Mechanisms of oxidative stress and vascular dysfunction
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The endothelium regulates vascular homeostasis through local elaboration of mediators that modulate vascular tone, platelet adhesion, inflammation, fibrinolysis, and vascular growth. Impaired vascular function contributes to the pathogenesis of atherosclerosis and acute coronary syndromes. There is growing pathophysiological evidence that increased generation of reactive oxygen species and oxidative stress participates in proatherogenic mechanisms of vascular dysfunction and atherothrombosis. In this review, the role of oxidative stress in mechanisms of vascular dysfunction is discussed, and potential antioxidant strategies are reviewed.

The endothelium plays a critical part in the regulation of vascular function through elaboration of paracrine factors that maintain vascular tone, inhibit platelet and inflammatory cell adhesion, promote fibrinolysis, and limit vascular proliferation. Endothelial dysfunction refers to a pathophysiological disease state in which homeostatic functions of endothelial cells are perturbed promoting vasospasm, thrombosis, intimal growth, inflammation, and plaque rupture leading to tissue ischaemia, atherothrombosis, and infarction. Impaired endothelial function is associated with atherothrombotic risk factors and atherothrombotic disease, is pathophysiological linked to acute cardiovascular syndromes, and provides prognostic information with regard to increased cardiovascular risk.

A central feature of impaired endothelial function in the presence of cardiac risk factors and under pathological conditions is impairment in endothelium-derived nitric oxide (EDNO) bioactivity. Nitric oxide is produced in endothelial cells from the conversion of L-arginine to L-citrulline through the tightly regulated activity of (endothelial) nitric oxide synthase. EDNO regulates vascular tone through a dilator action on vascular smooth muscle cells that depends on soluble guanylyl cyclase activation and consequent increase in intracellular cyclic 3',5'-guanosine monophosphate. Additional antiatherogenic functions of EDNO relate to inhibition of platelet activity, leucocyte adhesion, and vascular smooth muscle cell proliferation. Reduced nitric oxide synthesis or inactivation appears to be a common functional disturbance in the presence of cardiac risk factors and atherothrombosis. Other abnormalities in endothelial function relate, in part, to increased expression of adhesion molecules supporting inflammatory cell recruitment to the vessel wall; enhanced release of contractile agents such as angiotensin-II that promote vascular growth and alter vascular tone; and loss of antithrombotic function through reduced production of prostacyclin and fibrinolytic factors.

Mechanisms underlying impaired endothelial function in various disease states such as hypertension, diabetes mellitus, hypercholesterolaemia, and atherothrombosis are likely multifactorial. There is growing evidence that oxidative stress (defined as an imbalance between endogenous oxidants and antioxidants in favour of the former) contributes to mechanisms of vascular dysfunction. These observations fit well with the recognition that increased oxidative stress may be central to the atherogenic process. In this review, we will discuss the role of oxidative stress in endothelial dysfunction and its contribution to vascular disease, and discuss potential therapeutic antioxidant strategies.

VASCULAR OXIDANT STRESS, IMPAIRED EDNO BIOACTION, AND LOW DENSITY LIPOPROTEIN OXIDATION

Mammalian cells produce energy by reducing molecular oxygen to water during aerobic respiration. During this process, intermediates referred to as reactive oxygen species are generated that include superoxide anion, hydroxyl radicals, and hydrogen peroxide (fig 1). Under homeostatic conditions, these molecules likely play a regulatory role in cellular function, and antioxidant defences modulate their steady state balance. Owing to their highly biologically reactive properties, reactive oxygen species have the potential to interact with proteins, lipids, and DNA, and their excessive production has been implicated in the pathogenesis of various disease states including aging, reperfusion injury, dementia, and atherosclerosis.

A dominant mechanism of impaired vascular nitric oxide bioavailability relates to its oxidative inactivation by superoxide. Superoxide anion rapidly reacts with nitric oxide and eliminates its biological activity. There is considerable evidence that vascular production of superoxide is increased in hypercholesterolaemia, diabetes mellitus, hypertension, and cigarette use. Arterial tissue isolated from rabbits fed a hypercholesterolaemic diet releases increased amounts of superoxide anion that is associated with impaired

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Abbreviations: ACE, angiotensin converting enzyme; EDNO, endothelium-derived nitric oxide; eNOS, endothelial nitric oxide synthase; HOPE (study), Heart Outcomes Prevention Evaluation (study); LDL, low density lipoprotein; MAPK, mitogen activated protein kinase; NADH/NAD(P)H, nicotinamide dinucleotide/ (phosphate); NFκB, nuclear factor kappa B; ox-LDL, oxidised low density lipoprotein; SOD, superoxide dismutase
In addition to LDL oxidation in vivo are incompletely understood, endothelial dysfunction.

Inhibiting endogenous copper-zinc SOD in normal vascular tissue decreases nitric oxide action. In patients, the finding that an infusion of recombinant human superoxide dismutase (SOD) improves acetylcholine-mediated coronary dilation further supports the importance of increased superoxide anion production as a mechanism of endothelial dysfunction. Inhibiting endogenous copper-zinc SOD in normal vascular tissue decreases nitric oxide action. In addition to abrogating the antiatherogenic effects of nitric oxide, the combination of superoxide anion with nitric oxide generates peroxynitrite, a highly reactive intermediate that fuels lipid peroxidation, generation of reactive aldehydes and nitrogen oxides, and protein nitration supporting proatherogenic modification of low density lipoprotein (LDL). The “oxidative modification hypothesis of atherosclerosis” refers to the central role of oxidised LDL (ox-LDL) in the atherosclerotic process and provides the basis for a mechanistic link between hypercholesterolaemia and vascular disease. This hypothesis proposes that LDL initially localises in the vascular subendothelial space and is subsequently oxidatively modified by resident vascular cells. Although mechanisms of LDL oxidation in vivo are incompletely understood, endothelial cells, vascular smooth muscle cells, and monocytes are collectively able to oxidise LDL. Macrophages within the vessel wall internalise ox-LDL via scavenger receptors, and develop into lipid-rich “foam cells”. In contrast to regulated uptake of native (unoxidised) LDL by apo B/E receptors, the incorporation of ox-LDL into foam cells through scavenger receptor pathways is not subject to negative feedback regulation. Thus, progressive lipid accumulation within lipid laden macrophages occurs in an unchecked manner, and is believed to represent a dominant mechanism of subintimal fatty streak evolution that characterises the earliest manifestations of atherosclerosis. Evidence that LDL oxidation occurs in vivo is supported by studies demonstrating that antibodies against ox-LDL react with atherosclerotic lesions but not normal arteries, and their titres correlate with extent of atherosclerosis.

In addition to fuelling lipid accumulation in foam cells, ox-LDL contributes to vascular dysfunction and atherosclerotic plaque formation by additional mechanisms. Ox-LDL stimulates expression of proinflammatory signals including monocyte chemotactic protein-1 and intercellular adhesion molecule-1 that facilitate monocyte recruitment and adhesion to the vessel wall. Further, ox-LDL directly inactivates nitric oxide, is cytotoxic to endothelial cells, stimulates vascular smooth muscle cell proliferation, and upregulates tissue factor and plasminogen activator inhibitor-1 expression that have the potential to support atherothrombosis.

In addition to LDL oxidation, reaction of reactive oxygen species with cell membrane bound fatty acids can promote a vicious cycle of continued oxidative damage, resulting in alterations in cell membrane permeability and functional impairment in cellular transport and signalling. For example, superoxide anion may combine with transition metal ions to form hydroxyl radical and hydrogen peroxide, which are also relevant to the molecular underpinnings of cellular dysfunction.

**Sources of Reactive Oxygen Species**

A variety of enzymatic and non-enzymatic sources of reactive oxygen species exist in blood vessels. The primary biochemical source of reactive oxygen species in the vasculature, particularly of superoxide, appears to be the membrane-associated nicotinamide dinucleotide (phosphate) (NADH/NAD(P)H) oxidase enzyme complex. This system catalyses the reduction of molecular oxygen using NAD(P)H as an electron donor, generating superoxide. The function of this enzyme complex is most easily understood in the context of the activated neutrophil, wherein it generates large amounts of toxic superoxide anion and other reactive oxygen derivatives important in bactericidal function. NADH/NAD(P)H oxidases are also functional in membranes of vascular endothelial and smooth muscle cells, and fibroblasts providing a constitutive source of superoxide anion. Various cytokines and hormones relevant to the pathogenesis of vascular disease and reduced nitric oxide bioavailability (fig 2) including angiotensin II, thrombin, tumour necrosis factor-α, and platelet derived growth factor upregulate vascular NADH/NAD(P)H oxidase activity and superoxide production. NADH/NAD(P)H oxidase activity plays an important part in angiotensin II-mediated hypertension. Administration of angiotensin II to rats raises blood pressure and increases vascular superoxide production, and this effect is dependent on activation of membrane-associated oxidases. Impaired arterial relaxation to acetylcholine and increased production of superoxide anion are also features of angiotensin II-induced, but not catecholamine-induced, hypertension. The increase in superoxide production and impairment in vessel relaxation during angiotensin II infusion is prevented by concurrent oxidase activity and superoxide production.
administration of losartan, suggesting that activation of this
oxidase system occurs by an angiotensin II receptor depend-
ent mechanism. Increased NADH/NAD(P)H oxidase activity
may also be important in other cardiovascular diseases.
Superoxide is increased in aortic tissue of cholesterol-fed rab-
bbits and in blood vessels of patients with coronary artery dis-
case, hypercholesterolaemia, and diabetes mellitus. There is
increased expression of angiotensin converting enzyme (ACE)
in atherosclerotic plaques that serve as a source of local angio-
tensin II production. Shoulder regions of coronary lesions are
characterised by more abundant NADH/NAD(P)H oxidase
dependent superoxide activity that may be relevant to plaque
inflammation and propensity for rupture. The link between
angiotensin II, ACE activity, and superoxide anion production
underscores the general importance of the renin-angiotensin
system in cardiovascular disease.

Another source of vascular superoxide is the xanthine ox-
idoreductase enzyme system that catalyses the oxidation of
hypoxanthine to xanthine during purine metabolism.39 Early
stages of atherosclerosis are associated with increased
superoxide anion production by endothelial cells, and inhibi-
tion of xanthine oxidase activity with oxypurinol improves
impaired vasodilation in hypercholesterolaemic patients.38 A
third potential source of vascular reactive oxygen species pro-
duction is endothelial nitric oxide synthase (eNOS). eNOS is a
cytochrome P450 reductase-like enzyme that requires cofac-
tors including tetrahydrobiopterin, flavin nucleotides, and
NAD(P)H for transfer of electrons to a guanidino nitrogen
of L-arginine to form nitric oxide. L-arginine and tetrahydrobi-
operitin deficiency are associated with uncoupling of the
L-arginine-nitric oxide pathway resulting in decreased forma-
tion of nitric oxide, and increased eNOS-mediated generation
of superoxide (and peroxynitrite). Tetrahydrobiopterin reple-
tion improves endothelial function in chronic smokers,26 and
augments nitric oxide bioactivity in hypercholesterolaemic
humans.27 Additional intracellular sources of reactive oxygen
species include mitochondrial respiration, cyclo-oxygenases,
lipooxygenases, and cytochrome P450 mono-oxynogenase, but
the relative contribution and clinical relevance of these enzy-
matic sources remain incompletely understood.

The biological activity of reactive oxygen species depends
upon their relative balance in relation to intracellular antioxi-
dant defences. For example, SOD catalyses the metabolism
of superoxide to hydrogen peroxide. Hydrogen peroxide may
combine with transition metal ions to generate hydroxyl rad-
cal intermediates, or be detoxified to water by glutathione
reductase enzyme system that catalyses the oxidation of
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There is growing evidence to suggest that reactive oxygen
species, particularly superoxide and hydrogen peroxide, partici-
pate in vascular cell signalling and proatherogenic gene
expression by modulation of redox-sensitive transcription and
transduction pathways.40 In the setting of increased oxidative
stress, endothelial cells lose their protective phenotype, and
express proinflammatory molecules. These molecules include
vascular cell adhesion molecule-1, intercellular adhesion
molecule-1, and monocyte chemotactic protein-1, all of which
facilitate endothelial-leucocyte interactions and initiate early
stages of atherosclerosis. Expression of inflammatory signals
is, in part, controlled by a redox-sensitive transcriptional
regulatory protein nuclear factor kappa B (NF-κB).30 NF-κB is
also important in proliferative signals involved in vascular
smooth muscle cell growth, vascular remodelling, and athero-
genesis. Cultured cells overexpressing catalase exhibit sup-
pressed activation of NF-κB in response to tumour necrosis
factor-α,21 while those overexpressing SOD exhibit intracellu-
lar accumulation of hydrogen peroxide and NF-κB activation.

Further evidence for the involvement of reactive oxygen
species in NF-κB activity is provided by studies demonstrating
its inhibition by antioxidants such as N-acetylcysteine and
pyridoline dithiocarbamate.

Oxidant species also play a regulatory part in other aspects
of intracellular signalling. Mitogen activated protein kinase
(MAPK) and tyrosine kinases consist of key regulatory
proteins that control cellular response to growth and stress
signals.31 32 In vascular cells, growth factors and angiotensin II
are powerful activators of extracellular signal-regulated kinase
and p38 MAPK that stimulate smooth muscle cell prolifera-
tion and fibroblast migration through mechanisms that
involve hydroxyl peroxide. These proliferative responses drive
neointimal growth and likely play a part in atheroma develop-
ment and restenosis. Stimulation of vascular smooth muscle
cells by the mitogen platelet derived growth factor increases
intracellular production of hydrogen peroxide and tyrosine
phosphorylation.33 This process is abrogated by enhancing
intracellular concentrations of free radical-scavenging en-
zymes such as catalase, and by the antioxidant N-acetylcysteine. Reactive oxygen species modulate both Akt
kinase and caspase activity, which play a part in endothelial
cell proliferation and activation of apoptotic signals leading to
endothelial cell loss, respectively.34

Reactive oxygen species also modulate collagen matrix
metabolism through activation of proteolytic matrix metallo-
proteinases that play an important part in plaque behaviour
and stability.35 Matrix metalloproteinase expression is in-
creased in shoulder regions of atherosclerotic plaques where
its increased activity may increase the propensity for plaque
rupture.36 Atherectomy specimens from patients with unstable
coronary syndromes exhibit increased expression of reactive
oxygen species compared with individuals with stable angina,
supporting a mechanistic role of reactive oxygen species in
plaque composition and behaviour.37 N-acetylcysteine pre-
vents matrix metalloproteinases-9 expression and activation
in hypercholesterolaemic rabbits, implicating a potential role
for antioxidant treatment in modulating plaque stability.38

TREATMENT STRATEGIES
Antioxidant vitamins
The central role of oxidant stress in the pathogenesis of vascu-
lar dysfunction has generated considerable interest in antiox-
didant therapy for cardiovascular disease. As previously
discussed, several antioxidants such as ascorbic acid (vitamin
C), α-tocopherol (vitamin E), glutathione, tetrahydrobiopt-
erin, and N-acetylcysteine have been shown to improve
endothelial function and nitric oxide bioaction in cultured
cells, and in animal and human clinical studies of vascular
reactivity. In addition, epidemiological studies suggest that
individuals with higher antioxidant intake have reduced
cardiovascular risk.41 To date, vitamin E has been the predomi-
nant antioxidant tested in large clinical trials. Despite an ini-
tial small study demonstrating a therapeutic benefit of
vitamin E on reducing non-fatal myocardial infarctions,42
more recent randomised, placebo controlled, large scale trials
of vitamin E intake have been disappointing. In the GISSI-
Prevenzione study that involved 11 324 patients,
vitamin E supplementation (300 mg/day) to patients after
myocardial infarction had no significant effect on cardiovascular endpoints.46 In the Heart Outcomes Prevention Evaluation (HOPE) substudy, treatment with 400 IU/day of vitamin E failed to demonstrate a beneficial effect on cardiovascular outcomes after 4.5 years of therapy.47 In a three year double blind study, antioxidant treatment with a combined daily regimen of vitamin E (800 IU), vitamin C (1000 mg), β-carotene (25 mg), and selenium (100 μg) had no effect on angiographic coronary lesions or cardiovascular events.48 In the very recently completed Medical Research Council/British Heart Foundation Heart Protection Study of 20 536 high risk individuals with atherosclerotic disease or diabetes, treatment with vitamin E, vitamin C, and β-carotene for five years had no effect on mortality rate compared with placebo.49

On first look, it appears difficult to reconcile these negative studies in view of the large body of evidence supporting the role of oxidative stress in cardiovascular disease. On closer examination, several limitations of these trials may be brought to light before refuting a role for antioxidant treatment. Previous studies were conducted almost entirely on patients with existing coronary disease, and the role of antioxidant therapy for primary prevention remains an open question. In addition, there is considerable debate as to whether certain antioxidants, particularly vitamin E, have any significant in vivo activity to attenuate meaningfully all aspects of reactive oxygen species-mediated atherothrombotic mechanisms.44 45 For example, although vitamin E can inhibit LDL oxidation in vitro, it is unlikely to achieve sufficiently high concentrations in the vascular microenvironment to interfere effectively with all components of oxidative stress, and has limited activity against superoxide and peroxynitrite driven processes.45 Another limitation of the published clinical trials is the lack of biological markers that would identify individuals most likely to benefit from treatment, analogous to the relationship between plasma cholesterol and lipid lowering therapy. A recent study demonstrated that the ability of vitamin C to improve vascular dilation identifies patients at risk for cardiovascular events, and such investigations may represent initial steps towards defining a population that may benefit most from treatment.48 Lastly, there has been debate about duration of therapy, dosing regimens, and the potential role of antioxidant combinations on endpoints that are being addressed in ongoing clinical trials.

ACE inhibitors
ACE inhibitor therapy improves cardiovascular outcomes in patient with hypertension, congestive heart failure, and coronary artery disease. The recent HOPE trial demonstrated that ACE inhibitors produce a dramatic decrease in cardiovascular events independent of the effect on left ventricular function, and blood pressure lowering, supporting the idea that this intervention may have direct effects on vascular function.49 The most relevant evidence for such a mechanism was provided by the observation that quinapril treatment for six months improved coronary endothelial function in patients with coronary artery disease.50 Given the link between the renin-angiotensin system and vascular NAD(P)H oxidase activity, ACE inhibitors may act as “antioxidants” in part by limiting angiotensin II-mediated superoxide production by NAD(P)H oxidase at its source and, thus, preventing superoxide-mediated inactivation of EDNO. ACE inhibitors may also affect downstream effects of superoxide limiting hydrogen peroxide formation and vascular proliferation, consistent with observations that ramipril reduced progression of carotid intimal thickening.51 ACE inhibitor therapy may also limit peroxynitrite generation and lipid peroxidation, and downregulate activation of redox-sensitive proinflammatory signals.

Key references


Stats
Hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, were developed as a means to lower LDL cholesterol. Recent evidence, however, suggests that they are potent agents for improving endothelial function, and limiting inflammatory responses, including those mediated by NF-κB activation.41 These several actions of statins independent of their cholesterol lowering effects likely account for the benefits of these agents in improving outcomes in patients with coronary heart disease who had normal or low levels of LDL cholesterol.52 53 Importantly, owing to their anti-inflammatory effects, statins can be considered antioxidant, as well, since inflammatory responses, especially cytokine-mediated leucocyte and endothelial cell activation, promote reactive oxygen species generation. Thus, statins should be added to the list of antioxidant therapies that are currently available for the treatment of patients with atherothrombosis or risk factors for atherothrombosis.

In conclusion, oxidative stress alters normal endothelial function, supporting proinflammatory, prothrombotic, proliferative, and vasoconstrictor mechanisms that support the atherogenic process. Impaired nitric oxide bioactivity and increased oxidative stress are common features of disease states associated with atherosclerosis. Antioxidant treatment in clinical trials to date, predominantly with vitamin E, failed to improve cardiovascular outcomes, and ongoing clinical studies are designed to address the effects of alternative antioxidant regimens.

QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)
Q1. The principal biochemical source of reactive oxygen species in the vasculature is:
(A) NADH/NAD(P)H oxidase
(B) Xanthine oxidoreductase
(C) Superoxide dismutase
(D) Glucose-6-phosphate dehydrogenase

Q2. Reactive oxygen species contribute to mechanisms of atherosclerotic plaque vulnerability through activation of:
(A) Nitric oxide
(B) Matrix metalloproteinases
(C) Tetrahydrobiopterin
(D) Catalase

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Q3. Which of the following may exert their beneficial effects through antioxidant mechanisms?
(A) Angiotensin converting enzyme inhibitors
(B) Hydroxymethylglutaryl coenzyme A reductase inhibitors
(C) Both (A) and (B)
(D) None of the above

Q4. The endothelial form of nitric oxide synthase (eNOS) can be a source of reactive oxygen species: true or false

Q5. Reactive oxygen species up-regulate expression of inflammatory signals through nuclear factor kappa B: true or false

Q6. Superoxide enhances endothelium-derived nitric oxide activity: true or false

References

ANSWERS


3. (C). Both angiotensin converting enzyme inhibitors and hydroxymethylglutaryl coenzyme A reductase inhibitors may exert their potential beneficial actions through antioxidant mechanisms, independent of their blood pressure and lipid lowering effects.

4. True. Uncoupling of the L-arginine-nitric oxide pathway, via a deficiency of critical enzymatic cofactors, may result in increased superoxide production.

5. True. Nuclear factor kappa B is a redox-sensitive transcriptional regulatory protein important in upregulation of proinflammatory cell surface molecules.


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