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Contrast-Induced Nephropathy in Patients with Type 2 Diabetes Mellitus and Coronary Artery Disease: Update and Practical Clinical Applications

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1. Introduction

Contrast-induced nephropathy (CIN) is an injury to the kidney as a result of exposure to intravascular iodinated contrast medium. It represents an increasing health care burden and challenge as the frequency of diagnostic imaging and interventional studies increase, particularly among populations at risk of developing CIN. As the population ages, decreased renal function and increased atherosclerotic cardiovascular disease become more prevalent. An increasing incidence of obesity with resultant metabolic syndrome and/or type 2 diabetes mellitus also increases the population at risk for CIN (Toprak et al., 2006). Coronary artery disease is a major complication of type 2 diabetes mellitus. Thus, patients with type 2 diabetes mellitus often require coronary angiography and coronary intervention and are at risk of CIN.

2. Contrast-induced nephropathy in patients with type 2 diabetes mellitus and coronary artery disease

For clinical and research purposes, CIN is defined as an acute decline in renal function (rise in serum creatinine by 25% or greater than 0.5 mg/dL from baseline or fall in estimated glomerular filtration rate (eGFR) by greater than 25%) after systemic contrast medium administration in the absence of other causes. Typically, CIN onset occurs within 24-48 hours of exposure, serum creatinine levels peak in 3-5 days, and renal function returns to baseline in 7-21 days. If renal function does not return to baseline, other causes of acute renal injury, like atheroembolism or hypotension, should be suspected (Saleem et al., 1996). CIN is associated with both short-and long-term adverse outcomes, including the need for renal replacement therapy, increased length of hospital stay, major cardiac adverse events, and mortality. The incidence of CIN is less than 5% in patients with normal renal function and 15-50% in patients with baseline renal dysfunction (eGFR less than 60 mL/min/1.73m²). The increased risk of CIN in diabetic patients with reduced renal function is well documented (Parfrey et al., 1989). Yet, diabetic patients without overt renal dysfunction are also at risk as compromised renal function may not manifest until an acute renal insult

results from the administration of contrast medium. CIN carries short-term and long-term mortality. Acute renal failure after coronary intervention is associated with a 36% in-hospital mortality rate and a 19% 2-year survival rate. Thus, understanding why patients with type 2 diabetes are at increased risk of CIN and controlling factors to decrease the risk of CIN, has major short- and long-term benefits to patients with type 2 diabetes (Nikolsky et al., 2004). Most clinical studies on CIN have mainly been in patients with type 2 diabetes mellitus rather than type 1 diabetes mellitus and, thus, the remarks in this chapter will be confined to patients with type 2 diabetes kidney disease.

2.1 Mechanisms of contrast-induced nephropathy in patients with type 2 diabetes mellitus

The pathogenesis of CIN is complex with a cascade of contributing factors that are not fully understood. Factors contributing to CIN in patients with type 2 diabetes mellitus include decreased GFR, endothelial dysfunction and increased reactivity to intrarenal adenosine (Pfueger et al., 2000). After injection of contrast medium, renal blood flow increases transiently, followed by a more prolonged decrease, particularly at the corticomedullary junction of the kidney. The outer medulla is particularly susceptible to ischemic injury because of its high metabolic activity and low prevailing oxygen tension. Associated with the decrease in renal blood flow, there is a decrease in glomerular filtration rate due to afferent renal arteriolar vasoconstriction which is calcium-dependent with increased intrarenal adenosine and increased endothelin-1 activity as likely mediators of the vasoconstriction (Arakawa et al., 1996). The risk of CIN increases if there are inadequate compensatory vasodilatory responses, such as prostaglandins (E2 and I2) and nitric oxide.

Renal tubular cellular injury, in part, is mediated by generation of oxygen-free radicals. Intrarenal adenosine accumulates due to the depletion of adenosine triphosphate as a consequence of proximal tubular stress due to osmotic load and the large size of contrast media molecules. The renal toxicity from the direct effects of contrast media is reversible. It has been shown *in vitro* that renal tubular cells respond to contrast media exposure by increasing the concentrations of extracellular adenosine and by decreasing the activity of mitochondrial enzymes without altering viability. A late effect of intrarenal adenosine is oxygen-free radical production due to the catabolism of intrarenal adenosine to xanthine.

A role for intrarenal adenosine as a renal vasoconstrictor and substrate for oxygen-free radical formation is supported in human studies. Adenosine increases in urine following contrast medium; the magnitude of adenosine release and depression of creatinine clearance is proportional to the osmolality of the contrast agent, essentially a dose response relationship. Further, an inhibitor of adenosine uptake, dipyridamole, exacerbates the fall in GFR after contrast medium. In addition, blockade of the renal arterial adenosine receptors with theophylline attenuates the fall in GFR following contrast medium. Finally, following pretreatment with allopurinol (a xanthine oxidase inhibitor), urinary xanthine increases and the fall in GFR after contrast medium is lessened.

Endothelin is a potent renal afferent arteriolar vasoconstrictor, like intrarenal adenosine. Intravascular administration of contrast medium induces exacerbated release of urinary endothelin in patients with impaired renal function. Human studies show no significant increase in plasma endothelin levels until a volume of contrast media administered is greater than 150 mL (Clark et al., 1997). However, in diabetic patients or in patients with renal insufficiency, significant endothelin levels are detected when less than 100 mL of contrast medium are administered intraarterially.

In patients with normal GFR, the risk of CIN is likely less, not only because of more rapid clearance of contrast medium from the kidney (less time for generation of oxygen-free radicals), but, presumably, because of the presence of a variety of endogenous vasodilators that protect against renal ischemia, including prostaglandins (E2 and I2), atrial natriuretic peptide and nitric oxide. In patients with GFR of less than 60 mL/min/1.73 m2, the risk of CIN increases with prolonged clearance of contrast medium.

In summary, patients with type 2 diabetes mellitus appear to be at increased risk of CIN, not only because chronic renal disease is common in these patients, but also because there appears to be a greater vasoconstriction of the renal afferent arterioles to intrarenal adenosine and suppressed nitric oxide bioavailability in the kidney due to endothelial dysfunction (Komers & Anderson, 2003). Recent reports indicate that severe renal dysfunction need not be present to create a risk of CIN in diabetic patients with measured creatinine clearance of 100 mL/min and receiving proper hydration (Hardiek et al., 2008).

2.1.1 Prevention strategies to attenuate contrast-induced nephropathy in patients with type 2 diabetes mellitus and coronary artery disease

Since treatment of CIN after it has occurred is ineffective, efforts to prevent or attenuate the injury are the focus of ongoing investigations. Early diagnosis and careful long-term treatment of patients with type 2 diabetes mellitus and coronary artery disease includes 81 mg aspirin daily, angiotensin-converting enzyme inhibitor therapy or angiotensin II receptor blocker therapy and 3-hydroxyl-methylglutaryal coenzyme A reductase inhibitor therapy. Ideal goals for vascular risk factor modification include blood pressure of 130/80 mmHg or better, LDL cholesterol less than 70 mg/dL and hemoglobin A1C less than 7%. Successful accomplishment of these goals should decrease the progression of macro- and microvascular complications. In addition, if these goals are accomplished, endothelial function should be better. If the patient suddenly develops an acute coronary syndrome, the ability of the kidney to have a compensatory vasodilatory response in response to contrast medium should decrease the risk of CIN. Based on the assumption that acute renal adenosine and/or endothelia-medicated vasoconstriction and endothelial dysfunction are major interrelated pathogenic events in CIN, a type 2 diabetic patient meeting therapeutic goals should be at lower risk when coronary angiography and/or coronary intervention are required. When a patient with type 2 diabetes presents with an acute coronary syndrome, hyperglycemia is common, and increased risk of mortality in patients has been observed (Kosiborod & McGuire, 2010). Well-designed, large clinical outcome trials are required for better guidance as far as how hyperglycemia in the acute situation should be managed. Observational studies suggest that hypoglycemia should be avoided (Zoungas et al., 2010). Guidelines now recommend a therapeutic target of glucose control at 140 to 180 mg/dL in the critically ill patient which is a more liberal approach than prior recommendations (O'Keefe et al., 2011). Previously recommended more aggressive glucose lowering (including normalization of blood sugar) was not shown to have additional benefit and appeared to be harmful because of the increased incidence of hypoglycemia.

As mechanisms for CIN in patients with type 2 diabetes mellitus are better understood, there is a growing list of medications that may exacerbate the risk of CIN. Many of these medications are taken by patients with cardiovascular disease and should be addressed prior to proceeding with angiography. Medications that increase the risk of a patient developing CIN include nonsteroidal anti-inflammatory drugs which inhibit compensatory renal prostaglandin synthesis, diuretics that dehydrate the kidney and increase the risk of

medullary ischemia, and dipyridamole that blocks the normal cellular uptake of adenosine resulting in a greater renal adenosine – mediated vasconstrictive response.

In patients with type 2 diabetes mellitus requiring elective angiography, nonsteroidal anti-inflammatory medicines, diuretics and dipyridamole should be held prior to the procedure. While nonsteroidal anti-inflammatory medications are considered the cornerstone for managing the pain of osteoarthritis and other painful conditions, recent meta-analysis indicate significantly increased risk of myocardial infarction, stroke or death from cardiovascular disease compared to placebo with the chronic use of these medications. Contrary to some previous reports, the current meta-analysis found no suggestion that this increased cardiovascular risk is specific to cyclo-oxygenase-2 inhibitors. Data were available for naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib and lumiracoxib. Overall, naproxen appeared to be the least harmful nonsteroidal anti-inflammatory medication in terms of cardiovascular outcomes. Risks were greatest with ibuprofen, diclofenac, etoricoxib and lumiracoxib. Thus, chronic use of nonsteroidal anti-inflammatory medications in patients with type 2 diabetes who are at increased cardiovascular risk is discouraged. In regard to dipyridamole, recent data suggests superiority of clopidogrel over dipyridamole in patients who have suffered a cerebral vascular accident. Increasingly clopidogrel rather than dipyridamole is the recommended antiplatelet agent in addition to 81 mg aspirin in patients with type 2 diabetes after transient ischemic attacks or cerebral vascular accidents. Thus, if the patient with type 2 diabetes mellitus needs emergency angiography, the risk of dipyridamole contributing to CIN would no longer exist.

Patients with type 2 diabetes mellitus have a significantly greater risk of macrovascular disease, including coronary heart disease, stroke and peripheral vascular disease, in addition to the microvascular complications, such as retinopathy, neuropathy and nephropathy. Despite evidence of benefit for reduction of microvascular disease with glycemic control, to date, there is no such evidence for the role of glycemic control in macrovascular event reduction. In newly diagnosed patients with type 2 diabetes, besides initiation of diet, exercise and weight reduction, metformin is usually the recommended initial therapy unless contraindicated, such as renal disease (serum creatinine greater than 1.5 mg/dL in males and greater than 1.4 mg/dL in females). Although not relevant to CIN prevention, metformin should be temporarily discontinued at the time of or prior to use of contrast medium or major surgical procedures and withheld for 48 hours after the procedure. Metformin should be restarted after renal function has been reevaluated and found to be normal (Goergen et al., 2010). While the mortality rate for patients who develop lactic acidosis can be quite high, the actual number of people dying from metformin-induced lactic acidosis after contrast medium exposure is quite low using these guidelines.

Cigarette smoking is the most common cause of preventable morbidity and mortality in developed countries. In addition to it being a major risk factor for cardiovascular disease, lung disease and cancer, cigarette smoking is now recognized as an important independent risk factor of chronic kidney disease, including diabetic nephropathy, by increasing the rate of transition from microalbuminuria to proteinuria and promoting the progression to end-stage renal disease (Phisitkul et al., 2008). Furthermore, a recent cross-sectional analysis of participants in the National Health and Nutrition Examination Survey demonstrated a strong association between exposure to secondhand smoke and proteinuria, suggesting that passive smokers are also at increased risk of chronic kidney disease (Obert et al., 2011). Several clinical and experimental studies have demonstrated the role of transforming growth factor-beta in the pathogenesis of chronic kidney disease, including diabetic

Contrast-Induced Nephropathy in Patients with Type 2 Diabetes Mellitus
and Coronary Artery Disease: Update and Practical Clinical Applications
239

nephropathy. This cytokine is largely profibrotic and plays a significant role in diabetic nephropathy by increasing the production of extracellular matrix proteins, including fibronectin and collagen, in the glomerulus. It is also known that one cigarette paralyzes the ability of the endothelium to make nitric oxide for up to 24 hours. Thus, patients with type 2 diabetes mellitus should be counseled to discontinue smoking. Emphasizing that recommendation prior to elective angiography may decrease the incidence of CIN.

Another class of medication that warrants discussion in the long-term treatment of patients with type 2 diabetes mellitus, not only for the long-term metabolic advantages, but also because of the risk of CIN is beta-blocker therapy. Both nonselective and selective traditional beta-blockers have been shown to increase insulin resistance, facilitate weight gain of approximately 1 kilogram per six months and worsen hypertriglyceridemia by approximately 13%. In contrast, carvedilol in hypertensive diabetic patients has been found to have a neutral effect on insulin resistance, weight and triglycerides (Bakris et al., 2004). This favorable metabolic profile also suggests that carvedilol is a better choice compared to traditional beta-blockers in these high risk patients. Recent trials emphasize the class heterogeneity that exists for beta-blockers and provide a strong basis for preferred use of carvedilol in patients with type 2 diabetes. Carvedilol is a unique molecule that combines the properties of a nonspecific beta-blocker and a specific alpha-1-blocker in a ratio of 2:3. Carvedilol also possesses antioxidant properties. In hypertensive diabetic patients, carvedilol compared to metoprolol tartrate has been shown to reduce existing microalbuminuria and to decrease the risk of progression to microalbuminuria. These results suggest improved endothelial function and may be related to improvement in insulin resistance or an effect on oxidant stress in the kidney. Thus, in patients with type 2 diabetes mellitus that require beta-blocker therapy, carvedilol has become the recommended beta-blocker. There are also data to suggest that carvedilol compared to traditional beta-blockers attenuates CIN. Proposed mechanisms include unopposed alpha-medicated renal vasoconctriction causing more ischemia when on traditional beta-blockers and/or improved endothelial function due to the antioxidant properties of carvedilol.

There are other medicines that may attenuate the risk of CIN. Calcium-channel blocking medications attenuate both the magnitude and duration of renal vasoconstriction after contrast medium administration (Russo et al., 1990). In patients with type 2 diabetes mellitus and hypertension and/or angina requiring calcium-channel blocking medications, these medications should be continued if contrast medium administration is planned.

The adenosine receptor antagonists, theophylline and aminophylline, attenuate the decrease in GFR seen after contrast medium. Since patients with type 2 diabetes mellitus have an increased reactivity to intrarenal adenosine, theophylline prior to contrast medium administration warrants special consideration. The kidney responds to contrast media-induced stress with a tubuloglomercular feedback response which is largely medicated by adenosine when less than 100 mL of contrast medium is administered. This mechanism has been confirmed by both animal and clinical studies. Pretreatment with long-acting theophylline 3 mg/kg orally at least 30 minutes before contrast medium administration and 12 hours later in addition to hydration has been shown to attenuate the depression of creatinine clearance. It is critical that theophylline be administered before contrast medium injection, but prolonged treatment after angiography is unnecessary. Theophylline prophylaxis is effective, safe, and inexpensive. This dose of theophylline is manyfold greater than the minimum dose required to block renal vascular adenosine receptors and is well below that shown to affect renal cyclic nucleotide phosphodiesterase activity (Vassallo &

Lipsky, 1998). This dose of theophylline causes transient plasma theophylline levels of 7 mcg/mL which is below therapeutic levels required for treatment of asthma and unlikely to cause serious gastrointestinal, neurological, or cardiovascular adverse effects (Cooling, 1993; Shannon, 1999).

Adenosine receptor antagonists, theophylline and aminophylline, prophylaxis to attenuate CIN has not been strongly adopted except in patients at high risk for CIN. Some controlled trials have shown a significant reduction in the risk for CIN while others have shown no reduction (Abizaid et al., 1999; Erley et al., 1999; Erley et al., 1994; Gandhi et al., 1992; Huber et al., 2001; Huber et al., 2002; Huber et al., 2003; Kolonko et al., 1998; Shammas et al., 2001). However, these studies have been limited by small sample size, variation in timing and dosage of drug administration, and variation in the definition of CIN. Three meta-analyses have dealt specifically with the clinical use of theophylline for the prevention of CIN. Each of these gave extensive information concerning the way that the papers which were included were chosen, exactly what factors were chosen for matching across studies and which factors did not match. In addition, statistics were presented which addressed the concerns about selection bias and efforts were made to adjust for non-matching factors to the extent possible. No attempt will be made to describe each of these studies completely, however, we will give some summary information concerning each of them. One meta-analysis identified 10 studies in which theophylline was used for the prevention of CIN (Ix et al., 2004). Of the ten, seven were found to fulfill all the inclusion criteria and these constituted the final sample for the analysis. The studies included were reported between 1994 and 2003 and included a number of different protocols for the administration of the theophylline. The final conclusion reached by these investigators was that the prophylactic administration of theophylline appears to protect against contrast-induced declines in kidney function. They also reported that "the protective benefits appeared robust regardless of the study design, form or volume of contrast medium delivered, and the presence or absence of intravenous volume expansion." The investigators did indicate that they were unable to determine (given the available data) if theophylline reduced the number of patients who experienced large increases in serum creatinine concentrations or required dialysis. Another meta-analysis identified nine studies which met the study criteria for their protocol (Bagshaw & Ghali, 2005). Their conclusion was that the data they considered indicated that there is promising evidence supporting the use of theophylline for the prevention of CIN but the evidence is still not conclusive. They suggested that what was required to answer this question was a larger, well designed clinical trial for confirmation and assessment of risks before theophylline could be recommended routinely for the prevention of CIN. They also noted from their analysis of these papers that such a trial should include a hydration protocol and the routine use of low or iso-osmolar nonionic contrast media since those are now the current standards of care. These two meta-analyses focused primarily on theophylline and a comparison of the choices of papers from the two studies shows that seven papers included in the initial meta-analysis were also included in the nine chosen by the second meta-analysis. The latter authors included two papers which were in the same search time frame as the initial meta-analysis but were not selected under that study protocol. A third meta-analysis covered a number of drugs aimed at reducing the incidence of CIN (Kelly et al., 2008). The primary drug considered was N-acetylcysteine with theophylline being more secondary to the study. Only six of the studies considered dealt primarily with theophylline. Of the six considered, five were part of the set of studies considered by the second meta-analysis while four of them coincided with those used in the

Contrast-Induced Nephropathy in Patients with Type 2 Diabetes Mellitus
and Coronary Artery Disease: Update and Practical Clinical Applications
241

initial meta-analysis. The sixth paper which was unique to this analysis appeared in 2006 which was out of the range of years covered by the other two papers. One of the six papers common to both was not included by the initial meta-analysis. The conclusion of this paper with respect to the efficacy of theophylline was that it produced a large risk reduction but did not achieve statistical significance. Of these three meta-analyses, the first two are most comparable. Both reach the same conclusion. Each of these papers used slightly different statistical methods. Both contained a thorough discussion of the selection criteria used to choose the papers included and measures to check for selection bias. The general conclusions were favorable with the hypothesis that theophylline is protective against CIN. Unfortunately, neither group of authors was willing to report a definitive answer. There are some areas where the studies under review by these authors differed. One was in the area of how the theophylline was administered: as a fixed dose regardless of body weight or as a dose adjusted per kilogram of body weight. The broad conclusion reached is that a large, carefully designed clinical trial needs to be conducted to reach a final conclusion. The trial should be stratified according to ancillary risk factors such as age and diabetes. In addition, the effect of the dosing protocol and hydration methods needs to be considered. Finally, since it is known that certain beverages like coffee and tea also block adenosine vascular receptors, a study testing the benefit of theophylline should exclude other xanthine exposure during the time before contrast medium administration and for the 48 hours after while the subject is being followed.

Studies suggest two mechanisms by which intrarenal adenosine contributes to CIN. Early depression of renal function after contrast medium exposure is caused by A_1 receptor-mediated renal afferent arteriolar vasoconstriction and A_2 receptor-mediated efferent arteriolar vasodilatation resulting in decreased glomerular perfusion pressure. Later depression of renal function after contrast medium exposure is caused by oxygen-free radical production, in part, due to intrarenal adenosine catabolism to xanthine. Pretreatment with theophylline may attenuate CIN by maintaining GFR such that contrast medium is cleared from the kidney more rapidly, thus, decreasing direct cytotoxic effects from contrast medium and decreasing the potential for intrarenal adenosine-mediated oxygen-free radical production. Pretreatment with allopurinol has also been shown to attenuate CIN. To be effective, it is crucial to administer allopurinol at least 24 hours prior to exposure to contrast medium. Pretreatment allows time for production of oxypurinol, the chief metabolite of allopurinol, which is a much more potent xanthine oxidase inhibitor. Allopurinol administered in this fashion was renally protective. Decreasing renal xanthine oxidase decreases the catabolism of intrarenal adenosine to xanthine resulting in decreased oxygen-free radical production and less renal tubular cell injury.

Patients with type 2 diabetes mellitus are usually on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and/or direct renin inhibitor to decrease the progression of renal disease. Whether these agents need to be held or should be continued when contrast medium is administered requires clinical judgment. Intrarenal angiotensin II enhances adenosine-mediated vasoconstriction so theoretically blockade of the renin-angiotensin system should attenuate the risk of CIN. In support of this concept, preprocedure angiotensin-converting enzyme inhibitor use has been shown to lower the risk for CIN in patients with chronic renal disease (Dangas et al., 2005). Another clinical trial showed that periprocedural captopril, compared with an untreated control group, reduced the risk of CIN in patients with type 2 diabetes mellitus (Gupta et al, 1999). However, if an unstable patient has low cardiac output or hypotension, renin-angiotensin system blockade

is known to worsen glomerular perfusion (i.e. intrarenal angiotensin II is needed). In such patients, angiotensin-converting inhibitor therapy has increased the risk of CIN (Cirit et al., 2006; Holscher et al., 2008; Louis et al., 1996; Rosenstock et al., 2008). Given the long-term benefit of angiotensin-converting enzyme inhibitor and angiotensin II receptor antagonists, most believe these medications should be continued in patients with diabetes mellitus and chronic kidney disease requiring contrast medium administration unless the patient is hemodynamically unstable. However, if angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are held before contrast medium administration, they should be restarted when renal function is considered stable.

Recent research suggests that 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, or statins, may reduce the risk of CIN because they have beneficial effects on endothelial function, maintain nitric oxide production and reduce oxidative stress (Adel et al., 2010). Recent retrospective reviews of patients with renal impairment undergoing angiography suggests that the risk of CIN was lower in patients in whom a statin was initiated before the procedure (Khanal et al., 2005). These findings reinforce the rationale for the introduction of statin therapy before undergoing diagnostic or interventional coronary angiography, particularly in patients with type 2 diabetes mellitus (Attallah et al., 2004).

Hypomagnesemia, serum magnesium level less than 2 mEq/L, may also be a correctable risk factor for CIN in patients with renal dysfunction. Patients with type 2 diabetes mellitus frequently become hypomagnesemic due to poor control with glycosuria, the development of an acquired renal tubular defect and from chronic diuretic therapy. All three conditions decrease the renal tubular reabsorption of magnesium. Detecting hypomagnesemia and correcting it prior to angiography or coronary intervention may be indicated. The renal protective effect of magnesium is likely multifactorial. Besides its role as an antioxidant and as a coenzyme for compensatory sodium-potassium adenosine triphosphatase, magnesium has calcium channel blocking properties.

The universally accepted prevention strategy for CIN is adequate intravenous volume expansion. Extracellular volume expansion plays a well established role in reducing the risk of CIN although few trials have directly addressed the ideal protocol. Intravenous volume expansion before and after the administration of contrast medium appears to be more effective than either bolus volume expansion during the procedure or removal of restrictions on oral fluid intake. Isotonic saline has been found to be better than 0.45% saline and is given intravenously before and after administration of contrast medium for a total of 24 hours. An additional strategy that is under study is for patients to receive prophylactic volume expansion with isotonic sodium bicarbonate solution (Merten et al., 2004). It is thought that an alkaline environment decreases oxygen-free radical formation in the renal tubule. The findings of several recent trials and a meta-analysis indicate that volume expansion with sodium bicarbonate is more effective than volume expansion with saline. However, recent reports argue against a clear benefit for sodium bicarbonate volume expansion but examination of the various trials suggests that the dose given to accomplish an alkaline environment in the renal tubule is important. Isotonic sodium bicarbonate solution, administered at 3 mL/kg/h for one hour prior to angiography and at 1 mL/kg/h for, at least, six hours afterward accomplishes that goal. A major robust, well-designed trial comparing volume expansion with sodium bicarbonate versus normal saline is ongoing. At this time, the CIN consensus working panel concludes that no adjunctive medical pretreatment has been validated as effective for preventing CIN. Use of furosemide, mannitol or an endothelin receptor antagonist is potentially detrimental. Felodipine,

Contrast-Induced Nephropathy in Patients with Type 2 Diabetes Mellitus
and Coronary Artery Disease: Update and Practical Clinical Applications
243

dopamine, atrial natriuretic peptide and L-arginine have not been shown to be effective. Potentially beneficial strategies for attenuating CIN include theophylline, allopurinol, ascorbic acid, oral and intravenous N–acetylcysteine, hemodialysis of contrast medium and venous capture of contrast medium.

In regard to pretreatment approaches to limit oxygen-free radical injury following contrast medium, four pharmacologic approaches warrant further study with adequately powered, appropriately designed, randomized trials of high-risk diabetic patients, perhaps combined with theophylline pretreatment. One of these is isotonic sodium bicarbonate solution with the length of post-procedure treatment determined by the volume of contrast medium administered. Maintaining an alkaline environment should decrease oxygen-free radical formation in the renal tubule. As discussed above, one source of oxygen-free radical production after contrast medium is the catabolism of intrarenal adenosine to xanthine. Allopurinol, a xanthine oxidase inhibitor, 4 mg/kg orally daily starting 24 hours before administration of contrast medium has shown benefit. This dose of allopurinol, if given 24 hours before elective procedures, is metabolized into oxypurinol which is a more effective xanthine oxidase inhibitor than allopurinol. This 24-hour pretreatment approach has been shown to attenuate the fall in GFR after contrast medium exposure. Besides limiting oxygen-free radical formation, allopurinol may also protect the kidney from contrast medium exposure by its ability to inhibit adenine nucleotide degradation (thus, preservation of adenine nucleotide is required for recovery from renal injury). Allopurinol has also been found to markedly decrease the vasodilatation response to intravenous adenosine in the renal vasculature. Less adenosine-mediated efferent renal arteriolar vasodilatation would preserve glomerular perfusion pressure. In view of the possible role of oxidase stress and oxygen-free radical generation in CIN, ascorbic acid as an antioxidant warrants further study (Spargias et al., 2004). N-acetylcysteine, as an antioxidant and renal vasodilator, has not been shown to be consistently effective when given orally (Solomon, 2009). Perhaps a larger oral dose is needed or intravenous administration may be required. Allopurinol, ascorbic acid and N-acetylcysteine, if proven beneficial, require pretreatment and would be less helpful in diabetic patients requiring emergency diagnostic and/or interventional contrast medium usage.

To decrease the risk of CIN requires careful patient screening and selection, adequate patient hydration, limiting the volume of contrast medium administered and choosing a safe, non-ionic, low osmolar contrast agent. Based on comparisons of contrast media in proximal renal tubular cell culture and in recent robust head-to-head prospective clinical trials in high risk patients, however, iso-osmolar iodixanol and low-osmolar iopamidol are comparable and appear to be the contrast agents of choice to reduce renal risk for CIN.

The direct cellular toxicities of commonly used contrast medium have been compared in renal proximal tubular cells in culture (Hardiek et al., 2001). All contrast media, whether high-osmolar or iso-osmolar, ionic or non-ionic, stress renal proximal tubular cells. When renal proximal tubular cells in culture are exposed to contrast media, they respond by increasing extracellular adenosine concentrations because of the depletion of adenosine triphosphate due to osmotic load and the large size of contrast medium molecules. The renal toxicity from the direct effects of contrast medium is reversible, as has been shown *in vitro* in studies in which renal tubular cells respond to contrast media exposure by decreasing the activity of mitochondrial enzymes without altering viability. While all contrast medium may reduce mitochondrial enzyme activity, differences among agents are seen with iopamidol and iodixanol being the least toxic and the two ionic contrast media, ioxaglate and

diatrizoate, being the most toxic. The lesser the depression of mitochondrial function, the more rapidly renal proximal tubular cells can recover after contrast medium has been eliminated from the kidney suggesting that iopamidol and iodixanol are the least nephrotoxic molecules when studied in cell culture.

Earlier clinical trials comparing contrast medium risk in patients with type 2 diabetes for CIN had limitations that prevented valid conclusions: the studies were not blinded, the number of patients was small, the timing of outcome assessment was unclear, or the patients received contrast intra-arterially and/or intravenously. With proper hydration and identification of high-risk patients, the incidence of CIN after intra-arterial contrast medium administration is about 10%. More recent trials in high-risk diabetic patients given contrast medium intravenously suggest that the incidence of CIN is about 5%. More recent trials have been head-to-head, robust and prospective in high-risk patients with chronic renal failure (eGFR 59-20 mL/min) with intra-arterial contrast medium administration. Based on animal studies, concern about osmotoxicity in the pathogenesis of CIN emerged which led to the development of low-osmolar, and, later, iso-osmolar contrast medium. Of interest, in human prospective trials and meta-analysis, no specifically significant differences in nephrotoxicity between high-osmolar (1,400-2,000 mOsm/kg) and non-ionic low-osmolar (600-800 mOsm/kg) contrast have been found in patients with normal renal function (Solomon, 2005). Clinical trials published in the 1990s, however, showed that use of high-osmolar ionic monomer diatrizoate in patients with chronic renal disease who were undergoing coronary angiography had a higher incidence of CIN than that associated with non-ionic low-osmolar contrast medium. In general, lower osmolar contrast medium has now replaced diatrizoate for routine clinical use. It is less clear whether there are appreciable differences among various non-ionic low-osmolar contrast medium regarding the incidence of CIN. Because individual contrast medium has specific effects on renal tubular cells, head-to-head studies are required to compare the safer contrast medium in at risk patients undergoing angiography. With the development of the non-ionic iso-osmolar dimer, iodixanol, subsequent studies have evaluated whether a further reduction in osmolality would result in still more protection against CIN. In the first of these comparative studies ((Nephrotoxicity of High-Risk Patient Study of Iso-osmolar and Low-Osmolar Non-ionic Contrast Medium (NEPHRIC)) 129 patients with diabetes with chronic renal failure (baseline eGFR of 48 mL/min) and serum creatinine levels 1.5-3.5 mg/dL were randomized to the low-osmolar contrast medium iohexol or the iso-osmolar contrast medium, iodixanol (Aspelin et al., 2003). A higher rate of CIN defined as a serum creatinine rise of greater than 0.5 mg/dL after angiography was noted after iohexol (26.2%) than after iodixanol (3.1%).

Since the publication of NEPHRIC, subsequent prospective randomized trials involving high-risk patients with renal insufficiency and diabetes and the intra-arterial administration of contrast medium have not consistently found a lower incidence of CIN associated with iso-osmolar contrast medium. In general, a benefit favoring the non-ionic iso-osmolar dimer, iodixanol, is seen compared with the non-ionic low-osmolar monomer iohexol or the ionic low-osmolar dimer, ioxaglate. In contrast, when comparing non-ionic low-osmolar monomers, iopamidol or ioversol, in high-risk patients with iso-osmolar iodixanol, no additional protective effect is seen. There have been no head-to-head comparisons of iohexol with any other non-ionic, low-osmolar contrast agents in high-risk patients undergoing intra-arterial administration of contrast. Based on a recent systematic review of angiographic contrast medium in high-risk patients, however, the likely explanation of the

NEPHRIC findings is that low-osmolar, iohexol, appears to be more nephrotoxic than other low-osmolar contrast media, such as iopamidol and ioversol. Furthermore, a systematic review of angiographic contrast media in high-risk patients found no statistically significant difference in the risk of CIN between low-osmolar iopamidol and iso-osmolar iodixanol (Solomon, 2005). These comparisons in low-osmolar and iso-osmolar contrast medium administered intra-arterially in high-risk patients suggest that each molecule's safety must be based on robust clinical trials. These data also suggest that physical and/or chemical properties of each molecule, other than osmolarity, are implicated in the pathogenesis of CIN. Given this incidence of CIN, prospective randomized trials need larger patient populations to be properly powered to be certain of the conclusions. The recently published Cardiac Angiography in Renally-Impaired Patients (CARE) study fits these criteria by being a multicenter, double-blind, randomized study designed to prospectively compare the incidence of CIN after intra-arterial administration of low-osmolar iopamidol or iso-osmolar iodixanol in 414 patients with moderate to severe chronic kidney disease (eGFR of 20-59 mL/min/1.73 m^2) who underwent coronary angiography or percutaneous coronary intervention (Solomon et al., 2007). All patients received intravenous sodium bicarbonate prophylaxis. The primary endpoint was a post-dose serum creatinine increase of greater than 0.5 mL/dL over baseline. The renal effects of these two agents were comparable with no significant difference in occurrence of CIN and no significant difference in occurrence of CIN in the subgroup of chronic kidney disease patients with diabetes. More recently, a multicenter, randomized double-blind trial comparing the renal effects of non-ionic, iso-osmolar iodixanol versus non-ionic, low-osmolar iopamidol in 526 patients with impaired baseline renal function and diabetes undergoing diagnostic and/or therapeutic coronary angiography procedures was completed (Laskey et al., 2009). This trial showed overall rate of CIN in patients with chronic kidney disease and diabetes undergoing coronary angiographic procedures was 10.5%. There was no significant difference between iodixanol and iopamidol in either peak increase in serum creatinine or risk of CIN.

The renal effects of iodixanol and iopamidol are comparable in high-risk diabetic patients requiring contrast medium for diagnostic studies or intervention. The non-renal differences between these contrast agents should be considered when selecting an agent and when obtaining informed patient consent, however. Using a contrast medium with a higher iodine concentration per milliliter, such as iopamidol which has 370 mg/mL compared to iodixanol which has 320 mg/mL iodine content, may allow for a smaller volume to be used intravenously without sacrificing image quality. The higher iodine concentration of iopamidol may make complex plaques easier to appreciate during coronary angiography and intervention. Other considerations are that iodixanol is threefold more likely to cause contrast-induced delayed skin reactions compared to iopamidol. After percutaneous coronary intervention with bare-metal or drug-eluting stent placement, cardiac patients require antiplatelet therapy with clopidogrel, which may cause a rash within 5 to 7 days of treatment initiation, a timeline similar to that for delayed contrast-induced skin reactions. In clinical trials with clopidogrel, skin reactions are noted in 4.2% of patients. The choice of a contrast molecule, such as iopamidol, that is less likely to cause a delayed contrast-induced skin reaction makes decisions regarding the discontinuation of clopidogrel less frequent and more definitive. Finally, iopamidol is less expensive than iodixanol.

Gadolinium-based contrast agents were introduced, partly, because of the discovery that iodine-based contrast medium could cause CIN. However, recent reports suggest that gadolinium-based agents may also be nephrotoxic. Furthermore, after exposure to

gadolinium-based contrast, some patients with renal insufficiency have developed nephrogenic systemic sclerosis with scleroderma-like changes in the skin, connective tissues and other organs, which has sometimes been fatal (Grobner & Prischl, 2007). In diabetic patients with chronic renal failure, the use of any contrast agent should be avoided, if possible, but, if required, small volumes of a contrast agent, such as iodixanol or iopamidol with proper hydration appears to be the safest clinical management to reduce renal and long-term patient risk.

Ongoing investigation is searching for even more sensitive markers that may predict the development of CIN after percutaneous coronary interventions in patients with normal serum creatinine values (Kato et al., 2008). Future studies should include cystatin C which is an alternative serum measurement of kidney function that approximates direct measures of GFR more precisely than creatinine because its serum concentrations are independent of muscle mass and do not appear to be affected by age or sex. Cystatin C may identify a preclinical risk of kidney dysfunction after contrast medium that is not detected by serum creatinine or eGFR (Perkins et al., 2005). More recently, the value of neutrophil gelatinase-associated lipocalin (NGAL) has been highlighted as a novel biomarker for the early detection of acute renal failure (Ling et al., 2008). NGAL, a member of the lipocalin family, was originally isolated from the supernatant of activated human neutrophils, but it is also expressed at a low level in human tissues, including the kidney. Because of its small molecular size and resistance to degradation, NGAL is readily excreted and detected in urine. Thus, NGAL is highly accumulated in human kidney cortical tubules, blood and urine after renal injuries. NGAL might represent an early, sensitive and noninvasive urinary marker for the detection of CIN. Initial studies of NGAL after percutaneous coronary intervention showed an earlier increase in serum than in urine probably because NGAL was released into the circulation secondary to inflammatory activation of neutrophils initiated by percutaneous coronary intervention. Moreover, since NGAL is increased in atherosclerotic plaques, it might also be released in the circulation during the PCI. It has been found that predictors of serum NGAL 2 hours after PCI were serum creatinine, cystatin C, length of the percutaneous coronary intervention and the presence of diabetes. These findings have important implications for the clinical management of diabetic patients undergoing PCI. Since patients after PCI are often discharged the next day and CIN often occurs subsequent to discharge, NGAL needs to be investigated as a potential early marker for nephrotoxicity. Further studies in type 2 diabetes mellitus patients with chronic renal failure undergoing contrast medium administration are warranted to assess the use of NGAL with respect to earlier detection of CIN so that patients can be advised properly and medicines, such as metformin and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, can be restarted appropriately.

In patients undergoing cardiac catheterization, cystatin C may be useful in predicting before catheterization the risk of CIN. In contrast, urinary human liver-type fatty acid-binding protein (L-FABP) consistently appears to be the only marker for detecting transient renal tubular damage in patients with moderate renal disease. Thus, urinary L-FABP appears to be a useful marker of renal tubular damage caused by contrast medium. Other investigators have found that urinary intraleukin-18 (IL-18) is associated with the later cardiac outcomes in patients with CIN after coronary angiography. CIN, a form of acute kidney injury, has received increasing attention the past few years because of the recognition that CIN is associated with long-term adverse events. The increased incidence of adverse events after CIN is derived primarily from retrospective analysis of large data bases or observational

studies of patients who have undergone coronary angiography and/or percutaneous coronary intervention. A cause-and-effect relationship cannot be determined from such data. Patients with an increased burden of cardiovascular risk factors before contrast medium exposure may be more likely to develop CIN and independent of the occurrence of CIN may have more long-term adverse events (Shlipak et al., 2005). Alternatively, the occurrence of CIN may in some as yet undefined manner alter the future likelihood of adverse events (i.e., CIN triggers a pathophysiologic pathway that leads to adverse events). The Cardiac Angiography in REnally-impaired patients (CARE) study has allowed the opportunity to explore the association of CIN with long-term adverse events (Solomon et al., 2009). Patients were followed for the year after the trial, and adverse events were collected. The rate of long-term adverse events was higher in individuals who developed CIN. After adjustment for baseline comorbidities and risk factors, the adjusted incident ratio for adverse events was twice as high in those with CIN compared to the patients who did not develop CIN. It is also noted that randomization to iopamidol reduced the incidence of CIN and adverse events compared to iodixanol. Parallel decrease of incidence of CIN and adverse events in the iopamidol arm of this randomized trial supports a causal role for CIN in late adverse events in diabetic patients undergoing coronary angiography and/or coronary intervention. Why a transient decrease in renal function results in long-term increased risk of cerebrovascular accident, myocardial infarction and death is an area of intense study. Some investigators report that traditional cardiovascular risk factors have greater associations with cardiovascular mortality than novel risk factors. Thus, in patients that develop CIN, continued treatment of hypertension, hyperlipidemia and diabetes is recommended. Since multiple studies have demonstrated the important role of nitric oxide in endothelial physiology and the pathogenesis of vascular disease, ongoing studies are examining endogenous nitric oxide synthase inhibitors, such as the amino acid asymmetric dimethylarginine, in the pathogenesis of late adverse events (Chirinos et al., 2008). Additional studies are required to assess the prognostic value of measuring for this endogenous nitric oxide synthase inhibitor and assessing whether interventions limiting its effect will benefit patients at risk for future cardiovascular events.

2.1.1.1 Risks and benefits of prevention strategies to attenuate contrast-induced nephropathy in patients with type 2 diabetes mellitus and coronary artery disease

The risks of a short course of theophylline, either orally or intravenously, is low. If a patient is on theophylline, one cannot give adenosine as a coronary vasodilator as part of a flow wire analysis to assess the functional significance of a coronary stenotic lesion (Casella et al., 2003; Yoon et al., 2009). However, intravascular ultrasound can be used as the guide for functional significance, and, thus, pretreatment with theophylline to attenuate CIN may be more important than losing this one technique of assessing functional coronary stenosis. Of the various potential strategies for attenuating CIN, theophylline can be administered orally or intravenously within 30 minutes of the procedure and be beneficial. Antioxidant strategies, such as allopurinol, ascorbic acid, or N-acetylcysteine require pretreatment and will be less helpful in patients requiring emergency diagnostic and/or interventional contrast medium usage.

Volume expansion with normal saline or sodium bicarbonate is the universally agreed upon strategy to attenuate CIN. Bicarbonate therapy was initially explored because the generation of oxygen-free radicals is pH dependent through the Haber-Weiss reaction (Merten et al., 2004). Alkalinization of the urinary space is achieved very quickly with intravenous infusion

of sodium bicarbonate because normally there is little bicarbonate in the urine. Even a small increase in serum bicarbonate of 1 to 2 mEq/L will result in the 'dumping' of bicarbonate into the urine in most patients (Solomon, 2009). Such a change in serum is easily obtained with the infusion rate recommended. Sodium bicarbonate therapy is readily available, inexpensive, and safe. The question is whether it is efficacious for prevention of CIN. Of particular clinical interest from recent meta-analysis was the finding that sodium bicarbonate therapy is most effective in patients who experienced urgent or emergency contrast medium exposure (Meier et al., 2009). Presumably this selects a group of patients who are less likely to receive any other form of prophylaxis for CIN. This is of great potential importance for the emergency room and cardiac catheterization laboratory. Sodium bicarbonate therapy was also most effective in those receiving low osmolality contrast media compared with iso-osmolality contrast media. Low osmolality contrast is increasingly chosen because of its safety, lower costs, and higher iodine content. It has also been found that the addition of N-acetylcysteine to fluid expansion with sodium bicarbonate showed no additional reduction in the rate of CIN after the intra-arterial administration of iopamidol or iodixanol to high-risk patients with type 2 diabetes mellitus and chronic kidney disease (Staniloae et al., 2009).

CIN needs to be redefined using markers of kidney injury that are sensitive, specific, and predictive of adverse outcomes (Solomon, 2009). This will enable investigators to better address the question of how to attenuate this condition in the future. The most important question to be answered is whether prevention of kidney injury results in a change in short- and long-term adverse outcomes. Using iopamidol has been associated with a reduction in long-term adverse events (Solomon et al., 2007). The recent meta-analyses found that despite a reduction in the incidence of CIN, sodium bicarbonate therapy had no benefit on the need for dialysis or mortality (Meier et al., 2009). No matter how available, inexpensive, and safe a potential preventive therapy, to find an important role in clinical therapeutics, it must improve the 'downstream' adverse outcomes, an as yet elusive goal for the prevention and treatment of CIN (Solomon, 2009).

3. Conclusions

In summary, CIN remains an important clinical challenge in patients with type 2 diabetes mellitus with coronary artery disease. Reducing the incidence of CIN requires recognizing high risk patients, such as patients with type 2 diabetes mellitus. Long-term risk factor modification should improve endothelial function so a more normal renal compensatory response will occur should contrast medium administration be required. Lowest volume of iopamidol needed would appear to be the contrast agent of choice. In patients with type 2 diabetes mellitus, pretreatment with theophylline to block adenosine-mediated renal vasoconstriction combined with volume expansion with sodium bicarbonate to limit oxygen-free radical generation is a rational approach based on existing data. Appropriately designed robust randomized clinical trials combining pharmacologic approaches aimed at both the renal vasoconstriction and the oxygen-free radical generation are needed to confirm that this is the best preventive strategy in patients with type 2 diabetes mellitus.

4. Acknowledgement

5. References

Abizaid, A. S., C. E. Clark, G. S. Mintz, S. Dosa, J. J. Popma, A. D. Pichard, L. F. Satler, M. Harvey, K. M. Kent, & M. B. Leon. (1999). Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *American Journal of Cardiology* 83 (2):pp. ISSN 260-263, A265, 0002-9149.

Adel, A., Z. Abdel-Salam, & W. Nammas. (2010). Low-dose statin therapy improves endothelial function in type 2 diabetic patients with normal serum total cholesterol: a randomized placebo-controlled study. *J Clin Hypertens (Greenwich)* 12 (10):pp. 820-825, ISSN 1751-7176.

Arakawa, K., H. Suzuki, M. Naitoh, A. Matsumoto, K. Hayashi, H. Matsuda, A. Ichihara, E. Kubota, & T. Saruta. (1996). Role of adenosine in the renal responses to contrast medium. *Kidney International* 49 (5):pp. 1199-1206, ISSN 0085-2538.

Aspelin, P., P. Aubry, S. G. Fransson, R. Strasser, R. Willenbrock, & K. J. Berg. (2003). Nephrotoxic effects in high-risk patients undergoing angiography. *New England Journal of Medicine* 348 (6):pp. 491-499, ISSN 1533-4406.

Attallah, N., L. Yassine, J. Musial, J. Yee, & K. Fisher. (2004). The potential role of statins in contrast nephropathy. *Clinical Nephrology* 62 (4):pp. 273-278, ISSN 0301-0430

Bagshaw, S. M., & W. A. Ghali. (2005). Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Archives of Internal Medicine* 165 (10):pp. 1087-1093, ISSN 0003-9926.

Bakris, G. L., V. Fonseca, R. E. Katholi, J. B. McGill, F. H. Messerli, R. A. Phillips, P. Raskin, J. T. Wright, Jr., R. Oakes, M. A. Lukas, K. M. Anderson, & D. S. Bell. (2004). Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 292 (18):pp. 2227-2236, ISSN 1538-3598.

Casella, G., J. Rieber, T. M. Schiele, H. U. Stempfle, U. Siebert, M. Leibig, K. Theisen, U. Buchmeier, & V. Klauss. (2003). A randomized comparison of 4 doses of intracoronary adenosine in the assessment of fractional flow reserve. *Zeitschrift fur Kardiologie* 92 (8):pp. 627-632, ISSN 0300-5860.

Chirinos, J. A., R. David, J. A. Bralley, H. Zea-Diaz, E. Munoz-Atahualpa, F. Corrales-Medina, C. Cuba-Bustinza, J. Chirinos-Pacheco, & J. Medina-Lezama. (2008). Endogenous nitric oxide synthase inhibitors, arterial hemodynamics, and subclinical vascular disease: the PREVENCION Study. *Hypertension* 52 (6):pp. 1051-1059, ISSN 1524-4563.

Cirit, M., O. Toprak, M. Yesil, S. Bayata, N. Postaci, L. Pupim, & E. Esi. (2006). Angiotensin-converting enzyme inhibitors as a risk factor for contrast-induced nephropathy. *Nephron Clin Pract* 104 (1):pp. c20-27, ISSN 1660-2110.

Clark, B. A., D. Kim, & F. H. Epstein. (1997). Endothelin and atrial natriuretic peptide levels following radiocontrast exposure in humans. *American Journal of Kidney Diseases* 30 (1):pp. 82-86, ISSN 0272-6386.

Cooling, D. S. (1993). Theophylline toxicity. *Journal of Emergency Medicine* 11 (4):pp. 415-425, ISSN 0736-4679.

Dangas, G., I. Iakovou, E. Nikolsky, E. D. Aymong, G. S. Mintz, N. N. Kipshidze, A. J. Lansky, I. Moussa, G. W. Stone, J. W. Moses, M. B. Leon, & R. Mehran. (2005). Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *American Journal of Cardiology* 95 (1):pp. 13-19, ISSN 0002-9149.

Erley, C. M., S. H. Duda, D. Rehfuss, B. Scholtes, J. Bock, C. Muller, H. Osswald, & T. Risler. (1999). Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. *Nephrology, Dialysis, Transplantation* 14 (5):pp. 1146-1149, ISSN 0931-0509.

Erley, C. M., S. H. Duda, S. Schlepckow, J. Koehler, P. E. Huppert, W. L. Strohmaier, A. Bohle, T. Risler, & H. Osswald. (1994). Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. *Kidney International* 45 (5):pp. 1425-1431, ISSN 0085-2538.

Gandhi, M. R., P. Brown, C. A. Romanowski, S. K. Morcos, S. Campbell, A. M. el Nahas, & T. A. Gray. (1992). The use of theophylline, an adenosine antagonist in the prevention of contrast media induced nephrotoxicity. *British Journal of Radiology* 65 (777):pp. 838, ISSN 0007-1285.

Goergen, S. K., G. Rumbold, G. Compton, & C. Harris. (2010). Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology* 254 (1):pp. 261-269, ISSN 1527-1315.

Grobner, T., & F. C. Prischl. (2007). Gadolinium and nephrogenic systemic fibrosis. *Kidney International* 72 (3):pp. 260-264, ISSN 0085-2538.

Gupta, R. K., A. Kapoor, S. Tewari, N. Sinha, & R. K. Sharma. (1999). Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. *Indian Heart Journal* 51 (5):pp. 521-526, ISSN 0019-4832.

Hardiek, K., R. E. Katholi, V. Ramkumar, & C. Deitrick. (2001). Proximal tubule cell response to radiographic contrast media. *Am J Physiol Renal Physiol* 280 (1):pp. F61-70, ISSN 0363-6127.

Hardiek, K. J., R. E. Katholi, R. S. Robbs, & C. E. Katholi. (2008). Renal effects of contrast media in diabetic patients undergoing diagnostic or interventional coronary angiography. *Journal of Diabetes and Its Complications* 22 (3):pp. 171-177, ISSN 1056-8727.

Holscher, B., C. Heitmeyer, M. Fobker, G. Breithardt, R. M. Schaefer, & H. Reinecke. (2008). Predictors for contrast media-induced nephropathy and long-term survival: prospectively assessed data from the randomized controlled Dialysis-Versus-Diuresis (DVD) trial. *Canadian Journal of Cardiology* 24 (11):pp. 845-850, ISSN 1916-7075.

Huber, W., B. Jeschke, M. Page, W. Weiss, H. Salmhofer, U. Schweigart, K. Ilgmann, J. Reichenberger, B. Neu, & M. Classen. (2001). Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. *Intensive Care Medicine* 27 (7):pp. 1200-1209, ISSN 0342-4642.

Contrast-Induced Nephropathy in Patients with Type 2 Diabetes Mellitus
and Coronary Artery Disease: Update and Practical Clinical Applications

251

Huber, W., C. Schipek, K. Ilgmann, M. Page, M. Hennig, A. Wacker, U. Schweigart, L. Lutilsky, C. Valina, M. Seyfarth, A. Schomig, & M. Classen. (2003). Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. *American Journal of Cardiology* 91 (10):pp. 1157-1162, ISSN 0002-9149.

Ix, J. H., C. E. McCulloch, & G. M. Chertow. (2004). Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis. *Nephrology, Dialysis, Transplantation* 19 (11):pp. 2747-2753, ISSN 0931-0509.

Kapoor, A., S. Kumar, S. Gulati, S. Gambhir, R. S. Sethi, & N. Sinha. (2002). The role of theophylline in contrast-induced nephropathy: a case-control study. *Nephrology, Dialysis, Transplantation* 17 (11):pp. 1936-1941, ISSN 0931-0509.

Kato, K., N. Sato, T. Yamamoto, Y. K. Iwasaki, K. Tanaka, & K. Mizuno. (2008). Valuable markers for contrast-induced nephropathy in patients undergoing cardiac catheterization. *Circ J* 72 (9):pp. 1499-1505, ISSN 1346-9843.

Kelly, A. M., B. Dwamena, P. Cronin, S. J. Bernstein, & R. C. Carlos. (2008). Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Annals of Internal Medicine* 148 (4):pp. 284-294, ISSN 1539-3704.

Khanal, S., N. Attallah, D. E. Smith, E. Kline-Rogers, D. Share, M. J. O'Donnell, & M. Moscucci. (2005). Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. *American Journal of Medicine* 118 (8):pp. 843-849, ISSN 0002-9343.

Kolonko, A., A. Wiecek, & F. Kokot. (1998). The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. *J Nephrol* 11 (3):pp. 151-156, ISSN 1121-8428.

Komers, R., & S. Anderson. (2003). Paradoxes of nitric oxide in the diabetic kidney. *Am J Physiol Renal Physiol* 284 (6):pp. F1121-1137, ISSN 0363-6127.

Kosiborod, M., & D. K. McGuire. (2010). Glucose-lowering targets for patients with cardiovascular disease: focus on inpatient management of patients with acute coronary syndromes. *Circulation* 122 (25):pp. 2736-2744, ISSN 1524-4539.

Laskey, W., P. Aspelin, C. Davidson, M. Rudnick, P. Aubry, S. Kumar, F. Gietzen, & M. Wiemer. (2009). Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. *American Heart Journal* 158 (5):pp. 822-828 e823, ISSN 1097-6744.

Ling, W., N. Zhaohui, H. Ben, G. Leyi, L. Jianping, D. Huili, & Q. Jiaqi. (2008). Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. *Nephron Clin Pract* 108 (3):pp. c176-181, ISSN 1660-2110.

Louis, B. M., B. S. Hoch, C. Hernandez, N. Namboodiri, G. Neiderman, A. Nissenbaum, F. P. Foti, A. Magno, G. Banayat, F. Fata, N. L. Manohar, & H. I. Lipner. (1996). Protection from the nephrotoxicity of contrast dye. *Renal Failure* 18 (4):pp. 639-646, ISSN 0886-022X

Meier, P., D. T. Ko, A. Tamura, U. Tamhane, & H. S. Gurm. (2009). Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: a meta-analysis. *BMC Med* 7:pp. 23, ISSN 1741-7015.

Merten, G. J., W. P. Burgess, L. V. Gray, J. H. Holleman, T. S. Roush, G. J. Kowalchuk, R. M. Bersin, A. Van Moore, C. A. Simonton, 3rd, R. A. Rittase, H. J. Norton, & T. P. Kennedy. (2004). Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 291 (19):pp. 2328-2334, ISSN 1538-3598.

Nikolsky, E., R. Mehran, D. Turcot, E. D. Aymong, G. S. Mintz, Z. Lasic, A. J. Lansky, E. Tsounias, J. W. Moses, G. W. Stone, M. B. Leon, & G. D. Dangas. (2004). Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *American Journal of Cardiology* 94 (3):pp. 300-305, ISSN 0002-9149.

Obert, D. M., P. Hua, M. E. Pilkerton, W. Feng, & E. A. Jaimes. (2011). Environmental tobacco smoke furthers progression of diabetic nephropathy. *American Journal of the Medical Sciences* 341 (2):pp. 126-130, ISSN 1538-2990.

O'Keefe, J. H., M. Abuannadi, C. J. Lavie, & D. S. Bell. (2011). Strategies for optimizing glycemic control and cardiovascular prognosis in patients with type 2 diabetes mellitus. *Mayo Clinic Proceedings* 86 (2):pp. 128-138, ISSN 1942-5546.

Parfrey, P. S., S. M. Griffiths, B. J. Barrett, M. D. Paul, M. Genge, J. Withers, N. Farid, & P. J. McManamon. (1989). Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *New England Journal of Medicine* 320 (3):pp. 143-149, ISSN 0028-4793.

Perkins, B. A., R. G. Nelson, B. E. Ostrander, K. L. Blouch, A. S. Krolewski, B. D. Myers, & J. H. Warram. (2005). Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. *Journal of the American Society of Nephrology* 16 (5):pp. 1404-1412, ISSN 1046-6673.

Pflueger, A., T. S. Larson, K. A. Nath, B. F. King, J. M. Gross, & F. G. Knox. (2000). Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. *Mayo Clinic Proceedings* 75 (12):pp. 1275-1283, ISSN 0025-6196.

Phisitkul, K., K. Hegazy, T. Chuahirun, C. Hudson, J. Simoni, H. Rajab, & D. E. Wesson. (2008). Continued smoking exacerbates but cessation ameliorates progression of early type 2 diabetic nephropathy. *American Journal of the Medical Sciences* 335 (4):pp. 284-291, ISSN 0002-9629.

Rosenstock, J. L., R. Bruno, J. K. Kim, L. Lubarsky, R. Schaller, G. Panagopoulos, M. V. DeVita, & M. F. Michelis. (2008). The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. *International Urology and Nephrology* 40 (3):pp. 749-755, ISSN 0301-1623.

Russo, D., A. Testa, L. Della Volpe, & G. Sansone. (1990). Randomised prospective study on renal effects of two different contrast media in humans: protective role of a calcium channel blocker. *Nephron* 55 (3):pp. 254-257, ISSN 0028-2766.

Saleem, S., F. G. Lakkis, & M. Martinez-Maldonado. (1996). Atheroembolic renal disease. *Seminars in Nephrology* 16 (4):pp. 309-318, ISSN 0270-9295.

Shammas, N. W., M. J. Kapalis, M. Harris, D. McKinney, & E. P. Coyne. (2001). Aminophylline does not protect against radiocontrast nephropathy in patients

Contrast-Induced Nephropathy in Patients with Type 2 Diabetes Mellitus
and Coronary Artery Disease: Update and Practical Clinical Applications

253

undergoing percutaneous angiographic procedures. *Journal of Invasive Cardiology* 13 (11):pp. 738-740, ISSN 1042-3931.

Shannon, M. (1999). Life-threatening events after theophylline overdose: a 10-year prospective analysis. *Archives of Internal Medicine* 159 (9):pp. 989-994, ISSN 0003-9926.

Shlipak, M. G., L. F. Fried, M. Cushman, T. A. Manolio, D. Peterson, C. Stehman-Breen, A. Bleyer, A. Newman, D. Siscovick, & B. Psaty. (2005). Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 293 (14):pp. 1737-1745, ISSN 1538-3598.

Solomon, R. (2005). The role of osmolality in the incidence of contrast-induced nephropathy: a systematic review of angiographic contrast media in high risk patients. *Kidney International* 68 (5):pp. 2256-2263, ISSN 0085-2538.

Solomon, R. (2009). Preventing contrast-induced nephropathy: problems, challenges and future directions. *BMC Med* 7:pp. 24, ISSN 1741-7015.

Solomon, R. J., M. K. Natarajan, S. Doucet, S. K. Sharma, C. S. Staniloae, R. E. Katholi, J. L. Gelormini, M. Labinaz, & A. E. Moreyra. (2007). 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 (25):pp. 3189-3196, ISSN 1524-4539.

Solomon, R. J., R. Mehran, M. K. Natarajan, S. Doucet, R. E. Katholi, C. S. Staniloae, S. K. Sharma, M. Labinaz, J. L. Gelormini, & B. J. Barrett. (2009). Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol* 4 (7):pp. 1162-1169, ISSN 1555-905X.

Spargias, K., E. Alexopoulos, S. Kyrzopoulos, P. Iokovis, D. C. Greenwood, A. Manginas, V. Voudris, G. Pavlides, C. E. Buller, D. Kremastinos, & D. V. Cokkinos. (2004). Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 110 (18):pp. 2837-2842, ISSN 1524-4539.

Staniloae, C. S., S. Doucet, S. K. Sharma, R. E. Katholi, K. R. Mody, J. T. Coppola, & R. Solomon. (2009). N-Acetylcysteine added to volume expansion with sodium bicarbonate does not further prevent contrast-induced nephropathy: results from the cardiac angiography in renally impaired patients study. *J Interv Cardiol* 22 (3):pp. 261-265, ISSN 1540-8183.

Toprak, O., M. Cirit, M. Yesil, D. W. Byrne, N. Postaci, S. Bayata, K. M. Majchrzak, & E. Esi. (2006). Metabolic syndrome as a risk factor for contrast-induced nephropathy in non-diabetic elderly patients with renal impairment. *Kidney and Blood Pressure Research* 29 (1):pp. 2-9, ISSN 1420-4096.

Vassallo, R., & J. J. Lipsky. (1998). Theophylline: recent advances in the understanding of its mode of action and uses in clinical practice. *Mayo Clinic Proceedings* 73 (4):pp. 346-354, ISSN 0025-6196.

Yoon, M. H., S. J. Tahk, H. M. Yang, J. S. Park, M. Zheng, H. S. Lim, B. J. Choi, S. Y. Choi, U. J. Choi, J. W. Hwang, S. J. Kang, G. S. Hwang, & J. H. Shin. (2009). Comparison of the intracoronary continuous infusion method using a microcatheter and the intravenous continuous adenosine infusion method for inducing maximal

hyperemia for fractional flow reserve measurement. *American Heart Journal* 157 (6):pp. 1050-1056, ISSN 1097-6744.

Zoungas, S., A. Patel, J. Chalmers, B. E. de Galan, Q. Li, L. Billot, M. Woodward, T. Ninomiya, B. Neal, S. MacMahon, D. E. Grobbee, A. P. Kengne, M. Marre, & S. Heller. (2010). Severe hypoglycemia and risks of vascular events and death. *New England Journal of Medicine* 363 (15):pp. 1410-1418, ISSN 1533-4406.
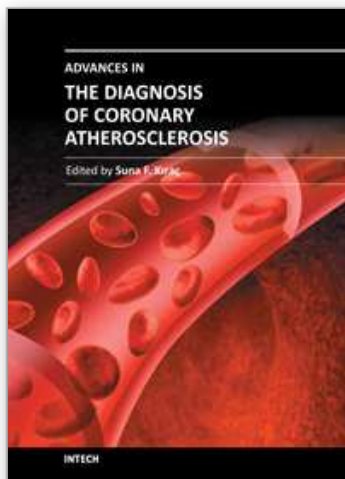
Advances in the Diagnosis of Coronary Atherosclerosis

Edited by Prof. Suna Kirac

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

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