Scientific Research and Essays Vol. 7(49), pp. 4151 -4159, 17 December, 2012
Available online at http://www.academicjournals.org/SRE
DOI: 10.5897/SRE11.1494
ISSN 1992-2248 ©2012 Academic Journals

Review

Role of reactive oxygen species in the pathogenesis of cardiovascular disease

O. B. L. Alinde, A. J. Esterhuyse and O. O. Oguntibeju*

Oxidative Stress Research Centre, Department of Biomedical Sciences, Faculty of Health and Wellness Sciences, Cape Peninsula University of Technology, Bellville, South Africa.

Accepted 11 December, 2012

Oxidative stress, in recent times, appears to be a major underlying risk factor in the occurrence of major diseases such as cardiovascular diseases (CVD) and inflammatory diseases. During oxidative stress, an overall dysfunction of the balance between the production of reactive oxygen species (ROS) and the antioxidant defence mechanism occurs and a shift is obtained in favour of ROS production. Consequently, this may cause severe molecular, cellular and histological damage of the heart and vascular membranes in both animal and human living system which may lead to more serious complications. Previous studies proposed that reactive oxygen species represent at a molecular basis a key aspect in the pathogenesis of endothelial dysfunction and atherosclerosis which in fact constitute major underlying pathologies of most CVD. In this review, we discuss the role of reactive oxygen species in the pathogenesis of cardiovascular disease.

Key words: Cardiovascular disease, reactive oxygen species, inflammation.

INTRODUCTION

An increasing body of evidence demonstrates that the overproduction of reactive oxygen species (ROS) coupled with impaired antioxidants defence system is a hallmark of the development of health-related disorders and aging (Chapple, 1996; Lavrovsky et al., 2000; Touyz and Schiffrin, 2004; Esterhuyse et al., 2005; Valko et al., 2007; Ha et al., 2008; George and Ojegbemi, 2009). In fact, it has now been well documented that oxidative stress and ROS-mediated damage affect the structures and the functions of different tissues, cells and molecules (Wiseman and Halliwell, 1996; Kumar et al., 2002; Berk, 2007). Reactive oxygen species are a family of short living molecules derived from oxygen metabolism and found in the environment and in all biological system (Wassmann et al., 2004; Touyz and Schiffrin, 2004).

Reactive oxygen species (such as superoxide anion $O_2^{\bullet-}$)/ reactive nitrogen species (RNS), such as nitric oxide ($NO^{\bullet}$) are constantly being formed in living organisms (Ceconi et al., 2003). ROS and RNS are well recognised to either be harmful or profitable to living systems (Devasagayam et al., 2004; Esterhuyse et al., 2006; Valko et al., 2007). Reactive oxygen species have oxidation ability and are classified either as free radicals (superoxide anion $O_2^{\bullet -}$, hydroxyl radical $HO^{\bullet}$, nitric oxide $NO^{\bullet}$) or as non-free radicals (hydrogen peroxide H_2O_2, peroxynitrite $ONOO^-$) (Higashi et al., 2006). Free radicals can be defined as molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals (Halliwell and Gutteridge, 1990). Oxygen free radical includes species such as superoxide anion ($O_2^{\bullet-}$), hydroxyl radicals ($HO^{\cdot}$), peroxyl ($RO_2^{\cdot}$) and alkoxyl ($RO^{\cdot}$). They are very short lived, with half-lived in milli-, micro or nanoseconds (Cai and Harrison, 2000; Devasagayam et al., 2004). Oxygen non free-radicals are oxidizing agents and/or easily converted into radicals, such as hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$)

*Corresponding author. E-mail: oguntibejuo@cput.ac.za or bejufemi@yahoo.co.uk. Tel: +27 21 953 8495. Fax: +27 21953 8490.

and hypochlorous acid (HOCl) (Cai and Harrison, 2000). Previous studies have shown the involvement of ROS in the physiological and pathophysiological conditions of cardiovascular diseases (CVD) (Hamilton et al., 2004; Fortuño et al., 2005; Berk, 2007, Heistad et al., 2009). At low concentration, ROS are produced in a controlled manner and function in normal cell signalling pathways (smooth muscle and endothelial cell growth, apoptosis and survival) and in the remodelling of vessel wall (Fortuño et al., 2005; Heistad et al*.,* 2009). At a regulated rate, ROS are implicated in defence against infectious agents, detoxification of xenobiotics by cytochrome P450, killing of cancer cells and generation of ATP in the mitochondria (Devasagayam et al*.,* 2004; Valko et al*.,* 2007). At high concentrations, ROS are identified as harmful compounds and constitute an important risk factor for the development of many diseases such as cardiovascular diseases (Touyz and Schiffrin, 2004; Heistad et al., 2009). Scientific evidence have suggested the implication of ROS and free radicals in the onset of cardiovascular diseases. Cardiovascular diseases (CVD) are non-communicable diseases that constitute one of the leading global threats to human health. Though the pathophysiology of CVD is multi-factorial, free radicals attack on the vascular vessel with subsequent endothelial dysfunction has been identified as a common feature occurring at an early stage of development of most CVD. The implication of ROS and free radicals in the onset of vascular diseases has been documented (Alexander, 1995; Sen and Packer, 1996; Cai and Harrison, 2000; Fortuño et al*.,* 2005).

This review will focus on the different mechanisms by which ROS have been implicated in the pathogenesis of cardiovascular diseases.

REACTIVE OXYGEN SPECIES

The intake of oxygen (O_2) by aerobic living organism through respiration is indispensable to sustain life (Nindl, 2004). However, during cellular respiration, 1 to 5% of all inhaled oxygen becomes reactive oxygen species (ROS) (Berk, 2007). The “primary ROS”, superoxide anion, is formed by the addition of one extra electron to molecular dioxygen (Chapple, 1996). It is a high reactive radical which generates “secondary” ROS (Chapple, 1996; Touyz and Schiffrin, 2004) such as hydrogen peroxide and peroxinitrite. Explicitly, superoxide anion favoured the production of hydrogen peroxide (H_2O_2) through the scavenging effect of superoxide dismutase (intracellular Cu/ Zn SOD, Mn SOD or extracellular Cu/Zn SOD) (Chapple, 1996; Hamilton et al., 2004): Hydrogen peroxide (H_2O_2) can also be reduced to form hydroxyl radical ($HO^{\cdot}$). Furthermore, overproduced superoxide anion favour the formation of toxic peroxynitrite ($ONOO^{-}$) by electron transfer to nitric oxide ($NO^{\bullet}$) (Darley-Usmar et al*.,* 1995; Liochev and Fridovich, 2002). Under physiologic conditions, ROS is known to regulate vascular functions by modulating cell growth, apoptosis, migration, inflammation, secretion, and extracellular matrix (Touyz and Schiffrin, 2004) (Figure 1).

SOURCES OF REACTIVE OXYGEN SPECIES

Many systems (enzymatic and non enzymatic) can be considered as sources of ROS in the living organism (Wiseman and Halliwell, 1996; Babior et al*.,* 2002; Turrens, 2003). Exogenously, ROS are produced from exposure to environmental agents such as ultra violet (UV) radiation and redox-cycling agents (Park et al*.,* 2002). Endogenously, ROS are derived mostly from the incomplete reaction of oxygen during aerobic metabolism *in vivo.* They are produced from mitochondrial electron transport chain, NADH/NADPH oxidases, arachidonic acid pathway enzymes, cyclo-oxygenase and lipoxygenase, NO synthase, peroxidases, xanthine oxidases, phagocytes-derived myeloperoxidase (Cai andHarrison, 2000; Szeto, 2006; Zalba et al*.,* 2006).

There is strong evidence showing that the principal source of superoxide anion in the vascular system prevails in the NADPH oxidase metabolism (Valko et al*.,* 2007). Nitric oxide synthase (NOS) is the enzyme primarily responsible for the production of nitric oxide (NO). Nitric oxide synthase has been reported to generate superoxide anion in condition of substrate (arginine) or cofactor (BH4) depletion (Stroes et al*.,* 1998; Silberman et al*.,* 2010). This condition has introduced the concept of “NOS uncoupling” whereby NOS favoured superoxide anion formation over nitric oxide production (Silberman et al*.,* 2010). Uncoupled NOS, is a dysfunctional endothelium NOS which promote an excessive release of superoxide anion and hydrogen peroxide subsequent to peroxynitrite-mediated cellular injury (Xia et al., 1996; Touyz and Schiffrin, 2004; Silberman et al*.,* 2010). Xanthine oxidoreductase (XOR) is a complex molybdoflavoenzyme that is readily available from mammalian or human milk (Vorbach et al., 2002; Harrison, 2006). Several studies reported that inhibition of XOR has been found to normalize the overproduction of superoxide anion which confirms XOR effects on the surplus production of ROS in vascular cells.

CARDIOVASCULAR DISEASES

According to the World Health Report 2003, CVD accounted for 16.7 million of total global deaths and is believed to be the leading cause of deaths in developing countries (WHO, 2003). Cardiovascular diseases are

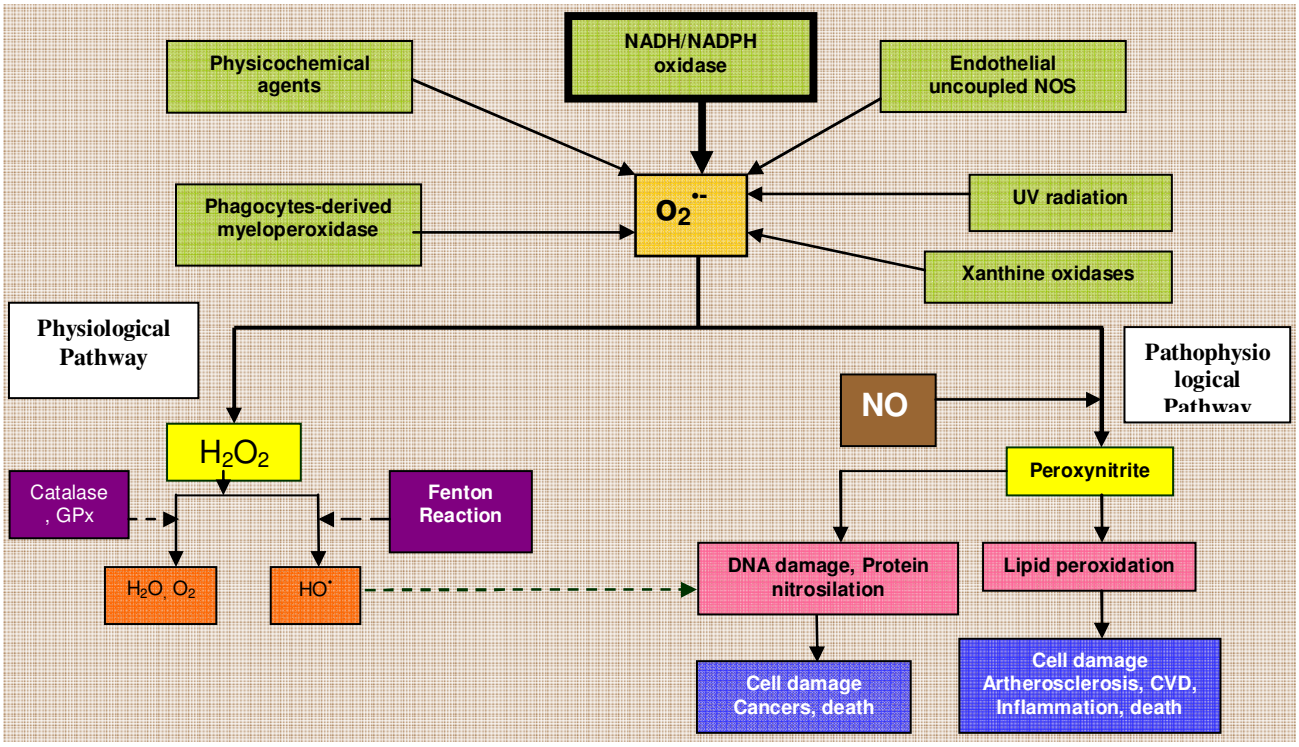

Figure 1. Reactive oxygen species pathways.

classified into many disorders such as coronary or ischaemic heart disease IHD (heart attacks), cerebrovascular disease (stroke), hypertension (raised blood pressure), congenital heart diseases, rheumatic heart diseases, heart failure, peripheral vascular diseases and cardiomyopathies (WHO, 2009). CVD affect both young and old people and the risk increases with age and are similar for men and women (WHO, 2004). On a global scale, high blood pressure, tobacco use, high blood cholesterol (hypercholesterolemia), diabetes mellitus, physical inactivity, low fruit and vegetable intake, obesity, aging and alcohol consumption have been reported as leading risk factors of CVD (WHO, 2004). Nevertheless, these traditional known risk factors do not provide a full explanation for all cases of CVD (Keaney and Vita, 1995; Sliwa et al., 2008). Recent research has identified what could be seen as novel risk factors that may assist to identify persons or populations at risk of developing CVD (Kadiri, 2005). One such novel risk factor is free and hydroxyperoxide radicals which promote oxidative stress. It has been reported that cardiovascular diseases are typically characterized by elevated levels of ROS, endothelial dysfunction and proinflammatory states (Fujii et al., 2006; Esterhuyse et al., 2006). As free and hydroxyperoxide radicals have the potential to damage biological compounds and structures such as proteins, membrane lipids, DNA and carbohydrates, they have thus been involved in the aetiology and pathogenesis of CVD (Kadiri, 2005; Thorogood et al., 2007). The pathophysiology of CVD although multi-factorial seems to have a common underlying pathogenesis factor in oxidative stress which is mediated by free radicals and other reactive products of oxygen metabolism. In the vascular vessel, free radicals and other ROS participate in the oxidation of fatty materials (mainly LDL cholesterol) which are deposited into the inner vascular wall of the cardiovascular system (Maxwell and Lip, 1997; Rudijanto, 2007; Heistad et al., 2009). The resultant effect of such free radicals attack is mostly the induction of endothelial dysfunction which is an early feature of chronic inflammation, atherosclerosis and vascular diseases (hypertension) (Heistad et al., 2009).

OXIDATIVE STRESS

The overall production of ROS is regulated by a set of scavenger systems called antioxidants. When the antioxidant system is depleted, pro-oxidants overwhelm antioxidant capacity, and this results in overload of ROS (Ceconi et al., 2003; Berk, 2007; Barbosa et al., 2008). This condition is called oxidative stress (Ha et al., 2008; Hassoun and Periandri-Steinberg, 2010). Oxidative

stress-mediated damages have been implicated in a variety of human disorders such as cancers, lung diseases, UV-mediated skin diseases, in aging and CVD (Stadtman, 2001; Park et al., 2002; Antoch and Kondratov, 2010; Palmer and Kitchin, 2010).

RELATIONSHIPS BETWEEN REACTIVE OXYGEN SPECIES (ROS) AND CARDIOVASCULAR DISEASES

Implication of lipid peroxidation in cardiovascular diseases (CVD)

Reports on the implication of lipid peroxidation in a wide range of health disorders continue to be acknowledged; especially, through promotion of oxidative stress. Free radicals, hydroperoxides and carbonyl compounds are toxic breakdown products of the peroxidation of unsaturated fatty acids. Park and co-workers (2002) demonstrated that lipid peroxidation is one of the important intermediary events in oxidative stress-induced cellular damage. Lipid peroxidation is believed to play a critical role in the pathophysiology of cardiovascular diseases such as atherosclerosis, stroke and hypertension (Heistad et al*.,* 2009). In the context of oxidative stress and its play in the pathogenesis of CVD, available evidence have shown that oxidative stress, mainly through lipid peroxidation, represents an important risk factor in the development of CVD and ischemic heart disease (IHD) (Waterfall et al*.,* 1997; Ceconi et al., 2003). In fact, oxidative stress, through lipid peroxidation of coronary and aortic vascular membranes, has been shown to cause membrane disruption and release of highly reactive free radicals (such as MDA, HNE) that severely alter the cellular function of the cardiovascular system (Waterfall et al., 1997; Ceconi et al*.,* 2003; Liu et al*.,* 2010).

Implication of oxidative stress in endothelial dysfunction: Relation to cardiovascular diseases (CVD)

Endothelial dysfunction is a hallmark of multiple vascular diseases such as hypertension, artherosclerosis and diabetes mellitus (Alexander, 1995; Griendling et al., 2000b), hence, a risk factor for CVD. Endothelial dysfunction is seen in patients with chronic heart failure (Landmesser et al*.,* 2002), with congestive heart failure condition (Katz, 1997), with congenital heart diseases (Oechslin et al*.,* 2005) and with other CVD. An important feature of endothelial dysfunction is the loss of the vasodilatation ability of the blood vessels in response to physiological stimuli (hormonal agonist, physiochemical, physical stimuli). The term endothelial dysfunction also reflects an impairment of anticoagulant and anti-inflammatory properties of the endothelium, a loss in modulation of vascular growth or in modulation of vascular remodelling (Gimbrone, 1995). Although, the mechanisms leading to endothelial and vascular dysfunction are multifactorial, oxidative stress has a major play in its incidence. Under oxidative stress, ROS become potent instruments of destruction with mild to severe cellular damages (Liu et al., 2010) and are implicated in endothelial dysfunction (Vaziri et al., 2000; Landmesser et al., 2002) through the alteration of different metabolic pathways.

Alteration in nitric oxide (NO) bioavailability: Cellular pathway

Alteration in NO bioavailability is generated by: an increase in vascular radical formation (Landmesser et al*.,* 2000, 2002) and also by impairment in NOS expression and activity (Kinoshita et al., 1997).

In the vasculature, an increase production of radicals by endothelial progenitor cells, xanthine oxidase, NADPH oxidase leads to superoxide overload (Mervalaa et al*.,* 2000; Landmesser et al*.,* 2002; Imanishi et al*.,* 2008). The rapid reaction of superoxide surplus with NO favours peroxynitrite formation and impairs both NO bioavailability and activity (Landmesser et al*.,* 2000; Wollin, 2000; Landmesser et al*.,* 2002; Wassmann et al, 2004; Wu and Johns, 2004; Fortuño et al., 2005). Nitric oxide depletion results in NO inactivation and subsequent losses in NO endothelium-relaxing properties, NO regulation of angiogenesis and NO neo-vascularisation which in overall leads to endothelial dysfunction (Ziche et al*.,* 1994; Parenti et al., 1997; Kondo et al., 2004; Murohara and Asahara, 2004; Roberts et al., 2007). Nitric oxide dysfunction promotes hypertension and impairment of cardiovascular functions (Kojda and Harrison, 1999; Cai and Harrison, 2000).

Likewise, newly formed peroxynitrite induces vasculopathies as a result of its damaging effects on the vascular membranes. Peroxynitrite and other potent oxidants attack vascular membranes and initiate lipid peroxidation (Brown and Borutaite, 2004). Evidences of peroxynitrite mediated-cellular injury have been reported in ischemia-reperfusion injury in isolated rat hearts (Yasmin et al., 1997) and in the pathogenesis of cytokines-induced myocardial dysfunction in dog *in vivo* (Cheng et al., 1999). Additionally, Milstien and Katusic (1999) demonstrated that peroxynitrite oxidises tetrahydrobiopterin (BH4), an important substrate of most NOS, into quinonoid 5,6-dihydrobiopterin as a primary target. Kinoshita et al. (1997) showed that in arteries depleted of tetrahydrobiopterin (BH4), synthesis of NO by NOS is impaired. In the vasculature, depleted BH4

favours the expression of uncoupled eNOS which rather produce superoxide anion and hydrogen peroxide instead of NO. These downstream radicals may lead to further increase of peroxynitrite-mediated cellular injuries and perpetuate the cycle.

In the coronary endothelium, endocardial endothelium, cardiac myocytes and cardiac neurons, NO is constitutively produced by the Ca^{2+}- dependent eNOS from oxygen and L-arginine (Schulz and Triggle, 1994). The magnitude of intracellular L-Arg depletion has also been revealed as a crucial factor which switches NOS from the production of NO to the generation of superoxide (Xia et al*.,* 1996). Moreover, in the vasculature, Lin et al. (2003) demonstrated that hydrogen peroxide may also contribute to cardiovascular dysfunction through an increase in spinal sympathetic tone by acting on sympathetic preganglionnic neurons.

Alteration in cellular signalling and in the expression of key regulatory protein: Molecular pathway

Cellular signalling or signal transduction can be simply defined as biological mechanisms by which "cells communicate with each other" (Valko et al*.,* 2007). At a molecular level, cell signalling can be defined as the mechanism by which extracellular messages are transduced across plasma membranes into the intracellular environment to regulate expression of a desired substrate (Abe and Berk, 1998). Indeed, extracellular signal such as hormones, neurotransmitter, growth factors or cytokines after internalisation triggers cell responses via redox signalling. Redox signalling is a regulatory process in which the signal is delivered through redox reactions to the nucleus. In the nucleus, a set of proteins called transcription factors regulate gene transcription and expression of the desired substrate. In the normal cellular signalling, ROS production plays a very important physiological role as a secondary messenger (Valko et al., 2007) but with increased production in ROS, the normal cell transduction is shifted to generate pathological conditions. Excessive ROS alter the tight regulated control of cell signal transduction. Reactive oxygen species induce the loss of coordination, growth and production of regulatory proteins which impair tight regulation of expression of genes. Reactive oxygen species subject the cells to uncontrolled production of inflammatory proteins, uncontrolled cell growth (cancers) and cell death (Valko et al., 2007).

In the onset of CVD, many pathways can provide an interesting insight into the pathogenic role of ROS-induced oxidative stress. One of the important pathways involved is the mitogen-activated protein kinase (MAPK) pathway. Mitogen-activated protein kinase family is a family of protein kinases encoded by a multi-gene family and activated by the phosphorylation of any of the inner residue of a well-defined inner motif. For instance, it has been reported that ROS produced by H_2O_2 stimulate mitogen activated protein kinases (MAPK) (Fialkow et al*.,* 1994). The involvement of ROS in CVD through signalling pathways have been documented by Abe and Berk (1998) and the study of Valko and co-workers (2007). Reactive oxygen species are also reported to activate regulatory proteins such as nuclear factor kappa B (NF-KB) and activator protein-1 (AP-1). The activator protein AP-1 and NF-KB/Rel transcription family are pro-inflammatory transcription factors. For instance, hydrogen peroxide has been reported to stimulate c-fos and c-jun gene expression (fos and jun as protooncoproteins) of the activator protein AP-1 and to enhance the binding activity of AP-1 to AP-1 responsive element in the regulatory domains of genes involved in proliferation of different cell types *(*Agnel and Karin, 1991; Stevenson et al., 1994; Lo and Cruz, 1995). Activation of NF-KB has been shown to play a key role in the onset of many inflammatory diseases such as rheumatoid arthritis and atherosclerosis which are also directly involved in the pathogenesis of CVD. Evidence have been provided by prior studies (Sen and Packer, 1996; Lavrosky et al*.,* 2000; Tak and Firestein, 2001; Valko, et al., 2007).

Implication of oxidative stress in the pathogenesis of atherosclerosis

Atherosclerosis, an inflammatory disease of vascular blood vessels, is also a critical factor in the pathogenesis of vascular diseases underlying the onset of the majority of cardiovascular diseases (Chancharme et al*.,* 1999; Frostegård, 2002). Atherosclerosis is one of the leading causes of death in the developed countries. It is a slow but progressive disease. Atherosclerotic lesions appear to be related to hypercholesterolemia: elevated plasma total cholesterol (TC), low-density lipoprotein (LDL) and decrease high-density lipoprotein (HDL) (Kim et al., 2006; Chancharme et al., 1999). Atherosclerosis is a pathology characterized by the formation of atherosclerotic plaques due to oxidation of fatty acids and deposition of low density lipoprotein cholesterol in the inner endothelium layer of the vessel wall (Adam et al*.,* 2008). The plaque formation, growth and rupture lead to compromise of the luminal diameter of the blood vessel which alters blood flow to the heart (Figure 2) (Higashi et al., 2009). Atherosclerosis is in most cases responsible for coronary heart diseases such as coronary artery diseases (CAD) but may also lead to angina and stroke (Chancharme et al., 1999). The coronary blood vessel luminal obstruction may result in death in most cases due to lack of nutrient and oxygen flow to the heart. This is clearly seen in myocardial infarction when the abrupt closure of the

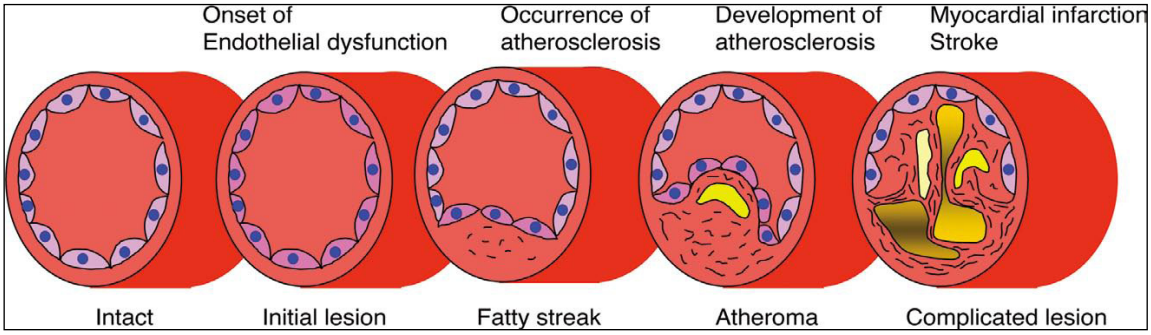

Figure 2. From endothelial dysfunction to myocardial infarction by atherosclerosis (Higashi et al., 2009).

coronary vessels results in myocardial necrosis leading to death (Figure 2).

Molecular mechanism of reactive oxygen species (ROS) damage in atherosclerosis

It has been shown that factors such as smoking, hypercholesterolemia, infections, and lipid peroxidation may damage the inner layer of the arteries (Harrison et al., 2003). Lesions initiate local inflammation. Once lesions occur in the intimal layer, LDL-cholesterol from blood can easily be trapped in the arterial wall. Various enzymatic and non enzymatic systems modified the trapped LDL which becomes oxidized LDL-c (oxLDL) (Jialal and Devaraj, 1996). The oxidation of LDL-c into oxLDL generates the formation of oxidative by-products of the cholesterol which plays an important role in the pathogenesis of atherosclerosis and cardiovascular diseases such as oxysterols and remnant lipoproteins (Yasunobu et al., 2001; Hiki et al., 2009). The oxLDL generated are thought to be particularly atherogenic. Several clinical and animal experimental studies have demonstrated that oxLDL and oxysterols play important role in atherogenesis. Oxidized- LDL induces morphological changes and increase stiffness of endothelial cells (Chouinard et al., 2008). Khan et al. (1995) demonstrated that oxLDL present at the site of lesions selectively augments redox-sensitive vascular adhesion molecule (VCAM-1) gene expression in vascular endothelium and therefore induce chemotactically the recruitment of monocytes and macrophages on the surface of endothelial cells. This allows monocytes and macrophages, at the site of lesions to enter the subendothelial space and initiate the so-called early atherosclerotic lesion (Yasunobu et al., 2001). Furthermore, oxLDL is more avidly taken up by macrophages via their scavenger receptors than unoxidized LDL (Adam et al., 2008). The OxLDL receptors on macrophage cells allow internalization of oxLDL cholesterol molecules. Macrophages embedded into the vascular tissue and enriched with oxLDL become large lipid laden cells called foam cells. Accumulation of foam cells in the vascular wall cause the formation of fatty streaks. The growth of fatty acids causes the formation of a fibrous capsule which surrounds the fatty streaks which develop into an atheromatous plaque: the artherosclerotic plaque. The plaque expansion is a threat to blood flow. As it starts growing into the inner vessels, it narrows the opening of the artery and the plaque becomes rigid due to the deposition of calcium. When the vessel affected is the coronary artery or any cardiac vessels, this obstruction may be fatal (Chien and Braunwald, 1999).

An important enzymatic pathway involved in the process of atherosclerosis has been identified in the oxidation of cholesterol lipoprotein by vascular ROS. Vascular NADPH oxidase excessively produce ROS under the stimulation of many factors such angiotensin II, cytokines, and physical forces. De Keulenaer et al. (1998) demonstrated how tumour necrosis factor α (TNF α) increase the vascular production of ROS involved in the pathogenesis of vascular diseases. Touyz and Schiffrin (2001) observed that angiotensin II increase NADPH oxidase-ROS generation in smooth muscle cells of hypertensive patients and may contribute to vascular remodelling in hypertension. Touyz and Schiffrin (2004) identified that angiotensin II activate protein kinase C through its action on the angiotensin II type 1 receptor. Activation of protein kinase C triggers an initial production of ROS, which stimulate the tyrosine kinase cellular Src and Src kinase. Src kinase initiates a chain of reaction which finally activates the GTPase Rac-1 unit of NADPH oxidase complex which facilitates its assembly (White et al., 1996; Griendling et al., 2000b).

Homocysteine is known as an independant risk factor of atherosclerosis. This compound directly damage blood vessels and its altered metabolism is involved in the oxidative process of atherogenesis (Adam et al., 2008). Wald et al. (2002), found strong evidence that the

association between homocysteine and CVD is causal and that lowering homocysteine level would reduce the risk of ischaemic heart diseases. Another risk factor has also been established in C-reactive protein (CRP). C-reactive protein has been suggested to participate in the development of atherosclerosis and atherothrombosis by promoting endothelial dysfunction and impairing endothelial progenitor cell survival and differentiation (Fujii et al., 2006).

CONCLUSION

The pathophysiology of CVD is multi-factorial but it has been shown that common underlying risk factor consists of oxidative stress-mediated damages. Excessive generation of vascular superoxide anion ($O_2^{\cdot-}$) and downstream ROS result in oxidative stress and constitute major risk factors in the pathogenesis of CVD. In this review, a brief outline of the involvement of ROS in the pathogenesis of CVD via lipid peroxidation, peroxynitrite mediated cell-damage, oxidation of LDLc in vascular bed, activation of regulatory protein and intracellular cell transduction have been highlighted. We however recommend further laboratory-based studies into the involvement and mechanisms ROS-mediated pathogenesis of CVD.

REFERENCES

Abe J, Berk BC (1998). Reactive oxygen species as mediators of signal transduction in cardiovascular disease. Trends Cardiovasc. Med. 8(2):59-64.

Adam SK, Soelaiman IN, Umar NA, Mokhtar N, Mohamed N, Jaarin K (2008). Effects of repeatedly heated palm oil on serum lipid profile, lipid peroxidation and homocysteine levels in a post-menopausal rat model. McGill J. Med. 11(2):145-151.

Agnel P, Karin M (1991). The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. Biochim. Biophys. Acta 1072(2-3):129-157.

Alexander RW (1995). Hypertension and the pathogenesis of atherosclerosis, oxidative stress and the mediation of arterial inflammatory response: A new perspective. Hypertension 25(2):155-61.

Antoch MP, Kondratov RV (2010). Circadian Proteins and Genotoxic Stress Response. Circ. Res. 106:68-78.

Babior BM, Lambeth JD, Nauseef W (2002). The neutrophil NADPH oxidase. Arch. Biochem. Biophys. 397(2):342-344.

Barbosa KB, Bressan J, Zulet MA, Martínez Hernández JA (2008). Influence of dietary intake on plasma biomarkers of oxidative stress in humans. An Sist. Sanit. Navar. 31(3):259-80.

Berk BC (2007). Novel approaches to treat oxidative stress and cardiovascular diseases. Trans. Am. Clin. Climatol. 118:209-14.

Brown GC, Borutaite V (2004). Inhibition of mitochondrial respiratory complex I by nitric oxide, peroxynitrite and S-nitrosothiols. Biochim. Biophys. Acta 1658(1-2):44-49.

Cai H, Harrison DG (2000). Endothelial Dysfunction in Cardiovascular Diseases: The Role of Oxidant Stress. Circ. Res. 87:840-844.

Ceconi C, Boraso A, Cargnoni A, Ferrari R (2003). Oxidative stress in cardiovascular disease: Myth or fact? Arch. Biochem. Biophys. 420(2):217-221.

Chancharme L, Thérond P, Nigon F, Lepage S, Couturier M, Chapman MJ (1999). Cholesteryl ester hydroperoxide lability is a key feature of the oxidative susceptibility of small, dense LDL. Arterioscler. Thromb. Vasc. Biol. 19(3):810-820.

Chapple ILC (1996). Role of free radicals and antioxidants in the pathogenesis of the inflammatory periodontal diseases. Clin. Mol. Pathol. 49(5):M247-M255.

Cheng X–S, Shimokawa H, Momii H, Oyama J, Fukuyama N, Egashira K, Nakazawa H, Takeshita A (1999). Role of superoxide anion in the pathogenesis of cytokine-induced myocardial dysfunction in dogs *in vivo*. Cardiovasc. Res. 42(3):651-659.

Chien KR, Braunwald E (1999). Molecular basis of cardiovascular disease: A companion to Braunwald's Heart disease. WB Saunders, Philadelphia.

Chouinard A, Grenier G, Khalil A, Vermette P (2008). Oxidized-LDL induce morphological changes and increase stiffness of endothelial cells. Exp. Cell. Res. 314(16):3007-3016.

Darley-Usmar V, Wiseman H, Halliwell B (1995). Nitric oxide and oxygen radicals: A question of balance. FEBS Lett. 369:131-135.

De Keulenaer GW, Alexander RW, Ushio-Fukai M, Ishizaka N, Griendling KK (1998). Tumour necrosis factor α activates a p22phox-based NADH oxidase in vascular smooth muscle. Biochem. J. 329:653-657.

Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD (2004). Free radicals and antioxidants in human health: Current status and future prospects. J. Assoc. Phys. India 52:794-804.

Esterhuyse A, Du Toit E, Benade A, van Rooyen J (2005). Dietary red palm oil improves reperfusion cardiac function in the isolated perfused rat heart of animals fed a high cholesterol diet. Prostaglandins Leukotrienes Essent. Fatty Acids 72(3):153-161.

Esterhuyse JS, van Rooyen J, Strijdom H, Bester D, du Toit, EF (2006). Proposed mechanisms for red palm oil induced cardioprotection in a model of hyperlipidaemia in the rat. Prostaglandins Leukotrienes Essent. Fatty Acids 75(6):375-384.

Fialkow L, Chan CK, Rotin D, Grinstein S, Downey GP (1994). Activation of the mitogen-activated protein kinase signaling pathway in neutrophils. Role of oxidants. J. Biol. Chem. 269(49):31234-31242.

Fortuño A, San José G, Moreno MU, Díez J, Zalba G (2005). Oxidative stress and vascular remodeling. Exp. Physiol. 90(4):457-466.

Fridovich I (1997). Superoxide Anion Radical ($O_2^{\bullet-}$), Superoxide Dismutases, and Related Matters. J. Biol. Chem. 272(30): 18515-18517.

Frostegård J (2002). Autoimmunity, oxidized LDL and cardiovascular disease. Autoimmun. Rev. 1:233-237.

Fujii H, Li S, Szmitko PE, Fedak PWM, Verma S (2006). C-reactive protein alters antioxidant defences and promotes apoptosis in endothelial progenitor cells. Arterioscler. Thromb. Vasc. Biol. 26:2476-2482.

George BO, Ojegbemi O (2009). Oxidative stress and the effect of riboflavin supplementation in individuals with uncompleted malaria infection. Afr. J. Biotechnol. 8(5):849-853.

Gimbrone MA (1995). Vascular Endothelium: An Integrator of pathophysiologic stimuli in atherosclerosis. Am. J. Cardiol. 75:67B-70B.

Griendling KK, Sorescu D, Lassegue B, Ushio-Fukai M. (2000b). Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology. Arterioscler. Thromb. Vasc. Biol. 20(10):2175-2183.

Ha H, Hwang IA, Park JH, Lee HB (2008). Role of reactive oxygen species in the pathogenesis of diabetic nephropathy. Diabetes Res. Clin. Pract. Suppl. 13(82 Suppl 1):S42-5.

Halliwell B, Gutteridge JM (1990). Role of free radicals and catalytic metal ions in human disease: An overview. Meth. Enzymol. 186:1-85.

Hamilton CA, Miller WH, Al-Benna S, Brosnan MJ, Drummond RD, McBride MW, Dominiczak AF (2004). Strategies to reduce oxidative stress in cardiovascular disease. Clin. Sci. 106(3):219-234.

Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H (2003). Role of Oxidative Stress in Atherosclerosis. Am. J. Cardiol. 91(Suppl):7A-11A.

Harrison R (2006). Milk xanthine oxidase: Properties and physiological roles. Int. Dairy J. 16:546-554.
Hassoun EA, Periandri-Steinberg SA (2010). Assessment of the roles of antioxidant enzymes and glutathione in 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126)-induced oxidative stress in the brain tissues of rats after subchronic exposure. Toxicol. Environ. Chem. 92(2):301-313.
Heistad DD, Wakisaka Y, Miller J, Chu Y, Pena-Silva R (2009). Novel aspects of oxidative stress in cardiovascular diseases. Circ. J. 73(2):201-207.
Higashi Y, Jitsuiki D, Chayama K, Yoshizumi M (2006). Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one), a novel free radical scavenger, for treatment of cardiovascular diseases. Recent Pat. Cardiovasc. Drug Discov. 1(1):85-93.
Higashi Y, Noma K, Yoshizumi M, Kihara Y (2009). Endothelial function and oxidative stress in cardiovascular diseases. Circ. J. 73(3):411-418.
Hiki M, Shimada K, Ohmura H, Kiyanagi T, Kume A, Sumiyoshi K, Fukao K, Inoue N, Mokuno H, Miyazaki T, Daida H (2009). Serum levels of remnant lipoprotein cholesterol and oxidized low-density lipoprotein in patients with coronary artery disease. J. Cardiol. 53(1):108-116.
Imanishi T, Tsujioka H, Akasaka T (2008). Endothelial Progenitor Cells Dysfunction and Senescence: Contribution to Oxidative Stress. Curr Cardiol. Rev. 4(4):275-286.
Jialal I, Devaraj S (1996). The role of oxidized low density lipoprotein in atherogenesis. J. Nutr. 126(4 Suppl):1053S-7S.
Kadiri S (2005). Tackling cardiovascular disease in Africa. Br. Med. J. (Clin. Res. Ed.) 331:711-12.
Katz SD (1997). Mechanisms and implications of endothelial dysfunction in congestive heart failure. Curr. Opin. Cardiol. 12(3):209-328.
Keaney JF, Vita JA (1995). Atherosclerosis, oxidative stress and antioxidant protection in endothelium-derived relaxing factor action. Prog. Cardiovasc. Dis. 38:129-54.
Khan BV, Parthasarathy SS, Alexander RW, Medford RM (1995). Modified low density lipoprotein and its constituents augment cytokine-activated vascular cell adhesion molecule-I gene expression in human vascular endothelial cells. J. Clin. Invest. 95(3):1262-1270.
Kim OS, Lee CS, Joe E, Jou I (2006). Oxidized low density lipoprotein suppresses lipopolysaccharide-induced inflammatory responses in microglia: Oxidative stress acts through control of inflammation. Biochem. Biophys. Res. Commun. 342:9-18.
Kinoshita H, Tsutsui M, Milstien S, Katusic ZS (1997). Tetrahydrobiopterin, nitric oxide and regulation of cerebral arterial tone. Prog. Neurobiol. 52:295-302.
Kojda G, Harrison DG (1999). Interactions between NO and reactive oxygen species: Pathophysiological importance in atherosclerosis, hypertension, diabetes and heart failure. Cardiovasc. Res. 43:562-571.
Kondo T, Kobayashi K, Murohara T (2004). Nitric oxide signaling during myocardial angiogenesis. Mol. Cell. Biochem. 264:25-34.
Kumar TR, Doreswamy K, Muralidhara BS (2002). Oxidative stress associated DNA damage of abnormal sperms and effects on fertility. Mutat. Res. 513:103-111.
Landmesser U, Merten R, Spiekermann S, Büttner K, Drexler H, Hornig B (2000). Vascular extracellular superoxide dismutase activity in patients with coronary artery disease: Relation to endothelium-dependent vasodilation. Circulation 101(19):2264-2270.
Landmesser U, Spiekermann S, Dikalov S, Tatge H, Wilke R, Kohler C, Harrison DG, Hornig B, Drexler H (2002). Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: Role of xanthine-oxidase and extracellular superoxide dismutase. Circulation 106(24):3073-3078.
Lavrovsky Y, Chatterjee B, Clark RA, Roy AK (2000). Role of redox-regulated transcription factors in inflammation, aging and age-related diseases. Exp. Gerontol. 35(5):521-532.
Lin HH, Chen C-H, Hsieh W-K, Chiu TH, Lai C-C (2003). Hydrogen peroxide increases the activity of rat sympathetic preganglionic neurons *in vivo* and *in vitro*. Neuroscience 121(3):641-647.
Liochev SI, Fridovich I (2002). Superoxide and nitric oxide consequences of varying rates of production and consumption: A theoretical treatment. Free Radic. Biol. Med. 33(1):137-141.
Liu J, Zhang J, Lu G, Qiu Y, Yang D, Yin G, Zhang X (2010). The effect of oxidative stress in myocardial cell injury in mice exposed to chronic intermittent hypoxia. Chin. Med. J. 123(1):74-78.
Lo YYC, Cruz TF (1995). Involvement of Reactive Oxygen Species in Cytokine and Growth Factor Induction of c-fos Expression in Chondrocytes. J. Biol. Chem. 270:11727-11730.
Maxwell SR, Lip GY (1997). Free radicals and antioxidants in cardiovascular disease. Br. J. Clin. Pharmacol. 44(4):307-317.
Milstien S, Katusic Z (1999). Oxidation of tetrahydrobiopterin by peroxynitrite: Implications for vascular endothelial function. Biochem. Biophys. Res. Commun. 263(3):681-684.
Murohara T, Asahara T (2002). Nitric Oxide and Angiogenesis in Cardiovascular Disease. Antioxid. Redox Sig. 4(5):825-831.
Nindl G (2004). Hydrogen Peroxide - From Oxidative Stressor to Redox Regulator. Cellscience 1(2):1-12.
Oechslin E, Kiowski W, Schindler R, Bernheim A, Julius B, Brunner-La Rocca HP (2005). Congenital heart disease: Systemic endothelial dysfunction in adults with cyanotic congenital heart disease. Circulation 112:1106-1112.
Palmer DM, Kitchin JS (2010). Oxidative damage, skin aging, antioxidants and a novel antioxidant rating. J. Drugs Dermatol. 9(1):11-15.
Parenti A, Morbidelli L, Cui X, Douglas JG, Hood JD, Granger HJ, Ledda F, Ziche M (1997). Nitric oxide is an upstream signal of vascular endothelial growth factor-induced extracellular signal-regulated kinase1⁄2 activation in postcapillary endothelium. J. Biol. Chem. 273(7):4220-4226.
Park JE, Yang J, Yoon SJ, Lee J, Yang ES, Park J (2002). Lipid peroxidation-mediated cytotoxicity and DNA damage in U937 cells. Biochimie 84:1198-1204.
Roberts DD, Isenberg JS, Ridnour LA, Wink DA (2007). Nitric Oxide and Its Gatekeeper Thrombospondin-1 in Tumour Angiogenesis. Clin. Cancer Res. 13(3):795-798.
Rudijanto A (2007). The Role of vascular smooth muscle cells on the pathogenesis of atherosclerosis. Acta Med. Indones. 39(2):86-93.
Schulz R, Triggle CR (1994). Role of NO in vascular smooth muscle and cardiac muscle function. Trends Pharmacol. Sci. 15(7):255-259.
Sen CK, Packer L (1996). Antioxidant and redox regulation of gene transcription. FASEB.10:709-720.
Silberman GA, Fan T-HM, Liu H, Jiao Z, Xiao HD, Lovelock JD, Boulden BM, Widder J, Fredd S, Bernstein KE, Wolska BM, Dikalov S, Harrison DG, Dudley SC (2010). Uncoupled cardiac nitric oxide synthase mediates diastolic dysfunction. Circulation 121:519-528.
Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, Stewart S (2008). Spectrum of heart disease and risk factors in a black urban population in South Africa (the heart of Soweto Study): A cohort study. Lancet 371:915-920.
Stadtman ER (2001). Protein Oxidation in aging and age-related diseases. Ann. N. Y. Acad. Sci. 928:22-38.
Stevenson MA, Pollock SS, Coleman CN, Calderwood SK (1994). X-irradiation, phorbol esters, and H_20_2 stimulate mitogen-activated protein kinase activity in NIH-3T3 cells through the formation of reactive oxygen intermediates. Cancer Res. 54:12-15.
Stroes E, Hijmering M, van Zandvoort M, Wever R, Rabelink TJ, van Faassen EE (1998). Origin of superoxide production by endothelial nitric oxide synthase. FEBS Lett. 438:161-164.
Szeto HH (2006). Mitochondria-Targeted Peptide Antioxidants: Novel Neuroprotective Agents. AAPS J. 8(3):E521-E531.
Tak PP, Firestein GS (2001). NF-kappa B: A key role in inflammatory diseases. J. Clin. Invest. 107(1):7-11.
Thorogood M, Connor M, Tollman S, Lewando Hundt G, Fowkes G, Marsh J (2007). A cross-sectional study of vascular risk factors in a rural South African population: Data from the Southern African Stroke Prevention Initiative (SASPI). BMC Public Health 7:1-10.
Touyz RM, Schiffrin EL (2001). Increased generation of superoxide by

angiotensin II in smooth muscle cells from resistance arteries of hypertensive patients: role of phospholipase D-dependent NAD (P) H oxidase-sensitive pathways. J. Hypertens. 19(7):1245-1254.
Touyz RM, Schiffrin EL (2004). Reactive oxygen species in vascular biology: implications in hypertension. Histochem. Cell Biol. 122:339-352.
Turrens JF (2003). Mitochondrial formation of reactive oxygen species. J. Physiol (Lond). 552(2):335-344.
Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J (2007). Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39(1):44-84.
Vaziri ND, Wang XQ, Oveisi F, Rad B (2000). Induction of oxidative stress by glutathione depletion causes severe hypertension in normal rats. Hypertension. 36:142-146.
Vorbach C, Scriven A, Capecchi MR (2002). The housekeeping gene xanthine oxidoreductase is necessary for milk fat droplet enveloping and secretion: Gene sharing in the lactating mammary gland. Genes Dev. 16:3223-3235.
Wald DS, Law M, Morris JK (2002). Homocysteine and cardiovascular disease: Evidence on causality from a meta-analysis. Br. Med. J. 325(7374):1202.
Wassmann S, Wassmann K, Nickenig G (2004). Modulation of oxidant and antioxidant enzyme expression and function in vascular cells. Hypertension 44(4):381-386.
White CR, Darley-Usmar V, Berrington WR, McAdams M, Gore JZ, Thompson JA, Parks DA, Tarpey MM, Freeman BA (1996). Circulating plasma Xanthine oxidase contributes to vascular dysfunction in hypercholesterolemic rabbits. Proc. Natl. Acad. Sci. U.S.A. 93(16):8745-8749.
Wiseman H, Halliwell B (1996). Damage to DNA by reactive oxygen and nitrogen species: Role in inflammatory disease and progression to cancer. Biochem. J. 313(Pt 1):17-29.
World Health Organisation (2003). The World Health Report 2003: Shaping the future. World Health Organisation, Switzerland.
World Health Organisation (2004). The Atlas of Heart Disease and stroke.http://www.who.int/cardiovascular_diseases/resources/atlas/en/[February 2009].
World Health Organisation (2009). Strategic priorities of the WHO Cardiovascular Disease programme. http://www.who.int/cardiovascular_diseases/priorities/en/ [October 2009].
Wu XC, Johns EJ (2004). Interactions between nitric oxide and superoxide on the neural regulation of proximal fluid reabsorption in hypertensive rats. Exp. Physiol. 89(3):255-261.
Xia Y, Dawson VL, Dawson TM, Snyder SH, Zweier JL (1996). Nitric oxide synthase generates superoxide and nitric oxide in arginine-depleted cells leading to peroxynitrite-mediated cellular injury. Proc. Natl. Acad. Sci. U.S.A. 93(13):6770-6774.
Yasmin W, Strynadka KD, Schulz R (1997). Generation of peroxynitrite contributes to ischemia-reperfusion injury in isolated rat hearts. Cardiovasc. Res. 33(2):422-432.
Yasunobu Y, Hayashi K, Shingu T, Yamagata T, Kajiyama G, Kambe M (2001). Coronary atherosclerosis and oxidative stress as reflected by autoantibodies against oxidized low-density lipoprotein and oxysterols. Atherosclerosis 155:445-453.
Zalba G, Fortuño A, Díez J (2006). Oxidative stress and atherosclerosis in early chronic kidney disease. Nephrol. Dial. Transplant. 21(10):2686-2690.
Ziche M, Morbidelli L, Masini E, Amerini S, Granger HJ, Maggi CA, Geppetti P, Ledda F (1994). Nitric oxide mediates angiogenesis *in vivo* and endothelial cell growth and migration *in vitro* promoted by substance P. J. Clin. Invest. 94(5):2036-2044.