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Contrast-induced nephropathy – a review of current literature and guidelines

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Summary

The use of iodine-based contrast agents always entails the risk of contrast-induced nephropathy (CIN). The recently observed dramatic increase in the number of examinations and therapeutic procedures using iodine-based contrast media led us to conduct a thorough analysis of the growing number of scientific reports and collective works devoted to contrast-induced nephropathy, based on current definitions, epidemiology, pathophysiology, risk factors, successful prophylaxis and guidelines of the European Society of Urogenital Radiology (ESUR).

Radiological contrast agents are the third most common cause of nephropathy among in-patients, accounting for 11–12% of cases. CIN is connected with some clinically significant consequences, including increased morbidity, prolonged hospitalisation, increased risk of complications, potential need for dialysis and increased mortality rate. A significant increase in the number of examinations applying iodine-based contrast media in the course of inpatient procedures requires close cooperation of the clinician and radiologist, supported by knowledge of all CIN issues. In order to protect patients from contrast-induced nephropathy, it is necessary to monitor their renal function, identify patients with risk factors, refer patients for examinations in a responsible manner, and undertake successful preventive measures.

key words: contrast-induced nephropathy • CIN • risk factors of CIN • CIN prevention

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BACKGROUND

A substantial increase in the number of multi-detector CT scanners in Poland, and a significant improvement in the quality of contrast media, has led in recent years to a marked rise in the number of examinations applying iodine-based contrast media. Despite a significant increase in the number of performed procedures [1,2], both in Poland and in other countries, the incidence of contrast-induced nephropathy fell in the last decade from 15% to 7% [3]. The currently applied non-iodine contrast agents cause a lower number of adverse effects; however, CIN still remains a significant problem, requiring the radiologist and the referring clinician to remain alert to threats and risk factors of nephropathy.

DEFINITION OF CONTRAST-INDUCED NEPHROPATHY

The number of diagnosed contrast-induced nephropathies depends directly on their definition and is significantly lower when the cases are diagnosed on the basis of an absolute increase in serum creatinine level. The European Society of Urogenital Radiology (ESUR) defines CIN as a state in which nephropathy (increase in blood serum creatinine level of more than 0.5 mg/dl or of more than 25% of the baseline value) occurs within 3 days from the moment of intravascular injection of the contrast medium, assuming that there is no alternative etiology [4]. In 2005 a survey was conducted of over 500 radiologists from 10 European countries by means of Internet or telephone. The survey evaluated their knowledge of the meaning of CIN and of CIN risk factors in patients who underwent contrast-enhanced computed tomography. Only 45% of the respondents agreed that patients develop CIN when the serum creatinine level exceeds 25% or 0.5 mg/dl, as compared to the baseline value, within 48 hours after contrast administration. Most radiologists (72%) thought that occurrence of CIN is connected with increased patient morbidity, but 56% did not believe that CIN results in a significant increase in the mortality rate. Although most of the respondents agreed that previous renal abnormalities (97%), dehydration (90%) and diabetes (89%) are CIN risk factors, as many as 26%, 30%, and 46% of radiologists (respectively) believed that old age, volume of the injected contrast agent, and congestive heart failure do not increase CIN. Only 7% of those responding to the survey were fully aware of the risk of CIN development [5]. We should therefore consider the best methods for renal function measurement for use in CIN epidemiology and pathophysiology, endeavor to identify patients at high risk, and introduce proper procedures to prevent patients from developing CIN.

Epidemiology

Use of radiological contrast media is the third most common cause of inpatient renal insufficiency, accounting for 11–12% of all cases [6,7]. CIN is connected with significant clinical outcomes, such as prolonged hospitalization, increased risk of nosocomial complications, potential need for dialysis and increased risk of death [5,8,9]. The incidence of CIN in the general population is estimated at 1–2%. However, in older patients with diabetes, in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI, congestive heart failure, or previous renal failure, the

risk of nephropathy may increase to 25–30% [10–14]. The population at particular risk includes patients with diabetes accompanied by renal failure, with a risk of 50% [15,16]. The mean intrahospital case mortality rate among patients who underwent contrast-enhanced examinations and did not develop CIN is 1–2%. In patients with CIN, the rate is significantly higher and reaches 7–22%, and 36% in CIN patients requiring dialysis [8,17–19]. The long-term mortality rate (within 1–5 years) among inpatients undergoing contrast-enhanced examinations is 6–12% in individuals not developing acute renal failure, and is as high as 44% in patients developing CIN after percutaneous coronary interventions (PCI), and 55% in patients after PCI with CIN and requiring dialysis [19,20].

Screening of the Basic Renal Function

Glomerular filtration rate (GFR) is an expression of the quantity of glomerular filtrate formed per unit time (usually each minute) in the nephrons of both kidneys. It indicates the volume of blood plasma filtrated per unit time by the glomeruli. GFR is usually given in ml/min or better, in ml/min * 1.72 m² (converted to a standard body surface area) [21].

The gold standard for measuring the GFR is inulin clearance. Inulin is uniquely treated by nephrons in that it is completely filtered at the glomerulus but is neither secreted nor reabsorbed by the tubules. This property of inulin allows the clearance of inulin to be used clinically as a highly accurate measure of GFR. This is clearly more accurate than the method of estimating GFR based on creatinine clearance, but is methodologically inconvenient. Unlike creatinine, inulin is not naturally present in the body. This is an advantage of inulin, because the amount infused will be known, but it is also a disadvantage because an infusion is necessary.

Inulin clearance is used more often in research than in clinical practice. Some studies have compared the determination of the inulin plasma clearance by 2 methods: the single injection and the continuous infusion method [22].

At present, the serum creatinine level remains the basic indicator of renal function. However, only the reduction of the glomerular filtration rate (GFR) by 50% leads to an increase in serum creatinine concentration, which is why its normal concentration does not exclude renal failure. In practice, this is not a reliable indicator of the glomerular filtration rate due to (inter alia) a high dependence on other factors such as diet, muscle mass, tubular secretion of creatinine, age and sex. A better indicator is the 12- or 24-hour creatinine clearance.

$$CCr = \frac{UCr \text{ (mg/dl)} \times V \text{ (ml)}}{SCr \text{ (mg/dl)} \times T \text{ (min)}}$$

CCr – Creatinine clearance,
UCr – Urine creatinine,
V – Volume of the collected urine,
SCr – Serum creatinine,
T – Time of urine collection.

Normal CCr values range from 97 to 137 ml/min for men and from 88 to 128 ml/min for women. The clearance method is a reliable indication of the glomerular filtration if the

difference between the first and the second measurement does not exceed 10% [21,23]. In case of CIN development, this condition is never met. Another marker used for evaluation of the renal function (in clinical trials rather than in everyday clinical practice) is cystatin C, produced by all cells with a nucleus (cell core containing the DNA), which is freely filtered at the glomerulus and not reabsorbed. This protein seems to be a slightly more sensitive indicator of mild GFR decreases than is creatinine, especially in diabetic patients. Correlation coefficients (r) with the GFR is in favor of cystatin C over creatinine and even more in favor of the Cockcroft-Gault formula ($r=74$) *vs.* ($r=67$) *vs.* ($r=88$). Moreover, the Cockcroft formula is more sensitive – 96% (in comparison to 87% for cystatin C and 77% for creatinine) [24,25]. Many studies have demonstrated that cystatin-C is a better marker of renal function, particularly in diabetic patients. As the Cockcroft-Gault equation calculates GFR proportional to body weight, it considerably overestimates GFR in obese subjects. This tendency is likely to increase because the mean BMI of subjects entering dialysis is increasing twice as fast as the BMI of the U.S. general population [24]. Cystatin C clearance is an alternative method for determination of GFR [24–26].

The National Kidney Foundation Kidney Disease Outcome Quality Initiative also recommends use of GFR based on Cockcroft's formula for clinical evaluation of renal function. The GFR should, as far as possible (emergency examinations), be established in each patient before testing using iodine contrast media [23,24,27].

$$GFR (man) = \frac{(140 - age) \times (body\ mass)}{72 \times (serum\ creatinine\ mg/dl)}$$

$$GFR (woman) = \frac{(140 - age) \times (body\ mass)}{85 \times (serum\ creatinine\ mg/dl)}$$

The Cockcroft-Gault formula should not be used for evaluation of renal function in children under the age of 13 years. In this group of patients, its concordance with GFR is the lowest and these are cases where serum cystatin C level or Schwartz formula for pediatrics should be established, being the most reliable indicators [28,29,30].

The Schwartz formula, creatinine-based prediction of GFR, depends on age, sex, body weight and serum creatinine [29].

$$GFR (pediatrics) = \frac{K (Height\ cm)}{(serum\ creatinine\ mg/dl)}$$

$K=0.33$ in premature infants,

$K=0.45$ in term infants to 1 year old,

$K=0.55$ in children to 13 years and adolescent females,

$K=0.65$ in adolescent males.

PATHOPHYSIOLOGY

Despite many studies, the mechanism of CIN development is still not fully understood, and many factors may be involved. The main cause is believed to be the coexistence of different mechanisms, with the most important ones being the following pathophysiological factors:

- vasoconstriction induced by angiotensin II,
- reduction of descending vasa recta luminal diameter by contrast media,
- nitric oxide (NO) level reduction,
- decreasing NO bioavailability,
- oxidative stress,
- viscosity of contrast media.

The principal CIN causes are renal ischemia from disequilibrium of vasodilatory and vasoconstrictive factors [31,32]. The most ischemia-susceptible region of the kidneys, distant from the vasa recta, is the ascending limb of the loop of Henle, which is the site of sodium reabsorption – a highly oxygen-consuming process. This process is the best explanation of the high partial pressure of oxygen in the renal cortex and a very low pO_2 of 20 mmHg in the medulla. The renal medulla, the site most sensitive to ischemia, is supplied from the vasa recta, which are very long and narrow vessels, and in consequence the ascending limbs in the renal medulla are areas of critical oxygen supply [33]. Use of contrast media decreases nitric oxide production, and the role of NO as a strong vasodilator has long been known. Vasoconstriction of these vessels is induced by reduced bioavailability of NO and in parallel intensifies angiotensin II-induced long-term spasm of the descending vasa recta by 50–60% in standard lumen [34]. NO inhibits salt reabsorption, thereby reducing oxygen demands within the outer medulla. Angiotensin II constricts the descending vasa recta, enhances sodium reabsorption and favors formation of oxygen free radicals. The narrowing of vessels caused by lower oxygen pressure generates necrosis and apoptosis of tubular cells and leads to tubular stenosis and collapse. The principal factor inducing this mechanism is the high viscosity of contrast media, not their osmolality. Osmolality of contrast media (CM) is widely regarded as the crucial parameter for the nephrotoxicity of CM. This assumption is based on the observation that ionic high-osmolar CM are associated with a greater risk of CIN than are low-osmolar CM [31,32]. Trial results show that iso-osmolar CM (high-viscosity dimers) is not associated with a significantly reduced risk of CIN compared with the low-osmolar CM (monomers) in patients with intravenous administration [35].

Risk factors for CIN

In spring 2008, on the basis of research results, the Contrast Media Safety Committee of the ESUR established risk factors for CIN development, dividing them into 2 groups: those connected with the patient and those connected with the contrast agents [4,36,37].

1. Patient-dependent risk factors:

- GFR <60 ml/min/1.73 m², or increase in serum creatinine level, especially when resulting from diabetic nephropathy,
- dehydration,
- congestive heart failure,
- gout,
- age over 70 years,
- concurrent application of nephrotoxic drugs such as NSAIDs, metformin, mannitol, loop diuretics, chronic use of ACE inhibitors, aminoglycosides.

MEDICAL HISTORY QUESTIONNAIRE

filled out by the physician referring the patient for an examination with the use of iodine contrast agents

- | | | |
|---|------|-----|
| 1. Mild or severe reactions to iodine contrast agents | Yes* | No* |
| 2. Allergic reactions requiring treatment | Yes | No |
| 3. Bronchial asthma | Yes | No |
| 4. Hyperthyroidism | Yes | No |
| 5. Heart failure | Yes | No |
| 6. Diabetes mellitus | Yes | No |
| 7. Renal disease | Yes | No |
| 8. Surgery on kidneys | Yes | No |
| 9. Proteinuria | Yes | No |
| 10. Hypertension | Yes | No |
| 11. Gout | Yes | No |
| 12. The last measurement of GFR or creatinine level | | |
| value | | |
| date | | |
| 13. Is the patient on the following medications?: | | |
| • Metformin | Yes | No |
| • Interleukin-2 | Yes | No |
| • NSAID | Yes | No |
| • Aminoglycosides | Yes | No |
| • Beta blockers | Yes | No |
| • Loop diuretics | Yes | No |

Date of history taking

Signature
Stamp of the physician

*Circle the right answer

Figure 1. Medical history questionnaire.

The following factors were also included in this group:

- diabetes,
- hypertension,
- low hematocrit,
- hypotension,
- low ejection fraction of the left ventricle <40%.

2. Risk factors connected with contrast agents:

- high doses of contrast agents (volume of less than 100 ml was considered relatively safe),
- high osmolality, viscosity.

CIN PROPHYLAXIS

On the basis of the current knowledge and available results of clinical and pathophysiological tests [36,38,39], the ESUR introduced a program of CIN prevention, recommending specific courses of action in particular groups of patients. The recommendations divide preventive measures against CIN into 3 groups applied before, during and after a contrast-enhanced examination.

Preventive measures undertaken before examination

1. Identification of patients with risk factors:
 - a. In patients with GFR <60 ml/min/1.73 m² or an elevated serum creatinine level, or a previously elevated serum creatinine level (nephropathy, proteinuria, hypertension, gout), the measurement of the serum creatinine level is recommended for the time period of 7 days after contrast agent administration.
 - b. In patients taking metformin:
 - i. If the creatinine level is normal, it is recommended to discontinue metformin for 48 hours from the time of contrast agent administration. Metformin treatment should be reinstated after 48 hours if the creatinine level is normal.
 - ii. If the creatinine level is elevated, it is recommended to discontinue metformin for 48 hours before contrast administration and for 48 hours after contrast administration. Metformin treatment should be reinstated only if the creatinine level does not increase after 48 hours from contrast agent administration.
2. Identification of patients taking nephrotoxic medications. It is recommended to discontinue nephrotoxic substances for at least 24 hours before contrast medium administration.
3. Hydration of patients with risk factors. It is recommended to administer 0.9% NaCl intravenously, in the dose of 1 ml/kg of body mass/hour, for 6 hours before contrast agent administration.

Prevention measures during examination include

- a. Application of the lowest possible volume of the contrast agent.
- b. Use of low- or iso-osmolal contrast agents.

Prevention measures after the examination

1. Patients with GFR <60 ml/min/1.73 m² or elevated creatinine level: continuation of hydration for at least 6 hours.
2. Patients taking metformin: indicated monitoring of GFR or serum creatinine level for 48 hours after contrast agent

administration. If the creatinine level is normal, metformin should be re-introduced.

In recent years there have been many attempts at evaluation of the effects of different factors on prevention of contrast-induced nephropathy [40–43]. Most studies examined normal saline, sodium bicarbonate, n-acetylcysteine, theophylline, dopamine, nitrendipine, furosemide, mannitol and ascorbic acid. The effectiveness of patient hydration with the use of different methods is still ambiguous. Finally, in 2008, there appeared results of a meta-analysis including 40 randomised controlled trials in which the following substances were administered: sodium bicarbonate, n-acetylcysteine, theophylline, dopamine, nitrendipine, statins, furosemide, mannitol, and ascorbic acid [44–49]. According to the results, only the administration of n-acetylcysteine or theophylline was more advantageous to patients than hydration with normal saline, while the use of furosemide significantly increased the risk of CIN [50–55]. Taking into consideration the large number of trials and their variable results, the ESUR took a definite stand on this matter and stated that no pharmacological manipulations could achieve comprehensive prevention of CIN. In most of the studies, hydration with 0.9% NaCl resulted in a significant reduction in the risk of contrast-induced nephropathy.

CONCLUSIONS

In everyday clinical practice, the key role in patient protection from contrast-induced nephropathy is the proper monitoring of renal function, identification of patients with risk factors, and introduction of effective preventive measures. One of the most important components of comprehensive prophylaxis is close cooperation between the radiologist and the clinician referring the patient for contrast-enhanced procedures. The result of such cooperation is unquestionably a responsible referral of the patients for examinations and proper preparation of these patients, for example by development of a proper medical history questionnaire (Figure 1), filled out before the examination, with involvement of the clinician, and allowing the radiologist to make conscious decisions and to plan the entire process before and after the examination.

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