

## Contrast induced acute kidney injury – is it a real problem these days?

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### ABSTRACT

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Acute kidney injury (AKI) is proven risk factor associated with higher mortality and morbidity among hospitalized patients. The widespread use contrast media opens the discussion about the acute kidney injury as a result of used contrast - contrast induced nephropathy (CIN). CIN is defined as an acute, generally reversible decline in renal function that occurs 48-72 hours after intravascular injection of contrast medium. Pre-existing renal insufficiency is characterised independent risk factor for occurrence of CI-AKI, other factors, such as diabetes mellitus, hypertension, advanced age or

hemodynamic instability increase the risk of AKI, but are not characterized as independent risk factors. Published new large retrospective single-center studies presented equal risk of AKI among patients receiving contrast enhanced computer tomography if compared to unenhanced computer tomography, based on serum creatinine levels. In our review we would like to present a persisting the problem of CIN after intravenous (iv) as well intra-arterial contrast media administration.

**Key words:** contrast media, contrast induced nephropathy, acute kidney injury

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## INTRODUCTION

Acute kidney injury (AKI) is proven risk factor associated with higher mortality and morbidity among hospitalized patients [1-4]. The aging population, growing percentage of people with diabetes mellitus and hypertension make the problem of kidney injury current and important. The one of the most important risk factors for acute kidney injury is chronic kidney disease (CKD), which estimated prevalence in Polish population is 5,8% [5-7]. Available data shows that about 16% of patients undergoing computer tomography (CT) suffer from CKD [6,8-9]. The increasing number of patients diagnosed with the use of CT, as also magnetic resonance and treated with percutaneous coronary interventions require the use of contrast media. The widespread use contrast media [10] opens the discussion about the acute kidney injury as a result of used contrast - contrast induced nephropathy (CIN). The first case report of CIN was observed in 1950's [11]. Nowadays contrast enhanced computer tomography is a standard diagnostic procedure. The incidence of CIN after contrast enhanced computer tomography is estimated at 2-12% depended on the analysed studies [12-19]. In our review we would like to present the problem of CIN after intravenous (iv) as well intra-arterial contrast media administration.

## REVIEW

### **The pathogenesis of contrast induced acute kidney injury (CI-AKI) after contrast media**

The pathogenesis of contrast induced acute kidney injury is complex. Iodinated contrast media injected intravenously or intra-arterial goes from vascular compartment to the extracellular space and is eliminated through glomerular filtration. It leads at the beginning to short increase of renal blood flow, followed by prolonged decreased blood flow resulting decreased glomerular filtration rate (GFR). It causes the ischemia of medulla, enlarges the damage of endothelial cells, among others the tubular epithelial cells [20-23]. The endothelium damage outside pre-existing clinical conditions is influenced by contrast media properties such as high osmolality and ionic strength [24-26]. Contrast media in in-vitro studies causes increase of renal tubular viscosity, tubular obstruction and elevates interstitial pressure [27].

### **Definition of contrast media induced acute kidney injury**

In order to reduce the risk of CIN European Society of Urogenital Radiology as also American College of Radiology and the Canadian Association of Radiologists have published guidelines for iv contrast medium administration. All mentioned study groups concentrated on basal

serum creatinine (SCr) levels, as a potential risk factor for later development of CIN [19,28,29].

Contrast-induced nephropathy (CIN) is defined as an acute, generally reversible decline in renal function that occurs 48-72 hours after intravascular injection of contrast medium [30,31]. CIN, depending on the route of administration of contrast media, is classified as intravenous or intra-arterial CIN [19].

The definition of contrast induced AKI is based on the same criteria as other forms of AKI and except changes in serum creatinine concentration it includes also urine creatinine output changes [32]. The term CI-AKI is usually defined as the serum creatinine concentration rise of  $\geq 0,5$ mg/dl ( $\geq 44$   $\mu$ mol/l) or a 25% increase from the baseline value occurs 24-48 hours, or up to 72 hours after intravenous or intra-arterial administration of contrast media and returns to the baseline within 14 days [29,32-34].

To standardize the definition for CIN The Acute Kidney Injury Network (AKIN) proposed new diagnostic criteria including the increase in serum creatinine level of  $>0.3$  mg/dl (26.4  $\mu$ mol/l) or a percentage increase in serum creatinine level of  $\geq 50\%$  from the baseline, or a reduction in urine output (oliguria of  $<0.5$  ml/kg/h for  $>6$  hours) within 48 hours after contrast administration. The AKIN highlights the fact that these thresholds may be over-sensitive and cause more false-positive cases [34-37].

### **Risk factors for CI-AKI**

These days the majority of radiological examinations are performed in outpatients. Also worth noting is aging population with coexisting many chronic diseases. In this situation it seems important to find patients with higher risk of CI-AKI in order to plan appropriate prevention procedures.

Pre-existing renal insufficiency, estimated in Polish population on 5,8% [7] is as a risk factor above other risk factors for occurrence of CI-AKI [32,38]

The discussion about the threshold of creatinine or eGFR, below which the risk of CIN increases, was the subject of various studies and meta-analysis. The CI-AKI Consensus Working Panel agreed that the prevention should be implemented among patients with baseline eGFR  $<60$  ml/min/1.73m<sup>2</sup> or even  $<45$  ml/min/1.73m<sup>2</sup> [32]. Large studies published in 2013 and 2014 proved that exposure to intravenous iodinated contrast media in patients with stable baseline eGFR  $\geq 45$  ml/min/1.73m<sup>2</sup> is not an independent nephrotoxic risk factor of AKI. Moreover, among patients with eGFR between 30-44 ml/min/1.73m<sup>2</sup> CI-AKI was observed less than expected [38-42]. What is worth a comment and need further analysis, that in only two of presented above study's authors characterized exposure on intravenous iodinated contrast material

as independent nephrotoxic risk factor in patients with eGFR < 30 ml/min/1.73m<sup>2</sup> [39,40].

Other risk factors predisposing the occurrence of CI-AKI, such as diabetes mellitus, hypertension, advanced age or hemodynamic instability increase the risk of AKI, but are not characterized as independent risk factors [38,41-43].

It is also important to differentiate the intravenous from intra-arterial administration of contrast media, which is related to higher risk of CI-AKI [19]. Patients undergoing angiographic procedures have higher risk of cardiovascular diseases or haemodynamic instability (hypotension, reduced cardiac output), as also the contrast media volume, depending on the procedure may be higher. Intra-arterial injection of contrast media causes higher iodine concentration in kidney capillaries, that might be related to later observed AKI [44-46]. It is important to notice, that through higher number of studies concentrating on cardiac angiography if compared to intravenous contrast media administration the risk of CIN among the second group might be over-estimated [47].

Abujudeh et al. as also Trivedi and Foley noticed that multiple, closely spaced iodinated intravenous contrast media doses may determine risk factor of higher CIN occurrence in studied populations [48,49]. There is no exact time interval which should be maintained between successive exposition on the contrast media. Some experts accept a 30-day limit in outpatients [28]. Repeated contrast media administration within 24-48 hours could positively influence the risk for CIN [50].

There are also contrast media related risk factors depending on contrast osmolality. Contrast media are divided into high-osmolar, low-osmolar and iso-osmolar contrast material. High-osmolar contrast media was identified as risk factor for CI-AKI, and because of this fact it is almost completely not in use any more [19,51,52].

### **Markers of AKI**

To get performed a contrast enhanced computer tomography outpatients are obliged to submit current creatinine level. Already in 1998 Choyke et al. [53] elaborated a list of risk factors in order to identify patients with impaired renal function. On the basis of available literature as also experts opinion the paper published in 2014 present a list of risk factors, the presence of which should require baseline serum creatinine concentration before the use of iodinated contrast medium administration. These factors include, among others: age >60, history of renal disease, hypertension or diabetes mellitus [28,54].

Acute kidney injury is diagnosed in everyday practice through serum creatinine levels measurements in time intervals. It is important to mention that serum creatinine changes are slowly following the onset of AKI. The steady state may be

reached days after the exposure to nephrotoxic factor. Based on serum creatinine eGFR is estimated. Unfortunately GFR reduction is observed when up to 50% of kidney function has been lost. Concluding serum creatinine, despite its widespread availability, is not a good marker for AKI [55,56]. The question remains open if creatinine as also eGFR are proper markers for detection of patients with higher risk of AKI.

Many available studies concentrate on intra-arterial contrast supply, especially in invasive cardiology procedures, which are associated with higher risk of CI-AKI than computer enhanced tomography. It may lead to overestimation of the CI-AKI risk in patients undergoing intravenous contrast media exposure. Such apparently similar, but in practice different studies should not be compared because of different kidney exposure on the contrast media [19,57].

Crucial studies were published by McDonald et al., who questioned the concept of CI-AKI after contrast media exposure. Over than 10,000 patients were retrospectively analyzed in this multiple propensity score matched trials, each trial with over 10000 patients. In the large retrospective single-center study they observed equal risk of AKI among patients receiving contrast enhanced computer tomography if compared to unenhanced computer tomography. AKI was based on serum creatinine level differences. The results suggest rather coincidental AKI in patients receiving contrast media, than statistically significant differences independently from basal renal function. [39,40]. The authors noticed some study limitations, among others the study population, who consisted on inpatients, as also exclusion of patients receiving multiple doses of contrast media. Published in 2013 systemic review, based on studies concerning AKI incidence among patients underwent enhanced and unenhanced CT, showed similar risk of AKI in both group of patients. Even the risk of dialysis and mortality was comparable in both groups [38]. Newhouse et al. [58] pointed out the problem of misinterpretation of serum creatinine levels. Daily variations in serum creatinine concentration might be interpreted as AKI.

### **CONCLUSIONS**

The debate about CI-AKI is still open and even more serious because of rising number of contrast enhanced computer tomography and angiography procedures. The anxiety of CI-AKI often leads to a refusal of performing the procedure, commonly in outpatients, what results prolongation of diagnostic procedures. Observed and analyzed since over 60 years problem of CI-AKI seems to be less serious than it was presumed. Non-controlled studies possibly exaggerated the risk of CI-AKI especially after intravenous exposure. New control

studies assume no risk of AKI after contrast media exposure in patients with proper renal function. The question of risk in patients with chronic kidney disease still remains open.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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