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Review

Endothelial safety of radiological contrast media: Why being concerned

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ABSTRACT

Iodinated radiocontrast media have been the most widely used pharmaceuticals for intravascular administration in diagnostic and interventional angiographic procedures. Although they are regarded as relatively safe drugs and vascular biocompatibility of contrast media has been progressively improved, severe adverse reactions may occur, among which acute nephropathy is one of the most clinically significant complications after intravascular administration of contrast media and a powerful predictor of poor early and long-term outcomes. Since radiocontrast media are given through the arterial or the venous circulation in vascular procedures, morphological and functional changes of the microvascular and macrovascular endothelial cells substantially contribute to the pathogenesis of organ-specific and systemic adverse reactions of contrast media. Endothelial toxicity of contrast media seems to be the result of both direct proapoptotic effects and morphological derangements, as well as endothelial dysfunction and induction of inflammation, oxidative stress, thrombosis, and altered vasomotor balance, with predominant vasoconstrictive response in atherosclerotic coronary arteries and kidney microcirculation. Further understanding of pathogenetic mechanisms underlying contrast media-induced adverse reactions in cellular targets, including endothelial cells, will hopefully lead to the development of novel preventive strategies appropriately curbing the pathogenesis of contrast media vasotoxicity.

Contents

1. Introduction

Contemporary medicine relies heavily on radiological angiographic procedures for diagnostic or interventional purposes. Since their introduction in the 1950s, iodinated radiocontrast media (CM) have been the most widely used pharmaceuticals for intravascular administration. The increasing number of angiographic examinations using CM in clinical practice and the relatively high amounts of CM used in the single procedures have raised critical concerns about their safety profile.

In fact, CM are not biologically inert. They can cause in-hospital and long-term adverse reactions, which vary from mild and self-limiting disturbances to rare severe life-threatening events. In this regard, the recognition of acute nephropathy as one of the most clinically important complications after an intravascular CM administration in patients with reduced renal function has spurred numerous experimental and clinical studies and a vast literature on CM safety aspects. In particular, since CM are given through the arterial or the venous circulation in diagnostic and interventional vascular procedures, these agents may affect microvascular as well as macrovascular endothelium, thus substantially contributing to the pathogenesis of organ-specific and systemic adverse reactions of CM (Aspelin et al., 2006). Therefore, in the last decades safety aspects of CM for the endothelium have drawn much attention in the scientific literature. The study by Ronda et al. published in the current issue of *Vascular Pharmacology* (2012, reference to be completed by the

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Publisher) provides novel insights into the potential mechanisms of direct CM toxicity for vascular endothelial cells, and supports the protective role of some pharmacological interventions, namely treatment with N-acetylcysteine (NAC) or statins, against such disturbances. We will here briefly review CM effects on endothelial cell morphology and function after a brief description of CM properties and the pathogenesis of their adverse reactions, with a special focus on contrast-induced nephropathy (CIN).

2. Properties of iodinated contrast media

All iodine-based CM are tri-iodinated benzene derivatives that rely on iodine for their radio-opacity, and are characterized by low-molecular weight, water solubility, and low protein-binding (Sandler, 2003). They are classified according to their osmolality (high-, low- or iso-osmolal), ionicity (ionic *vs* non-ionic), viscosity, and the number of benzene rings (monomers and dimers). Development of new CM over the last decades has aimed at reducing their chemotoxicity and osmotoxicity. The *first-generation* or conventional CM (diatrizoate, iothalamate, metrizoate) are ionic monomers with the first carbon of the benzene ring occupied by an ionizing carboxyl group, and are therefore extremely hyperosmolar relative to plasma (about 2000 mOsm/L, high-osmolar CM, HOCM). Developed in the late 1960s, the *second-generation* CM are either ionic dimers (ioxaglate) or non-ionic monomers (iohexol, ioversol, iopamidol, iopromide, iomeprol), with increased hydrophilicity. These compounds are referred to as "low-osmolar" CM (LOCM) with an osmolality lower than that of first-generation agents but still higher relative to plasma (about 400–800 mOsm/L). The *third-generation* CM (iodixanol, iotrol) are dimers of two benzene rings and are virtually iso-osmolar (IOCM) to plasma (290 mOsm/L) (Sandler, 2003). However, the low osmolality of IOCM came at the price of increased viscosity, which may represent a disadvantage in terms of biocompatibility (Seeliger et al., 2012) as well as for the procedural technique during angiography (higher resistance to catheter injection). To achieve adequate contrast, large volumes of highly concentrated CM (about 250–400 mg of iodine/mL) are often injected intravenously or intra-arterially. After injection, they rapidly distribute in the vascular and extravascular compartments, being eliminated unmetabolized mainly *via* renal excretion within the first 24 h, without tubular reabsorption. The elimination half-life (1–2 h in normal condition) increases with an increasing renal impairment, even in patients with mild renal impairment. It has been estimated that the maximum plasma concentration following a diagnostic dose occurs immediately after the intravascular injection and falls rapidly after 5–10 min (Rosati, 1994). Some studies have also documented CM cellular intake *via* pinocytosis (Nordby et al., 1990).

CM exert organ-specific (*e.g.*, renal, cardiac) and systemic effects, the latter induce changes in the functional properties of blood constituents (platelets, leukocytes, erythrocytes) and of the endothelium. Systemic effects include, among others, direct cellular toxicity, thrombosis, hemodynamic changes (vasoconstriction/vasodilatation), as well as changes in blood rheology, and are thought to be caused by the chemical nature of CM, their electrical charge (chemotoxicity), viscosity and osmolality, although a contribution by pharmaceutical excipients and pH cannot be ruled out (Aspelin et al., 2006). Ionicity of HOCM has been particularly involved in toxic reactions and may influence membrane integrity, hemocompatibility (inhibition of blood coagulation and platelet function), electrolyte balance, nerve conduction and cardiac performance. Although the marked anticoagulant and antiplatelet properties of ionic CM might be advantageous in preventing thrombosis in the setting of coronary interventional procedures, clinical data found no significant difference between ionic and non-ionic CM with regard to major cardiac events, with non-ionic CM featuring better vascular biocompatibility, and a lower incidence of hypersensitivity and adverse reactions (Bertrand et al., 2000). Therefore, given their clinically-proven greater tolerability and safety profile, non-ionic LOCM and IOCM are gradually replacing ionic HOCM in current routine practice.

3. Contrast-induced nephropathy: pathogenesis and impact of iodinated contrast media

CIN (otherwise called contrast-related acute kidney injury — AKI) is the leading life-threatening side effect following the intravascular administration of CM, and is a form of an acute kidney injury. It is the third most common cause of in-hospital acute renal failure (12%), with an incidence of 2–25% after percutaneous coronary interventions (PCI) (Perrin et al., 2012). Most authors define CIN as a relative ($\geq$25%) or an absolute ($\geq$0.5 mg/dL) rise in serum creatinine, a surrogate marker for glomerular filtration rate, at 48 h after CM exposure (Perrin et al., 2012). Patients at risk for CIN have co-morbidities, including diabetes mellitus, chronic kidney disease, acute hypotension, heart failure, advanced age, anemia, and often feature the concomitant use of nephrotoxic drugs. Procedural issues, such as the total amount and type of CM administered, and its route of administration (arterial *vs* venous), are additional risk factors for CIN (Perrin et al., 2012). In most cases, CIN is transient and free of clinically significant consequences, although an irreversible deterioration or even complete loss of renal function may rarely occur. The importance of preventing CIN is supported by a growing body of evidence demonstrating a clinically significant association of CIN with poor short- and long-term outcomes, including death, stroke, myocardial infarction, end-stage renal disease, as well as increased costs and hospital stay (Solomon et al., 2009).

The pathogenesis of CIN is multifactorial and still incompletely understood. Current understanding of CIN pathophysiology suggests a complex interaction between vascular and tubular effects of CM, thus making it unlikely that a single preventive intervention is successful. A combination of direct cytotoxicity, renal medullary hypoxia resulting from renal vasoconstriction, rheological changes of hemodynamics and tubulodynamics, as well as inflammation and endothelial dysfunction have been implicated (Seeliger et al., 2012). The relative importance of such mechanisms varies with the CM used, the kind and degree of pre-existing individual risk factors, and the patient's hydration status (Seeliger et al., 2012).

CM direct cytotoxicity, resulting in apoptosis/necrosis of renal tubular cells and vascular endothelial cells, has been well documented in both *in vitro* and *in vivo* studies, where ionic HOCM feature the highest toxicity (Ramponi et al., 2007; Hsu et al., 2010; Wu et al., 2010). With regard to the vasoactive effects of CM, while most vascular beds respond to CM primarily with vasodilatation (Morcos et al., 1998; Limbruno et al., 2000), it has been demonstrated that CM administration induces a biphasic response in renal hemodynamics, characterized by an initial transient increase in renal blood flow, followed by a 50% sustained reduction in renal blood flow (Seeliger et al., 2012). These hemodynamic changes are probably the result of several mechanisms, including: a) an increase in intratubular pressure, leading to raised interstitial pressure and compression of the vasa recta, thus decreasing renal blood flow; b) an increase in tubular osmotic load, causing diuresis and natriuresis that stimulate the macula densa to release adenosine, resulting in vasoconstriction of the afferent arteriole by a tubule-glomerular feedback; c) a direct vasoconstrictive effect of CM, for effects on smooth muscle cells; and d) an unbalanced production of endothelium-dependent vasoactive substances in both the cortex and the medulla (see below), resulting from endothelial dysfunction (Seeliger et al., 2012). Perturbations of erythrocyte shape and deformability probably contribute to medullary hypoperfusion (Aspelin et al., 2006).

It has also been proposed that oxidative stress, *i.e.*, an unbalanced relative overproduction of reactive oxygen species (ROS), is an important contributor to the pathogenesis of CIN (Heyman et al., 2010). Animal and human studies have shown increased levels of oxidative stress markers after CM administration (Bakris et al., 1990; Fiaccadori et al., 2004), and the beneficial effect of antioxidants, including NAC, for CIN prevention, supporting ROS-mediated mechanisms in the pathogenesis of CIN (Drager et al., 2004). ROS generation, presumably in endothelial and tubular cells, during CM-induced renal hypoxia as well as during

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the reoxygenation of the diseased artery may be exacerbated by most of the risk factors for CIN, mainly diabetes, chronic kidney disease, and atherosclerosis (Heyman et al., 2010), which are characterized by ROS overproduction, compromising homeostatic mechanisms and predisposing to a higher susceptibility to CM-induced injury. Once formed, ROS may trigger vasoconstriction, direct vascular endothelial and tubular injuries, and hence endothelial dysfunction and dysregulation of tubular transport, intensifying renal tissue hypoxia (Heyman et al., 2010).

All commercially available CM can cause CIN, with different pathophysiological impact of osmolality, viscosity, ionicity, and the amount of administered CM. Clinical trials comparing HOCM with LOCM indicated a statistically significant benefit for LOCM (<800 mOsm/L) in terms of renal function only among patients with pre-existing renal dysfunction (Barrett and Carlisle, 1993). The development of IOCM raised hope for an even further reduction in the risk of CIN. In fact, the pioneering study by Aspelin et al. (2003) reported significantly fewer nephrotoxic effects of iodixanol, an IOCM, compared with iohexol, a LOCM, in a small group of high-risk patients undergoing arteriography. However, recent meta-analyses have produced conflicting results. On the one hand, some studies have apparently confirmed a significant advantage of IOCM, in particular iodixanol, only when compared with ioxaglate, an ionic LOCM, and iohexol (a non-ionic LOCM), but not in comparison with other LOCM (From et al., 2010). IOCM indeed feature iso-osmolality at the price of higher viscosity, the latter also playing a role in the pathophysiology of CIN, especially in patients not sufficiently hydrated (Seeliger et al., 2012). On the other hand, another meta-analysis has raised the possibility of iodixanol superiority over a pool of LOCM in the interventional cardiology setting (Dong et al., 2012). Therefore, the verdict on this subject still remains open.

4. Effects of contrast media on endothelial cell morphology

The alteration of endothelial cell morphology and physical integrity due to apoptotic/necrotic processes contributes to altered vascular homeostasis, including pro-coagulant and pro-thrombotic properties, as well as changes in permeability and tone, vessel growth and angiogenesis. Although CM biocompatibility has been progressively improved, all currently available CM still have some direct cytotoxicity, which is probably caused not only by iodine, but also by specific physico-chemical properties, such as osmolality, viscosity and ionic strength (Sendeski, 2011). In general, from *in vitro* and *in vivo* studies, it appears that iodinated CM may directly injure glomerular and vascular endothelial cells in a time- and concentration-dependent manner, by inducing cytotoxic, cytostatic and pro-apoptotic effects, as documented by morphological changes (shrinkage, swelling, detachment) (Franke et al., 2008), as well as changes in the indices of apoptosis/necrosis and cell proliferation (Zhang et al., 1999, 2000; Ramponi et al., 2007; Zhao et al., 2009) (Fig. 1). Hyperosmolality has been proposed to significantly contribute to cell injury. Some *in vitro* studies found that HOCM as well as hyperosmotic mannitol solution caused cell shrinkage and prominent pro-apoptotic and cytostatic effects on cultured endothelial cells even after a 1-minute exposure (Zhang et al., 2000). Potential contributory mechanisms include activation of tyrosine and stress kinases, elevation of intracellular calcium (Malek et al., 1998), and the regulation of apoptosis-related proteins, including increased levels of p53 and Bax (pro-apoptotic) and decreased Bcl-2 (anti-apoptotic) (Zhang et al., 1999). Supportively, HOCM have been associated with a greater risk for CIN than LOCM in clinical practice (Barrett and Carlisle, 1993). However, it has been increasingly clear that high osmolality is not the only factor in

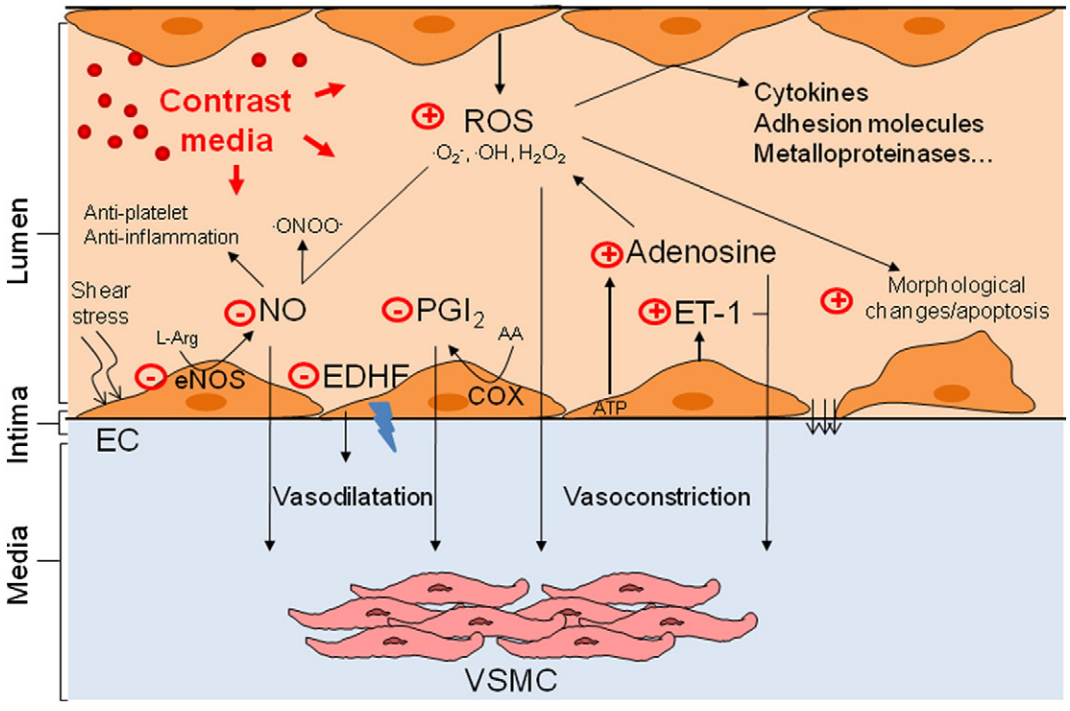

Fig. 1. Effects of contrast media on endothelial cells with relevance to vascular and renal dysfunctions. Intravascular contrast media (CM) administration can induce specific patterns of morphological changes in endothelial cells, including partial cell–cell and cell–matrix detachment and bulging, which may be accompanied by apoptosis. In addition to decreasing NO synthesis through inhibition of eNOS activity and expression, CM can induce endothelial dysfunction and inflammatory responses *via* ROS generation (directly or through adenosine catabolism), which further reduces NO bioavailability by uncoupling eNOS and directly scavenging NO. CM also decrease PGI_2 and EDHF releases, while also increasing ET-1 and adenosine releases, thus tipping the vasomotor balance toward vasoconstriction, particularly in the kidney and in atherosclerotic coronary arteries in the presence of CAD. Plus and minus signs indicate induction and inhibition by CM, respectively. AA = arachidonic acid; ATP = adenosine triphosphate; CAD = coronary artery disease; COX = cyclooxygenase; EC = endothelial cells; EDHF = endothelium-derived hyperpolarizing factor; eNOS = endothelial nitric oxide synthase; ET-1 = endothelin-1; NO = nitric oxide; ONOO = peroxynitrite; PGI_2 = prostacyclin; ROS = reactive oxygen species; VSMC = vascular smooth muscle cells.

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endothelial injury by iodinated CM, where ionicity may also play a significant role through mechanisms involving cell membrane damage and interference with enzymes, through CM binding to proteins and lipids. In this regard, it has been shown that, at comparable osmolality, ionic agents can acutely induce more marked morphological alterations and cytostatic or cytotoxic effects in endothelial cells than non-ionic ones (Morgan and Bettmann, 1989; Ramponi et al., 2007). Ionic CM-induced endothelial injury has also been associated with increased platelet depositions in an isolated perfused rabbit carotid artery model, with possible relevance to coronary interventions, specifically with regard to acute vessel occlusion and chronic restenosis (Riemann et al., 1993). *In vitro* data reported some inhibitory effects on endothelial cell viability also for non-ionic LOCM and IOCM agents, including iodixanol (Ramponi et al., 2007), but these effects were generally observed only after prolonged exposure (24 h) to a high concentration (100 mg/mL) of CM, which is reached immediately after intravascular injection and just for few minutes in the vascular compartment. Whether the reported endothelial cell apoptosis occurs through the induction of ROS via the activation of the intrinsic/mitochondrial pathway of apoptosis, as already reported in renal epithelial cells (Quintavalle et al., 2011), has not been well elucidated yet. However, *in vivo* data found no significant changes in endothelial cell morphology and signs of apoptosis after the intravascular administration of non-ionic agents, particularly iso-osmolar dimers including iodixanol (Zhao et al., 2011), which thus appears to feature better endothelial biocompatibility.

5. Endothelial cell function and dysfunction: a contributing role to contrast agent-induced adverse reactions

The endothelium is now recognized as a crucial homeostatic organ, fundamental for the regulation of vascular structure and function. Physiologically, the endothelium contributes to vascular homeostasis acting at different levels: maintaining a relaxed vascular tone, primarily by the regulated secretion (and clearance) of powerful vasoactive mediators, such as the vasodilators nitric oxide (NO), prostacyclin (PGI_2), endothelium-dependent hyperpolarizing factor (EDHF), and the vasoconstrictor endothelin (ET)-1; tightly regulating vascular permeability, smooth muscle cell growth/migration, platelet adhesion and aggregation, leukocyte infiltration and thrombosis (De Caterina et al., 2007; Deanfield et al., 2007). However, in response to noxious stimuli, including inflammatory, oxidative and metabolic triggers, the endothelium may undergo phenotypic modulation to a non-adaptive state, a condition referred to as "endothelial dysfunction", characterized by the loss or dysregulation of critical homeostatic mechanisms and the acquisition of a pro-adhesive, pro-inflammatory/mitogenic and pro-thrombotic phenotypes, increased oxidative stress, and abnormal modulation of vasoactive pathways, leading to different clinical manifestations, including – but not limited to – impaired endothelium-dependent vasodilatation (De Caterina et al., 2007; Deanfield et al., 2007). The endothelium plays an important early role in the inflammatory responses by promoting tissue accumulation/activation of leukocytes through increased expression of adhesion molecules, chemoattractants and cytokines, mainly through the activation of redox-sensitive transcription factors including nuclear factor (NF)-κB. Interestingly, microvasculopathy with functionally altered endothelial cells and interstitial inflammation are hallmarks of ischemic AKI, and inhibition of NF-κB by intrarenal transfection of decoy oligonucleotides resulted in attenuated ischemic AKI (Devarajan, 2006). Vascular inflammation and thrombotic complications after intravascular administration of CM may be clinically relevant in PCI, procedures that invariably damage the endothelium. The risk of thrombosis induced by CM may be accounted for by a combined effects on platelets, endothelial cells, and coagulation factors. However, since, in general, CM display antiplatelet and anticoagulant properties, thrombotic complications may be mainly attributable to CM-induced endothelial dysfunction. To this regard, CM influence on some markers of endothelial activation, inflammation and thrombogenicity, including leukocyte adhesion molecules, cytokines, and von Willebrand Factor (vWF), has been little investigated (Fauser et al., 2001). A human study reported an acute increase in serum von Willebrand Factor (vWF) following CM injection (Blann et al., 2001). An increased NF-κB activation and cytokine release has been found in cultured epithelial cells after CM treatment (Andreucci et al., 2011), leading to the hypothesis that similar direct proinflammatory pathways might be operative also in endothelial cells.

Routinely used CM have complex vasoactive effects with iso-osmolar dimers inducing the smallest changes in vascular tone (Morcos et al., 1998). The hemodynamic effects of CM certainty involve actions on the heart and vascular smooth muscle cells (Morcos et al., 1998), but it is also reasonable to expect actions through the endothelium *via* the modulation in the production of vasoactive substances, given the direct exposure of the endothelium to locally high concentrations of CM (Fig. 1). The mechanisms responsible for contrast-induced vasomotor changes are not fully elucidated. They are likely to be multifactorial, and attributable to hyperosmolality, chemotoxicity, ion content of the medium, and flow-mediated changes in vascular tone (Morcos et al., 1998). Both vasoconstriction and vasodilatation can be observed after iodinated CM injection, with the only exception of the kidney where vasoconstriction appears to predominate (Morcos et al., 1998). Most often, vasodilatation is observed in peripheral vascular beds, contributing to the sensation of warmth and even pain following CM injection. A direct endothelium-independent action on vascular smooth muscle cells has been shown to play a role in mediating non-ionic CM-induced vasodilatation in pulmonary as well as peripheral circulation, by modulating ion exchange mechanisms and transport systems, as demonstrated in isolated rat pulmonary arteries as well as in rabbit aortic rings (Pugh et al., 1995; Pitman et al., 1996; Wang et al., 1997). Importantly, atherosclerosis may impinge on the type of contrast-induced vasomotor reaction in coronary arteries, where vasodilatation predominates in patients without coronary artery disease (CAD), and vasoconstriction in CAD patients, which feature blunted endothelial control of vascular tone due to the underlying endothelial dysfunction (Limbruno et al., 2000). In addition, in normal coronary arteries, vasodilatation does not apparently involve flow-mediated vasodilatation or endothelial NO synthesis, but a cyclooxygenase (COX) product, possibly PGI_2 or EDHF (Limbruno et al., 2000).

The sustained contrast-induced vasoconstriction observed in the kidney is widely believed to be caused primarily by an increased endothelial release of vasoconstrictors, such as ET-1, adenosine, angiotensin II, ROS, and a reduction in vasodilators including NO, PGI_2 and EDHF (Fernandez-Rodriguez et al., 2009; Zhao et al., 2011) (Fig. 1). NO is the main vasodilator produced by endothelial cells exerting numerous vasculoprotective effects, such as smooth muscle cell relaxation, inhibition of platelet adhesion/aggregation and endothelial adhesion molecule expression (Forstermann and Sessa, 2012). NO is also generally regarded as a protective molecule against renal injury (Cowley et al., 2003). In animal models of CIN, inhibitors of endothelial NO synthase (eNOS) rapidly predispose to tubular necrosis by impairing renal medullary perfusion, and the CM-induced deleterious effect on renal function may be ameliorated by L-arginine, the eNOS endogenous substrate (Agmon et al., 1994; Prasad et al., 2001). Furthermore, it has been shown that CM (iodixanol included) inhibit endothelial NO release evoked by fluid shear stress in isolated arteries (Hutcheson et al., 1999), as well as glomerular and aortic eNOS expression *in vivo* (Zhao et al., 2011), through mechanism(s) not directly correlated with osmolality or iodine concentration. Accordingly, plasma levels of nitrite, the principal circulating metabolite of NO, are depressed following clinical angiography with CM (Murakami et al., 2002). Reduced renal NO bioavailability may also be the result of an increased clearance by virtue of ROS generation: superoxide anion has indeed been shown to induce endothelial dysfunction by scavenging NO and generating the very potent ROS peroxynitrite, leading to altered renal microcirculation (Heyman et al., 2010). The demonstration of a concomitant depression in EDHF-dependent vasodilatation

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by CM, through modulation of endothelial calcium homeostasis (Fernandez-Rodriguez et al., 2009), suggests a global inhibition of endothelium-dependent relaxation, and may be particularly detrimental in disease states such as diabetes and heart failure, where EDHF is widely thought to compensate for depressed NO bioavailability. Another important endothelium-derived vasodilator is PGI_2, an eicosanoid produced by the action of COX-PGI synthase pathway and the levels of which have been shown to be reduced by CM (Heyman et al., 1994). The PGI_2 analog iloprost reduced CIN risk in patients with renal dysfunction undergoing coronary procedures (Spargias et al., 2009). ET-1 is an endothelial-derived vasoactive substance with potent and long-lasting vasoconstrictive action. Several observations support the hypothesis that ET-1 contributes to CIN pathogenesis. Animal and human studies reported an increase in plasma and urinary ET-1 levels, as well as an associated reduced renal blood flow, following angiographic procedures (Heyman et al., 1992; Zhao et al., 2011), at least in part because of the induction of endothelial ET-converting enzyme (ECE)-1 (Khamaisi et al., 2008). On the contrary, the ET-A receptor antagonist partially prevented CM-induced reduction in renal blood flow (Liss et al., 2003). As demonstrated by studies using antagonists or knockout mice (Lee et al., 2006), CM-induced hemodynamic changes in the kidney have been shown to involve also adenosine, the production of which *via* ATP hydrolysis is dramatically increased after CM injection due to the increased tubular transport and energy metabolism. Adenosine predominantly causes vasoconstriction *via* A_1 receptor of the afferent arterioles, although it may exert vasodilating effect *via* A_2-mediated generation of NO in the efferent arterioles and medullary capillaries (Hansen et al., 2005). Moreover, adenosine catabolism, along with hypoxia, contributes to ROS generation, which dampens NO bioavailability.

Therefore, direct and indirect adverse endothelial effects, from induction of apoptosis to unbalanced vasoactive and inflammatory responses, may be involved in CM-induced endothelial dysfunction and kidney injury. Although many underlying molecular mechanisms are not fully understood, it appears they are all the result of a complex interplay among osmolality, viscosity and direct pharmacological properties of CM.

6. Strategies for the prevention of contrast-induced adverse reactions based on the underlying pathophysiology

The multifactorial and incompletely understood pathogenesis of CM adverse reactions makes it hard to improve diagnostic and therapeutic tools, and also suggests that combined multiple protective measures curbing specific pathogenetic mechanisms (endothelial dysfunction, oxidative stress, vasoconstriction, inflammation) may be more effective than single protective measures. Besides periprocedural hydration, some pharmacological interventions have received considerable attention in recent years for CIN prevention. Statins are widely used in patients with CAD due to their cholesterol-lowering effect and cholesterol-independent effects, such as the improvement of endothelial function as well as the reduction of oxidative stress and inflammation (Zhang et al., 2011). According to a recent meta-analysis, chronic statin treatment would reduce the risk of CIN, with no significant effect of a short-term (periprocedural) high-dose therapy (Zhang et al., 2011). Therefore, the current clinical data are not conclusive as to whether statins are protective for CIN, and uncertainties remain about statin timing and dosage. More consistently, the thiol antioxidant NAC has received much attention as a potentially effective (as well as inexpensive, readily available and relatively safe) preventive strategy against contrast-induced adverse reactions. NAC has the potential to blunt oxidative stress by directly scavenging ROS, increasing intracellular glutathione, NO stabilization and inhibition of angiotensin-converting enzyme (Heyman et al., 2010). However, since the first positive clinical trial addressing NAC for CIN prevention (Tepel et al., 2000), several subsequent studies found conflicting results (Kelly et al., 2008; ACT Investigators, 2011), and NAC efficacy has become a matter of dispute leading to widely varying recommendations for its use.

Other preventive interventions have been tested in animal and clinical studies, including sodium bicarbonate, adenosine receptor antagonists, additional antioxidants, with some encouraging results (Heyman et al., 2010). In view of the lack of preventive strategies with clear-cut proven benefit, further mechanistic studies on CM toxicity in probable cellular targets, including endothelial cells – such as the one by Ronda et al. (this issue) of *Vascular Pharmacology* – are certainly warranted, and should eventually lead to the development of preventive tools appropriately addressing the pathogenesis of CM vasotoxicity.

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