International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Role of oxidative stress in the process of vascular remodeling following coronary revascularization

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ARTICLE INFO

Article history:
Received 14 March 2018
Received in revised form 17 April 2018
Accepted 14 May 2018
Available online xxxx

Keywords:
Coronary revascularization
Restenosis
In-stent thrombosis
Reactive oxygen species
NADPH
Mitochondria
Vascular smooth muscle cells

ABSTRACT

Percutaneous coronary interventions (PCI), including balloon angioplasty and implantation of both bare metal and drug eluting coronary stents, are associated with risk of restenosis and in-stent thrombosis. A better understanding of signals that regulate cellular proliferation, neointimal formation and vessel wall thickening following PCI may contribute to identify novel preventive and therapeutic strategies aimed to reduce the atherosclerosis progression and the consequent vascular sequelae.

Among the possible mechanisms, an increased level of reactive oxygen species (ROS) is associated with endothelial dysfunction and vascular smooth muscle cells (VSMCs) proliferation and migration involved in the post-procedural remodeling process.

This review article provides an overview of the current knowledge on the contribution of increased oxidative stress to the post-procedural pathological vascular changes. We discuss the role of nicotinamide adenine dinucleotide phosphate oxidase, nitric oxide synthase, and of proteins regulating the mitochondrial function and dynamics. We will also highlight new knowledge on the atypical Fat1 cadherin that appears to play a key role in VSMCs proliferation. In fact, its induction after vascular injury serves as a physiological regulator of VSMCs growth. Specific molecular mechanisms, including Pin1- and H2S-mediated pathways, have been identified in the vascular complications of type 2 diabetic patients.

The identification of novel key players may expand our perspectives and promote the development of new tools for future preventive and therapeutic strategies in order to reduce the adverse vascular remodeling following PCI. The latter represents one of the major goals in the development of innovative technologies with relevance for clinical practice.

1. Introduction

Coronary interventions, including percutaneous transluminal coronary angioplasty (PTCA) and coronary stent implantation, are associated with increased occurrence of vascular consequences such as vascular remodeling, in-stent restenosis (ISR) and in-stent thrombosis [1].

Restenosis after percutaneous coronary interventions (PCI) involves proliferation and migration of vascular smooth muscle cells (VSMCs) and of adventitial myofibroblasts [2,3]. In fact, proliferation of VSMCs is essential for repair of injured arteries, but its excess can cause vascular obstruction eventually leading to tissue ischaemia and/or infarction [4].

ISR is defined as a progressive lumen diameter reduction post-PCI that can begin in the early hours following the barotrauma determined by PCI. The incidence of ISR dropped from 32 to 55% in the pre-stent era [5,6] to 17–41% in the bare-metal stent (BMS) era [7]. A further step in ISR reduction was obtained with the advent of drug-eluting stents (DES), which led to a <10% occurrence [8].

The occurrence of ISR is significantly higher in patients with multivessel disease, when compared with those with one-vessel disease [9,10]. ISR is also more frequent in the presence of conditions such as

Abbreviations: ATP, adenosine triphosphate; BES, biolimus-eluting stents; BMS, bare-metal stent; cGMP, cyclic guanosine monophosphate; DES, drug-eluting stents; DRP 1, dynamin-related protein 1; EES, everolimus eluting stent; eNOS, endothelial NOS; FAD, flavin adenine dinucleotide; Fis 1, fission protein1; GADPH, glyceraldeide 3-phosphate dehydrogenase; GSK-3β, glycogen synthase kinase-3β; H_2O_2, hydrogen peroxide; H2S, hydrogen sulfide; ICAM-1, intercellular adhesion molecule-1; ISR, in-stent restenosis; MAPK, mitogen–activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MEK, mitogen-activated protein kinase; Mfn, mitofusin; mRNA, messenger ribonucleic acid; mtDNA, mitochondrial DNA; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor Kappa B; NO, nitric oxide; NOS, nitric oxide synthase; $O2^{\bullet -}$, superoxide anion; Opa1, optic atrophy 1; oxLDL, oxidized low-density lipoproteins; OXPHOS, oxidative phosphorylation; PCI, Percutaneous coronary interventions; PDGF, platelet derived growth factor; PES, paclitaxel-eluting stent; PGC-1α, peroxisome proliferator-activated receptor-coactivator-1α; PKC, protein kinase C; PLA2, phospholipase A2; PLD, phospholipase D; PTCA, percutaneous transluminal coronary angioplasty; ROS, reactive oxygen species; SES, sirolimus-eluting stents; SOD, superoxide dismutases; SQR, sulfide quinone reductase; T2D, type 2 diabetes mellitus; TGF, transforming growth factor; VCAM-1, vascular cell adhesion molecule-1; VSMCs, vascular smooth muscle cells; ZES, zotarolimus-eluting stent; α-SMA, alpha-smooth muscle actin.

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https://doi.org/10.1016/j.ijcard.2018.05.046
0167-5273/

diabetes mellitus, complex lesions, bypass grafts, bifurcations, and deployment of longer stents [11,12]. There are significant overlaps in the cause of restenosis after BMS and DES deployment, although emerging data indicate that subtle differences may exist (i.e. development of in-stent neoatherosclerosis) that are more common and faster after DES deployment [13].

The three major pathogenic mechanisms that underlie restenosis are the early elastic return (recoil), the vascular remodeling and the neointimal hyperplasia. In particular, the stent deployment after balloon dilatation causes denudation of endothelial cells within the stented segment. The resulting healing arterial ulcers promote ISR and thrombosis by interfering with the local endothelial repair processes and by perturbation of local flow hemodynamics [14].

Another important pathological consequence after PCI is the in-stent thrombosis. Acute and early stent thrombosis are related to mechanical issues with the stents, inadequate platelet inhibition, or prothrombotic risk factors [15], delayed re-endothelialization and inhibition of vascular repair after DES deployment [13,16].

2. Role of oxidative stress

Augmented reactive oxygen species (ROS), as a result of an excess in ROS generation not counterbalanced by the intrinsic antioxidant defense system, contribute significantly to the endothelial dysfunction, to the VSMCs proliferation and the consequent vascular complications following coronary revascularization [17,18]. Production of ROS is a strongly regulated process and plays a role in preserving cellular oxidative homeostasis and propagation of cellular signalling pathways. ROS are produced by various biological systems, including uncoupling of nitric oxide synthase (NOS), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondrial uncoupled respiration, xanthine oxidase, and cyclooxygenase [19]. Mechanisms responsible of ROS depletion are superoxide dismutases (SOD), uncoupling proteins and thioredoxins [19].

In this article, we will review knowledge on the role of increased oxidative stress in the promotion of endothelial dysfunction, vascular remodeling, ISR and in-stent thrombosis that may occur after coronary revascularization.

2.1. Cytoplasmic ROS production

Seven isoforms of NADPH oxidase or Nox (Nox1, Nox2, Nox3, Nox4, Nox5, Duox1 and Duox2) are transmembrane proteins with multiple cytosolic and transmembrane subunits [19]. They are activated by several molecular pathways, such as protein kinase C (PKC), phospholipase D (PLD), phospholipase A2 (PLA2), Rho Kinase. The p47phox, p67phox and p40phox subunits are located in the cytosol, whereas p22phox and the catalytic gp91phox subunits are located in the cell membrane forming the complex cytochrome *b*558 [19].

When stimulated, p47phox becomes phosphorylated and the cytosolic subunits translocate to the cell membrane. Herein, together with NOXA1 and Rac 1/2, forms a complex with Nox1 and p22phox. This event allows the transfer of electrons from the substrate to O_2, forming the superoxide anion $O2^{\bullet -}$. Nox2 is constitutively expressed in endothelial cells [20], whereas Nox1 and Nox4 are upregulated by pro-inflammatory cytokines, growth factors, hormones, vasoactive agents, oxidized lipoproteins [19].

All isoforms of the homodimeric enzyme NOS (neuronal, endothelial and inducible) utilize L-arginine as substrate and O_2 and NADPH as co-substrates. The electron transfer from NADPH to L-arginine is facilitated by the essential cofactor tetrahydrobiopterin [21]. In case of suboptimal bioavalability of tetrahydrobiopterin or L-arginine, NOS becomes uncoupled and generates $O2^{\bullet -}$ instead of nitric oxide (NO) [22].

The homodimer xanthine oxidoreductase catalyzes the terminal two reactions in purine degradation: oxidation of hypoxanthine to xanthine and of xanthine to uric acid. Each subunit consists of four redox center: a molybdenum cofactor, one flavin adenine dinucleotide (FAD) site and two Fe/S clusters [23]. During inflammatory conditions, the dehydrogenase form of the enzyme is converted into the oxidase one, xanthine oxidase, which is characterized by an increased affinity for O_2 at the FAD site, resulting in univalent and divalent electron transfer to O_2, producing $O2^{\bullet -}$ and hydrogen peroxide (H_2O_2) respectively [23].

2.2. Mitochondrial ROS production

Mitochondria are particularly abundant in muscle cells due to their role in the energy production in eukaryotic cells. They include four compartments: the outer membrane, the intermembrane space, the inner membrane and the matrix. The inner membrane includes the respiratory complexes and the ATP synthase [24].

Mitochondria produce ATP with a mechanism mediated by the oxidative phosphorylation (OXPHOS) via electron transfer through the multimeric complexes of the respiratory chain [25]. During this process, anion superoxide is produced by the Nox4 subunit of NADPH oxidase through the one-electron reduction of O_2. Superoxide is the proximal ROS produced and it is transformed into H_2O_2 through the action of SODs within both the mitochondria and the cytosol. Sites wherein electrons can early reduce O_2, producing superoxide, are present in the Complexes I, II, and III of the OXPHOS chain [26,27]. Complex III produces ROS on both sides of the mitochondrial inner membrane, whereas complexes I and II produce ROS only into the matrix [28]. Complex III accepts electrons donated to coenzyme Q by mitochondria complexes I and II and transfers them to cytochrome *c* which reduces only one electron. The coenzyme Q, instead, is able to accept two electrons from the complexes I or II. The complex III sequentially removes each electron from reduced coenzyme Q (ubiquinol, QH2). After removal of the first electron, the radical ubisemiquinone (QH) is formed from ubiquinol. The unpaired electron of ubisemiquinone is transferred to the cytochrome *b* center of complex III. However, this electron can also react with O_2 to form $O2^{\bullet -}$ (27). In addition, Nox2 increases the production of mitochondrial ROS by reverse electron transfer, due to the interaction between mitochondria and NADPH oxidase-derived $O_2^{\bullet -}$ [29].

Changes in respiratory rate or mitochondrial inner membrane potential, post-translational modifications or damage to the respiratory chain can influence the rate of ROS production. ROS increase when mitochondria redox potential is significantly reduced or oxidized, this occurring at the extremes of intracellular and intra-mitochondrial redox potential. The latter depends on redox couples involved in both ROS generation (NADH/NAD+) and ROS scavenging (NADPH/NADP+) [27,30].

ROS-mediated insult causes lipid, protein, and, most of all, mitochondrial DNA (mtDNA) damage [26].

3. Oxidative stress and the consequences of coronary interventions on vascular remodeling

PCI, PTCA and stent deployment induce pathophysiological levels of vascular ROS production, reduction of nitric oxide (NO) bioavailability and an impairment of endothelium-dependent vasodilatation [31,32] (Fig. 1).

The endothelial dysfunction correlates to the type of procedure and to the type of the inserted stent. BMS deployment has been associated with more severe impairment of endothelium dependent vasomotor function in comparison with balloon angioplasty [33]. Endothelial dysfunction after DES is multifactorial and more pronounced than after BMS implantation [34]. The direct influence of the eluting drug promotes a decrease in endothelial NO synthesis and of its protective functions [35] which, in physiological conditions, prevent VSMCs growth, platelet aggregation, and leukocyte adhesion [36].

Several studies involving animal models analyzed at the molecular level the consequences of PCI, with or without the deployment of different types of stents, on vascular remodeling.

Please cite this article as: G. Gallo, et al., Role of oxidative stress in the process of vascular remodeling following coronary revascularization, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.05.046