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STATE-OF-THE-ART PAPER

Oxidative Stress and Pathological Changes After Coronary Artery Interventions

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Oxidative stress greatly influences the pathogenesis of various cardiovascular disorders. Coronary interventions, including balloon angioplasty and coronary stent implantation, are associated with increased vascular levels of reactive oxygen species in conjunction with altered endothelial cell and smooth muscle cell function. These alterations potentially lead to restenosis, thrombosis, or endothelial dysfunction in the treated artery. Therefore, the understanding of the pathophysiological role of reactive oxygen species (ROS) generated during or after coronary interventions, or both, is essential to improve the success rate of these procedures. Superoxide $O_2^{\cdot-}$ anions, whether derived from uncoupled endothelial nitric oxide synthase, nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase, or mitochondria, are among the most harmful ROS. $O_2^{\cdot-}$ can scavenge nitric oxide, modify proteins and nucleotides, and induce proinflammatory signaling, which may lead to greater ROS production. Current innovations in stent technologies, including biodegradable stents, nitric oxide donor-coated stents, and a new generation of drug-eluting stents, therefore address persistent oxidative stress and reduced nitric oxide bioavailability after percutaneous coronary interventions. This review discusses the molecular mechanisms of ROS generation after coronary interventions, the related pathological events—including restenosis, endothelial dysfunction, and stent thrombosis—and possible therapeutic ways forward. (J Am Coll Cardiol 2013;61: 1471–81) © 2013 by the American College of Cardiology Foundation

Oxidative stress, characterized by an imbalance between the generation reactive oxygen species (ROS) and the capacity of the intrinsic antioxidant defense system, has been implicated in the pathogenesis of cardiovascular diseases. ROS are produced by various biological systems, including uncoupling of nitric oxide synthase (NOS), nicotinamide adenine dinucleotide phosphate oxidase (NOX), mitochondrial uncoupled respiration, xanthine oxidase, and cyclooxygenase (Fig. 1). NOS is a homodimeric enzyme that produces superoxide ($O_2^{\cdot-}$) when uncoupled, that is, because of a deficiency in tetrahydrobiopterin or a lack of L-arginine (1). Seven isoforms of NOX are transmembrane proteins with multiple cytosolic and transmembranous subunits that are able to transport electrons across the membrane to produce $O_2^{\cdot-}$ (2). Mitochondria is the nonenzymatic source of ROS that mainly emerges from complex I and III of the respiratory chain (3,4). Another vascular source of ROS is xanthine oxidase, which uses O_2 as an electron acceptor to produce $O_2^{\cdot-}$. In addition, $O_2^{\cdot-}$ can be generated as a product of arachidonic acid metabolism by cyclooxygenase (5). Although excessive ROS production is damaging, a lack of ROS generation (i.e., reductive stress) also is detrimental (6). The redox window hypothesis suggests that a shift in the redox state to an overly reductive or oxidative environment is harmful and that only when the redox environment is in balance can these radicals be biologically beneficial (7).

Percutaneous coronary interventions (PCI), for example, percutaneous transluminal coronary angioplasty (PTCA) and stent deployment, induce pathophysiological levels of vascular ROS production (8,9), leading to post-procedural pathological changes, including restenosis, stent thrombosis, and endothelial dysfunction. This review discusses the generation of ROS after different types of PCI and the post-procedural pathological consequences and summarizes possible preventive and therapeutic strategies.

ROS Generation After PTCA

Immediately or several days after balloon injury, $O_2^{\cdot-}$ levels are elevated in the vessel wall (8,10), which colocalize to smooth muscle cells (SMC) (8). In addition, $O_2^{\cdot-}$ generation is observed in the adventitial layers, implying the role of

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Abbreviations and Acronyms

BES = biolimus-eluting stent(s)

BMS = bare-metal stent(s)

DES = drug-eluting stent(s)

eNOS = endothelial nitric oxide synthase

NO = nitric oxide

NOS = nitric oxide synthase

NOX = nicotinamide adenine dinucleotide phosphate oxidase

$O_2^{\cdot-}$ = superoxide

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

PTCA = percutaneous transluminal coronary angioplasty

ROS = reactive oxygen species

SES = sirolimus-eluting stent(s)

SMC = smooth muscle cells

fibroblasts in the production of the free radical. This is mediated by NOX, because the $O_2^{\cdot-}$ generation was abolished after diphenyleneiodonium administration (11). Further, messenger ribonucleic acid and protein expression of nox1, nox4, gp91 phox, and p22phox are upregulated in rat carotid arteries after balloon injury (8). Xanthine oxidase does not seem to be involved in $O_2^{\cdot-}$ generation after balloon angioplasty (11). It also has been suggested that inducible NOS is not involved in the generation of $O_2^{\cdot-}$ because the inhibition of this enzyme does not affect the level of ROS after balloon injury in pig coronaries (11). $O_2^{\cdot-}$ anions can promote proliferation of vascular SMC and fibroblasts (11). Indeed, balloon angioplasty rapidly induces p38 mitogen–activated protein kinase, which also is activated by ROS and is involved in SMC hypertrophy and neointimal hyperplasia (12). NOS may play a significant role in the prevention of neointimal formation and, thereby, restenosis after balloon injury (13,14). Nevertheless, the underlying mechanisms remain to be elucidated. Studies regarding PTCA-associated oxidative stress are summarized in Table 1.

ROS Production After Bare-Metal Stent Deployment

Similar to balloon angioplasty, bare-metal stent (BMS) deployment in human coronary arteries can induce oxidative stress (9). A significant increase of $O_2^{\cdot-}$ production after BMS deployment also has been reported in the rabbit arterial wall, which is associated with increased expression of 2 NOX subunits, p22phox and gp91phox (15). Studies regarding BMS-associated oxidative stress are summarized in Table 1.

ROS Production After DES Deployment

Paclitaxel-eluting stent (PES) deployment in pig coronary arteries induces a higher production of $O_2^{\cdot-}$ compared with BMS deployment and decreased nitric oxide (NO) bioavailability (16). Paclitaxel causes ROS generation by enhancing NOX activity (17) and stimulating mitochondrial ROS production (18). Sirolimus administration increases $O_2^{\cdot-}$ production in the aorta and heart of rats, leading to reduced NO bioavailability. Here, NOX and mitochondria were found to be the major ROS generators (19). Importantly, patients with stable coronary artery disease who received sirolimus-eluting stents (SES) have a different behavior of oxidative stress compared with those with BMS, and this could contribute to the difference in restenosis rates between these 2 types of stents (9). See also Table 1.

PCI-Associated Pathological Events

Restenosis. ROS contribute to the initial apoptosis, proliferation, and migration of vascular SMC and adventitial myofibroblasts, processes that occur shortly after balloon angioplasty or stent deployment, leading to restenosis (Figs. 2 and 3) (20,21). As in injuries occurring after balloon angioplasty, restenosis after BMS deployment can be explained by ROS-associated neointimal formation (22,23). Administration of an angiotensin II type 1 receptor blocker attenuates in-stent restenosis by reducing NOX expression, leading to a decrease in $O_2^{\cdot-}$ production in stented rabbit iliac artery (15). An association between NOX and restenosis has been investigated in NOX2$^{-/-}$ mice that showed reduced neointimal proliferation and leukocyte accumulation after wire-induced vascular injury in the femoral arteries (24). Inflammatory response after balloon angioplasty or BMS deployment also has been associated with neointimal formation (25). Because inflammatory cells are capable of generating $O_2^{\cdot-}$, their recruitment may lead to oxidative stress enhancement and induction of restenosis. It has been shown in stented human coronary arteries that ROS production by activated neutrophils plays a role in the mechanism of restenosis (26).

The precursors of antiproliferative drugs eluted from drug-eluting stents (DES), including sirolimus (Cypher, Cordis, Miami Lakes, Florida), paclitaxel (Taxus, Boston Scientific, Natick, Massachusetts), zotarolimus (Endeavor and Resolute, Medtronic, Minneapolis, Minnesota), and everolimus (Xience, Abbott, Illinois, and Promus Element, Boston Scientific Corporation, Natick, Massachusetts), exert a potent antimitotic action. Sirolimus (rapamycin) and paclitaxel are cell cycle inhibitors working by inhibiting mammalian target of rapamycin (27) and interfering with microtubule assembly (28), respectively. Despite their efficacy, restenosis still occurs and is more frequent in some circumstances, for example, diabetes mellitus, complex lesions, bypass grafts, bifurcations, and deployment of longer stents (29). There are significant overlaps in the cause of restenosis after BMS and DES deployment, although emerging data indicate that subtle differences may exist (e.g., development of in-stent neoatherosclerosis) that are more common and faster after DES deployment (30). The biological effect of DES on neointimal proliferation has uncovered the contribution of 2 other aspects of restenosis after BMS: mechanical-related failures (31) and technique-related factors (32). Further, hypersensitivity to BMS and

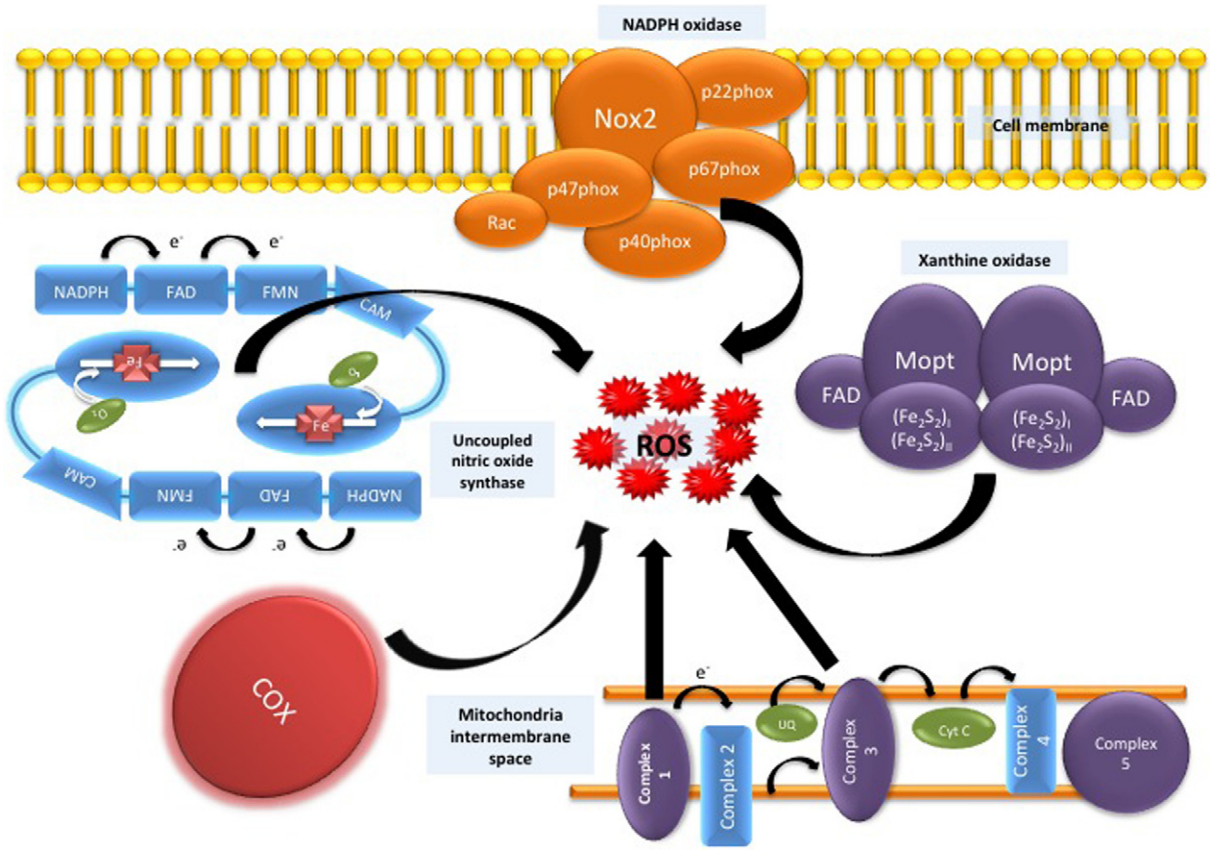

Figure 1 **Reactive Oxygen Species Production in the Vascular Wall**

Reactive oxygen species (ROS) can be generated by different enzymatic systems, namely nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), uncoupled nitric oxide synthase (NOS), xanthine oxidase (XOD), and cyclooxygenase (COX). Complex 1 and 3 in the respiratory chain in mitochondria also contribute to ROS production in the vasculature. CAM = calmodulin; Cyt C = cytochrome C; e^- = electron; FAD = flavin adenine dinucleotide; Fe = iron; Fe_2S_2 = ferredoxin; FMN = flavin mononucleotide; Mopt = molybdopterine; O_2 = oxygen; UQ = ubiquitine.

DES has been implicated in the inflammatory process leading to restenosis (33,34). Different factors contributing to restenosis are depicted in Figure 4.

Endothelial dysfunction. BMS deployment has been associated with more severe impairment of endothelium-dependent vasomotor function in comparison with balloon angioplasty (35). Endothelial dysfunction after DES is more pronounced than after BMS implantation (36). Both PES and SES impair endothelium dependent relaxation responses to acetylcholine in the adjacent and remote distal nonstented segments (37). Further, PES are able to induce paradoxical vasoconstriction in the proximal and distal segments of the stented vessel (38). Paclitaxel, sirolimus, and everolimus reduce endothelial nitric oxide synthase (eNOS) expression (39), leading to decreased NO bioavailability, which may explain vasomotor disturbance after DES deployment. The use of multiple stents to cover long segments of blood vessels also decreases production of NO and other endothelium-derived vasodilators, leading to endothelial dysfunction (40).

The pathogenesis of DES-induced endothelial dysfunction is multifactorial. A major determinant is a decrease in endothelial NO synthesis resulting from direct influence of the eluting drug (41). As previously mentioned, sirolimus administration increases $O_2^{\cdot -}$ production, leading to reduced NO bioavailability (19). In addition, PES deployment induces high production of $O_2^{\cdot -}$, leading to decreased NO levels and impairment of endothelium-dependent relaxation (16). ROS generation also interferes with other NO protective functions, for example, preventing vascular SMC growth, platelet aggregation, and leukocyte adhesion (42). Another explanation for DES-related endothelial dysfunction is an acute or delayed hypersensitivity reaction to DES components, for example, the strut, polymer, eluting drug, or a combination thereof (16).

In-stent thrombosis. Acute and early stent thrombosis are related to mechanical issues with the stents, inadequate platelet inhibition, or prothrombotic risk factors (43). Late and very late stent thrombosis have been associated with delayed re-endothelialization and inhibition of vascular

Table 1 Studies Regarding Coronary Intervention-Associated Oxidative Stress

Source of ROS	Species	Parameter(s)	First Author, Year (Ref. #)
Balloon angioplasty-induced ROS			
Medial and neointimal SMCs and adventitial fibroblasts	Rat carotid artery	$O_2^{\cdot-}$ production, NOX mRNA expression	Szocs et al., 2002 (8)
Cells present in the media and neointima	Pig coronary artery	$O_2^{\cdot-}$ production, vitamin C and E levels	Nunes et al., 1997 (10)
Adventitial fibroblasts	Pig coronary artery	$O_2^{\cdot-}$ production, NOX expression and activity, SOD activity	Shi et al., 2001 (11)
BMS-induced ROS			
Blood	Human coronary artery	Blood total peroxides levels, restenosis	Kochiadakis et al., 2009 (9)
Iliac ring	Cynomolgus monkey and rabbit iliac artery	$O_2^{\cdot-}$ production, NOX mRNA expression, proinflammatory markers mRNA expression, neointimal thickness	Ohtani et al., 2006 (15)
DES-induced ROS			
Coronary artery	Pig coronary artery	$O_2^{\cdot-}$ production, endothelial vasomotor function, neointimal thickness	Pendyala et al., 2009 (16)
Blood	Human blood	total peroxide levels	Kochiadakis et al., 2009 (9)
Aortic ring	Rat aorta (continuous sirolimus infusion)	$O_2^{\cdot-}$ production, NOX expression, NO synthesis, eNOS protein expression	Jabs et al., 2008 (19)

BMS = bare-metal stent(s); DES = drug-eluting stent(s); eNOS = endothelial nitric oxide synthase; mRNA = messenger ribonucleic acid; NO = nitric oxide; NOS = nitric oxide synthase; $O_2^{\cdot-}$ = superoxide; ROS = reactive oxygen species; SMC = smooth muscle cells; SOD = superoxide dismutase.

repair after DES deployment (44,45). The high rates of stent thrombosis in the first generation of DES had raised safety concerns. Therefore, a new generation of DES have been developed. A meta-analysis showed that late stent thrombosis was significantly lower with cobalt-chromium everolimus-eluting stent than with BMS, PES, SES, or zotarolimus-eluting stent (46). The pathological changes, including stent thrombosis, endothelial dysfunction, restenosis, and their relation with ROS generation, occurring after DES deployments are summarized in Figure 5.

Antioxidant and Concomitant Medical Therapies in PCI

Ascorbic acid, α-tocopherol, probucol, and succinobucol. Protective effects of antioxidants ascorbic acid and α-tocopherol on cardiovascular diseases have been conflicting (47–50). Regarding the use of these antioxidants after PCI, although animal studies show a protective effect on neointimal formation (51,52), clinical trials show contrary outcomes (53,54). Several clinical studies (55,56) showed a reduction in restenosis after probucol administration. Although reducing restenosis after angioplasty, probucol has no effect on stent restenosis after BMS deployment (57). It is only protective when combined with other drugs, such as cilostazol (58) or candesartan (59). This discrepancy may be the result of the difference in treatment duration (57) or the presence of confounding factors (60). Nevertheless, probucol is no longer available for clinical use because of its proarrhythmogenic effect (61). Succinobucol is a derivate of probucol with an antioxidant effect (62) that lacks proarrhythmogenic properties (63). Succinobucol administration after balloon angioplasty and stent deployment leads to reduction of restenosis (63).

β-adrenergic receptor blockers. The third-generation β-blocker nebivolol reduces $O_2^{\cdot-}$ levels by inhibiting vascular NOX expression and activity (64) and by preventing eNOS uncoupling (65). In addition, this drug increases eNOS activity (66) and restores endothelium-dependent vasodilation (67). A clinical trial of the antioxidant effect of carvedilol on restenosis showed negative results (68). However, a pitfall in the study design may invalidate the conclusions of this study (69). Implantation of carvedilol-eluting stents resulted in reduction of neointimal hyperplasia in porcine coronary arteries (70). A small trial in patients reported that carvedilol-eluting stents show a tendency to inhibit neointimal hyperplasia (71). The antioxidant property of β-blockers seems to be limited only to the third-generation groups (64).

Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists. Stimulation of angiotensin II type 1 receptors after arterial injury induces oxidative stress, leading to neointimal formation. Treatment with angiotensin-converting enzyme inhibitors (72) and angiotensin II type 1 receptor antagonists (73) decreases ROS generation by reducing activity of NOX, attenuating eNOS uncoupling, and increasing $O_2^{\cdot-}$ dismutase levels (74). Despite evidence of neointimal inhibition in animal models of restenosis (75), 2 large-scale trials with angiotensin-converting enzyme inhibitors failed to show any benefit of these drugs (76,77). Although the angiotensin II type 1 receptor antagonist prevents neointimal formation in animal studies (78,79), the results of clinical trials seem to be conflicting (80,81). A protective effect of candesartan, however, was observed in the subgroup of patients with smaller vessel diameters, suggesting that angiotensin II type 1 receptor blockers are only beneficial for certain groups of patients (81).

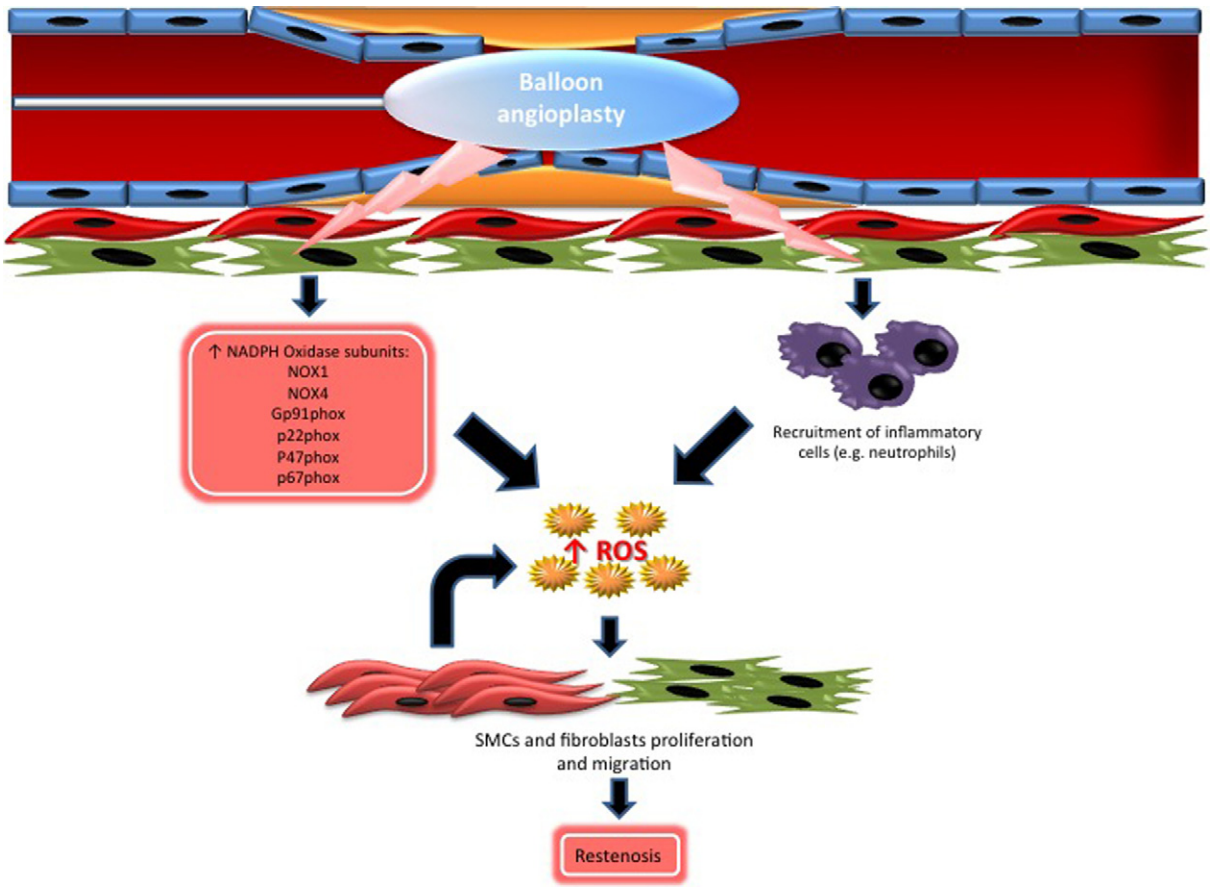

Figure 2 **ROS Generation and Associated Pathological Changes After Balloon Angioplasty**

Balloon angioplasty induces an increase in ROS production from vascular smooth muscle cells (SMC) and adventitial fibroblasts via the NOX pathway and vascular injury-induced inflammatory response. ROS stimulate SMC and fibroblast proliferation and migration through the internal elastic lamina to form a neointimal layer leading to restenosis. Proliferative neointimal cells also generate ROS, enhancing the oxidative stress after balloon angioplasty. Abbreviations as in Figure 1.

Statins. Among the pleiotropic effects of statins, their antioxidant effect may explain additional beneficial contribution of these drugs to ameliorate various pathological processes. Statins inhibit $O_2^{\cdot -}$ formation by preventing isoprenylation of p21 RAC, which is essential for assembling NOX (82) and reducing NOX4, p47phox (83), and p22phox (84) expression. Further, statins up-regulate vascular eNOS expression and activity (83) and prevent the formation of NOS-derived $O_2^{\cdot -}$ (85). Administration of statins in patients undergoing stent deployment reduces the risk of myocardial injury (86) and stent thrombosis (87). Statins exert antiproliferative effects without endothelium impairment. It has been shown that cerivastatin-eluting stents significantly decrease neointimal hyperplasia and inflammatory responses, without endothelial dysfunction, in porcine coronary arteries (88).

Other concomitant therapies with antioxidant properties. The antioxidant effect of aspirin is mediated through cyclooxygenase-2 inhibition and its interaction with NOX (89). The role of aspirin in the prevention of restenosis after PCI has not been explored thoroughly. Amlodipine has been studied for its effect on restenosis prevention. Although it did not decrease luminal loss, the incidence of repeated interventions was reduced significantly (90). Pentaerythritol tetranitrate is a long-acting nitrate that reduces eNOS uncoupling and NOX activation (91), leading to prevention of endothelial dysfunction and plaque formation in animal models (92,93). Despite their potential as a therapeutic strategy against restenosis, there is no study so far investigating the role of long-acting nitrate in PCI.

The results demonstrated by the above-mentioned trials indicate that the effect of antioxidant treatment to ameliorate restenosis or thrombosis after PCI deployment remains debatable. The conflicting results are probably the result of differences in type of antioxidants (broad spectrum vs. specific targeting antioxidants), dosage, supplementation methods and duration (94), and the type of stented vessel and lesions (81). In addition, genetic factors influence individual response to antioxi-

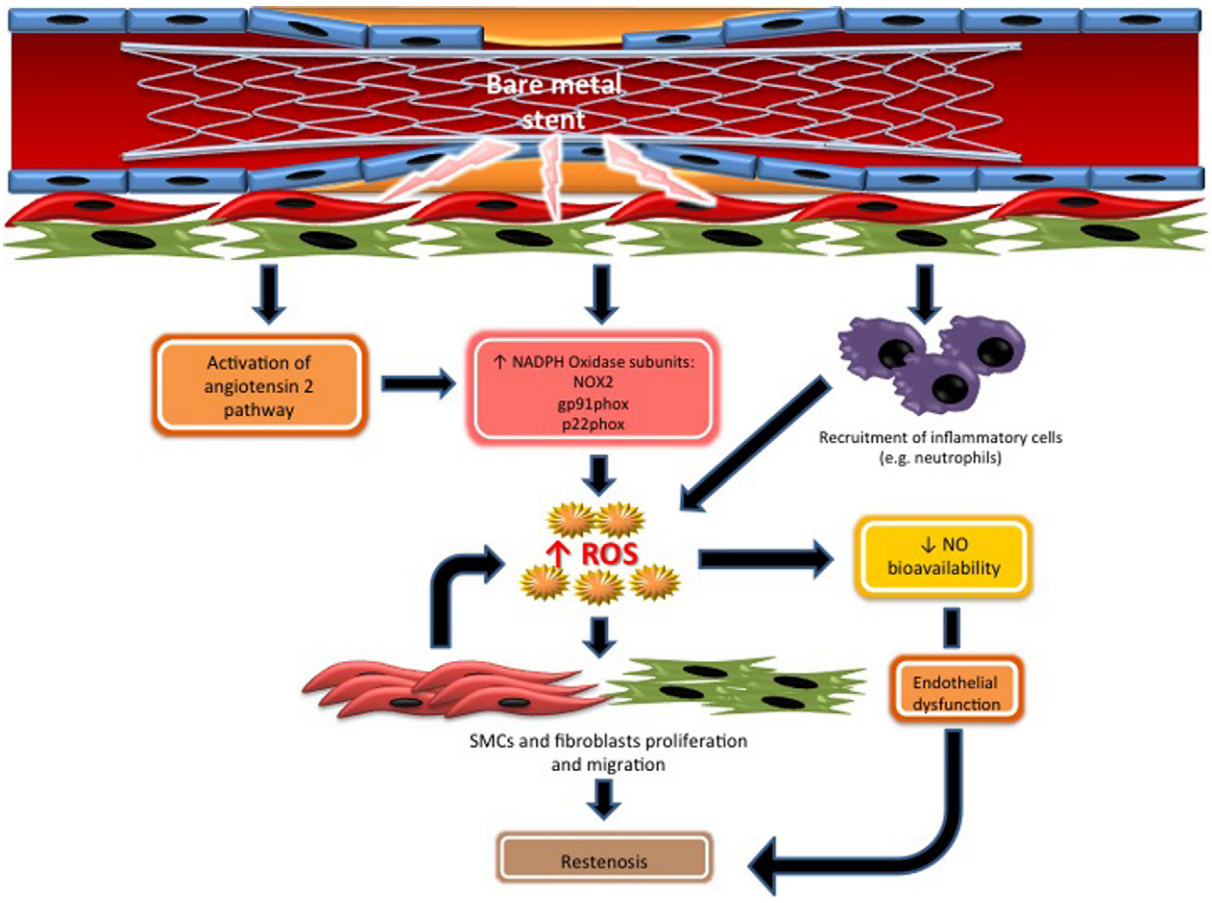

Figure 3 **Bare-Metal Stents Induce ROS Production with Subsequent Vascular Damage**

After bare-metal stent (BMS) deployment, there is recruitment of inflammatory cells, such as neutrophils. These cells produce ROS, which contribute to the vascular pathological characteristics after BMS deployment. BMS deployment increases expression of NOX subunits leading to additional superoxide ($O_2^{\cdot -}$) production. This pathway is considered to be the main ROS-generating pathway during coronary stent implantation. $O_2^{\cdot -}$ anions induce vascular SMC and fibroblast proliferation and migration, leading to neointimal growth and restenosis. The proliferating neointimal cells produce ROS, leading to more accumulation of the radicals that may react with nitric oxide (NO), resulting in decreased NO bioavailability with subsequent endothelial dysfunction also contributing to restenosis. Abbreviations as in Figures 1 and 2.

dants, (95) suggesting that only some individuals respond well to certain therapies.

Perspectives

The high levels of $O_2^{\cdot -}$ produced after various coronary interventions have been associated with the initiation of migration and proliferation of SMC, leading to restenosis and reduction of NO bioavailability, which results in an impairment of endothelium-dependent vasodilatation and development of stent thrombosis. Therefore, ROS seem to play a significant role in the development of those pathological events after coronary interventions. The sources of ROS are not completely clear, but NOX seems to play a major role.

The use of coronary artery stents, especially DES, remains hampered by the occurrence of adverse events of endothelial dysfunction and late-stent thrombosis (96,97). To overcome these problems, several attempts have been made to improve the stent design and polymer and drug coating the stents. Incorporation of endothelium-specific factors into the stent coating can provide improved clinical treatment. Several NO-releasing materials have been studied in the form of films or hydrogels and have been shown to reduce platelet adhesion and intimal hyperplasia in vitro and in vivo (98–100). A use of a nanofibrous matrix containing NO leads to stimulation of in vitro proliferation of endothelial cells, reduction of SMC proliferation, and decline in platelet attachment (101). Such an NO-eluting nanofibrous matrix has the potential of being applied to various cardiovascular implants, thereby providing a physiological-like endothelial environment. EES have some important differences in comparison with the first-generation DES, including a thinner stent strut, a lower durable polymer load, a newer drug, and a lower drug dose (102). These stents have been proven superior with a better safety profile than the first-generation DES in a number of

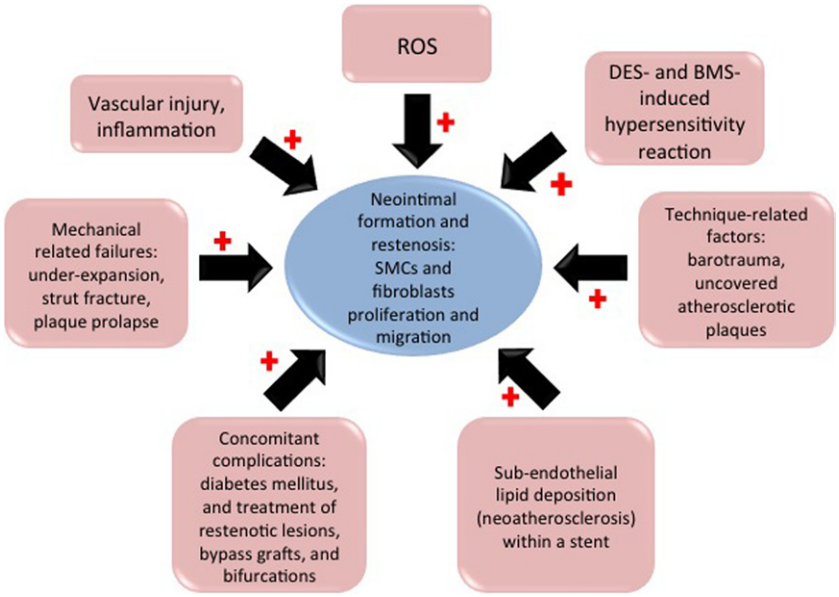

Figure 4 **Different Factors Contributing to Restenosis**

Several stent-related factors (i.e., ROS formation, vascular injuries, stent-induced hypersensitivity, subendothelial lipid deposition, and mechanical- and technique-related failures) can induce SMC and fibroblast proliferation and migration, leading to restenosis. Concomitant complications also can increase the rate of restenosis after stent deployment. DES = drug-eluting stent(s). Abbreviations as in Figures 1, 2, and 3.

randomized controlled trials (103–105) and meta-analyses (46,102), and therefore are the most widely used DES at present in the United States. In addition to everolimus, biolimus is another sirolimus derivative that has been studied increasingly. Biolimus is the -limus family member that was developed specifically for local delivery to coronary arteries (106). Biolimus-eluting stents (BES) (Nobori, Terumo, Leuven, Belgium) are equipped with a biodegradable polymer, polylactic acid, in which the biolimus is incorporated and applied only to the abluminal surface of a flexible stainless steel stent (107). Several large clinical trials have compared BES and SES (107–110). BES performance is superior in some subpopulations such as in myocardial infarction patients with ST-segment elevation (109), and these stents show a lower risk of very late stent thrombosis (110). By reducing the risk of very late stent thrombosis-related cardiac events, this stent may improve long-term clinical outcomes for up to 4 years compared with SES.

Another attempt to improve coronary stents is to reduce polymer-induced inflammation or hypersensitivity by incorporating biodegradable polymer into the stents. SES with biodegradable polymer have been shown to be noninferior to permanent polymer-based SES in terms of clinical efficacy and stent thrombosis (111,112). Another biodegradable polymer-based DES is BES, which better preserve endothelium-dependent coronary vasomotor response in comparison with SES and PES (36,113).

The role of eNOS increasingly has been studied to develop a new strategy to reduce PCI-induced adverse pathological reactions. As mentioned, several NO-releasing material-based stents show promising outcomes. However, whether the addition of an NO donor to the stent coating would be sufficient to prevent endothelial dysfunction induced by a coronary intervention, because administration of NO does not reduce the eNOS uncoupling-dependent ROS generation, is unclear. eNOS-eluting stents have been tested in vivo and shown to reduce restenosis and to accelerate re-endothelialization (114,115). Although NOX seems to play an important role in ROS generation after vascular damage, a role for eNOS cannot be excluded. Uncoupled eNOS generates ROS and it seems that antiproliferative drugs used in DES reduce functional eNOS with subsequent declined NO bioavailability, which may lead to stent thrombosis and vasomotor disturbance (39,40). The increased level of oxidative radicals in the dog coronary sinus after PTCA was reduced after inhibition of eNOS with NG-nitro-L-arginine (116). Modulation of eNOS by administration of tetrahydrobiopterin or folic acid is another potential way to overcome complications after coronary interventions (117).

Conclusions

Various coronary interventions, namely balloon angioplasty and implantation of BMS and DES, can induce ROS generation from different enzymatic systems and mitochondria, leading to pathological-related events, including restenosis, endothelial dysfunction, and stent thrombosis.

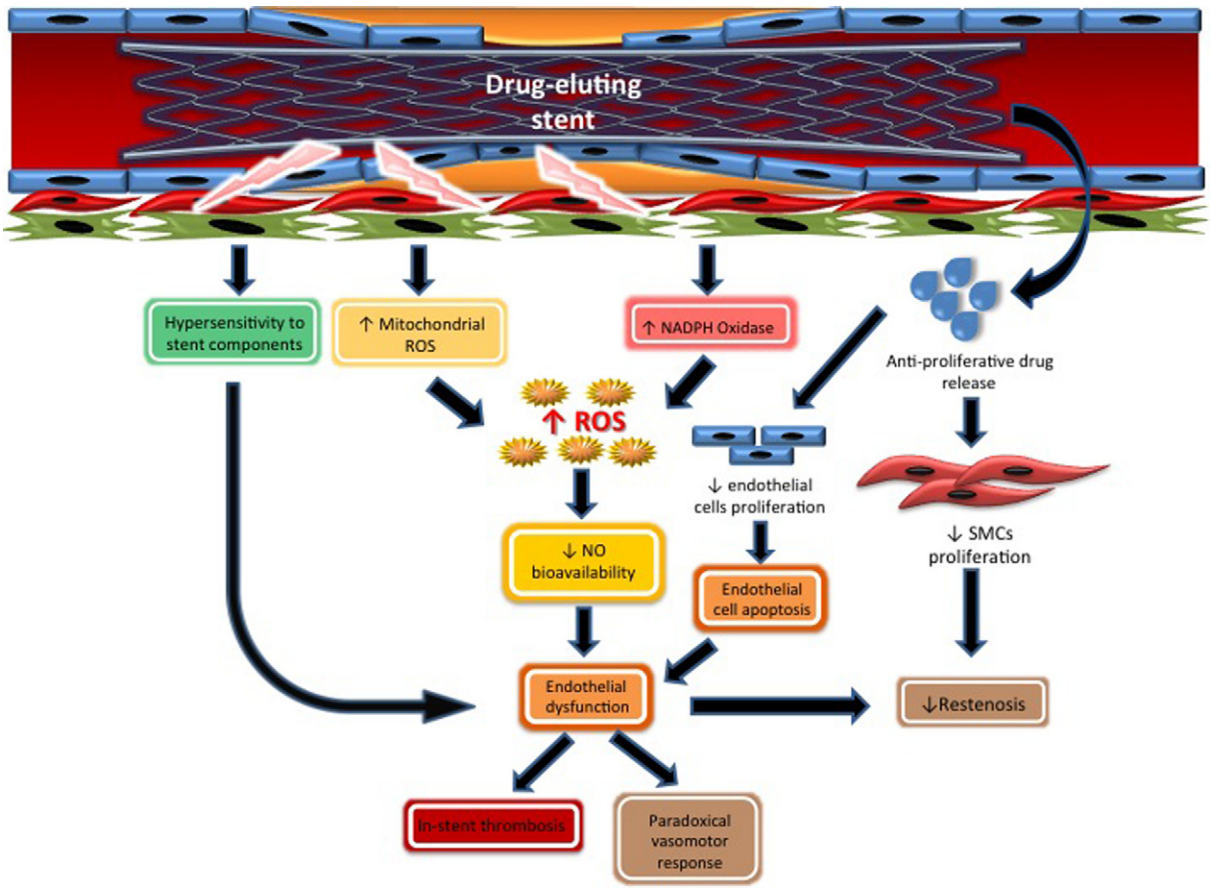

Figure 5 **DES-Induced Oxidative Stress and Related Pathological Changes in the Blood Vessel Wall**

DES are a double-edged sword. On the one hand, they prevent restenosis by elution of an antiproliferative drug that inhibits SMC proliferation and migration. On the other hand, they contribute to vascular abnormalities by induction of ROS in the vessel wall. NOX and mitochondria play a role in the vascular ROS generation after DES deployment, leading to reduced NO bioavailability and endothelial dysfunction. Another cause of endothelial dysfunction after DES deployment is an acute or delayed hypersensitivity reaction to DES components. The endothelial dysfunction ultimately leads to development of late in-stent thrombosis, disturbed vasomotor response, and restenosis. Abbreviations as in Figures 1, 2, 3, and 4.

Given that coronary interventions reduce eNOS with subsequent decline in NO bioavailability, the role of eNOS in generating $O_2^{\cdot-}$ after coronary interventions cannot be disregarded.

Several new approaches are being developed to overcome the adverse events after coronary interventions, including improvement of stent design, incorporation of biodegradable stents, newer DES, and eNOS-based coated stents. Because there is no single approach available that can completely overcome PCI-induced adverse reactions, more innovations are needed to improve the efficacy and safety profile of the coronary intervention further.

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Key Words: bare-metal stent(s) ■ drug-eluting stent(s) ■ endothelial dysfunction ■ nitric oxide synthase ■ percutaneous coronary intervention ■ reactive oxygen species ■ superoxide.