Journal of Integrative Cardiology

Short Communication ISSN: 2058-3702

Contrast-induced nephropathy

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Contrast-induced nephropathy remains a common complication of radiographic procedures and the third most common cause of hospital acquired renal failure, after decreased renal perfusion and nephrotoxic medications. Contrast-induced nephropathy (CIN) is typically defined as an increase in serum creatinine of 25% over baseline, or an absolute increase of 0.5mg/dL (44.2µmol/l), within 48-72 hours of contrast administration [1,2] that persists for 2-5 days. Estimated GFR is most commonly calculated with formula and eCCr by using the Cockcroft-Gault formula. This equation account for differences in muscle mass in adult populations based on several variables (age, gender, race, weight) and are thought to result in more sensitive and specific measurements of renal function than serum creatinine alone. It is important to remember that these formulas were developed for assessment of patients with chronic renal disease, not acute renal dysfunction (Table 1).

Contrast-induced nephropathy occurs in less than 2% of patients with normal renal function, but in up to 50% of those with pre-existing renal impairment (with estimated creatinine clearence less than 60), diabetes [3], anemia, shock, sepsis, dehydration, concurrent administration of nephrotoxic drugs, administration of >100ml of contrast medium. Other nonmodifiable risk factors are congestive cardiac failure with ventricular dysfunction (<40%), age over 75 years [4-8].

The pathophisiology of CIN is very complex but one of the most important problems in CIN would be the injury of renal medulla caused by osmotic effect, and a direct toxic effect of contrast media on tubular epithelial cells. The tubular injiury is thought to be due to intrarenal vasoconstriction. Contrast agents are thought to produce prolonged vasoconstriction of the arteriole and stasis of contrast material in the renal vasculature, resulting in medullary ischemic injury and death of proximal and distal renal tubular cells [9,10]. The decreased blood flow caused by vasoconstriction is amplified further as blood viscosity increases, resulting in medullary hypoxia.

Prevention of CIN

To prevent CIN the first step is discontinuing of administration of nephrotoxic drugs like Amphotericin B, Vancomycin, Chemotherapeutic agents, Aminoglycosides, Metformin, Nonsteroidal anti-inflammatory agents [11], because these drugs in combination with contrast media can have an additive injurious effect through different mechanisms (Table 2).

Among the prevention strategies the most effective [12] is the intravenous hydration, inexpensive and risk free procedure, with sodium chloride, administrated 12 h before and 6 h after the prcedure (1ml/kg per hour). However the prophylactic hydration would be most effective, for some authors, with sodium bicarbonate, alkalinizing renal tubular fluid and reducing the injury of free radical. Free-radical formation is promoted by an acidic environment typical of tubular urine [13-14] but is inhibited by the higher pH of normal extracellular fluid. The urine alkalinization is obtained with administration of N-acetylcysteine with normal saline infusione (the oral dose suggested is 1200mg twice a day 48 hours before and 48 hours after the procedure or 600mg; there isn't a recommended dose for intravenous dose) [15-16].

However, despite extensive research, any benefit offered by acetylcysteine or sodium bicarbonate infusion remains unclear; while the most important innovation remains the administration of iso-osmolar contrast agents (280mOsm/kg) that replaced the old hyperosmolar (1500 - 1800mOsm/kg) and low-osmolar (600 - 850mOsm/kg) and which cause less CIN.

To prevent CIN is important the correct function of the nephrons (about 1 milion in a kidney) and the glomerular filtration; it is due to a balance of 3 forces: plasma-colloid osmotic pressure, Bowman capsule hydrostatic pressure, and, most important, glomerular capillary blood pressure. The plasma-colloid osmotic pressure (15mm Hg) and Bowman hydrostatic pressure (30mm Hg) are influenced by protein concentration, whereas the glomerular capillary pressure (55 mm Hg) is controlled by constriction and dilatation of the afferent and efferent vessels. The glomerular capillary pressure is the highest and most dominant force in glomerular filtration. Glomerular capillary pressure favors filtration as it pushes fluid from the blood, counteracting the opposing osmotic and hydrostatic pressures, which pull fluid according to protein concentration. A net filtration pressure results from the glomerular capillary pressure (55mm Hg) and the opposing plasma-colloid osmotic pressure (15mm Hg) and Bowman hydrostatic pressure (30mm Hg): 55mm Hg - (30mm Hg + 15mm Hg) = 10mm Hg. A normal

Table 1. Formulas for assessment of patients with chronic renal disease.

Stage	Description	GFR (Ml/min/1.73m^2)
1	Kidney damage with normal/increased GFR	>90
2	Kidney damage with mild decrease in GFR	60-89
3	Kidney damage with moderate decrease in GFR	30-59
4	Kidney damage with severe decrease in GFR	15-29
5	Kidney failure	<15

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Received: January 15, 2015; **Accepted:** February 10, 2015; **Published:** February 14, 2015

Table 2. Medications to be discontinued.

Drug	Effect
Vancomycin	Mechanism of nephrotoxic effect is unknown
Amphotericin B	Binds to tubular epithelial cells, alters cell permeability, and causes vasoconstriction of intrarenal arteries and arterioles
Chemotherapeutic agents	Cumulative nephrotoxic effects related to tubular epithelial cell necrosis
Aminoglycosides	Intracellular accumulation of medication in proximal tubule cells thought to interfere with cellular function, eventually leading to cell death and decreased glomerular filtration rate
Metformin	Not a nephrotoxic medication; however, has been associated with spontaneous lactic acidosis resulting in acute kidney injury, systemic complications, and death
Non steroidal anti-inflammatory agents	Two deleterious effects: Interstitial inflammation Decreased production of vasodilatory prostaglandins, thereby potentiating the effect of adenosine, increasing vasoconstriction

net filtration pressure allows fluid from the blood to be forced through the highly permeable glomerular membrane (glomerular filtration) [17].

A modern system designed to reduce the toxic effects that contrast media can have on the kidneys of high risk patients is Renal Guard therapy that replace urine output by infusion of a matched volume of sterile replacement solution to maintain a patient's intravascular fluid volume [18]. The damage was reduced through: - increasing urine rates, - increasing the patient level of hydration, - reducing the workload of the kidney, which will reduce the oxidative stress on nephrons.

At the end another option not only to prevent but to treat CIN is the hemofiltration, throug we can remove low-osmolality media after a procedure that requires contrast material, without depleting volume, and has shown some benefit.

However, hemofiltration is expensive, requires intensive care, and should be used only in very high-risk patients.

Considerations and conclusions

In the attempt to prevent CIN some authors try to find some new marker of GFR for a earlier diagnosis of CIN like "Serum cystatin C concentration", a small cysteine protease that is secreted at a fixed rate by all nucleated cells and is not affected by diet or muscle mass. In CIN, serum cystatin concentration peaks and normalizes more rapidly than creatinine [19]. Other markers were Urinary KIM-1 that has been shown to be an earlier diagnostic indicator of kidney injury when compared to conventional biomarkers such as creatinine [20]. NGAL is a protein bound to gelatinase in specific granules of neutrophils whose synthesis may be induced in epithelial cells in the setting of inflammation [21]. The earlier diagnosis of kidney failure we may consider the first step to prevent it. In these years were proposed many measures to prevent CIN without a definitive conclusion. In the summary we may identify some steps: the first one is the complete risk stratification of patient and determination of the necessity of contrast administration; the correction of modifiable risk factors; hydration; urine alkalinization; choice of contrast agents and the techniques for minimizing contrast dose during radiologic procedures; they are often not discussed in the literature although they remain critically important to reduction of contrast dose during procedures. Because contrast volume is related to the risk for contrast nephropathy; any method for decreasing iodinated contrast load may be potentially beneficial.

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