIN" [126].

It is important that, before any radiographic procedure using the IRCA, renal function of the patient is measured, preferably using eGFR. It is also important to monitor renal function also after the procedure once daily for 5 days [38, 101].

It has been also suggested to discontinue potentially nephrotoxic drugs, such as aminoglycosides, vancomycin, amphotericin B, metformin and nonsteroidal anti-inflammatory drugs [101].

It is important to choose the least nephrotoxic radiocontrast agent: iodixanol (IOCM) and iopamidol (LOCM) appear to be the IRCA of choice to reduce risk of CIN [127]; and to use it with the lowest dosage possible. Before the advent of CT, intravenous urography and angiography were the major indications for IRCA. In the pre-CT era, most radiologists were utilizing 30–50 ml HOCM and with hand injection rates of less than 1 ml/s for urography. The average IRCA dose for CT is approximately 100–150 ml and with power injection rates of up to 3–4 ml/s [128].

High doses of IRCA are required in coronary angiography and percutaneous coronary intervention. For these procedures, some formulas have been suggested to calculate their least dangerous dosage:

(A) Cigarroa's formula: 5 mL of IRCA/kg b.w./SCr (mg/dL). The maximum dose acceptable is 300 mL for diagnostic coronary arteriography [129].

(B) Laskey's formula: volume of IRCA to calculated CrCl ratio with a cut-off point of the ratio at 3.7 [130]; a cut-off point of the ratio at 2.0 is better: below a ratio of 2.0 CIN would be a rare complication; it would increase dramatically at a ratio of 3.0 [127, 131].

(C) Ratio of grams of iodine to the calculated CrCl; a ratio of 1.42, or even better a ratio of 1.0, would prevent CIN [127].

Since ROS may play an important role in the pathogenesis of CIN, it has been suggested to use antioxidants to prevent CIN. The first antioxidant used for this purpose was N-acetylcysteine (NaC) [132]. Reddan et al. [119] have conducted a systematic literature review of the evidence available from published reports, between 2000 and 2008, of prospective, randomized, controlled trials comparing contrast media and preventive strategies. Among 27 studies, all but 1 reported the use of prophylactic volume expansion as part of the protocol. The majority of trials compared NaC with no NaC: 6 demonstrated a significant benefit, 1 showed a borderline benefit in favor of NaC and 1 found a

significant disadvantage in NaC use [133]; 15 failed to detect a difference in CIN incidence between treatment with NaC and no treatment [134].

Also, short-duration pretreatment with NaC has been shown to reduce IRCA-induced cytotoxicity in human embryonic kidney cells treated with the ioxithalamate, iopromide and iodixanol [135] and to ameliorate the ischemic renal failure in animal models [136]. The suggested dosage is 600 mg orally twice daily, one day before and on the day of procedure [38] or, in patients unable to take the drug orally, with an i.v. dose of 150 mg/kg b.w. over half an hour before the procedure or 50 mg/kg b.w. administered over 4 hours [137].

But overall, the efficacy of NaC against CIN is still controversial, for whilst some Authors have reported protective results [31, 137, 138], others have denied it [125, 133, 139–144].

The efficacy of ascorbic acid, another antioxidant, is also controversial [135, 145–148]. The dosage of ascorbic acid that has been suggested to prevent CIN is 3 g orally 2 hours before the procedure and 2 g during the night and in the morning after the procedure [145, 146].

A comparison between different antioxidants has shown that NaC, at a dose of 1,200 mg orally twice a day before and on the day of coronary catheterization, is more beneficial in preventing CIN than ascorbic acid, particularly in diabetic patients with renal insufficiency undergoing coronary angiography [148]. Recently, a meta-analysis, with 1536 patients who completed the trial, has suggested that ascorbic acid decreased by 33% the risk of developing CIN [149].

Also the antioxidant vitamin E has been used to prevent CIN. The oral administration of either 350 mg/day of α-tocopherol or 300 mg/day of γ-tocopherol (5 days prior to the coronary procedure and continued for a further 2 days post-procedure) in combination with 0.9% saline (1 mL/kg/h for 12 hours before and 12 hours after) has been shown to be effective in protecting against CIN in patients with CRF undergoing coronary procedures with Iopromide: CIN developed in 14.9% of cases in the placebo group, but only in 4.9% and 5.9% in the α- and γ-tocopherol groups, respectively [150].

Nebivolol is a third-generation β1-adrenergic receptor antagonist [151, 152]. It has been used, at a dosage of 5 mg/day for one week or 5 mg every 24 hours for 4 days, to protect the kidney against CIN through its antioxidant and NO-mediated vasodilating action [153–155].

Statins have been demonstrated to prevent CIN in patients undergoing PCI [156–163]. Rosuvastatin, at a dosage of 10 mg/day for five days, two days before, three days post the procedure, reduced the risk of CIN in patients with diabetes mellitus and chronic kidney disease undergoing coronary/peripheral arterial angiography [164]. Simvastatin had a dose-dependent nephroprotective effect in experimental rats treated with IRCA [162]. Patients on pravastatin had a lower incidence of CIN than patients on simvastatin

[165, 166]. Atorvastatin has been used at a dosage of 40 mg/day 3 days before the procedure [167] as well as at a dosage of 80 mg 12 hours before intervention with another 40 mg pre-procedure, followed by long-term treatment of 40 mg/day [168].

Renal outer medulla hypoxia is a crucial point in the pathogenesis of CIN. As we have mentioned, this hypoxia is due both to low O_2 delivery because of normal local hypoperfusion due to anatomical reasons and to the high O_2 consumption due to the high active sodium reabsorption in the thick ascending limb of Henle' loops. The osmotic diuresis induced by IRCA causes an increased delivery of tubular fluid to the thick ascending limb of Henle's loops, thereby increasing the active sodium reabsorption and consequently O_2 demand, thereby aggravating hypoxia. Thus, it has been thought that furosemide, by decreasing sodium reabsorption in this tubular segment [169], would reduce medullary O_2 consumption and decrease renal medullary hypoxia.

Unfortunately, several studies have demonstrated no protection against CIN when utilizing this diuretic or even deleterious effects [170–172], mainly related to the salt depletion caused by furosemide. Thus, it has been concluded that diuretics should be avoided before contrast exposure [86].

To overcome the problem of hypovolemia caused by the diuretic, a perfect combination of hydration plus furosemide has been suggested: this is obtained by delivering i.v. fluid in an amount exactly matched to the volume of urine produced by the patient under the effect of furosemide [173]. This procedure is accomplished by a special device, called 'RenalGuard', that would guide the physician in achieving high urine output while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia.

The availability of the device RenalGuard allowed Briguori et al. [173] to perform a multicenter, randomized, investigator-driven study comparing 2 different strategies to prevent CIN in patients at high risk [174]. All consecutive patients from January 2009 to December 2010 with CRF scheduled for coronary and/or peripheral angiography and/or angioplasty, who had an eGFR of $\leq$30 mL/min/1.73 m^2 were included in the trial. Patients were randomly assigned to either the Control Group or the RenalGuard Group. Patients of the Control Group received 154 mEq/L sodium bicarbonate in dextrose and H_2O (an initial intravenous bolus of 3 mL/kg per hour for at least 1 hour before contrast injection, followed by the same fluid at a rate of 1 mL/kg per hour during contrast exposure and for 6 hours after the procedure). All patients received also NaC orally at a dose of 1200 mg twice daily the day before and the day of administration of the contrast agent; an additional NaC dose (1200 mg diluted in 100 mL normal saline) was administered intravenously during the procedure. (The total NaC dose was $\geq$6 g). Patients of the RenalGuard Group were treated by hydration with normal saline plus NaC controlled by the RenalGuard system: an initial bolus of 250 mL was

infused over 30 minutes; then furosemide (0.25 mg/kg b.w.) was administered intravenously to achieve an optimal urine flow of $\geq$300 mL/h. When this urine flow was reached, the patient was moved into the catheterization laboratory, and the procedure was started. Controlled hydration by the *RenalGuard* system continued during the procedure and for 4 hours after the procedure; urine flow was monitored and maintained at the target value throughout the procedure and during the next 4 hours. NaC was administered to the patients of *RenalGuard* Group only intravenously (1500 mg in 1 L saline) throughout the observation time (i.e. before, during and after the radiographic procedure). Iodixanol was the IRCA used in all patients. The results were remarkable: the incidence of CIN (increase in SCr concentration $\geq$0.3 mg/dL above the baseline value at 48 hours after administration of IRCA or the need for dialysis) was 16% in the Control Group (standard hydration) and 5% in the *RenalGuard* Group.

Similar results have been obtained by Marenzi et al. [175]. In patients with CRF undergoing coronary procedures, furosemide-induced high urine output with matched hydration significantly reduced the risk of CIN ($\geq$25% or $\geq$0.5 mg/dL rise in SCr over baseline) with an incidence of 4.6% versus 18% of controls ($p = 0.005$).

Calcium channel blockers have also been suggested to prevent CIN, based on what was mentioned earlier regarding the fact that, after IRCA injection, NCX may reversely extrude Na^+ for Ca^{2+} influx and result in intracellular Ca^{2+} overload, that is believed to be a key factor in ischemic cell injury in CIN [84]. Thus, calcium channel blockers have been hypothesized to have protective effects against CIN. But their use have given controversial results, protective for some Authors [176, 177], non-protective according to others [67, 178].

It has also recently been reported that a crude fruit extract could reverse the loss in cell viability due to the HOCM sodium diatrizoate in human renal proximal tubular cells *in vitro* [179].

8. Dialytic Measures for Prevention of CIN

The preventive measures just mentioned are particularly useful in patients with eGFR of >30 mL/min.

What can be done with patients with eGFR of $\leq$30 mL/min ? Fortunately, the IRCA are easily dialyzed because of their poor binding to serum albumin. Thus, the use of either hemodialysis or hemofiltration has been suggested to remove IRCA immediately after the radiographic procedure. Schindler et al. [180] demonstrated, in patients with CRF (most of whom were in chronic dialysis), that different dialysis techniques do remove IRCA (iopromide or iomeprol), with high-flux hemodialysis and hemodiafiltration being more effective than low-flux hemodialysis and hemofiltration. But Lehnert et al. [181] demonstrated that, although hemodialysis eliminates contrast media, it does not prevent CIN. Vogt et al. [182] performed a randomized

trial to test whether CIN can be avoided by prophylactic hemodialysis immediately after the administration of low-osmolality contrast media in patients with impaired renal function (baseline serum creatinine level >2.3 mg/dL); renal function was recorded before and during the 6 days after administration of contrast media.

The prophylactic hemodialysis did not diminish the rate of CIN. These results suggested that, even if dialysis is carried out immediately, the early damage has already triggered a cascade of pathogenic events, which cannot be reversed [183]. Hence, the effects of hemodialysis have been negative [184] with only a few exceptions. Good results were obtained by Lee et al. [185], who evaluated 82 patients with CrCl of 13 mL/min undergoing coronary angiography; hemodialysis with polisulfon decreased the incidence of CIN (5% vs 35% in non-dialyzed controls) and mortality (0 vs. 13%). Marenzi et al. [186] have demonstrated that hemofiltration is an effective strategy for CIN prevention in patients with CRF (CrCl $\leq$30 mL/min) who are undergoing cardiovascular procedures provided that is performed for 6 hours before and for 18 to 24 hours after contrast exposure.

Better results have been obtained with continuous venovenous hemofiltration (CVVH). Thus, Guastoni et al. [187] performed CVVH in 53 consecutive patients with eGFR <30 ml/min/1.73 m^2 undergoing diagnostic or interventional coronary procedures using iopamidol; CVVH was started immediately after the angiographic procedure. Six-hour CVVH resulted in iopamidol removal comparable with that of 12-hour diuresis (i.e. 43% vs 42%). CIN occurred in only 7.5% of patients in the whole population.

Acknowledgment

Abbreviations

IRCA: Iodinated radiographic contrast agents;
CT: computed tomography;
i.v.:   intravenous;
CTU: CT Urography;
CECT: Contrast Enhanced Computed Tomography;
CCTA: Coronary CT angiography;
PCI: Percutaneous coronary intervention;
PTCA: Percutaneous transluminal coronary angioplasty;
HOCM: High-Osmolar Contrast Media;
LOCM: Low-Osmolar Contrast Media;
IOCM: Iso-Osmolar Contrast Media;
CIN: Contrast-Induced Nephropathy;
CI-AKI: Contrast-Induced Acute Kidney Injury;

ARF: Acute Renal Failure;
SCr: serum creatinine;
eGFR: estimated glomerular filtration rate;
CrCl: creatinine clearance;
MDRD: Modification of Diet in Renal Disease;
CKD- Chronic Kidney Disease Epidemiology
EPI: Collaboration;
RBF: renal blood flow;
NO: nitric oxide;
ROS: reactive oxygen species;
CRF: chronic renal failure;
ACEi: angiotensin-converting enzyme inhibitors;
ARBs: angiotensin II receptor blockers;
NaC: N-acetylcysteine;
CVVH: continuous venovenous hemofiltration;
Cps: viscosity in centipoise.

References

[1] P. Dure-Smith, The dose of contrast medium in intravenous urography: a physiologic assessment, *Am J Roentgenol Radium Ther Nucl Med*, **108**, no. 4, 691–697, (1970).

[2] B. Korkmaz, K. Buharalioglu, S. Sahan-Firat, T. Cuez, A. Tuncay Demiryurek, and B. Tunctan, Activation of MEK1/ERK1/2/iNOS/sGC/PKG pathway associated with peroxynitrite formation contributes to hypotension and vascular hyporeactivity in endotoxemic rats, *Nitric Oxide*, **24**, no. 3, 160–172, (2011).

[3] S. Komatsu, T. Kamata, A. Imai, et al., Coronary computed tomography angiography using ultra-low-dose contrast media: radiation dose and image quality, *Int J Cardiovasc Imaging*, **29**, no. 6, 1335–1340, (2013).

[4] B. A. Herzog, L. Husmann, I. Valenta, et al., Determinants of vessel contrast in BMI-adapted low dose CT coronary angiography with prospective ECG-triggering, *Int J Cardiovasc Imaging*, **25**, no. 6, 625–630, (2009).

[5] A. P. Pazhenkottil, L. Husmann, R. R. Buechel, et al., Validation of a new contrast material protocol adapted to body surface area for optimized low-dose CT coronary angiography with prospective ECG-triggering, *Int J Cardiovasc Imaging*, **26**, no. 5, 591–597, (2010).

[6] M. Andreucci, R. Solomon, and A. Tasanarong, Side Effects of Radiographic Contrast Media: Pathogenesis, Risk Factors, and Prevention, *BioMed Research International*, **2014**, Article ID 741018, 20 pages, (2014).

[7] R. W. Katzberg, Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity, *Radiology*, **204**, no. 2, 297–312, (1997).

[8] J. Singh and A. Daftary, Iodinated contrast media and their adverse reactions, *J Nucl Med Technol*, **36**, no. 2, 69–74, (2008)., quiz 76-67.

[9] M. C. Heinrich, M. K. Kuhlmann, A. Grgic, M. Heckmann, B. Kramann, and M. Uder, Cytotoxic effects of ionic high-osmolar, nonionic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells in vitro, *Radiology*, **235**, no. 3, 843–849, (2005).

[10] P. Aspelin, P. Aubry, S. G. Fransson, R. Strasser, R. Willenbrock, and K. J. Berg, Nephrotoxic effects in high-risk patients undergoing angiography, *N Engl J Med*, **348**, no. 6, 491–499, (2003).

[11] B. J. Barrett, Contrast nephrotoxicity, *J Am Soc Nephrol*, **5**, no. 2, 125–137, (1994).

[12] B. J. Barrett and E. J. Carlisle, Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media, *Radiology*, **188**, no. 1, 171–178, (1993).

[13] C. P. Taliercio, R. E. Vlietstra, D. M. Ilstrup, et al., A randomized comparison of the nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography, *J Am Coll Cardiol*, **17**, no. 2, 384–390, (1991).

[14] M. C. Heinrich, L. Häberle, V. Müller, W. Bautz, and M. Uder, Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials, *Radiology*, **250**, no. 1, 68–86, (2009).

[15] L. Bolognese, G. Falsini, C. Schwenke, et al., Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial), *Am J Cardiol*, **109**, no. 1, 67–74, (2012).

[16] M. Reed, P. Meier, U. U. Tamhane, K. B. Welch, M. Moscucci, and H. S. Gurm, The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials, *JACC Cardiovasc Interv*, **2**, no. 7, 645–654, (2009).

[17] R. J. Solomon, M. K. Natarajan, S. Doucet, et al., Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease, *Circulation*, **115**, no. 25, 3189–3196, (2007).

[18] N. Chalmers and R. W. Jackson, Comparison of iodixanol and iohexol in renal impairment, *Br J Radiol*, **72**, no. 859, 701–703, (1999).

[19] K. Dyvik, K. Dyrstad, and A. Tronstad, Relationship between viscosity and determined injection pressure in angiography catheters for common roentgen contrast media, *Acta Radiol Suppl*, **399**, 43–49, (1995).

[20] G. Jost, H. Pietsch, J. Sommer, et al., Retention of iodine and expression of biomarkers for renal damage in the kidney after application of iodinated contrast media in rats, *Invest Radiol*, **44**, no. 2, 114–123, (2009).

[21] E. Seeliger, D. C. Lenhard, and P. B. Persson, Contrast Media Viscosity versus Osmolality in Kidney Injury: Lessons from Animal Studies, *BioMed Research International*, **2014**, (2014).

[22] M. Andreucci, *G Ital Nefrol*, **31**, p. 5, (2014), [Radiographic contrast nephropathy].

[23] M. Andreucci, T. Faga, F. Perticone, and A. Michael, Radiographic contrast agents, drugs useful for diagnostics, but with contrast-induced nephropathy as side effect, *J Nephrol Urol*, **2**, no. 2, 013, (2015).

[24] A. S. Levey, J. P. Bosch, J. B. Lewis, T. Greene, N. Rogers, and D. Roth, A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation, *Ann Intern Med*, **130**, no. 6, 461–470, (1999).

[25] A. S. Levey, L. A. Stevens, C. H. Schmid, et al., A new equation to estimate glomerular filtration rate, *Ann Intern Med*, **150**, no. 9, 604–612, (2009).

[26] D. W. Cockcroft and M. H. Gault, Prediction of creatinine clearance from serum creatinine, *Nephron*, **16**, no. 1, 31–41, (1976).

[27] G. Bragadottir, B. Redfors, and S. E. Ricksten, Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury–true GFR versus urinary creatinine clearance and estimating equations, *Crit Care*, **17**, no. 3, p. R108, (2013).

[28] S. Robert, B. J. Zarowitz, E. L. Peterson, and F. Dumler, Predictability of creatinine clearance estimates in critically ill patients, *Crit Care Med*, **21**, no. 10, 1487–1495, (1993).

[29] V. E. Andreucci, G. Fuiano, D. Russo, and M. Andreucci, Vasomotor nephropathy in the elderly, *Nephrol Dial Transplant*, **13**, suppl 7, 17–24, (1998).

[30] V. E. Andreucci, G. Fuiano, P. Stanziale, and M. Andreucci, Role of renal biopsy in the diagnosis and prognosis of acute renal failure, *Kidney Int Suppl*, **66**, S91–S95, (1998).

[31] C. Briguori, A. Colombo, A. Violante, et al., Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity, *Eur Heart J*, **25**, no. 3, 206–211, (2004).

[32] M. Andreucci, S. Federico, and V. E. Andreucci, Edema and acute renal failure, *Semin Nephrol*, **21**, no. 3, 251–256, (2001).

[33] L. M. Curtis and A. Agarwal, HOpe for contrast-induced acute kidney injury, *Kidney Int*, **72**, no. 8, 907–909, (2007).

[34] R. Solomon, Contrast-induced acute kidney injury: is there a risk after intravenous contrast? *Clin J Am Soc Nephrol*, **3**, no. 5, 1242–1243, (2008).

[35] S. D. Weisbord and P. M. Palevsky, Prevention of contrast-induced nephropathy with volume expansion, *Clin J Am Soc Nephrol*, **3**, no. 1, 273–280, (2008).

[36] R. W. Katzberg and J. H. Newhouse, Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? *Radiology*, **256**, no. 1, 21–28, (2010).

[37] R. Mehran and E. Nikolsky, Contrast-induced nephropathy: definition, epidemiology, and patients at risk, *Kidney Int Suppl*, **69**, no. 100, S11–S15, (2006).

[38] T. G. Gleeson and S. Bulugahapitiya, Contrast-induced nephropathy, *AJR Am J Roentgenol*, **183**, no. 6, 1673–1689, (2004).

[39] M. Dong, Z. Jiao, T. Liu, F. Guo, and G. Li, Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials, *J Nephrol*, **25**, no. 3, 290–301, (2012).

[40] L. Byrd and R. L. Sherman, Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review, *Medicine (Baltimore)*, **58**, no. 3, 270–279, (1979).

[41] D. R. Campbell, B. K. Flemming, W. F. Mason, S. A. Jackson, D. J. Hirsch, and K. J. MacDonald, A comparative study of the nephrotoxicity of iohexol, iopamidol and ioxaglate in peripheral angiography, *Can Assoc Radiol J*, **41**, no. 3, 133–137, (1990).

[42] A. S. Gomes, J. D. Baker, V. Martin-Paredero, et al., Acute renal dysfunction after major arteriography, *AJR Am J Roentgenol*, **145**, no. 6, 1249–1253, (1985).

[43] S. Harkonen and C. Kjellstrand, Contrast nephropathy, *Am J Nephrol*, **1**, no. 2, 69–77, (1981).

[44] R. W. Katzberg and B. J. Barrett, Risk of iodinated contrast material–induced nephropathy with intravenous administration, *Radiology*, **243**, no. 3, 622–628, (2007).

[45] G. A. Khoury, J. C. Hopper, Z. Varghese, et al., Nephrotoxicity of ionic and nonionic contrast material in digital vascular imaging and selective renal arteriography, *Br J Radiol*, **56**, no. 669, 631–635, (1983).

[46] R. D. Moore, E. P. Steinberg, N. R. Powe, et al., Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial, *Radiology*, **182**, no. 3, 649–655, (1992).

[47] G. Deray, F. Martinez, P. Cacoub, B. Baumelou, A. Baumelou, and C. Jacobs, A role for adenosine calcium and ischemia in radiocontrast-induced intrarenal vasoconstriction, *Am J Nephrol*, **10**, no. 4, 316–322, (1990).

[48] G. Fuiano, D. Mancuso, C. Indolfi, et al., Early detection of progressive renal dysfunction in patients with coronary artery disease, *Kidney Int*, **68**, no. 6, 2773–2780, (2005).

[49] R. J. Bruce, A. Djamali, K. Shinki, S. J. Michel, J. P. Fine, and M. A. Pozniak, Background fluctuation of kidney function versus contrast-induced nephrotoxicity, *AJR Am J Roentgenol*, **192**, no. 3, 711–718, (2009).

[50] M. S. Davenport, S. Khalatbari, J. R. Dillman, R. H. Cohan, E. M. Caoili, and J. H. Ellis, Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material, *Radiology*, **267**, no. 1, 94–105, (2013).

[51] M. Andreucci, T. Faga, A. Pisani, M. Sabbatini, and A. Michael, Pathogenesis of Acute Renal Failure induced by iodinated radiographic contrast media, *Austin J Nephrol Hypertens*, **1**, no. 1, 1005, (2014).

[52] M. Sendeski, A. Patzak, T. L. Pallone, C. Cao, A. E. Persson, and P. B. Persson, Iodixanol, constriction of medullary descending vasa recta, and risk for contrast medium-induced nephropathy, *Radiology*, **251**, no. 3, 697–704, (2009).

[53] R. W. Katzberg, T. W. Morris, G. Schulman, et al., Reactions to intravenous contrast media. Part I: severe and fatal cardiovascular reactions in a canine dehydration model, *Radiology*, **147**, no. 2, 327–330, (1983).

[54] S. W. Murphy, B. J. Barrett, and P. S. Parfrey, Contrast nephropathy, *J Am Soc Nephrol*, **11**, no. 1, 177–182, (2000).

[55] S. Detrenis, M. Meschi, S. Musini, and G. Savazzi, Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art, *Nephrol Dial Transplant*, **20**, no. 8, 1542–1550, (2005).

[56] S. N. Heyman, S. Rosen, and C. Rosenberger, Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy, *Clin J Am Soc Nephrol*, **3**, no. 1, 288–296, (2008).

[57] M. Andreucci, T. Faga, A. Pisani, M. Sabbatini, and A. Michael, Acute kidney injury by radiographic contrast media: pathogenesis and prevention, *Biomed Res Int*, **2014**, Article ID 362725, (2014).

[58] A. J. Giaccia, M. C. Simon, and R. Johnson, The biology of hypoxia: the role of oxygen sensing in development, normal function, and disease, *Genes Dev*, **18**, no. 18, 2183–2194, (2004).

[59] M. Sabbatini, M. Santillo, A. Pisani, et al., Inhibition of Ras/ERK1/2 signaling protects against postischemic renal injury, *Am J Physiol Renal Physiol*, **290**, no. 6, F1408–F1415, (2006).

[60] S. N. Heyman, S. Rosen, M. Khamaisi, J. M. Idée, and C. Rosenberger, Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy, *Invest Radiol*, **45**, no. 4, 188–195, (2010).

[61] P. Dawson, M. J. Harrison, and E. Weisblatt, Effect of contrast media on red cell filtrability and morphology, *Br J Radiol*, **56**, no. 670, 707–710, (1983).

[62] M. M. Sendeski, Pathophysiology of renal tissue damage by iodinated contrast media, *Clin Exp Pharmacol Physiol*, **38**, no. 5, 292–299, (2011).

[63] A. Pisani, E. Riccio, M. Andreucci, T. Faga, M. Ashour, A. Di Nuzzi, A. Mancini, and M. Sabbatini, Role of reactive oxygen species in pathogenesis of radiocontrast-induced nephropathy, *BioMed Research International*, **2013**, Article ID 868321, (2013).

[64] P. Pacher, J. S. Beckman, and L. Liaudet, Nitric oxide and peroxynitrite in health and disease, *Physiol Rev*, **87**, no. 1, 315–424, (2007).

[65] A. Pisani, M. Sabbatini, E. Riccio, et al., Effect of a recombinant manganese superoxide dismutase on prevention of contrast-induced acute kidney injury, *Clin Exp Nephrol*, **18**, no. 3, 424–431, (2014).

[66] S. N. Heyman, B. A. Clark, N. Kaiser, et al., Radiocontrast agents induce endothelin release in vivo and in vitro, *J Am Soc Nephrol*, **3**, no. 1, 58–65, (1992).

[67] A. Caiazza, L. Russo, M. Sabbatini, and D. Russo, Hemodynamic and tubular changes induced by contrast media, *BioMed Research International*, **2014**, (2014).

[68] M. Andreucci, T. Faga, G. B. De Sarro, and A. Michael, The toxicity of Radiographic Contrast Agents in the Clinical Practice, *J Nephrol Advances*, **1**, no. 1, 1–41, (2015).

[69] M. Andreucci, G. Fuiano, P. Presta, et al., Radiocontrast media cause dephosphorylation of Akt and downstream signaling targets in human renal proximal tubular cells, *Biochem Pharmacol*, **72**, no. 10, 1334–1342, (2006).

[70] M. Andreucci, G. Lucisano, T. Faga, et al., Differential activation of signaling pathways involved in cell death, survival and inflammation by radiocontrast media in human renal proximal tubular cells, *Toxicol Sci*, **119**, no. 2, 408–416, (2011).

[71] M. Andreucci, T. Faga, D. Russo, et al., Differential activation of signaling pathways by low-osmolar and iso-osmolar radiocontrast agents in human renal tubular cells, *J Cell Biochem*, **115**, no. 2, 281–289, (2014).

[72] X. Gong, G. Celsi, K. Carlsson, S. Norgren, and M. Chen, N-acetylcysteine amide protects renal proximal tubular epithelial cells against iohexol-induced apoptosis by blocking p38 MAPK and iNOS signaling, *Am J Nephrol*, **31**, no. 2, 178–188, (2010).

[73] H. C. Lee, S. H. Sheu, H. W. Yen, W. T. Lai, and J. G. Chang, JNK/ATF2 pathway is involved in iodinated contrast media-induced apoptosis, *Am J Nephrol*, **31**, no. 2, 125–133, (2010).

[74] A. Michael, T. Faga, A. Pisani, E. Riccio, P. Bramanti, M. Sabbatini, M. Navarra, and M. Andreucci, Molecular mechanisms of renal cellular nephrotoxicity due to radiocontrast media, *BioMed Research International*, **2014**, Article ID 249810, (2014).

[75] M. Andreucci, A. Michael, C. Kramers, et al., Renal ischemia/reperfusion and ATP depletion/repletion in LLC-PK(1) cells result in phosphorylation of FKHR and FKHRL1, *Kidney Int*, **64**, no. 4, 1189–1198, (2003).

[76] M. Andreucci, [Contrast media and nephrotoxicity: a molecular conundrum], *G Ital Nefrol*, **28**, no. 4, p. 355, (2011).

[77] M. Andreucci, T. Faga, G. Lucisano, et al., Mycophenolic acid inhibits the phosphorylation of NF-kappaB and JNKs and causes a decrease in IL-8 release in H_2O_2-treated human renal proximal tubular cells, *Chem Biol Interact*, **185**, no. 3, 253–262, (2010).

[78] M. C. Mendoza, E. E. Er, and J. Blenis, The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation, *Trends Biochem Sci*, **36**, no. 6, 320–328, (2011).

[79] B. D. Manning and L. C. Cantley, AKT/PKB signaling: navigating downstream, *Cell*, **129**, no. 7, 1261–1274, (2007).

[80] M. Andreucci, G. Fuiano, P. Presta, et al., Downregulation of cell survival signalling pathways and increased cell damage in hydrogen peroxide-treated human renal proximal tubular cells by alpha-erythropoietin, *Cell Prolif*, **42**, no. 4, 554–561, (2009).

[81] T. Yano, Y. Itoh, T. Kubota, et al., A prostacyclin analog prevents radiocontrast nephropathy via phosphorylation of cyclic AMP response element binding protein, *Am J Pathol*, **166**, no. 5, 1333–1342, (2005).

[82] S. P. Wood, Contrast-induced nephropathy in critical care, *Crit Care Nurse*, **32**, no. 6, 15–23, (2012).

[83] P. A. McCullough and J. A. Tumlin, Prostaglandin-based renal protection against contrast-induced acute kidney injury, *Circulation*, **120**, no. 18, 1749–1751, (2009).

[84] D. Yang, D. Yang, R. Jia, and J. Tan, Na+/Ca2+ exchange inhibitor, KB-R7943, attenuates contrast-induced acute kidney injury, *J Nephrol*, **26**, no. 5, 877–885, (2013).

[85] S. B. Duan, F. Y. Liu, J. A. Luo, et al., Nephrotoxicity of high- and low-osmolar contrast media. The protective role of amlodipine in a rat model, *Acta Radiol*, **41**, no. 5, 503–507, (2000).

[86] J. A. Neyra, S. Shah, R. Mooney, G. Jacobsen, J. Yee, and J. E. Novak, Contrast-induced acute kidney injury following coronary angiography: a cohort study of hospitalized patients with or without chronic kidney disease, *Nephrol Dial Transplant*, **28**, no. 6, 1463–1471, (2013).

[87] M. C. Martín-Mateo, M. Sánchez-Portugal, S. Iglesias, A. de Paula, and J. Bustamante, Oxidative stress in chronic renal failure, *Ren Fail*, **21**, no. 2, 155–167, (1999).

[88] D. M. Okamura, S. Pennathur, K. Pasichnyk, et al., CD36 regulates oxidative stress and inflammation in hypercholesterolemic CKD, *J Am Soc Nephrol*, **20**, no. 3, 495–505, (2009).

[89] O. Toprak, Conflicting and new risk factors for contrast induced nephropathy, *J Urol*, **178**, no. 6, 2277–2283, (2007).

[90] A. Pflueger, T. S. Larson, K. A. Nath, B. F. King, J. M. Gross, and F. G. Knox, Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus, *Mayo Clin Proc*, **75**, no. 12, 1275–1283, (2000).

[91] M. Khamaisi, I. Raz, V. Shilo, A. Shina, C. Rosenberger, R. Dahan, Z. Abassi, R. Meidan, S. Lecht, and S. N. Heyman, Diabetes and radiocontrast media increase endothelin converting enzyme-1 in the kidney, *Kidney Int.*, **74**, no. 1, 91–100, (2008).

[92] K. J. Hardiek, R. E. Katholi, R. S. Robbs, and C. E. Katholi, Renal effects of contrast media in diabetic patients undergoing diagnostic or interventional coronary angiography, *J Diabetes Complications*, **22**, no. 3, 171–177, (2008).

[93] S. Morabito, V. Pistolesi, G. Benedetti, et al., Incidence of contrast-induced acute kidney injury associated with diagnostic or interventional coronary angiography, *J Nephrol*, **25**, no. 6, 1098–1107, (2012).

[94] O. Toprak, M. Cirit, M. Yesil, et al., Impact of diabetic and pre-diabetic state on development of contrast-induced nephropathy in patients with chronic kidney disease, *Nephrol Dial Transplant*, **22**, no. 3, 819–826, (2007).

[95] M. R. Rudnick, S. Goldfarb, and J. Tumlin, Contrast-induced nephropathy: is the picture any clearer? *Clin J Am Soc Nephrol*, **3**, no. 1, 261–262, (2008).

[96] V. E. Andreucci, D. Russo, B. Cianciaruso, and M. Andreucci, Some sodium, potassium and water changes in the elderly and their treatment, *Nephrol Dial Transplant*, **11**, suppl 9, 9–17, (1996).

[97] S. K. Morcos, Contrast media-induced nephrotoxicity–questions and answers, *Br J Radiol*, **71**, no. 844, 357–365, (1998).

[98] A. Kolonko, F. Kokot, and A. Wiecek, Contrast-associated nephropathy–old clinical problem and new therapeutic perspectives, *Nephrol Dial Transplant*, **13**, no. 3, 803–806, (1998).

[99] D. Yang, S. Lin, D. Yang, L. Wei, and W. Shang, Effects of short- and long-term hypercholesterolemia on contrast-induced acute kidney injury, *Am J Nephrol*, **35**, no. 1, 80–89, (2012).

[100] M. Andreucci, Side effects of radiographic contrast media, *BioMed Research International*, **2014**, Article ID 872574, (2014).

[101] M. Andreucci, T. Faga, M. Sabbatini, A. Pisani, D. Russo, and A. Michael, How to prevent Contrast-Induced Nephropathy in clinical practice, *J Clin Nephrol Res*, **1**, no. 1, Article ID 1002, (2014).

[102] C. Mueller, Prevention of contrast-induced nephropathy with volume supplementation, *Kidney Int Suppl*, **69**, no. 100, S16–S19, (2006).

[103] C. E. Balemans, L. J. Reichert, B. I. van Schelven, J. A. van den Brand, and J. F. Wetzels, Epidemiology of contrast material-induced nephropathy in the era of hydration, *Radiology*, **263**, no. 3, 706–713, (2012).

[104] M. Andreucci, T. Faga, A. Pisani, M. Sabbatini, D. Russo, and A. Michael, Prevention of contrast-induced nephropathy through a knowledge of its pathogenesis and risk factors, *ScientificWorldJournal*, **2014**, Article ID 823169, (2014).

[105] H. S. Thomsen, Guidelines for contrast media from the European Society of Urogenital Radiology, *AJR Am J Roentgenol*, **181**, no. 6, 1463–1471, (2003).

[106] J. H. Ellis and R. H. Cohan, Prevention of contrast-induced nephropathy: an overview, *Radiol Clin North Am*, **47**, no. 5, 801–811, v, (2009)., v.

[107] R. Solomon and H. L. Dauerman, Contrast-induced acute kidney injury, *Circulation*, **122**, no. 23, 2451–2455, (2010).

[108] G. J. Merten, W. P. Burgess, L. V. Gray, et al., Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial, *JAMA*, **291**, no. 19, 2328–2334, (2004).

[109] M. Masuda, T. Yamada, T. Mine, et al., Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure, *Am J Cardiol*, **100**, no. 5, 781–786, (2007).

[110] E. E. Ozcan, S. Guneri, B. Akdeniz, et al., Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial, *Am Heart J*, **154**, no. 3, 539–544, (2007).

[111] A. Tamura, Y. Goto, K. Miyamoto, et al., Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure, *Am J Cardiol*, **104**, no. 7, 921–925, (2009).

[112] S. D. Navaneethan, S. Singh, S. Appasamy, R. E. Wing, and A. R. Sehgal, Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: a systematic review and meta-analysis, *Am J Kidney Dis*, **53**, no. 4, 617–627, (2009).

[113] E. A. Hoste, J. J. De Waele, S. A. Gevaert, S. Uchino, and J. A. Kellum, Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis, *Nephrol Dial Transplant*, **25**, no. 3, 747–758, (2010).

[114] M. Joannidis, M. Schmid, and C. J. Wiedermann, Prevention of contrast media-induced nephropathy by isotonic sodium bicarbonate: a meta-analysis, *Wien Klin Wochenschr*, **120**, no. 23-24, 742–748, (2008).

[115] F. Assadi, Acetazolamide for prevention of contrast-induced nephropathy: a new use for an old drug, *Pediatr Cardiol*, **27**, no. 2, 238–242, (2006).

[116] M. Pakfetrat, M. H. Nikoo, L. Malekmakan, et al., A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial, *Int Urol Nephrol*, **41**, no. 3, 629–634, (2009).

[117] J. S. Jang, H. Y. Jin, J. S. Seo, et al., Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury – a systematic review and meta-analysis –, *Circ J*, **76**, no. 9, 2255–2265, (2012).

[118] C. Briguori, F. Airoldi, D. D'Andrea, et al., Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies, *Circulation*, **115**, no. 10, 1211–1217, (2007).

[119] D. Reddan, M. Laville, and V. D. Garovic, Contrast-induced nephropathy and its prevention: what do we really know from evidence-based findings? *J Nephrol*, **22**, no. 3, 333–351, (2009).

[120] S. Zoungas, T. Ninomiya, R. Huxley, et al., Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy, *Ann Intern Med*, **151**, no. 9, 631–638, (2009).

[121] S. S. Brar, A. Y. Shen, M. B. Jorgensen, et al., Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial, *JAMA*, **300**, no. 9, 1038–1046, (2008).

[122] S. S. Brar, S. Hiremath, G. Dangas, R. Mehran, S. K. Brar, and M. B. Leon, Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: a systematic review and meta-analysis, *Clin J Am Soc Nephrol*, **4**, no. 10, 1584–1592, (2009).

[123] L. Shavit, R. Korenfeld, M. Lifschitz, A. Butnaru, and I. Slotki, Sodium bicarbonate versus sodium chloride and oral N-acetylcysteine for the prevention of contrast-induced nephropathy in advanced chronic kidney disease, *J Interv Cardiol*, **22**, no. 6, 556–563, (2009).

[124] A. Vasheghani-Farahani, G. Sadigh, S. E. Kassaian, et al., Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial, *Am J Kidney Dis*, **54**, no. 4, 610–618, (2009).

[125] A. M. From, B. J. Bartholmai, A. W. Williams, S. S. Cha, A. Pflueger, and F. S. McDonald, Sodium bicarbonate is associated with an increased incidence of contrast nephropathy: a retrospective cohort study of 7977 patients at mayo clinic, *Clin J Am Soc Nephrol*, **3**, no. 1, 10–18, (2008).

[126] D. Fliser, M. Laville, A. Covic, et al., A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy, *Nephrol Dial Transplant*, **27**, no. 12, 4263–4272, (2012).

[127] J. J. Keaney, C. M. Hannon, and P. T. Murray, Contrast-induced acute kidney injury: how much contrast is safe? *Nephrol Dial Transplant*, **28**, no. 6, 1376–1383, (2013).

[128] R. W. Katzberg and C. Haller, Contrast-induced nephrotoxicity: clinical landscape, *Kidney Int Suppl*, **69**, no. 100, S3–S7, (2006).

[129] R. G. Cigarroa, R. A. Lange, R. H. Williams, and L. D. Hillis, Dosing of contrast material to prevent contrast nephropathy in patients with renal disease, *Am J Med*, **86**, no. 6 Pt 1, 649–652, (1989).

[130] W. K. Laskey, C. Jenkins, F. Selzer, et al., Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention, *J Am Coll Cardiol*, **50**, no. 7, 584–590, (2007).

[131] H. S. Gurm, S. R. Dixon, D. E. Smith, et al., Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions, *J Am Coll Cardiol*, **58**, no. 9, 907–914, (2011).

[132] R. Safirstein, L. Andrade, and J. M. Vieira, Acetylcysteine and nephrotoxic effects of radiographic contrast agents–a new use for an old drug, *N Engl J Med*, **343**, no. 3, 210–212, (2000).

[133] L. C. Coyle, A. Rodriguez, R. E. Jeschke, A. Simon-Lee, K. C. Abbott, and A. J. Taylor, Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics, *Am Heart J*, **151**, no. 5, 1032.e9–1032.e12, (2006).

[134] C. Sandhu, A. M. Belli, and D. B. Oliveira, The role of N-acetylcysteine in the prevention of contrast-induced nephrotoxicity, *Cardiovasc Intervent Radiol*, **29**, no. 3, 344–347, (2006).

[135] H. C. Lee, S. H. Sheu, I. H. Liu, et al., Impact of short-duration administration of N-acetylcysteine, probucol and ascorbic acid on contrast-induced cytotoxicity, *J Nephrol*, **25**, no. 1, 56–62, (2012).

[136] J. DiMari, J. Megyesi, N. Udvarhelyi, P. Price, R. Davis, and R. Safirstein, N-acetyl cysteine ameliorates ischemic renal failure, *Am J Physiol*, **272**, no. 3 Pt 2, F292–F298, (1997).

[137] C. S. Baker, A. Wragg, S. Kumar, R. De Palma, L. R. Baker, and C. J. Knight, A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study, *J Am Coll Cardiol*, **41**, no. 12, 2114–2118, (2003).

[138] M. Tepel, M. van der Giet, C. Schwarzfeld, U. Laufer, D. Liermann, and W. Zidek, Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine, *N Engl J Med*, **343**, no. 3, 180–184, (2000).

[139] J. D. Durham, C. Caputo, J. Dokko, et al., A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography, *Kidney Int*, **62**, no. 6, 2202–2207, (2002).

[140] S. Allaqaband, R. Tumuluri, A. M. Malik, et al., Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy, *Catheter Cardiovasc Interv*, **57**, no. 3, 279–283, (2002).

[141] I. Goldenberg, M. Shechter, S. Matetzky, et al., Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature, *Eur Heart J*, **25**, no. 3, 212–218, (2004).

[142] N. Pannu, B. Manns, H. Lee, and M. Tonelli, Systematic review of the impact of N-acetylcysteine on contrast nephropathy, *Kidney Int*, **65**, no. 4, 1366–1374, (2004).

[143] F. Ferrario, M. T. Barone, G. Landoni, et al., Acetylcysteine and nonionic isosmolar contrast-induced nephropathy–a randomized controlled study, *Nephrol Dial Transplant*, **24**, no. 10, 3103–3107, (2009).

[144] H. S. Gurm, D. E. Smith, O. Berwanger, et al., Contemporary use and effectiveness of N-acetylcysteine in preventing contrast-induced nephropathy among patients undergoing percutaneous coronary intervention, *JACC Cardiovasc Interv*, **5**, no. 1, 98–104, (2012).

[145] K. Spargias, E. Alexopoulos, S. Kyrzopoulos, et al., Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention, *Circulation*, **110**, no. 18, 2837–2842, (2004).

[146] E. Alexopoulos, K. Spargias, S. Kyrzopoulos, et al., Contrast-induced acute kidney injury in patients with renal dysfunction undergoing a coronary procedure and receiving nonionic low-osmolar versus iso-osmolar contrast media, *Am J Med Sci*, **339**, no. 1, 25–30, (2010).

[147] A. Boscheri, C. Weinbrenner, B. Botzek, K. Reynen, E. Kuhlisch, and R. H. Strasser, Failure of ascorbic acid to prevent contrast-media induced nephropathy in patients with renal dysfunction, *Clin Nephrol*, **68**, no. 5, 279–286, (2007).

[148] S. H. Jo, B. K. Koo, J. S. Park, et al., N-acetylcysteine versus AScorbic acid for preventing contrast-Induced nephropathy in patients with renal insufficiency undergoing coronary angiography NASPI study-a prospective randomized controlled trial, *Am Heart J*, **157**, no. 3, 576–583, (2009).

[149] U. Sadat, A. Usman, J. H. Gillard, and J. R. Boyle, Does ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography: a systematic review with meta-analysis of randomized, controlled trials, *J Am Coll Cardiol*, **62**, no. 23, 2167–2175, (2013).

[150] A. Tasanarong, A. Vohakiat, P. Hutayanon, and D. Piyayotai, New strategy of α- and γ-tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures, *Nephrol Dial Transplant*, **28**, no. 2, 337–344, (2013).

[151] A. Veverka, D. S. Nuzum, and J. L. Jolly, Nebivolol: a third-generation beta-adrenergic blocker, *Ann Pharmacother*, **40**, no. 7-8, 1353–1360, (2006).

[152] S. S. Sule and W. Frishman, Nebivolol: new therapy update, *Cardiol Rev*, **14**, no. 5, 259–264, (2006).

[153] O. Toprak, M. Cirit, M. Tanrisev, et al., Preventive effect of nebivolol on contrast-induced nephropathy in rats, *Nephrol Dial Transplant*, **23**, no. 3, 853–859, (2008).

[154] E. Avci, M. Yeşil, S. Bayata, N. Postaci, E. Arikan, and M. Cirit, The role of nebivolol in the prevention of contrast-induced nephropathy in patients with renal dysfunction, *Anadolu Kardiyol Derg*, **11**, no. 7, 613–617, (2011).

[155] O. Günebakmaz, M. G. Kaya, F. Koc, et al., Does nebivolol prevent contrast-induced nephropathy in humans? *Clin Cardiol*, **35**, no. 4, 250–254, (2012).

[156] S. Khanal, N. Attallah, D. E. Smith, et al., Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions, *Am J Med*, **118**, no. 8, 843–849, (2005).

[157] G. Patti, A. Nusca, M. Chello, et al., Usefulness of statin pretreatment to prevent contrast-induced nephropathy and to improve long-term outcome in patients undergoing percutaneous coronary intervention, *Am J Cardiol*, **101**, no. 3, 279–285, (2008).

[158] M. Leoncini, A. Toso, M. Maioli, F. Tropeano, and F. Bellandi, Statin treatment before percutaneous cononary intervention, *J Thorac Dis*, **5**, no. 3, 335–342, (2013).

[159] B. C. Zhang, W. M. Li, and Y. W. Xu, High-dose statin pretreatment for the prevention of contrast-induced nephropathy: a meta-analysis, *Can J Cardiol*, **27**, no. 6, 851–858, (2011).

[160] M. Andreucci, [Statins in CIN: a problem at least partly solved?], *G Ital Nefrol*, **30**, no. 3, p. gin/30.3.9, (2013).

[161] M. Sabbatini, A. Pisani, F. Uccello, et al., Atorvastatin improves the course of ischemic acute renal failure in aging rats, *J Am Soc Nephrol*, **15**, no. 4, 901–909, (2004).

[162] K. E. Al-Otaibi, A. M. Al Elaiwi, M. Tariq, and A. K. Al-Asmari, Simvastatin attenuates contrast-induced nephropathy through modulation of oxidative stress, proinflammatory myeloperoxidase, and nitric oxide, *Oxid Med Cell Longev*, **2012**, (2012).

[163] C. Quintavalle, D. Fiore, F. De Micco, et al., Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury, *Circulation*, **126**, no. 25, 3008–3016, (2012).

[164] Y. Han, G. Zhu, L. Han, et al., Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease, *J Am Coll Cardiol*, **63**, no. 1, 62–70, (2014).

[165] S. Yoshida, H. Kamihata, S. Nakamura, et al., Prevention of contrast-induced nephropathy by chronic pravastatin treatment in patients with cardiovascular disease and renal insufficiency, *J Cardiol*, **54**, no. 2, 192–198, (2009).

[166] M. A. Muñoz, P. R. Maxwell, K. Green, D. W. Hughes, and R. L. Talbert, Pravastatin versus simvastatin for prevention of contrast-induced nephropathy, *J Cardiovasc Pharmacol Ther*, **16**, no. 3-4, 376–379, (2011).

[167] S. Acikel, H. Muderrisoglu, A. Yildirir, et al., Prevention of contrast-induced impairment of renal function by short-term or long-term statin therapy in patients undergoing elective coronary angiography, *Blood Coagul Fibrinolysis*, **21**, no. 8, 750–757, (2010).

[168] G. Patti, E. Ricottini, A. Nusca, et al., Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty–contrast-induced nephropathy] trial, *Am J Cardiol*, **108**, no. 1, 1–7, (2011).

[169] M. Andreucci, D. Russo, G. Fuiano, R. Minutolo, and V. E. Andreucci, Diuretics in renal failure, *Miner Electrolyte Metab*, **25**, no. 1-2, 32–38, (1999).

[170] R. Solomon, C. Werner, D. Mann, J. D'Elia, and P. Silva, Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents, *N Engl J Med*, **331**, no. 21, 1416–1420, (1994).

[171] J. M. Weinstein, S. Heyman, and M. Brezis, Potential deleterious effect of furosemide in radiocontrast nephropathy, *Nephron*, **62**, no. 4, 413–415, (1992).

[172] L. S. Weisberg, P. B. Kurnik, and B. R. Kurnik, Risk of radiocontrast nephropathy in patients with and without diabetes mellitus, *Kidney Int*, **45**, no. 1, 259–265, (1994).

[173] C. Briguori, G. Visconti, A. Focaccio, et al., Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury, *Circulation*, **124**, no. 11, 1260–1269, (2011).

[174] C. Briguori, G. Visconti, B. Ricciardelli, G. Condorelli, and R. I. Investigators, Renal insufficiency following contrast media administration trial II, (REMEDIAL II): RenalGuard system in high-risk patients for contrast-induced acute kidney injury: rationale and design, *EuroIntervention : Journal of EuroPCR in Collaboration With the Working Group on Interventional Cardiology of the European Society of Cardiology*, **6**, no. 9, 1117–1122, (2011).

[175] G. Marenzi, C. Ferrari, I. Marana, et al., Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial, *JACC Cardiovasc Interv*, **5**, no. 1, 90–97, (2012).

[176] D. Russo, A. Testa, L. Della Volpe, and G. Sansone, Randomised prospective study on renal effects of two different contrast media in humans: protective role of a calcium channel blocker, *Nephron*, **55**, no. 3, 254–257, (1990).

[177] H. H. Neumayer, W. Junge, A. Küfner, and A. Wenning, Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial, *Nephrol Dial Transplant*, **4**, no. 12, 1030–1036, (1989).

[178] B. Spångberg-Viklund, J. Berglund, T. Nikonoff, P. Nyberg, T. Skau, and R. Larsson, Does prophylactic treatment with felodipine, a calcium antagonist, prevent low-osmolar contrast-induced renal dysfunction in hydrated diabetic and nondiabetic patients with normal or moderately reduced renal function? *Scand J Urol Nephrol*, **30**, no. 1, 63–68, (1996).

[179] M. Andreucci, T. Faga, A. Pisani, et al., Reversal of radiocontrast medium toxicity in human renal proximal tubular cells by white grape juice extract, *Chem Biol Interact*, **229**, 17–25, (2015).

[180] R. Schindler, C. Stahl, S. Venz, K. Ludat, W. Krause, and U. Frei, Removal of contrast media by different extracorporeal treatments, *Nephrol Dial Transplant*, **16**, no. 7, 1471–1474, (2001).

[181] T. Lehnert, E. Keller, K. Gondolf, T. Schäffner, H. Pavenstädt, and P. Schollmeyer, Effect of haemodialysis after contrast medium administration in patients with renal insufficiency, *Nephrol Dial Transplant*, **13**, no. 2, 358–362, (1998).

[182] B. Vogt, P. Ferrari, C. Schönholzer, et al., Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful, *Am J Med*, **111**, no. 9, 692–698, (2001).

[183] V. L. Esnault, Radiocontrast media-induced nephrotoxicity in patients with renal failure: rationale for a new double-blind, prospective, randomized trial testing calcium channel antagonists, *Nephrol Dial Transplant*, **17**, no. 8, 1362–1364, (2002).

[184] C. Guastoni, S. De Servi, and M. D'Amico, The role of dialysis in contrast-induced nephropathy: doubts and certainties, *J Cardiovasc Med (Hagerstown)*, **8**, no. 8, 549–557, (2007).

[185] P. T. Lee, K. J. Chou, C. P. Liu, et al., Renal protection for coronary angiography in advanced renal failure patients by prophylactic hemodialysis. A randomized controlled trial, *J Am Coll Cardiol*, **50**, no. 11, 1015–1020, (2007).

[186] G. Marenzi, G. Lauri, J. Campodonico, et al., Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients, *Am J Med*, **119**, no. 2, 155–162, (2006).

[187] C. Guastoni, N. Bellotti, F. Poletti, et al., Continuous venovenous hemofiltration after coronary procedures for the prevention of contrast-induced acute kidney injury in patients with

severe chronic renal failure, *Am J Cardiol*, **113**, no. 4, 588–592, (2014).

[188] J. J. Pasternak and E. E. Williamson, Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the non-radiologist, *Mayo Clin Proc*, **87**, no. 4, 390–402, (2012).