INTRODUCTION

Contrast Induced Nephropathy has gained increased attention in the clinical setting, particularly during cardiac intervention but also in many other radiological procedures in which iodinated contrast media are used. There is at present good clinical evidence from well-controlled randomized studies that CIN is a common cause of acute renal dysfunction[1,2]. CIN is the acute deterioration of renal function after parenteral administration of radiocontrast media in the absence of other causes. CIN is generally defined as an increase in serum creatinine concentration of >0.5 mg/dL (>44 μmol/L) or 25% above baseline within 48 hours after contrast administration[3–7].

Although the exact mechanisms of CIN have yet to be fully elucidated, several causes have been described. Increased adenosine-, endothelin-, and free radical–induced vasoconstriction and reduced nitric oxide– and prostaglandin-induced vasodilatation have been observed. These mechanisms cause ischemia in the deeper portion of the outer medulla, an area with high oxygen requirements and remote from the vasa recta supplying the renal medulla with blood. Contrast agents also have direct toxic effects on renal tubular cells, causing vacuolization, altered mitochondrial function, and apoptosis[8]. Atopy does not play a role in the pathogenesis of CIN.

The incidence of CIN in the general population has been calculated to be <2%. In high-risk patients, i.e., patients with chronic renal impairment, diabetes mellitus, congestive heart

failure, and older age, the incidence has been calculated to be >20% to 30%[3–7]. CIN has been associated with increased morbidity, extended length of hospital stay, and increased costs[9]. Several risk factors have been described for CIN[10–12]. A risk score for prediction of CIN after percutaneous coronary intervention has been reported by **Mehran et al.**[12] That risk score includes hypotension (5 points, if systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive heart failure (5 points, if class III/IV by New York Heart Association classification or history of pulmonary edema), age (4 points, if >75 years), anemia (3 points, if hematocrit <39% for men and <36% for women), diabetes mellitus (3 points), contrast media volume (1 point per 100 mL), estimated glomerular filtration rate (GFR; GFR in mL/min per 1.73 m^2; 2 points, if GFR 60 to 40; 4 points, if GFR 40 to 20; 6 points, if GFR <20). A risk score of <6, 6 to 10, 11 to 16, and >16 indicates a risk for CIN of 7.5%, 14%, 26%, and 57%, respectively.[12] It should be emphasized that higher contrast volume is an important risk factor for CIN[10–12]. Although no definite proof has been obtained yet, the risk of nonsteroidal antiinflammatory drugs or angiotensin-converting enzyme inhibitors to exacerbate CIN has been reported because of their effects on renal perfusion or tubulotoxicity[13,14]. It is thus clear that CIN is a potentially harmful condition. The reason that problems seem to be increasing is that the number of angiographies and CT examinations in clinical practice is increasing, and today higher doses are administered to sicker and older patients[3–7,15].

AIM OF THE WORK

This study aims to observe the effect of contrast agents on renal functions in patients with renal impairment undergoing percutaneous coronary intervention.

CONTRAST INDUCED NEPHROPATHY

Introduction

Increasing use of contrast media during radiological procedures has resulted in an increasing incidence of contrast-induced nephropathy (CIN), an iatrogenic disorder caused by exposure to contrast material.

CIN is a complex syndrome of acute renal failure occurring after the administration of iodinated contrast media. The definition includes absolute or relative increase in creatinine level after exposure to contrast agent compared with baseline value, when alternative explanations for renal impairment have been excluded. It occurs within 24–48hr of the exposure, with creatinine level typically peaking 3–5 days after procedure and returning to baseline or near baseline value in 1–3 weeks[1]. The cut-off increase in creatinine defining CIN differs in various studies (from 20 to 50% or in absolute values from 0.5 to 1.0 mg/dL), making it difficult to compare the results. The most common definition used lately is ≥25% relative increase or an absolute increase of ≥0.5 mg/dL in serum creatinine from baseline value at 48 to 72hr after exposure to contrast media. On the basis of this definition, the overall incidence of CIN in the general population is reported to be 1.2 to 1.6%[2,3]. The incidence of CIN is even higher in selected subsets of patients with cardiovascular pathology, which is not surprising given the high prevalence of risk factors for CIN in this population. On the basis of the data

registry of the Mayo Clinic including 7,586 patients who underwent percutaneous coronary interventions (PCI), the incidence of CIN was 3.3%[4]. In a smaller study of **McCullough et al.**[5] that analyzed data on 1,826 patients undergoing PCI, CIN occurred in 14.5% of the cases. Dialysis as a result of CIN in these two series was required in 0.7% and 0.3% of patients, respectively.

Pathogenesis of CIN

The pathogenesis of CIN is not clearly understood. Thus far, several pathophysiological mechanisms of CIN have been proposed, including direct toxicity to renal tubular epithelium, oxidative stress, ischemic injury, and tubular obstruction[6,7]. Low blood flow in the medulla leading to medullary hypoxia might result from increased perivascular hydrostatic pressure, increased intratubular pressure secondary to contrast-induced diuresis, vasoconstriction due to redundance of vasoactive substances as adenosin and endothelin, and decrease of nitric oxide and prostaglandins[8,9]. Excretion of the contrast medium requires significant urine volume to clear the osmotic load. Exposure of renal tissues to high osmotic loads results in characteristic histopathologic changes called “osmotic nephrosis” Changes consistent with osmotic nephrosis were observed in 22.3% of patients undergoing renal biopsy within 10 days of contrast exposure[10]. After injection of contrast media, a transient increase is followed by a more prolonged decrease in renal blood flow in animals and humans[11]. Endothelin-1 has been implicated as the

most likely causative agent in a number of studies[12,13]. The vasoactive effect of adenosine in different organs is dependent on the ratio of adenosine A_1 and A_2 receptors. In kidneys, in contrast to heart, adenosine causes vasoconstriction and is also thought to play a role in pathogenesis of CIN due to increase of renal adenosine concentrations as a result of enhanced adenosine triphosphate hydrolysis[14]. Reactive oxygen species, which are generated during hypoxia, also probably contribute to renal injury[15].

Risk factors of CIN

Risk factors for the development of CIN have been thoroughly examined in several studies. They may be divided into two categories: fixed (nonmodifiable) and modifiable.

The best recognized nonmodifiable risk factors include older age, diabetes mellitus, preexistent renal insufficiency, congestive heart failure, hemodynamic instability, and nephrotic syndrome.

Age

The elderly are at increased risk of CIN with reported incidence of 11% in patients older than 70 years[3]. The reasons for higher risk of developing CIN in the elderly have not been studied specifically and probably are multifactorial, including age-related change in renal function as diminished glomerular filtration rate (GFR), tubular secretion and concentration ability,

as well as more difficult vascular access requiring greater amount of contrast, presence of multivessel disease, etc. Importantly, by multivariate analysis, age older than 70 years appeared to be an independent predictor of CIN in some studies[16–18].

Preexisting Renal Disease

Preexisting renal disease with an elevated level of creatinine is a crucial risk factor in the development of CIN; rates in patients with underlying renal disorder are extremely high, ranging from 14.8 to 55%[4,5,19]. In multivariate analysis, baseline creatinine represented an independent predictor of CIN in the majority of the studies[3–5,19]. In contrast, the risk of CIN is minimal (<10%) in patients who have normal renal function at the time of contrast-medium exposure.

Higher baseline creatinine values are associated with greater risk of CIN[20]. As shown in study by Hall[21] if baseline plasma creatinine level is ≤1.2 mg/dL, the incidence of CIN was only 2%. However, in patients with values of creatinine in the range of 1.4–1.9 mg/dL, the incidence of CIN increased to 10.4%, and in patients with baseline creatinine level ≥2.0 mg/dL, 62% developed CIN after angiography. A model that predicted CIN by the serum creatinine level showed an exponential increase in the risk for nephrotoxicity if the baseline level was 1.2 mg/dL or higher[22]. Generally, estimated GFR <60 mL/min/1.73m^2 is considered a cut-off value for increased risk of CIN[23].

Diabetes Mellitus

Diabetes mellitus has been identified as an independent risk factor for CIN in numerous studies[3–5,24]. The incidence of CIN in diabetics varies from 5.7 to 29.4%[2,25,26]. Given the high prevalence of diabetes in the general population and its ability to cause broad spectrum of cardiovascular diseases, which require radiological procedures for their diagnosis and treatment, diabetic patients represent a significant proportion of those undergoing contrast exposure. Risk of CIN is increased even in diabetics with preserved renal function[24,27]. Presence of other risk factors, such as renal insufficiency or proteinuria, in diabetics further increases the risk for CIN. In study by **Berns et al.**[1], CIN occurred in 27% of diabetics with baseline serum creatinine 2.0 to 4.0 mg/dL and in 81% of those with serum creatinine >4.0 mg/dL. In a study by **Toprak et al.**[28], a total of 421 patients with Cockcroft–Gauldt estimated creatinine clearance between 15 and 60 mL/min were divided into three groups: diabetes mellitus (n = 137; glucose ≥ 126 mg/dL), pre-diabetes (n = 140; glucose between 100 and 125 mg/dL), and normal fasting glucose (n = 144; glucose < 100 mg/dL). CIN, defined as an increase of ≥25% in creatinine over baseline within 48hr of angiography, occurred in 20% of diabetics, 11.4% of pre-diabetics, and 5.5% of patients with normal fasting glucose level.

Congestive Heart Failure and Hemodynamic Instability

Since reduced renal perfusion is probably a major mechanism of renal injury in CIN, it is not surprising that several clinical situations associated with hemodynamic impairment were shown to predispose to CIN. Congestive heart failure has been associated with increased risk for CIN in several studies[3,4,24,29]. Anterior myocardial infarction as well as indicators of hemodynamic instability, such as periprocedural hypotension and use of an intra-aortic balloon pump, were shown to be predictors of CIN in patients undergoing primary PCI[29,30].

Renal Transplant

Concomitant use of nephrotoxic drugs (cyclosporine) along with higher prevalence of diabetes and renal insufficiency results in high risk of CIN in patients with renal transplant. **Ahuja et al.**[31] retrospectively assessed the data on 144 patients with functioning renal allograft who were exposed to contrast media. The incidence of CIN was 21.2% in the whole group, and was especially high (42.8%) among those who have not received hydration before the procedure.

Volume of Contrast Media

Volume of contrast media administered during the procedure is of primary importance in the development of CIN[26]. It is a main modifiable risk factor for CIN. However, growing

complexity of coronary procedures inevitably causes an increased use of contrast media per procedure and consequently enhances the risk of CIN. The correlation between the amount of contrast and the risk of CIN was documented in a number of studies[32,33]. According to **McCullough et al.**[5], the risk of CIN is minimal in patients receiving <100 mL of contrast media.

Nephrotoxic Drugs

It is anticipated that concomitant use of nephrotoxic drug and contrast administration will increase risk of CIN. Alamartine reported a trend toward a higher incidence of CIN (*P*=0.07) in patients receiving nephrotoxic drugs (including diuretics, nonsteroidal anti-inflammatory drugs, coxibs, aminoglycosides, amphotericin B)[34]. It is a common clinical practice to avoid any other nephrotoxic insults, if it is feasible, when contrast medium is administered.

The contribution of angiotensin-converting enzyme (ACE) inhibitors to risk of CIN is still controversial. In a study by **Kini et al.**[17], patients receiving ACE inhibitors had a significant increase in serum creatinine after the procedure compared with patients without this therapy. Similarly, in study by Cirit[35], patients with renal insufficiency receiving ACE inhibitors had a higher incidence of CIN after contrast administration than patients who did not receive ACE inhibitors (15.6% vs. 5.8%; *P*=0.015). However, another study showed that preprocedure ACE inhibitor use was associated with a lower risk for CIN in patients with

chronic renal disease (OR, 0.61; P=0.005)[24]. Similarly, another clinical trial showed that periprocedural captopril reduced the risk for CIN, compared with an untreated control group[36].

Anemia

In a large registry of 6,773 consecutive patients treated with PCI, low baseline hematocrit was identified as an independent predictor of CIN by multivariate analysis[27]. CIN (increase of ≥25% or ≥0.5 mg/dL over preprocedure serum creatinine, at 48 hr postprocedure) rates steadily increased with baseline hematocrit quintile decrements (from 10.3% in the highest quintile to 23.3% in the lowest quintile) (P for trend <0.0001).

Type of Contrast Agent

Despite the structural similarity of currently used contrast media (all of them represent derivatives of bensoic acid), there are substantial differences in the chemical properties of these various agents, including the number of iodine molecules, sodium content, and osmolar composition. These latter properties define such characteristics of contrast media as osmolarity, ionicity, and viscosity. Properties of contrast media are listed in the following table.

Table (1): Properties of Contrast Media

Generic name	Osmolarity	Ionicity
Diatrizoate	High-osmolar	Ionic monomer
Iothalamate	High-osmolar	Ionic monomer
Ioxithalamate	High-osmolar	Ionic monomer
Ioxaglate	Low-osmolar	Ionic dimer
Iohexol	Low-osmolar	Nonionic monomer
Iopamidol	Low-osmolar	Nonionic monomer
Ioversol	Low-osmolar	Nonionic monomer
Iopromide	Low-osmolar	Nonionic monomer
Iobitridol	Low-osmolar	Nonionic monomer
Iomeprol	Low-osmolar	Nonionic monomer
Iodixanol	Iso-osmolar	Nonionic dimer

Numerous studies comparing different contrast agents have been conducted. **Barrett et al.**[37] published in 1993 a meta-analysis of 31 randomized trials comparing low-osmolality contrast media and high- osmolality contrast media. Pooled odds of a rise in serum creatinine level of more than >0.5 mg/dL with low-osmolality contrast media was 0.61 (95% confidence interval [CI], 0.48–0.77) times that after high-osmolality contrast media. The effect of low-osmolality contrast media in reducing the risk of a rise in serum creatinine of >0.5 mg/dL was significant in patients with renal impairment (OR 0.5; CI, 0.36–0.68) but not in those with normal renal function (OR 0.75; CI, 0.52–1.1). The authors concluded that use of low-osmolality contrast media may be beneficial in patients with existing renal failure [37]. These finding were confirmed in a prospective, randomized, double-blind multicenter trial by **Rudnick et al.**[19] comparing low-

osmolar nonionic contrast agent, iohexol, and the high-osmolar ionic contrast agent, diatrizoate, in 1,196 patients undergoing cardiac angiography. Acute nephrotoxicity (increase in serum creatinine of ≥1 mg/dL, at 48 to 72hr postprocedure) was observed in 7% of patients receiving diatrizoate compared with 3% of patients receiving iohexol (P<0.002). Differences in nephrotoxicity between the two contrast groups were confined to patients with previous renal insufficiency or renal insufficiency combined with diabetes mellitus.

A pooled analysis of 16 double-blind, randomized, controlled trials (n=2,727) comparing nephrotoxicity of iso-smolar contrast medium iodixanol with low-osmolar contrast media was recently published[38]. The maximum creatinine increase within 3 days after contrast medium administration was significantly smaller in the iodixanol group compared with the low-osmolar contrast media group (0.06 mg/dL vs. 0.10 mg/dL; P<0.001). CIN, defined as an increase in creatinine ≥0.5 mg/dL within 3 days after contrast media administration, occurred less frequently in the iodixanol group than in the low-osmolar contrast media group in all patients (1.4% vs. 3.5%, P<0.001), in renal insuficiency patients (2.8% vs. 8.4%, P=0.001), and in patients with combination of renal insufficiency and diabetes mellitus (3.5% vs. 15.5%, P=0.003). In recently published RECOVER[39] and ICON[40] trials, patients with chronic renal insufficiency were randomly assigned either to iso-osmolar contrast media iodixanol or low-osmolar contrast media ioxaglate. The incidence of CIN,

defined as ≥25%, or ≥0.5 mg/dL increase of creatinine, was significantly lower with iodixanol (7.9%) than with ioxaglate (17.0%; *P*=0.021) in RECOVER trial[39], but there was no significant difference between both group (16.2% vs. 24.2%, respectively; *P*=0.285) in ICON trial[40].

Generally, use of non-ionic low-osmolar contrast media leads to lower rates of CIN than the high-osmolar contrast media, especially in patients with renal impairment. Recent data suggests that use of the iso-osmolar iodixanol is associated with smaller rises in creatinine and lower rates of CIN than low-osmolar contrast media, especially in patients with renal insufficiency and with combination of renal insufficiency and diabetes mellitus[38,39].

Cumulative Risk Assessment

Risk factors for development of CIN usually occur in combination in individual patients**. Mehran et al.** developed single risk score for prediction of CIN in patients after PCI[29]. **Bartholomew et al.**[41] suggested another score system based on 8 variables associated with CIN: creatinine clearance <60 mL/min, use of intra-aortic balloon pump, urgent coronary procedure, diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease, and contrast volume.

Figure 1: Risk score for prediction of contrast-induced nephropathy by **Mehran et al.** IABP, intra-aortic balloon pump; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate.

Prognosis of CIN

Today, CIN is one of the most common sources of acute renal failure among hospitalized patients. It is associated with prolonged in-hospital stay and increased morbidity, mortality, and costs. Previous studies have shown that 12–14% of patients who develop acute renal insufficiency during hospitalization do so after procedures involving radiographic contrast[5,42]. A retrospective analysis of 16,248 patients exposed to contrast media showed that even apparently small decreases in renal function can lead to excessive mortality rates independent of other risk factors, and given that small rises in serum creatinine levels actually represent a significant drop in GFR[43]. In-hospital mortality rates were almost fivefold higher in patients that developed CIN (34%) compared with those without renal failure (7%)[43]. Prognosis is especially unfavorable in patients with preexisting renal disease, in whom contrast material causes further deterioration of renal function, and those on dialysis [44]. In-hospital mortality in these subsets was 14.9% and 27.5%, respectively, versus 4.9% in patients with preserved renal function[44,45]. In the Mayo Clinic registry, in-hospital mortality in patients undergoing PCI and developing CIN was 22% compared with only 1.4% in patients without CIN[4]. In-hospital mortality is especially high (36%) in patients that require dialysis after the radiocontrast procedure[5].

During the first year after exposure to contrast, rates of mortality in patients with underlying renal disease remain very