Contrast-induced nephropathy (CIN) in the actual essence of the term refers to renal damage induced by a contrast medium. The ultimate clinical manifestation of CIN is renal failure requiring dialysis, and this article will concentrate on CIN as a clinical outcome. However, transient rises in serum creatinine have been frequently used as a surrogate marker that is suggested to predict renal failure, and these transient rises are usually also termed CIN. The definition and the pitfalls of this surrogate marker will also be part of this review, but in order to maintain a clear nomenclature the focus will be on CIN as a clinical outcome in coronary intervention. This article will also discuss the effectiveness of proposed strategies for prophylaxis of CIN.

Incidence of Actual Renal Failure in Coronary Intervention

The incidence of renal failure requiring dialysis following coronary intervention is very low, amounting to 0.1–0.5%.1,2 The incidence is higher in risk patients, i.e. patients with pre-existing chronic kidney disease, increasing to 1% in high-risk patients and up to 13% in very high-risk patients.1 What needs to be appreciated, however, is that not all cases of renal failure requiring dialysis after coronary intervention are actually caused by the administered contrast medium. In fact, there are several other possible causes for such an event, e.g. atheroemboli or other procedural-related causes, as well as procedure-unrelated progress of disease in risk patients. Still, renal failure requiring dialysis is a serious complication after percutaneous coronary intervention (PCI) associated with a significantly poorer prognosis for the respective patient, which is to be avoided as much as possible.

Pathophysiology of Contrast-induced Nephropathy

The pathophysiology of CIN is not completely understood, but it is certain to involve the interplay of multiple factors leading to hypoxia of the outer medulla.1 Several characteristics of contrast media (CM) have been suggested as possible causes of CIN, e.g. osmolality, direct tubular cytotoxicity, and, more recently, viscosity.

The role of one of these factors, osmolality, may have been over-interpreted. A widespread explanation for the development of CIN is that hyperosmotic CM cause diuresis, which activates tubuloglomerular feedback and subsequently compromises renal blood flow and glomerular filtration. However, this theory is not a likely explanation for CIN, as pioneering animal experiments have already shown that osmolality has no effect on tubuloglomerular feedback.4

Animal experiments have demonstrated that direct toxic effects on the tubular cells occur with all CM, but to varying degrees. Opinion varies as to the pathophysiological relevance of the direct effects of CM on tubular cells, but it seems likely that these effects do play a role in the development of CIN.4

The viscosity of CM is probably the most relevant characteristic for the pathophysiology of CIN.5 The viscosity of CM may in fact increase the viscosity of tubular fluid such that tubular resistance and renal interstitial pressure are increased, which will ultimately result in reduced renal medullary flow. This in turn results in a fall in the glomerular filtration rate (GFR).

Prophylaxis of Contrast-induced Nephropathy—How Are Preventive Strategies Validated?

Usually, preventive strategies should be validated in clinical trials. Randomized, controlled clinical trials looking for the hard, patient-outcome end-point of CIN—i.e. renal failure requiring dialysis—would require very high numbers of patients well beyond the scope and budget of a regular clinical trial, as the incidence of the event is very low. Clinical studies on CIN therefore usually measure a surrogate end-point for renal failure. One definition describes this surrogate as a relative increase of serum creatinine ≥25% or an absolute increase of serum creatinine ≥0.5mg/dl within 72 hours post-contrast-enhanced intervention.5 The incidence of this...
Contrast-induced Nephropathy in Coronary Intervention

surrogate CIN is much higher than true CIN, amounting to 10–50% depending on the indication and risk profile of the patients. However, this surrogate marker has not been validated, although there is evidence that serum creatinine increases are a marker for increased morbidity and mortality. The surrogate definition of CIN—maybe partly due to the lack of validation—is neither universally accepted nor universally employed. Some key CIN trials have used variations of this definition regarding both the increase in serum creatinine and the time-frame of observation.

The surrogate definition of CIN employing serum creatinine has some serious limitations, which are not fully appreciated in the vast CIN-pertaining literature. Serum creatinine is in itself a poor marker for renal function. More importantly, the lack of consistency of the application of the surrogate definition of CIN considerably hampers the interpretation of results across trials or even within one trial if several definitions are used. Spurious effects on serum creatinine are the least known and least appreciated limitation of the CIN surrogate marker, although it may have grave consequences for the interpretation of study data. Serum creatinine is employed as a surrogate marker for the GFR. However, overall renal creatinine excretion is, in addition to the quantitatively more important glomerular filtration, also achieved by tubular secretion. Iodinated CM might interfere with the tubular excretion, leading to an increase of serum creatinine and feigning a decrease of GFR. This spurious interference can have several consequences: it can inflate or decrease the incidence of surrogate CIN considerably, and it might even feign differences between, for example, different contrast agents if interference with tubular excretion varies between those agents.

Given the limitation of the surrogate marker as outlined above, any prophylactic strategy for CIN (i.e. choice of contrast agent and additional pharmacological measures) that is not within the scope of good medical practice/common sense, should not be recommended for clinical routine unless the effectiveness has been demonstrated in studies using hard clinical outcomes as end-points.

The Controversy Around the Osmolality of Iodinated Contrast Agents

Classes of iodinated contrast agents vary in terms of their osmolality, viscosity, and chemical structure. The first generation of CM had about seven-fold greater osmolalities than blood and were subsequently termed high-osmolar CM (HOCM). The viscosity of these ionic monomers was, however, very close to normal blood viscosity. The rate of adverse events with this class of compounds is considerable and significantly higher than that of the next generation of low-osmolar CM (LOCM), and it was widely assumed that the key feature in this switch was the reduction of osmolarity to twice that of blood. Renal tolerance of LOCM in risk patients is also higher compared with ionic HOCM, but this is most likely much more related to the reduced chemotoxicity of the compounds than to the reduced osmolality. Ionic HOCM have been substituted by LOCM in the vast majority of indications and patients in highly industrialized countries.

LOCM achieved a reduction of osmolality while maintaining favorably low viscosity values. These new compounds are non-ionic monomers, such as iohexol (Omnipaque®, GE Healthcare), iopamidol (Isovue®, Bracco), lopromide (Ultravist®, Bayer Schering Pharma), or ioversol (Optiray®, Tyco). LOCM are remarkably well-tolerated substances and have been administered in well over 500 million patients globally.

In the quest to further reduce osmolality, a new class of CM—termed iso-osmolar CM (IOCM)—was created in the mid-1990s, which achieved iso-osmolality by creating a non-ionic dimeric structure; however, this came at the price of a considerably increased viscosity at similar iodine concentration. Iodixanol (Visipaque™, GE Health) is today the only representative of this class for intravascular use on the market.

Since the publication of the NEPHRIC trial—a hypothesis-generating trial in 129 patients—in early 2003, which claimed better renal tolerance of IOCM over LOCM in high-risk patients, there has been an ongoing intense debate as to whether IOCM indeed have a better renal tolerance than do the established LOCM. As of mid-2007, the NEPHRIC study results have not been truly confirmed in any of the conducted clinical trials. Only one randomized, controlled study claims, despite its results, to support the NEPHRIC findings; on the other hand, five studies of similar design and size found no significant differences in favor of iodixanol.

As outlined above, clinical trials employing the surrogate definition of CIN are of limited value. Registry studies that look for hard clinical end-points in a large enough number of patients are much more appropriate to elucidate this scientific discussion. The results of the Swedish registry study, which included data on over 57,000 patients undergoing coronary intervention, strongly indicate that high-viscous, iso-osmolar iodixanol shows no better renal safety than contrast agents with combined low osmolality and low viscosity. In fact, the study results suggest that the opposite might be the case, in line with the hypothesis that higher viscosity of CM is associated with an inferior renal tolerance.

The volume of contrast media, particularly for high-risk patients, should be the minimum amount needed for diagnosis and intervention.

Recommendations For Prophylaxis of Contrast-induced Nephropathy

Due to the high scientific interest in CIN there are by now countless recommendations and guidelines on how to avoid or reduce the incidence of CIN. All guidelines, however, agree on the following prophylactic measures.
**Contrast-induced Nephropathy**

The most immediate task for the physician is to identify the patients at risk. The key risk factor is the degree to which the patient’s renal function is impaired. This is usually identified by assessing serum creatinine levels, preferably by estimating creatinine clearance using, for example, the modification of diet in renal disease (MDRD) formula. Other risk factors, such as diabetes, hypertension, heart failure, myeloma, and treatment with nephrotoxic drugs, also need to be considered. In the presence of risk factors, a careful risk–benefit analysis must be performed, although the number of alternatives in case of need of coronary intervention might be limited. If the coronary intervention is warranted, patients should be in an optimal volume status at the time of contrast exposure. Although there is no consensus as to how ‘optimal volume status’ is defined, dehydration is a clear risk factor for coronary intervention, and hydration is thus the key prophylactic measure. To minimize the risk, patients should be encouraged to drink water liberally during the 12 hours before receiving the contrast media. For inpatients, intravenous (IV) volume expansion prior to contrast exposure should be considered; however, the specific degree of volume expansion will depend on individual patient characteristics.

With regard to renal safety, LOCM should be used in all patients. The volume of contrast media, particularly for high-risk patients, should be the minimum amount needed for diagnosis and intervention. Drugs with an adverse effect on renal function should be withheld prior to and immediately after contrast exposure, provided that this does not place the patient at an increased risk. There is currently no compelling evidence that any additional prophylactic strategy, such as N-Acetylcysteine or sodium bicarbonate, is of additional value.

Summarizing the recommendations, it is fair to say that unfortunately there is no easy recipe to prevent CIN; however, there is a set of measures that, when adapted by the physician according to the individual patient’s needs, will reduce the likelihood of the occurrence of CIN. A recent publication by Mosucci et al. impressively confirms this strategy. In a large-scale registry study involving different PCI centers, a comprehensive set of continuously evaluated and updated quality measures—which included stringent hydration and reduction of dose of CIN—resulted in a significant reduction of the rate of adverse outcomes compared with historical controls as well as with centers that did not implement this set of continuous quality measures; these outcomes included, but were not restricted to, renal failure requiring dialysis. The study by Mosucci et al. confirms that, although there is no easy solution for CIN, comprehensive, patient-oriented best clinical practice approaches do result in significant benefits for the patients.

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