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Conference Paper

Use and Misuse of a Biomarker: Contrast-Medium-Induced Nephropathy and Serum Creatinine

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Two different types of contrast media are being used: low-osmolar and isoosmolar contrast media (LOCM, IOCM). Both types induce renal failure. Serum creatinine is routinely used as a marker of renal impairment in many clinical settings. A variety of studies and meta-analyses addressed the differential safety of contrast media with divergent osmolarity. Unfortunately, research in this field is lacking standardized endpoints, as different levels of creatinine increase are used as a surrogate for renal failure, and additionally, serum creatinine levels are influenced by a variety of pathophysiological conditions and thus susceptible for marker artifacts. This is one explanation why conflicting results have been published regarding the different safety of contrast media favoring either LOCM or IOCM. Viscosity which is higher in IOCM rather than osmolarity determines the potential of a CM to induce renal failure. High viscosity reduces flow in renal tubules and vessels and thus impairs renal filtration. Thus, the most effective prevention measure for renal failure is reducing the concentration of contrast media and adequate hydration. In emergency situations, hydration as well as kidney status is commonly unknown, and LOCM are indicated due to their lower viscosity and to their greater water-binding capacity to reduce the risk of renal failure.

1. Introduction

Reflecting the recommendations given by the cardiologic societies (ESC/ACC/AHA) during the past years, major changes regarding the use of contrast media during coronary angiography (CA) and percutaneous coronary intervention (PCI) have occurred. These recommendations are mainly based on studies using surrogate markers for renal impairment. Unfortunately, research regarding the use of serum creatinine as a marker for renal impairment in the setting of coronary angiography is biased by overinterpretation, marker artifacts, statistical shortcomings, wishfulness, and even ethical limitations. These topics will be elucidated in the following passages.

2. Results

2.1. Types of Contrast Media. Cardiologists usually use contrast media during CA and PCI. There are many different types of contrast media, but in Germany, only nonionic contrast media are currently being used. Nonionic contrast media are subgrouped by their osmolarity into low-osmolar contrast media (LOCM, monomers) and iso-osmolar contrast media (IOCM, dimers) (Figure 1).

Low-osmolar contrast media are still hyperosmolar compared to human blood. Thus, LOCM do have a higher osmolarity compared to IOCM. Their denomination is descended from times when all prior used contrast media had a higher osmolarity. Besides osmolarity, another important, if not

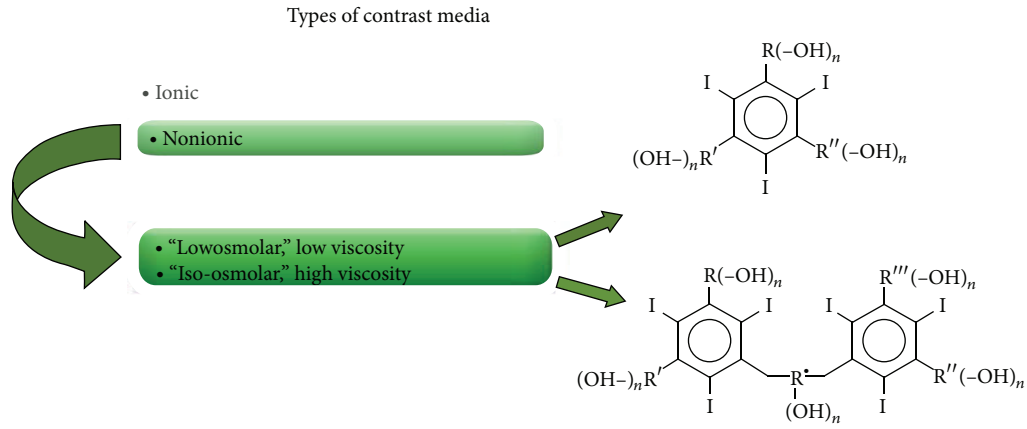

Figure 1: Different types of contrast media in current use.

more important, characteristic of contrast media is viscosity, which, until recently, did not receive much attention. LOCM have a lower viscosity than IOCM. IOCM are characterized by plasma osmolarity and a higher viscosity. Their water-binding potential is half as high as that of LOCM. In the year 2005, the first IOCM were introduced and promoted as having a better nephron safety.

2.2. Recommendations regarding the Use of Contrast Media in the Guidelines. In most of the nephrologic, cardiologic, and radiologic guidelines, it is stated that iso-osmolar and low-osmolar contrast media are comparable with regard to nephrotoxicity (Figure 2). The American Heart Association/ACC guidelines in 2007 were the only recent key guidelines recommending the use of IOCM in chronic kidney disease: "In chronic kidney disease patients undergoing angiography, iso-osmolar contrast agents are indicated and are preferred. (Level of Evidence: A)" [1]. This recommendation was mainly based on the results of the RECOVER trial, where 300 patients were studied in a randomized trial comparing iodixanol (IOCM) and ioxaglate (LOCM) and on the results of a meta-analysis with 16 randomized clinical trials and 2,727 patients [2, 3].

In the new guidelines in 2011, this recommendation was deleted [4] due to several clinical trials and 2 meta-analyses reporting no difference in nephrotoxicity when comparing IOCM and LOCM [5–10].

2.3. Pathophysiology of CIN. From the physiological perspective, slightly higher osmolarity is not a great danger to the kidney. The kidney is the only organ which is adapted to osmolar stress to a high extent. In the kidney medulla, where nephric damage occurs after coronary angiography, physiological osmolarities up to 1,200 mosmol/kg H_2O can occur, as compared to the osmolarity of contrast media (LOCM) of about 700 mosmol/kg H_2O. The first diuretics, which are now older than 100 years, were osmodiuretics. They have a similar osmolarity compared to LOCM and a high nephron safety. The only indication for those diuretics today is early kidney insufficiency, and this is due to the fact that they actually have kidney-protective effects.

2.4. Marker Artifacts regarding Serum Creatinine as a Surrogate for CIN. Serum creatinine is released from the skeletal muscle and is eliminated almost entirely by the kidneys. Only 10% of creatinine is secreted and 90% is eliminated by free filtration. Unfortunately, a variety of factors can lead to artifacts (Figure 3):

(1) skeletal muscle injury,
(2) amount of muscle mass,
(3) special diets,
(4) pharmaceutics,
(5) infections,
(6) hydration status.

Thus, interpretation of serum creatinine levels can be challenging, especially when keeping in mind that a creatinine increase is not linear but exponential.

2.5. Statistical Shortcomings

2.5.1. Definitions of Contrast-Medium-Induced Nephrotoxicity (CIN). In the current literature, different definitions of contrast-medium-induced nephropathy are being used.

Increases in serum creatinine by

(1) ≥0.5 mg/dL (or ≥1.0 mg/dL),
(2) >25% (or >50%)

within 1–7 days.

Even in the manual of contrast media (Version 7.0, 2010), it is stated: "There is no standard definition for reporting contrast-media-induced nephropathy" [11]. As a result, the definition of CIN used for individual publications might be driven by the study data rather than defining applied cutoffs beforehand.

The currently most robust definition is an increase in serum creatinine of over 50% above the baseline value.

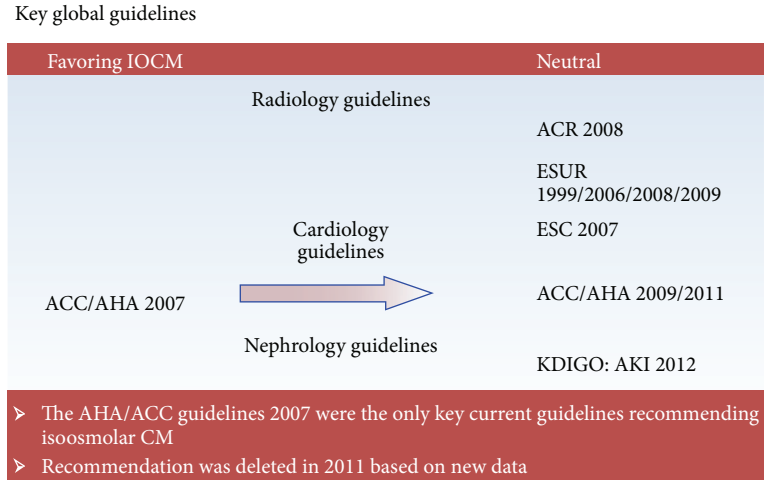

Figure 2: Changes in guidelines regarding contrast media.

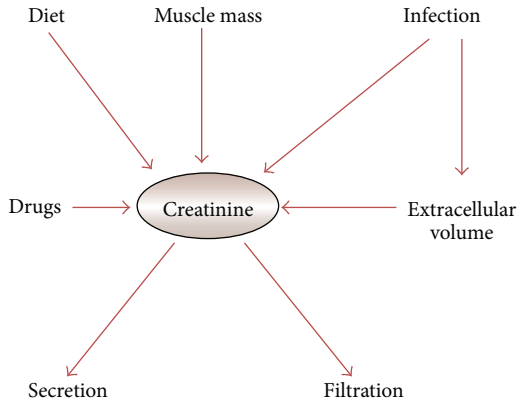

Figure 3: Factors that can perturb creatinine determination.

2.5.2. Surrogate versus Endpoint. Over 60% of contrast-media-induced mortality is not caused by allergic reactions but by renal failure. If serum creatinine is increased over 0.5 mg/dL for one or two months, only 20% of the patients survive 4 years, indicating that serum creatinine is a very important prognostic factor [12].

Studies investigating contrast-induced acute kidney injury usually focus on minute changes of serum creatinine as an endpoint. Changes in serum creatinine can occur in response to several factors (Figure 3). More robust endpoints such as clinically relevant acute kidney injury diagnosed by an expert, dialysis, or mortality are usually not used, since very many patient observations would be required.

2.5.3. CIN, a Rare Event. In one of the biggest studies regarding CIN with 562 patients, different levels of creatinine increase were compared [13]. When using the most robust endpoint (>50% increase), only one patient was identified as having CIN. An increase of serum creatinine over 50% can be considered as the more robust endpoint used in comparing the effects of contrast media. This is because the threshold is higher than the other commonly used endpoints. Thus, artifacts due to arbitrary changes in serum creatinine are less likely to occur. When using the lower cutoff of 25% increase in serum creatinine, CIN detection was very much higher. But the lower the increase in serum creatinine is the weaker the endpoint definition resulting in a higher incidence of CIN is and data become hardly interpretable.

2.5.4. Lack of Control Groups. One other reason why studies regarding CIN might be biased is the lack of control groups, which is caused by the obvious ethical reasons. Controls are mainly hospital based; patients who received contrast media were age, gender, and morbidity matched with patients who did not receive contrast media. In one study by Newhouse et al., patients who were comparable to patients receiving contrast media, but, did not receive contrast media, were studied to compare creatinine kinetics [14]. In comparison, creatinine increases above the different levels of CIN definitions occur to an equal percentage in patients receiving and not receiving contrast media (Figure 4).

2.6. Mechanism behind CIN. Contrast media are freely filtrated in the glomeruli but can develop a high viscosity. In the kidney, fluids are concentrated up to 100-fold during elimination, and thus, contrast media are accumulated 100-fold (Figure 5). Urine viscosity after application of contrast media was measured by our study group using a viscometer. The resulting viscosity after IOCM were given is extremely high [15] and comparable to the viscosity of maple syrup. High viscosity results in a very high pressure and reduces flow in tubules and vessels, and filtration is impaired up to a filtration arrest. This is comparable to the pathomechanism in rhabdomyolysis.

Fortunately, the increase in viscosity in the glomeruli can be avoided very easily by adequate hydration which aims to reduce the concentration of contrast media. For cardiologists, this can be challenging, especially in patients with heart failure since a decision has to be made between heart and kidney!

2.7. Hydration Lowers Incidence of CIN. The most common risk factor for CIN is dehydration. Thus, every study participant needs to be hydrated adequately because other study

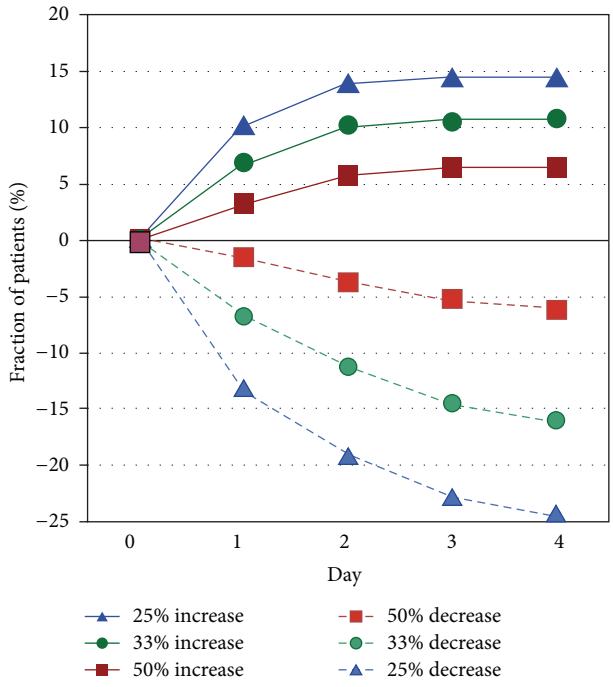

FIGURE 4: Changes of serum creatinine in hospital patients not receiving contrast media [14].

designs would be unethical. The disadvantage from a statistical perspective is that the incidence of cases will become very low, when patients are adequately hydrated. Thus, thousands of patients have to be investigated to study CIN. This is not possible in prospective, controlled trials. Thus, prospective, controlled trials often use weaker endpoints and therefore do not provide much insight into the actual occurrence of clinically relevant CIN. In many clinical settings, adequate hydration is not always possible. These real-world situations are not reflected by the prospect is randomized trials available on CIN. The effectiveness of hydration was recently demonstrated by Balemans et al. In their study, hydration was very effective in CIN prevention [16]. The frequency of CIN was almost the same in the low-risk group as compared to the high-risk group after adequate hydration.

A Swedish research group and I conducted a retrospective study with 57,925 patients in Sweden and compared the incidence of CIN at discharge after cardiac catheterization was conducted in patients with STEMI and NSTEMI receiving either IOCM or LOCM [17] (Figure 6). The hydration scheme of these patients was under usual clinical conditions; no uniform hydration protocol existed, and it can be assumed that several patients were not adequately hydrated. Clinically relevant renal failure was diagnosed by the treating physician and not defined by a serum creatinine increase only. In this study, the incidence of clinically relevant renal failure was three times higher in patients who were treated with IOCM. The incidence is still quite small, and that is the reason why it is impossible to study CIN in a few hundred persons.

A comparable study was conducted in Michigan, where 58,000 patients were studied [18]. In the raw data, the results were the same as shown above, but after adjustment to certain risk factors, the differences diminished. Deductively, IOCM do not seem to have any advantage over LOCM.

2.8. Sponsor Bias. As many of the clinical studies on contrast media are sponsored by the pharmaceutical companies producing them, sponsor bias should also be considered. Conflict of interests may cause delayed publication.

3. Discussion

Hydration is effective in minimizing the risk for CIN during coronary angiography. If the patient is well hydrated, IOCM can be used without any disadvantage—but also without any benefit for the kidney. In the case of an unknown hydration status, which is usually the case in emergency situations, LOCM should be preferred. LOCM bind a higher amount of water compared to IOCM and thus cannot be concentrated in the kidney as much as seen for IOCM. In conclusion, LOCM monomers should be preferably used when the status of hydration or kidney function is unclear. Considering the fact that the relation between viscosity and concentration is exponential, a critical viscosity is rapidly attained.

In CIN, injury occurs not only on the tubular side of the kidney, but also on the vascular side [15]. Vascular concentration of contrast medium leads to injuries of the endothelium and causes oxidative stress. Free oxygen radicals can bind nitric oxide and in consequence vasa recta (the vessels supplying the area at risk) constrict [15]. Some pharmaceutics like acetylcysteine and sodium bicarbonate are meant to neutralize those free oxygen radicals, but a sufficient concentration of these substances will be hardly achieved. Sodium bicarbonate is almost completely reabsorbed in the proximal tubules and do not reach the place of injury. If instead sodium chloride is supplemented, at least 30% dilution of contrast media is achieved in the kidney. Current meta-analyses show no evidence for a benefit of acetylcysteine or sodium bicarbonate over hydration only.

Transition of guidelines and recommendations for hydration into clinical reality can be challenging. Guidelines recommend administering infusions 12 hours prior to the procedure, which is often not possible in clinical routine. From the pathophysiological perspective, hydration leads to a lower concentration of contrast medium in the collecting ducts of the kidney due to the diminished release of the antidiuretic hormone (vasopressin) from the posterior lobe of the pituitary gland. The same effect can be achieved very effectively within 20 minutes by drinking tap water. Sodium chloride should be used to maintain hydration during the examination because it remains in the vessels for a longer period of time, but the effect of oral hydration with tap water is faster than iso-osmolar sodium chloride administration before the procedure.

Patients with heart failure and cardiac decompensation pose a clinical challenge to cardiologists. Those patients seem to be "overhydrated," and water retention occurs by aldosterone release. This leads to an iso-osmolar volume expansion, and thus, even in those patients, the drinking of tap water may be preventive. Cardiologists have to decide

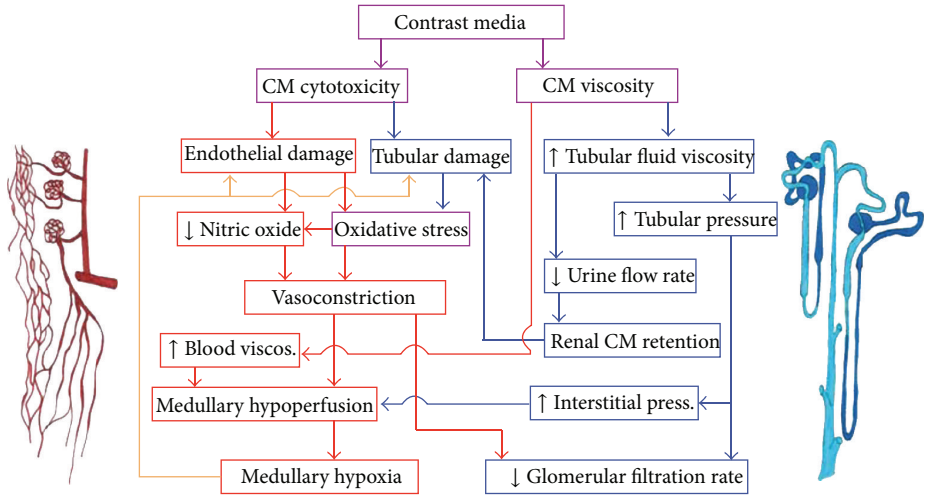

Figure 5: Mechanisms that can lead to contrast-induced acute kidney injury. Damage can occur either from the vascular side or from the tubular network. Reprinted by permission of European Society of Cardiology [15].

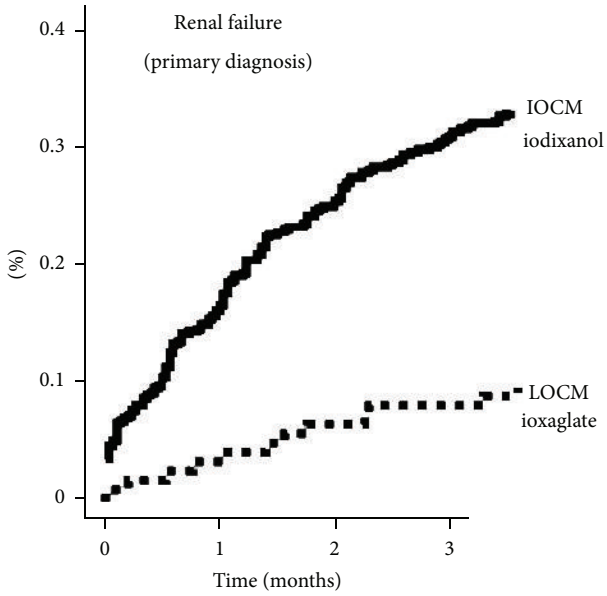

Figure 6: Renal failure in patients perceiving contrast media. This study with many observations was retrospective. In contrast to previous studies, the observations referred to real-life conditions; that is, there was no uniform hydration regime or protocol. Reprinted by permission from Macmillan Publishers Ltd: Kidney International [17] copyright 2013.

whether a patient is stable enough to be orally hydrated or not; for the kidney, this will usually be a benefit.

4. Conclusions

Creatinine has been overestimated as a marker of kidney injury after contrast media exposure. Several studies on the differential safety of IOCM and LOCM need to be interpreted with caution. Due to the limited evidence, guidelines underwent rapid changes in the past, but lately all international publications no longer prefer a specific IOCM over LOCM. In fact, due to pathophysiological data, LOCM should be preferred whenever kidney, or hydration, status is unknown, for example, in all emergency situations. The most data-based prophylactic measure is hydration which should be performed in all patients undergoing contrast-media-based examinations.

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