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Oxidative stress and inflammation in the development of cardiovascular disease and contrast induced nephropathy

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Abstract

Utilization of contrast media to visualize vasculature structures in the setting of cardiovascular disorders (CVD) can lead to acute kidney injury, referred to as contrast-induced nephropathy (CIN). CIN can potentiate mortality and hospitalization in aged individuals, patients with CVD, nephropathy, enhancing kidney damage, and cardiac events. Preventing CIN by identifying risk factors is important. The underlying mechanisms of CIN pathology are unclear, but the key factors include direct cytotoxicity, oxidative stress, vascular and endothelial dysfunction and inflammatory processes. Reactive Oxygen Species and inflammatory mediators have been proposed as key factors influencing the development of CIN and CVD, and the elucidation of the interplay between the mechanisms evoked by them may provide a better understanding of the signaling processes happening in these conditions, thereby potentially enabling early identification, prevention and characterization of novel drug targets.

Keywords: Contrast induced nephropathy, cardiovascular disorders, oxidative stress, inflammation, reactive oxygen species

INTRODUCTION

Inflammation is an immune system response to pathogenic insults and is physiologically important to protect the organism from injury. Inflammatory responses are triggered by harmful stimuli and lead to a removal of invading pathogens and initiation of the healing process[1]. Reactive oxygen species (ROS) modulate the inflammatory processes[2-5]. ROS include chemically heterogeneous free radicals (e.g., superoxide) and non-radicals (e.g., hydrogen peroxide) vital for cell development, survival and signaling[6]. Redox signaling occurs through posttranslational oxidation of proteins (e.g., cysteine residues)[7,8]. Moreover, there is also a known cross-talk between ROS and neutrophil inflammation clearance and pro-inflammatory markers[5,9]. Usually, these mechanisms are tightly regulated and when sustained and aberrant, inflammatory responses and ROS can lead to tissue damage and disease.

Environmental stress can cause oxidative stress, often defined by cell/tissue injury and attendant oxidative macromolecule damage[10]. Moreover, ROS have been highlighted as a cause of several inflammatory diseases like cardiovascular diseases (CVD), type II diabetes and cancer.

Due to its role promoting inflammation and lipid peroxidation, ROS have been tightly linked to CVD[11]. Thus, both inflammatory elements and ROS are CVD risk factors, described as underlying participants in the progression of atherogenesis. In addition, chronic inflammatory diseases, characterized by an involvement of oxidative stress in their pathogenesis, promote high risk and influence CVD susceptibility[12,13]. Inflammatory molecules and ROS have been proposed as possible predictors and drug targets in CVDs, reviewed by Cervantes Gracia, Llanas-Cornejo, & Husi, 2017[14,15]. Interestingly, target organ damage, described as the strong association with high blood pressure and functional changes in the heart, brain, eyes and kidney, is known to have significant implications in CVD onset[16,17]. Furthermore, CVD is a characteristic hallmark of severe kidney failure. Patients with chronic kidney disease (CKD) have been well characterized to carry a significantly higher risk of developing and dying from severe CVDs[18-20]. Therefore, management of chronic kidney disease progression has been proposed as strategy to reduce the incidence of cardiovascular events[21]. Conversely, the presence of CVDs have also been associated with a higher risk of renal impairment and CKD progression[22]. However, the influence that one disease has over the other, as well as the underlying molecular mechanisms remain to be elucidated.

To add to this pathology, kidney failure exacerbated by coronary intervention procedures relying on contrast media (CM), known as contrast induced nephropathy (CIN), constantly increases the incidence of comorbidities in this group of patients undergoing interventions and its prevention is challenging[23-26]. Since pre-existing CKD is the most common cause of CIN[27,28], the interplay among the underlying mechanisms of CVD and kidney failure are important. Additionally, inflammation and ROS have been identified as risk factors of CIN and as potential targets for prophylaxis or treatment[29-34]. Hence, the elucidation of CIN/CVD interplay in this setting would improve understanding of the signaling processes and progression of the diseases, leading the way to different approaches to either early detection or to identification of novel drug targets.

CIN PATHOPHYSIOLOGY IN THE CONTEXT OF CVD

According to the WHO, non-communicable diseases (NCD) account for 71% of all deaths world-wide and CVDs are responsible for most NCD deaths. CVDs were responsible for about 17.8 million deaths in 2017[35,36], and are the primary cause of death globally. Notably, angioplasty is the most common percutaneous coronary intervention (PCI) method for CVD treatment[37,38], and diagnostic angiography and PCI routinely utilize iodinated CM for vascular visualization[39,40]. Although angiograms and PCI can effectively diagnose and treat CVD patients, this can potentially lead to acute kidney diseases such as CIN induced by CM[41-46]. CM can be retained by the kidney where they have the potential to cause toxicity,

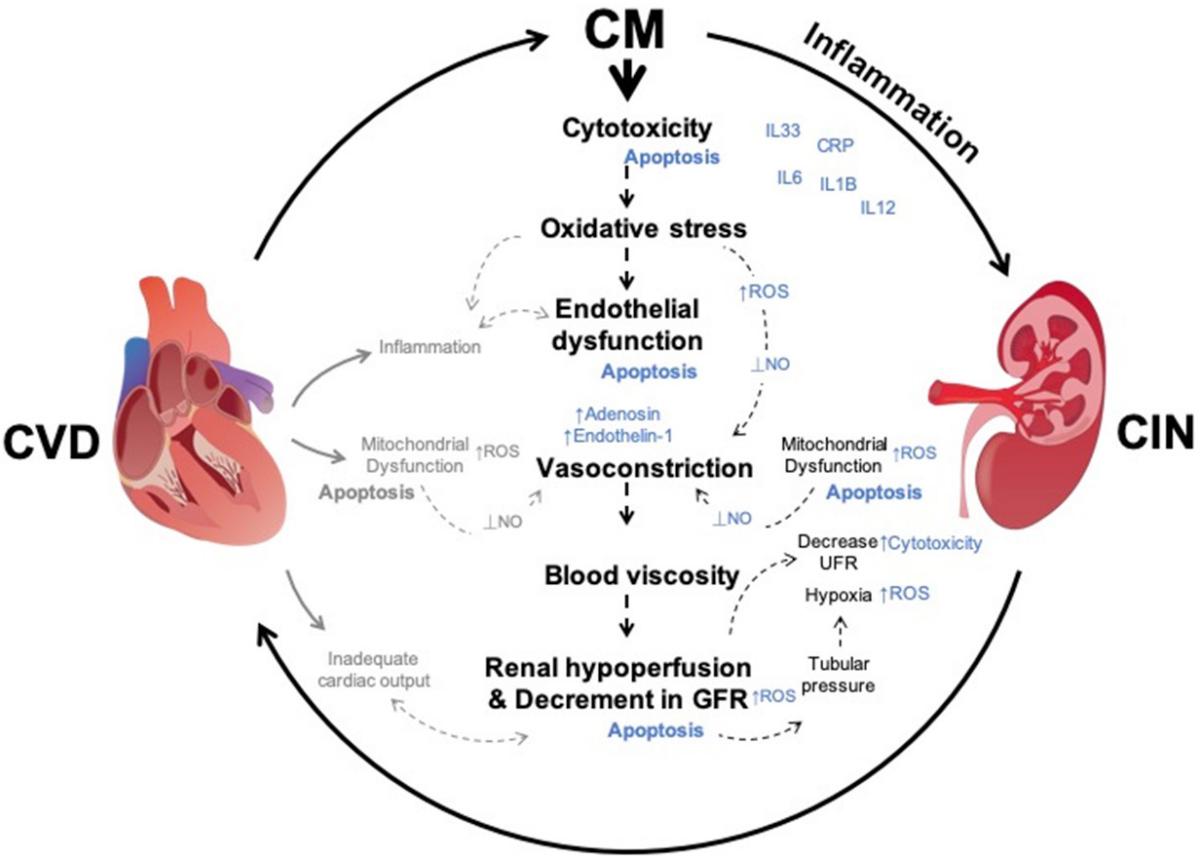

Figure 1. Contrast induced nephropathy and cardiovascular disorders pathophysiology interaction. Mechanisms triggered by Contrast Media (represented in black) lead to CIN. Their interaction promotes mitochondrial dysfunction, excessive ROS, promotes cytotoxicity and apoptosis. CIN enhances CVD pathophysiology. CVD processes (represented in grey) show CIN/CVD potential interaction creating a feedback loop that will enhance heart and kidney malfunction. Outcome from CM induced processes are represented in blue. ⊥: repression/reduction; ↑: overproduction; ROS: reactive oxygen species; NO: nitric oxide; UFR: urine flow rate; IL: interleukin; CRP: C-reactive protein; CIN: contrast induced nephropathy

resulting in acute renal injury[47]. Alternative CM have been developed to perform these procedures, but patients with risk factors such as kidney malfunction, diabetes, advanced age, CVD, anemia and hypotension are at high-risk and remain vulnerable to CIN[48,49].

CIN is a reversible form of acute renal injury that becomes evident after 48-72 h of intravascular administration of iodinated CM, manifesting in an increase of at least 25% in the serum creatinine level from baseline[50-52]. Although CIN can be transient, and in most of the cases serum creatinine level normalizes in 5-10 days, it can be irreversible and is associated with increased mortality and morbidity[25,45,50,53,54]. CIN is known to increase hospitalization, cardiovascular events, hepatic failure, dialysis and cardiac mortality, thus being directly associated with detrimental cardiac outcomes[50,55-57]. Additionally, CIN is attributable for a third of all hospital-acquired acute kidney injuries and its incidence can be as high as 50% in high-risk patients undergoing any procedure relying on intravascular contrast[26,47,58-60]. Regarding CIN treatment, it is limited and mainly supportive[60], thus early identification of at-risk patients is crucial and can be a potential approach for its management.

Although the precise pathophysiology of CIN is incompletely understood, crucial mechanisms have been associated with CIN, such as vasoconstriction in the renal vasculature, oxidative stress, renal medullary hypoxia, direct renal tubular cytotoxicity, and viscosity[45,53,61] [Figure 1]. It has been proposed

that the interplay of cytotoxicity and viscosity caused by CM, may be key in CIN pathophysiology. CM causes damage and apoptosis in surrounding endothelial cells (EC) and tubules of the nephron through iodine[62,63]. Moreover, vasoconstriction is known to increase blood viscosity after CM administration. CM increased viscosity and tubular pressure, exacerbating renal hypoperfusion and promote a decrease in urine flow rate, leading to its retention and allowing its continuous cytotoxicity [Figure 1][64,65]. Furthermore, blood viscosity is a key player in CVD pathophysiology and is associated with increased risks of CVD[66,67]. It has also been reported in the context of renal dysfunction and is associated with an increased risk of CVD and CKD development[68].

Vasoconstrictor mediators (endothelin, adenosine, angiotensin II, vasopressin) are known to play a key role CIN and CVD pathogenesis[65,69-73]. CM is known to cause immediate vasoconstriction and vasodilation impairment, reduce renal blood flow, decrease glomerular filtration rate (GFR) and cause renal hypoperfusion, which leads to an inadequate delivery of oxygen, promoting ischemic injury [Figure 1]. These processes are associated with oxidative stress promoted by CM[74,75]. Decrease in GFR has also been associated with increased risk in CVD mortality, a feature that reflects kidney damage[76]. Regarding vasodilatation impairment, it has been suggested to be induced by CM through decreased nitric oxide (NO) bioavailability. This event has been proposed to be a result of loss of vasoactive NO and cellular damage on account of generation of peroxynitrite ($ONOO^-$). Under physiological conditions, ROS production is attributed to nephron tubular transport regions with dense mitochondria populations, an important source of ROS[77,78]. Additionally, mitochondrial dysfunction is a key player in acute kidney injury[79,80] and is a characteristic feature of ageing, and chronic diseases, including diabetes and CVD, which are considered to be major risk factors for CIN[81,82]. Mitochondria are also abundant within cardiac cells due to the high energy demands, and notably mitochondrial ROS production is associated with CVD development[15,83]. Deleterious events such as arterial hypertension, endothelial dysfunction, atherosclerotic plaque formation and heart failure are associated with mitochondrial dysfunction[84-86]. Mitophagy removes damaged mitochondria and its impairment is a feature in CVD development as well. Moreover, ROS can induce damage in mitochondrial DNA, and damaged mitochondria are important sources of ROS; therefore, ROS overproduction due to mitophagy impairment disturbs homeostasis and leads to inflammation and apoptosis[87,88]. As in CIN, excessive ROS production from mitochondria is also associated with NO vasodilator impairment and it is tightly linked with endothelial dysfunction in cardiac event[89]. To add to CIN pathophysiology, oxygen imbalance under hypoxic conditions also leads to ROS production by the conversion of adenosine triphosphate (ATP) into hypoxanthine and its further reduction by xanthine oxidase. Mitochondrial dysfunction is also responsible for reduction in ATP synthesis, and will add to the cellular apoptotic state [Figure 1]. Interestingly, it has been recently reported that CKD in a rat model can influence cardiac pathologies by changing the function of cardiac tissue and inducing mitochondrial swelling and damage[90].

Inflammation is also a CIN hallmark, since the mechanisms previously described can trigger inflammatory processes. Notably, the presence of inflammatory elements has also been set as a feature for the population at high risk of CIN. Several studies have reported that the presence of active inflammatory processes biomarkers in patients with CVD may attribute its high-risk to developing CIN after CM exposure[30,31,91-94].

Cardiac insufficiency is also accountable for renal function impairment, emphasizing the complex interactions between heart and kidney where dysfunction in one organ can result in injury of the other[95]. Since CVD is a high-risk factor in CIN, and CIN can exacerbate CVD mortality, it is important to identify potential biomarkers for early detection and development of appropriate treatments. CIN processes that induce the release of vasoconstrictors, ROS and inflammatory cytokines have also been defined as hallmarks in CVDs due to the promotion of myocardial damage[50,96,97]. Additionally, a drastic decline in renal function may accelerate cardiovascular impairment by triggering inflammatory pathways[95,98].

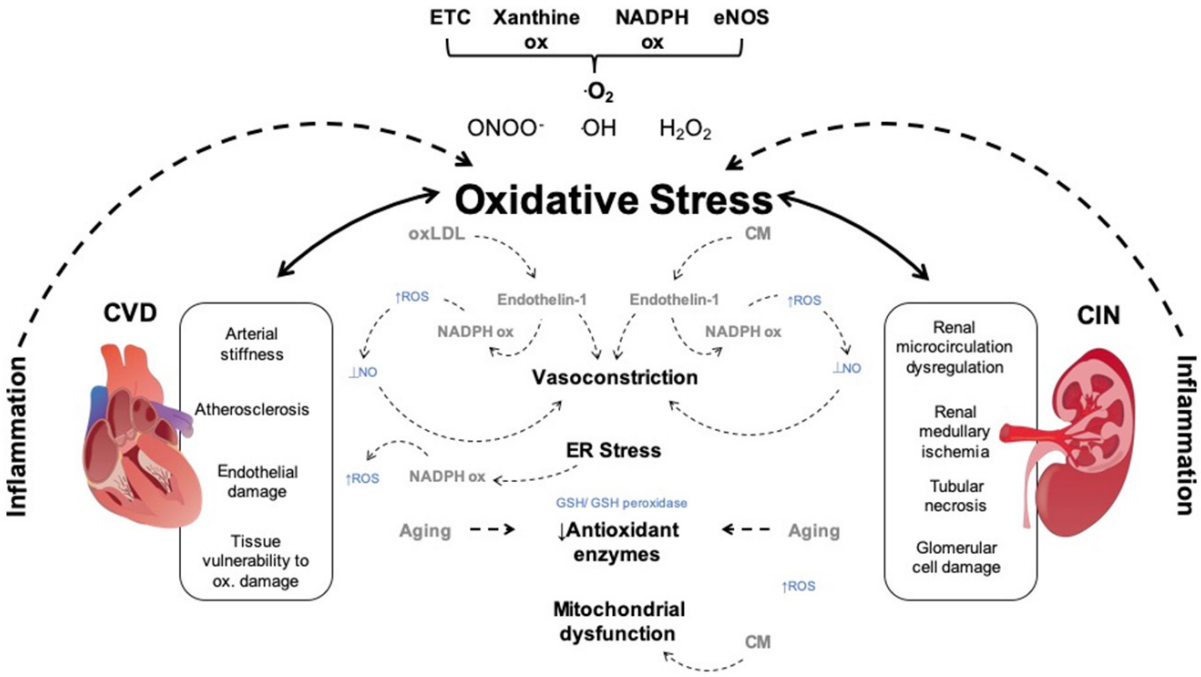

Figure 2. Oxidative stress mechanisms in contrast induced nephropathy and cardiovascular disorders. $ONOO^-$, OH, O_2 and H_2O_2 are physiologically relevant ROS in the vascular endothelium. Processes involved in oxidative stress are represented in bold black. Left side represent mechanisms described in CVD, right side represent mechanisms described in CIN. Boxes show effects of oxidative stress in CIN and CVD. Oxidative stress mechanisms lead to inflammation which in turn generates a feedback loop in ROS production. ROS, NO, and antioxidant enzymes are represented in blue. ⊥: repression/reduction; ↑: overproduction; ↓: decrease; ROS: reactive oxygen species; NO: nitric oxide; ER: endoplasmic reticulum; ox: oxidases; ETC: electron transfer chain; eNOS: endothelial nitric oxide synthase; $ONOO^-$: peroxynitrite; OH: hydroxyl radical; O_2: superoxide anion; H_2O_2: hydrogen peroxide; CIN: contrast induced nephropathy; CVD: cardiovascular disorders

Although an association of these events has been suggested for many years, its interplay remains to be described. Elucidating the possible interplay between oxidative stress and inflammation is important.

OXIDATIVE STRESS IN CVD AND CIN

ROS play a significant role as second messengers within cells and regulate normal cellular functions, including gene transcription, signal transduction and homeostasis[99]. Many sources of ROS exist within cells and amongst ROS, the free radical superoxide (O_2^-), is often a proximal ROS. O_2^- can lead to peroxynitrite ($ONOO^-$), hydroxyl radical (OH) and hydrogen peroxide (H_2O_2) production. Univalent reduction of molecular oxygen (a diradical) by the mitochondrial electron transport chain (ETC), as well as by xanthine oxidase, uncoupled endothelial nitric oxide synthase and Nicotinamide adenine dinucleotide phosphate oxidases (NOXs) leads to O_2 production[100].

Mitochondria are responsible for the bulk ATP synthesis via chemiosmotic oxidative phosphorylation (OXPHOS). OXPHOS involves mobile electron carriers shuttles (NADH, cytochrome C and Coenzyme Q), protein complexes (complexes I-IV and the ATP-synthase complex) and a sequence of redox reactions where electrons are transported across the complexes of the respiratory chain up to complex IV, where molecular oxygen is reduced to water. The proton pumps establish an electrochemical proton motive force necessary for OXPHOS. Mitochondrial ROS can directly disturb the functionality of the ETC complexes by oxidizing iron-sulfur clusters and protein thiols [Figure 2][101-103]. Although mitochondria are a major source for ROS production, no clinical studies have been reported for mitochondrial-targeted antioxidants. This is largely due to the complications surrounding the targeted antioxidant delivery of injured mitochondria. Another cause for concern is that the role of mitochondrial ROS differs from cytosolic ROS as they

are responsible for intracellular functions, which are maintained at a delicate equilibrium that could be negatively influenced by the careless use of antioxidants[104].

It is understood that ageing is associated with cardiovascular oxidative stress[105]; tissue vulnerability to oxidative damage and is likely to be a key contributor in the development of cardiovascular disease[106]. Direct CM-induced toxicity on renal tubular epithelial cells appears to be a major contributing factor in CIN. CM induces renal vasoconstriction, through increased adenosine and endothelin-1 secretion, and diversion of blood flow from the medulla to the cortex [Figure 2]. Consequently, renal blood flow to the medulla and GFR is reduced, followed by ischemia in the renal medulla[107,108].

Atherosclerosis is the main cardiovascular disorder in which the association with oxidative stress became evident. Oxidized low density lipoprotein (oxLDL) plays a critical role in the pathogenesis of atherosclerosis. Studies have shown a clear link between arterial stiffness and oxLDL concentration, independent of the typical CVD risk factors[109]. It remains uncertain whether oxLDL as an oxidative stress biomarker has any predictive property in cardiovascular patients[110].

Vascular NOXs are important ROS generating enzymes and in human vascular cells, NOX1, NOX2, NOX4 and NOX5 are expressed. NOX are transmembrane enzyme complexes with a few regulatory subunits and a core catalytic subunit, except for NOX5[111]. NOX activation results in the generation of O_2 from molecular oxygen by the transfer of electrons from NADPH[112]. NADPH oxidase in humans was thought to be phagocyte specific as the two membrane bound units, $gp91^{phox}$ and $p22^{phox}$ form a heterodimer and mediate bacterial killing by generating O_2 ($gp91^{phox}$ produces a burst of O_2 and $p22^{phox}$ acts to stabilize $gp91^{phox}$, enhancing O_2 production)[113]. $P22^{phox}$ expression in non-phagocytic cells directed the discovery of NOX1 in non-phagocytic cells which then led to the identification of the other NOX proteins[111].

NOX4 plays a key regulatory role, generating athero-protective ROS that inhibits inflammation and vascular remodeling. Decreased levels of effector T cells and chemokines, increased regulatory T-cells and reduced lesion formation was seen in apolipoprotein E-deficient mice expressing ectopic endothelial NOX4[114]. However, reduced levels of endothelial H_2O_2 and phosphorylated mothers against decapentaplegic homolog 3 (p-SMAD3), along with the elevated expression of profibrotic connective tissue growth factor has been seen when NOX4 was downregulated in human aortic endothelial cells[115]. NOX4 knockdown *in vivo* has also been shown to elevate fibrillar collagens I and III production in plaques, which is linked to increased p-SMAD3 levels and transforming growth factor-β expression in diabetic lesions[116]. During the development of arteriosclerosis, NOX4 and H_2O_2 regulate the response of EC to endoplasmic reticulum (ER) stress [Figure 2][117]. ER stress leads to elevated ER H_2O_2 in a NOX4-dependent manner which then results in Ras-specific guanine nucleotide releasing factor (RasGRF) activation, the oxidation of thiols in the Ca^{2+}-ATPase of sarcoplasmic reticulum microsomes and increased cytosolic calcium levels. In addition, NOX produced ROS affects X-box-binding protein 1 (KBP1) splicing, a key protein that promotes EC apoptosis and atherosclerosis formation[118].

As well as the increased production of oxLDL, an additional contributor to cardiovascular morbidity appears to be oxidative endothelial damage. In healthy adults of varying ages, brachial artery flow-mediated dilation appeared to inversely correlate with the concentration of nitrotyrosine (produced, for example, via nitrogen dioxide radical and tyrosine radical recombination) in vascular EC[119]. ET-1, as well as being a powerful vasoconstrictor, has also demonstrated proinflammatory and prooxidant properties and consequently, it has been associated with oxidative endothelial damage[120]. In EC, oxLDL has been shown to stimulate endothelin-1 production, and elevated levels of endothelin-1 is known to generate ROS by NADPH oxidase [Figure 2][121]. Furthermore, the cardiovascular system inflammatory response is induced by oxidative stress and proinflammatory cytokines additionally induce oxidative damage in a positive, reverse feedback mechanism [Figure 2][122].

Antioxidant defense mechanisms decrease with age[123], therefore age is a major risk factor of CIN. The unique anatomy of the renal medulla requires the thick ascending limbs of the loop of Henle to carry out energetically challenging ion transport in a state of relative hypoxia compared to the renal cortex. It has been proposed that a discrepancy between the metabolic requirements of these thick ascending limbs and the medullary blood supply could generate O_2[124]. The thick ascending limb is associated with ROS generation mostly due to the extremely high mitochondrial density and therefore, mitochondrial ROS generation[125]. Reduced renal blood flow can induce oxidative stress and osmotic necrosis consequently generating ROS, via a positive feedback mechanism, leading to acute tubular necrosis[114,123]. Renal microcirculation is compromised by ROS production, which affects renal vascular function by facilitating the production of vasoconstrictors such as endothelin-1 and ameliorating the effects of vasodilators, such as NO[126]. Direct toxicity of CM in renal tubular cells can also result in mitochondrial dysfunction and, combined with elevated levels of ROS, leads to extensive damage of glomerular cells by compromising the cellular membrane, ultimately resulting in apoptosis[127].

A crucial factor in the production of ROS in the kidney is renal hypoxia. There are, however, conflicting reports relating to the extent to which oxidative stress is a cause or epiphenomena. ROS are regularly involved in cellular inflammatory responses and it is proposed that ROS are formed during renal parenchymal hypoxia, following CM exposure, resulting in vascular endothelial injury. This aggravates renal parenchymal hypoxia resulting in endothelial dysfunction[125]. O_2 can lead to the accumulation of $ONOO^-$, the production of which reduces NO bioavailability. In addition, ROS activate p38 MAPK stress kinases and c-Jun N-terminal kinases, that are involved in the activation of caspase-3 and caspase-9, which are associated with the induction of apoptosis[128]. Mitochondrial dysfunction can induce apoptosis by releasing cytochrome c and activating caspase-9, which in turn activates caspase-3. Caspase-3 plays a major role in apoptotic signaling by mediating death receptor-dependent and mitochondria-dependent apoptosis pathways[129].

In response to excessive oxidative stress, cells activate/induce their own antioxidant defense mechanisms. Glutathione (GSH), is an important endogenous thiol that is essential to a variety of detoxification processes. Mammalian cells contain high concentrations of GSH (3-5 mmol/L) which is used in numerous diverse roles as well as hepatic detoxification. GSH can donate reducing equivalents for the activity of specific antioxidant peroxidase enzyme, such as GSH peroxidase (GPx), and can react directly with certain ROS (e.g., carbonate radical). Intracellular levels of GSH are tightly controlled by the enzymes glutamate-cysteine ligase and GSH synthase (involved in synthesis), GSH reductase (involved in recycling of oxidized glutathione back to GSH) and GSH transferases (involved in utilization)[130]. Redox enzymes include thioredoxin, catalase, GPx, peroxiredoxins and superoxide dismutase (SOD)[100].

ROLE OF INFLAMMATION IN CIN/CVD

One of the factors that is central to the prevalence of CIN is chronic inflammation. The role of inflammation in CIN has been extensively studied and clinical trials in humans and animal models have been performed to help elucidate this role[131-134]. One of the main features of intravascular iodinated CM is that it causes vasodilation followed by a prolongation in vasoconstriction[135,136]. The vasodilation/vasoconstriction occurs in all patients that require a CM procedure, but this effect has not been found to work alone in the increase of CIN risk among patients. Two additional pathways suggested to promote this increase are cellular toxicity and elevated urinary viscosity that can cause obstructions through stone formation[137].

Although the global prevalence of CIN does not constitute a public health threat, at risk populations, such as those suffering from higher presence of infectious diseases, have a higher incidence of inflammation than populations that are not affected by these diseases[138]. A close relationship between inflammatory

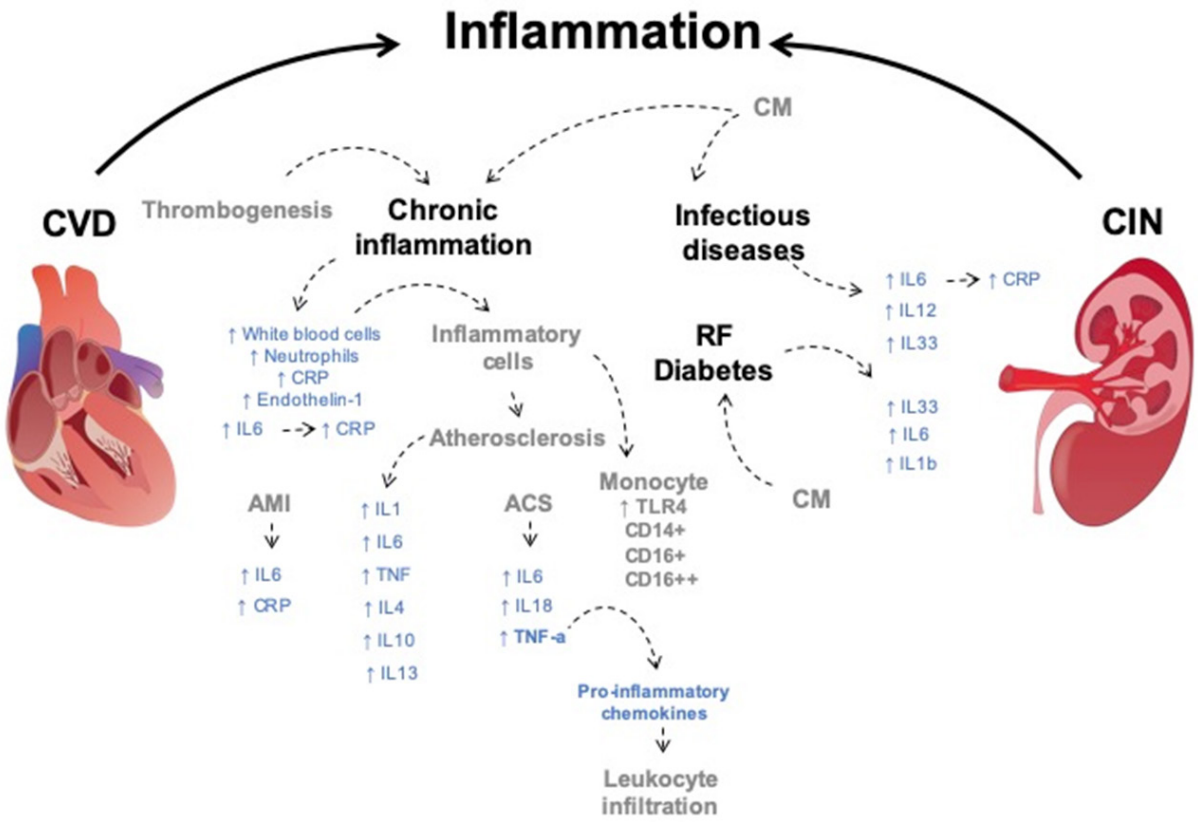

Figure 3. Inflammatory molecules in CIN and CVD. Inflammatory states have been associated with CIN and CVD risk factors. Inflammatory cells and molecules are considered as potential risk factors in CVD and CIN. Inflammatory risk factors highlighted in blue. CM, Disease states and cellular types related to inflammatory risk factors represented in grey. ↑: overproduction. CM: contrast media; RF: risk factors; AMI: acute myocardial infarction; ACS: acute coronary syndrome; IL: interleukin; CRP: C reactive protein; TNF-α: tumor necrotic factor-α; TLR4: toll like receptor 4; CIN: contrast induced nephropathy; CVD: cardiovascular disorders

molecules and thrombogenesis has been well reported[139]. The acute inflammatory state is a landmark of infectious diseases and one of the main type of molecules that derive from it are interleukins (ILs). IL-6 and IL-12 have been targeted as disruptors of homeostasis within inflammatory processes. IL-6 promotes the expression of the C reactive protein (CRP), which is being used as a current acute inflammation marker [Figure 3][140].

One of the studies that assessed the increased risk for CIN due to inflammation was performed by Kwasa *et al.*[132]. They performed a prospective cohort study of patients undergoing a contrast-enhanced CT (CECT) scan. 423 patients were recruited and grouped into those without inflammation having serum CRP levels ≤ 5mg/dL and those with evidence of inflammation having CRP levels > 5 mg/dL. Serum creatinine (SCr) was measured before the CECT and 48 h following the CECT with CIN diagnosed by an increase of > 25% in SCr from the baseline [Figure 3]. The observed incidence of CIN was 9.92%. Of the patients with inflammation, 29 (13.5%) developed CIN, while 13 (6.25%) of those without inflammation developed CIN. No significant relation was found between the increase of CIN prevalence and biophysical variables (age, sex, height, weight, *etc.*)[132]. Another study reported by Oweis *et al.*[30] showed serum levels of IL-33 as significant predictor for development of CIN. Of the total 202 patients, 30 (14.8%) developed CIN. The incidence rate was 21.1% among females and 12.4% among males [Figure 3].

Additional biomarkers of inflammation have been studied to assess their potential as predictors of CIN in different conditions. Cell types that are associated chronic inflammation have been proposed as predictors

of increased risk of developing CIN: the study published by Yuan *et al.*[92] in 2017 found in 1,061 patients that white blood cell count, neutrophil count, neutrophil lymphocyte ratio, CRP level, and big ET-1 level were all associated with an increased risk of CIN development. It is important to mention that all of the patients in this study went through emergency PCI.

Regarding the assessment of multiple markers to predict the development of CIN, different studies have reported combinations between proteins that can be measured in human serum. The study performed by Satilmis *et al.*[141], presented an assessment of the ratio between 2 inflammatory markers, CRP and albumin. 205 patients with non-ST-elevation myocardial infarction that underwent PCI were subsequently assessed for development of CIN. The prevalence of CIN in this study was 10.2%. Multivariate logistic regression analysis showed significant association between CRP: albumin ratio and the development of CIN; advanced age, diabetes, dyslipidemia and left ventricular ejection fraction were also associated with the condition.

Animal models have also been used in the search for the potential role of inflammation in the development of CIN. Demirtas *et al.*[29] evaluated the role of IL-33 in the pathogenesis of CIN in diabetic rats. 30 male Sprague-Dawley rats were divided into 3 groups (healthy, diabetic and diabetic with CIN). Significantly increased presence of IL-33 was found in the kidney tissue of the diabetic group after induction of CIN when compared with the healthy and diabetic groups. Serum levels of IL-33, IL-6, and IL-1β were also significantly increased in the diabetic + CIN group when compared to the healthy and diabetic groups [Figure 3].

Prophylactic use of carotenoids has been studied in animal models to assess the relation between oxidative stress induced inflammation and CIN development. The studies presented by Buyuklu *et al.*[142,143] aimed to investigate the effects of lycopene and curcumin as protection against the development of CIN in rats. 28 male Wistar albino rats were divided into 4 groups, they included a normal control group, CIN group, CIN + lycopene and CIN + curcumin groups. Significant increase in urea, creatinine and malondialdehyde were observed in the CIN group when compared with the control group. Additionally, histological tests showed significant increase of infiltrated inflammatory cells and necrotic degenerative changes in the CIN group when compared against the control[142,143].

The role of the inflammatory state in CVD was addressed in an extensive literature[14]. The search for markers has two principal aims: to look into the understanding of the mechanisms of disease and to identify molecules that can be detected more accurately to predict the risk of cardiovascular events. The role of inflammation in CVD development has been assessed throughout different populations and experimental models, critical importance has been given to events such as acute myocardial infarction (AMI) and atherosclerosis due to their high incidence and mortality rates[144]. Inflammation in CVD includes a vast number of processes which can occur at the site of disease, in the bloodstream and at sites far from the disease[145]. Immune response takes the spotlight when addressing inflammation and CVD. In AMI a signaling cascade induces the expression and recruitment of proinflammatory molecules, accelerating both damage and further repair of injured cardiac tissue. Elevated levels of high-sensitivity CRP and IL-6 in plasma have been found correlated with unfavorable outcomes in patients [Figure 3][146].

Rajendran *et al.*[147] assessed both IL-6 and hs-CRP in a Chennai based population. 93 patients with AMI and 102 healthy subjects as a control group were analyzed. Both IL-6 and hs-CRP were found to be significantly increased when compared with the control group. Pro-inflammatory cytokines IL-6, IL-10, IL-18 and TNF-α were evaluated in a study published in 2019 including 120 patients with acute coronary syndrome (ACS) and 60 healthy controls. Serum levels of IL-6, IL-18 and TNF-α were significantly higher in the ACS group when compared to the healthy group [Figure 3]. No significant difference in serum levels of IL-10 was found[148]. Additionally, TNF-α has been found to promote the release proinflammatory

chemokines and adhesion molecule synthesis in damaged myocardium and causing additional leukocyte infiltration in mice[149].

Toll-like receptors (TLRs) may be key to understanding heart failure. TLR4 deficiency is associated with decreased in size of damage by infarct and reduction of systemic inflammation in mice[150]. In humans, the activation of TLR4 in monocytes is associated with the development of cardiac failure after AMI [Figure 3][151]. By contrast, deficiencies in the function of TLR2 were found to reduce myocardial fibrosis and improve ventricular remodeling after AMI in a murine model[152].

Atherosclerosis is often described as a chronic inflammatory process. Deregulation in the endothelium is mediated by cell adhesion molecules, such as ICAM1, P-selectin and VCAM1. Additionally, the secretion of cytokines has a role in atherogenesis, namely IL-1, IL-6, TNF, IL-4, IL-10 and IL-13 [Figure 3]. The detection of some of these molecules in plasma has identified associations that could help to predict atherosclerosis severity. Moreover, the identification of cell types through flow cytometry has proven to be a promising predictor for atherogenic levels of severity. The amount $CD^{14+}CD^{16++}$ monocytes present in circulation has been found to be inversely correlated to plasma HDL levels while CD^{16+} monocytes levels are proportional to severe atherosclerosis [Figure 3][153].

CVD AND CIN BIOMARKERS

The identification of rapid, predictive biomarkers for CIN is essential as current targets are relatively slow to be useful, or the assays are just too expensive to be launched in a clinical setting. Some of the postulated biomarkers for CIN and CVD are shown on Table 1. An early predictive biomarker of AKI is human neutrophil gelatinease-associated lipocalin (NGAL). NGAL is a small protein of the lipocalin superfamily that was initially identified from the supernatant of activated human neutrophils in 1993. Successive studies have recognized renal NGAL as a unique, specific biomarker for the early detection of AKI in critically ill patients and after CM administration. Urinary and serum levels of NGAL increase well before the increase of serum creatinine levels (~2 h). As a result, NGAL is increasingly studied as a marker of AKI[154-157]. Another proposed sensitive, early, non-invasive biomarker for AKI kidney injury is urinary neutrophil gelatinase-associated lipocalin (uNGAL) also known as lipocalin-2. uNGAL is an iron-transporting protein that rapidly accumulates in the urine and kidney tubules after nephrotoxic and ischemic insults. Zappitelli *et al.*[158] concluded that uNGAL is an effective predictor of AKI which is triggered in advance of increases in serum creatinine concentration. Despite these findings, the use of uNGAL is still experimental.

Liver type fatty acid binding protein (L-FABP) is an intracellular lipid chaperone and is expressed in renal proximal tubule cells and secreted into the urine in response to hypoxia caused by a decrease in peritubular capillary blood flow. Although L-FABP concentration is significantly increased in CIN patients after 24 hours, the specificity of this biomarker for CIN is low on account of a range of potential confounders[159].

Tissue plasminogen activator (tPA), a part of the serine protease family, is a plasma protein involved in the breakdown of blood clots and a key fibrinolytic agent that takes part in the recruitment of inflammatory cells. Some other roles of tPA involve the turnover of extracellular matrix components via activation of matrix metalloproteinases and immune-modulatory functions. Plasminogen activator inhibitor-1 is the main physiological inhibitor of endogenous fibrinolysis which functions through the inhibition of tPA and the urokinase type activator (uPA)[160,161]. A recent study[162] reported a relationship between increased serum tPA levels with an increased rate of mortality of dialysis-dependent AKI (AKI-D) patients. Elevated tPA expression has been detected in the proximal tubular epithelial cells of ischemic kidneys, in animal models. Removing tPA by antisense treatment had reduced the influx of neutrophils and helped protect renal function during ischemia-reperfusion injury. This suggests tPA inhibition as a novel strategy to improve ischemic AKI[163]. Many additional studies have also implied the involvement of tPA in the process of kidney fibrosis that leads to progression of CKD[164-166].

Table 1. Origin and mechanisms of potential biomarkers for prediction of CIN and CVD

Biomarkers	Etiology	Mechanisms	Organism	Ref.
IL-6, IL-12, IL-8	CIN and CVD	Induction of the production of CRP	Human	Alladina *et al.*[171] (2016) Kwasa *et al.*[132] (2014) Rajendran *et al.*[147] (2012)
C reactive protein	CIN and CVD	Response to chronic inflammation	Human	Kwasa *et al.*[132] (2014) Rajendran *et al.*[147] (2012)
TNF-α	CVD	Upregulated in inflammation in acute myocardial infarction, modulates cardiac contractility and peripheral resistance. Promotes leukocyte infiltration in mice	Human Mice	Senguttuvan *et al.*[148] (2019) Maekawa *et al.*[149] (2002)
$CD14^{+}CD16^{++}$ monocytes	CVD	Presence inversely correlated to plasma HDL levels	Human	Schlitt *et al.*[153] (2004)
$CD16^{+}$ monocytes	CVD	Levels proportional to severe atherosclerosis	Human	Schlitt *et al.*[153] (2004)
Neutrophil/Lymphocyte ratio	CIN	Elevated in subclinical inflammation	Human	Yuan *et al.*[92] (2017)
CRP/Albumin ratio	CIN	CRP levels are found increased in chronic inflammation and albumin levels are negatively correlated in the presence of acute inflammation	Human	Satilmis *et al.*[141] (2020)
IL-33 and IL-1β	CIN and CVD	Proinflammatory cytokines, IL-33 binds to immune cells and promotes secretion of cytokines resulting in inflammation	Human and Sprague-Dawley rat	Oweis *et al.*[30] (2018) Demirtas *et al.*[29] (2016)
NGAL	CIN	Accumulates in urine, blood and renal cortical tubules following ischaemic and nephrotoxic injury. Antioxidant protection against CIN development	Human Wistar albino rat	Malyszko *et al.*[156] (2009) Buyuklu *et al.*[143] (2014)
L-FABP	CIN	Specifically binds to intracellular, free unsaturated fatty acids during hypoxic tissue injury	Human	Nakamura *et al.*[159] (2006)
tPA	CIN and CVD	Tissue type fibrinolytic agent involved in the breakdown of blood clots and the recruitment of inflammatory cells	Human	Baramova *et al.*[160] (1997) and Stringer *et al.*[161] (1997)
uPA	CIN and CVD	Urokinase type fibrinolytic agent involved in the breakdown of blood clots and the recruitment of inflammatory cells	Human	Baramova *et al.*[160] (1997) and Stringer *et al.*[161] (1997)
PAI-1	CIN and CVD	Primary physiological inhibitor of tPA and uPA	Human	Baramova *et al.*[160] (1997) and Stringer *et al.*[161] (1997)
KIM-1	CIN	Localised to the proximal tubules of the human kidney following toxic or ischaemic injury	Human	Nogare *et al.*[172] (2012)
IL-18	CIN and CVD	Proinflammatory cytokine	Human Mice	Ling *et al.*[168] (2008)
CysC	CIN	Produced by all nucleated cells and displays a stable rate of production. Freely filtered by the glomerulus	Human	Soto *et al.*[174] (2010)
Serum Creatinine	CIN	Resulting product of creatine phosphate from protein and muscle metabolism. Exhibits a stable rate of production and is freely filtered by the glomerulus	Human	Slocum *et al.*[173] (2012)

IL: interleukin; TNF: tumor necrotic factor; CRP: C reactive protein; NGAL: neutrophil gelatinase-associated lipocalin; L-FABP: liver type fatty acid binding protein; tPA: tissue plasminogen activator; uPA: urokinase plasminogen activator; PAI: plasminogen activator inhibitor; KIM-1: kidney injury molecule 1; CysC: Cystatin C; CIN: contrast induced nephropathy; CVD: cardiovascular disorders; CRP: C reactive protein

IL-6 is an interleukin that can act as both an anti-inflammatory myokine and a pro-inflammatory cytokine and is encoded by the IL6 gene in humans. Osteoblasts produce and release IL-6. The role of IL-6 role as an anti-inflammatory cytokine is facilitated via the interleukins inhibitory effects on IL-1 and TNF-α, and activation of IL-10 and IL-1ra[167]. Studies have demonstrated a close correlation between AKI and IL-6

expression in many animal models[168,169]. Resident kidney cells, such as tubular epithelial cells, endothelial cells, mesangial cells and podocytes can all produce and release IL-6. A study has shown that, in a model of ischemia-reperfusion injury, after leukocytes penetrated the injured kidney, maladaptive IL-6 was produced in response to their TLR-4 receptors interacting with high mobility group box 1 protein released by the injured renal cells[170]. Raised levels of the pro-inflammatory cytokines, IL-8 and IL-6, have been seen early on in AKI patients and were linked to prolonged mechanical ventilation[171].

The transmembrane protein, kidney injury molecule 1 (KIM-1), recognizes apoptotic cells and leads them to lysosomes. Additionally, it acts as a receptor for oxidized lipoproteins and is therefore adept at recognizing apoptotic cell signals. KIM-1 is undetectable in normal kidney tissue but is highly expressed following toxic or ischaemic injury in differentiated proximal tubule epithelial cells from rodent and human kidneys[172,173]. Plasma cystatine-C (CysC), is a low molecular weight protein produced at a predictable rate by all nucleated cells. CysC is filtered across the glomerular membrane but is neither reabsorbed nor secreted during its passage through the nephron. Given that CysC is almost entirely catabolized in the proximal tubule, it is impossible to measure its renal clearance. However, the plasma or serum concentration of CysC accurately reflects the GFR and significant increases in CysC are detected in CIN patients after 8 h. However, a similar increment has also been seen in several other conditions, including thyroid dysfunction, age, an increase in muscle mass, systemic inflammation, corticosteroids administration and neoplasia[174] limiting its utility as a CIN biomarker.

The key diagnostic criterion for CIN is the elevation of serum creatinine concentration by more than 25% over baseline, after eliminating any other possible causes. Other laboratory findings may also be present such as hyperkalaemia and acidosis. Although patients may have normal urine output, they can also suffer from anuria (failure of the kidneys to produce urine) or oliguria (low output of urine > 80 mL/day, < 400 mL/day). Findings on urine analysis are normally non-specific[175]. Normally a delay of 24-48 h is seen between contrast exposure and changes in serum creatinine concentration, which makes creatinine a late indicator of renal function changes[176].

Since a close correlation among inflammatory molecules and kidney injury in CIN has been observed, as described above, they have also been proposed as potential CIN biomarkers [Table 1]. IL-8 and IL-6, have been seen early on in AKI patients and were linked to prolonged mechanical ventilation[171]. Successive studies have recognized renal NGAL as a unique, specific biomarker for the early detection of AKI in critically ill patients and after CM administration[154-157]. Other proposed biomarkers, despite being effective predictors of AKI, such as uNGAL triggered preceding increases in serum creatinine concentration[157,158] are still experimental. Other potential biomarkers have been deemed as non-specific, such as L-FABP, although significantly increased in CIN patients after 24 h, where potential confounders lower its specificity[159].

CONCLUSION

Oxidative stress influences cardiovascular morbidity mainly through increased peripheral vascular resistance [Figure 1]. However, although the generation of ROS could affect renal blood flow by facilitating the production of vasoconstrictors and impacting the effects of vasodilators, the influence of oxidative stress in the development of CIN is uncertain.

Inflammation results in the alteration of homeostasis in both the circulatory and renal systems. These alterations can be intrinsic of cellular damage or can be mediated by external factors such as CM. Immune response to CM cytotoxicity causes a rapid increase in the migration and accumulation of cytokines such as ILs and TNF-α in the progression of both CVD and CIN. Additionally, the presence of cellular types found in response to inflammation is a feature in early development of CVD and CIN. The main interplay

between CIN and CVD in the context of inflammation may rely on endothelial dysfunction and immune response. The signaling pathways activated through endothelial dysfunction in cardiac events result in the generation of systemic inflammation which has been found to affect the kidneys and made them more susceptible to local inflammation processes driven by CM cytotoxicity.

Current CIN prevention strategies, such as the use of carotenoids, for instance curcumin and lycopene[142,143], to limit the oxidative effects of CM are questionable due to the inconclusive evidence to support the oxidative capacity of CM. Existing biomarkers for CIN are either non-specific, such as L-FABP, or late indicators of renal function changes, such as changes in serum creatinine, making them poor predictive markers at best. The relationship between CVD and CIN and the underlying mechanisms responsible for CIN are unclear. Identifying novel biomarkers, be it genetic, redox or serum protein markers, for the early detection of CIN will help gain a better understanding of the underlying mechanisms. Greater mechanistic understanding is required to better predict and treat CIN.

DECLARATIONS

Authors' contributions

Design and conception of the original draft: Cervantes-Gracia K, Raja K, Llanas-Cornejo D
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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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