Environmental and physiological angiogenesis in causing CVD with oxidative pattern

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Abstract
Oxidative stress (OS) is a mechanical pathway that regulates cellular function in different pathophysiology. Correlating mechanisms of metabolic diseases with OS has a growing interest in pharmaceuticals and life science research. The therapeutic solution requires the collaboration of different biopathway analyses using bioinformatics tools. However, OS has both environmental and physiological disturbances in treating cardiovascular diseases. Oxidative stress plays a vital role in cardiac remodeling and heart failure pathophysiology. OS induces insidious modification in the intracellular pathways, redox signaling, and causes cellular dysfunction and damage. The discovery of a wide variety of hypertrophy signaling kinases and transcription factors knowledge can provide gene/protein relations for new drug design and discovery. A good non-resistant anti-angiogenic medicine might better treat cardiac complications at any age. The alternative of VEGF or its combinatorial therapeutic approach might provide a better solution in the new treatment paradigm.

Key Words: Oxidative stress; ROS; Angiogenesis; Cardiovascular disease; Metabolic risk.

Introduction
Cardiovascular disease (CVD) is the principal global cause of death, accounting for 17.3 million deaths per year, which is suspected to rise to 23.6 million by 2030. Expenditures associated directly or indirectly with CVD and stroke cost more than $320.1 billion including medical expenses and loss in productivity (Abegunde et al., 2007). Therefore, CVD is considered an important cause of mortality and morbidity in Bangladesh. Many risk factors have already been established related to CVD such as smoking, hypertension, high lipid, diabetes, obesity, etc. (Yoshikawa & Naito, 2000). In addition, several emerging risk factors were identified through continuous surveillance and research on CVD that need special attention to be paid (Chowdhury et al., 2018). Oxidative stress is one such risk factor.

Oxidative stress
Oxidative stress is described best as an overweening bioavailability of Reactive Oxygen Species (ROS) in a physiological condition caused due to an imbalance between generation and wipeout of ROS (the latter one being scavenged by antioxidants) (Yoshikawa & Naito, 2000). Any condition where the oxidant metabolites (e.g., singlet oxygen, superoxide, or other free radicals) exert toxic effects due to their excessive production or modified cellular mechanisms of protection can be referred to as oxidative stress. The influence of oxidative stress can be determined by observing the cellular accumulation of peroxides (e.g., lipid peroxides) or by-products, such as malondialdehyde (MDA), and by oxidized glutathione. Oxygen itself has a radical nature and can be called a diradical, but it does not exert any major reactivity (Fearon &
Figure 1. Oxidative stress and cellular responses. Oxidative stress can be triggered through both endogenous and exogenous sources. ROS produced due to oxidative stress can activate different signaling kinases and transcription factors. As a result, systems that maintain intracellular redox state is impaired resulting in cellular responses such as DNA damage, abrupt of protein synthesis and chromosomal abnormalities. In case of cancer cells, oxidative stress promotes cell survival and thus promote the prognosis of cancer. The balance between ROS production and cellular antioxidant systems is important for maintaining intracellular redox state of the cell.

Figure 2. Sources of reactive oxygen species and their cellular effects. Superoxide dismutase (SOD) plays pivotal role in regulation of reactive oxygen species in the cell. Electron transport chain components and cytosolic enzymes, phagocytic and non-phagocytic cells as well as environmental factors affects the generation of ROS in a cell. In response to increased ROS and resultant oxidative stress, various enzymes (kinases) and cell signaling pathways as well as critical transcription factors are activated. These changes due to ROS production is responsible for various cellular responses such as apoptosis, cellular dysfunction, endothelial dysfunction and cardiovascular dysfunctions.
Oxidative stress has been defined as harmful because oxygen-free radicals attack biological molecules such as lipids, proteins, and DNA. Besides the cytotoxic effect, oxidative stress also plays an essential role in the modulation of messengers that regulate crucial cell membrane activities, which is critical for survival (Ando & Fujita, 2009). It influences the intracellular redox status, activating protein kinases which include a series of receptor and non-receptor tyrosine kinases, protein kinase C, and the MAP kinase cascade, and as a result, induces various cellular responses (Fig. 1) (Finkel, 2003).

A consistent body of evidence suggests an association of oxidative stress to medical conditions such as cardiovascular disease, angiogenesis, diabetes mellitus (DM), neoplasias, respiratory diseases, and neurological disorders. In addition, oxidative stress can influence many biological processes such as apoptosis, viral proliferation, and inflammatory reactions (Roberts & Sindhu, 2009).

Reactive oxygen species (ROS) can play a role in cell signaling. Numerous intracellular signaling pathways can be activated by oxidative stress via ROS-mediated modulation of different enzymes and the activation of critical transcription factors in response to an increase in ROS or oxidative damage which continues from the cytoplasm to the nucleus of a cell and binds to the promoter regions of particular genes (Hamanaka & Chandel, 2010). These stress-activated pathways significantly impact gene expression, which will ultimately affect a cell’s fate (e.g., apoptosis, proliferation, and cytokines). The balance between ROS production, cellular antioxidant defenses, activation of stress-related signaling pathways, and the production of various gene products, as well as the effect of aging on these processes, will determine whether a cell exposed to an increase in ROS will be destined for survival or death (Bigarella et al., 2014).

**Reactive oxygen species (ROS)**

Reactive oxygen species (ROS) include both free radicals (that typically have oxygen- or nitrogen-based unpaired electrons in their outer orbitals) and other species (e.g. hydrogen peroxide) that act as oxidants. ROS include superoxide (O$_2^-$), hydroxyl radical (OH), hydrogen peroxide (H$_2$O$_2$), and peroxynitrite (ONOO$^-$). The mitochondria and cellular membrane oxidases (e.g., NADPH oxidase) are major sources of ROS (Finkel & Holbrook, 2000).

Production of ROS occurs through various generating systems (Fig. 2). Oxygen radicals are involved as fundamental intermediates in metabolic reactions, including spontaneous and enzyme-mediated physiological processes. In most cells, the bulk amount of oxygen is reduced through the mitochondrial cytochrome oxidase pathway e.g. in the heart (Forman & Torres, 2002).

Reactive oxygen species (ROS) are involved in cell growth, differentiation, progression, and death. Low concentrations of ROS may be beneficial and higher amounts of ROS play a role in several human disease states like cardiovascular diseases, aging, cancer, etc. (Finkel, 2011). ROS not only has harmful effects on organisms. ROS plays a very important role in cellular processes.

**Oxidative stress in cardiovascular disease**

Oxidative stress has a major role in the development of cardiovascular diseases. ROS mediates various pathological processes in the endothelium, smooth muscle cells, and inflammatory cells. Several unwanted pathways were found to be correlated to the raised oxidative stress. This promotes the formation of oxidized LDL (O-LDL) and oxidized cholesterol leading to the accumulation of cholesterol in arterial tissues. Oxidative DNA damage occurs spontaneously from ROS produced during normal metabolic events in all organisms. ROS ( Reactive Oxygen Species) also affects mtDNA (Mitochondrial DNA) damage in vascular cells. Mitochondrial ROS could contribute to tenacious cardiovascular disorders (Katoch et al., 2013).

According to the “oxidative stress theory”, cumulative and irreversible accruement of physiological damages due to ROS influences certain critical aspects of the aging process and leads to afflicted physiological activities, increased rate of disease, and a reduced life span. Emerging evidence suggests that reactive oxygen species (ROS) such as nitric oxide (NO), superoxide (O$_2^-$), and peroxynitrite (OONO$^-$) undergo reactions according to the oxidative stress of the environment and mediate numerous effects in the cardiovascular system promoting various disease like hypertension, angina, arrhythmia, etc. (He & Zuo, 2015). ROS can also damage the components of ETC (Electron Transport Chain) and mitochondrial DNA, resulting in further rise in intracellular ROS levels and a fall in mitochondrial function. Alterations in membrane structure caused due to ROS-mediated disturbed lipid profile or lipid peroxidation are one of the most important and potent risk factors that usually lead to ischemic heart disease (IHD) like angina pectoris (Vijaya et al., 2010).

There are both direct and indirect pieces of evidence of increased oxidative stress in humans with heart failure. In patients with heart failure, the lipid peroxidation product malondialdehyde (MDA) is increased in plasma. Direct evidence of increased myocardial oxidative stress is also obtained from the fact that the level of 8-iso-prostaglandin F$_2$as increased in the pericardial fluid of patients with heart failure (Heitzer et al., 2001). The involvement of oxidative stress in heart failure is further supported by the prevention of the progression of several pathological processes such as cardiac hypertrophy, cardiac myocyte apoptosis, ischemia-reperfusion and myocardial stunning.

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leading to heart failure can be prevented by antioxidants such as vitamin E, hydroxyanisole, and catalase (Lakshmi et al., 2009).

An important source of ROS is the intra-mitochondrial electron transport chain. Free radicals produced in mitochondria can cause point mutations, DNA cross-link, and DNA strand breaks in mitochondrial genes. The damage to the mitochondrial genome results in impaired respiration. Several studies have reported impaired mitochondrial function and increased production of superoxide associated with reperfusion-related events (Schnabel & Blankenberg, 2007).

Myocardial cell damage and myocyte apoptosis mediated by free radicals and oxidative stress are early-stage events of CVD. Mitochondria-mediated apoptosis pathway initiates by releasing cytochrome c from mitochondria and activating caspase-9 (Singal, 1998).

Scientific evidence suggests that oxidative stress plays a key role in the onset of chronic diseases, such as CVD, and obesity, but especially DM2. In this case, the role of oxidative stress in MS is not yet fully understood, but its importance, this case, lies mainly in the manifestations associated with MS, such as atherosclerosis, hypertension, obesity, and insulin resistance. For this reason, it has been suggested that oxidative stress may be a primary event triggering MS, not a subsequent event (Tsutsui et al., 2011).

**Oxidative stress and angiogenesis**

ROS, although proven as detrimental to tissue damages and responsible for chronic vascular conditions; in essential or transient amounts, is also able to activate signaling pathways that lead to the progress of angiogenesis. Angiogenesis is a systemic process of formation of new blood vessels from previously existing vasculature, a process which is vital for many physiological courses of events, such as growth and development, repair and regeneration of tissues and organs, skin renewal, and wound healing (Fig. 3). This process involves multiple cell types including blood cells, inflammatory and endothelial cells. Multiple cytokines also play important role in this process, termed proangiogenic factors such as endothelial growth factor (VEGF), fibroblast growth factors (FGF), platelet-derived growth factor (PDGF), placental growth factor (PGF), angiopoietin-1 (Ang-1), etc.; and antiangiogenic factors, such as angiotatin, and endostatin, etc. (Kim & Byzova, 2014). In the physiological concentration of ROS, these pro- and anti-angiogenic factors act in a balanced way to stimulate and sustain angiogenesis as required. But pathological or excessive angiogenesis may proceed if such a balance gets upset.

In many conditions, proangiogenic factors themselves induce the recruitment of inflammatory cells, such as monocytes and neutrophils at their functional site. Excessive ROS load in these inflammatory cells generates oxidative stress, which further contributes to angiogenesis, and at the same time, causes oxidative tissue damage, ultimately leading to several vascular pathological situations (Xian et al., 2019). Therefore, directly or indirectly, oxidative stress may contribute in both directions to the vascular development system.

**Association of angiogenesis with cardiovascular disease**

The role of angiogenesis in atherosclerosis, the buildup of plaque inside the artery, remains a highly disputative issue. It is still a puzzle whether angiogenesis is a key cause in the pathogenesis of atherosclerotic plaque formation or is a way to treat coronary heart disease. Several studies found atherosclerotic plaques causing acute coronary syndromes to be associated with intralesion angiogenesis (Khurana et al., 2005; Nasreen et al., 2021). These vulnerable plaques are prone to rupture and lead to intra-arterial occlusion which can cause a sudden and catastrophic restriction of the blood supply to the heart resulting in acute
coronary syndrome to a fatal loss of cardiac function. Again, angiogenesis itself may play a vital role in such cases since it is suggested from the evidence that endogenous VEGF may play an arterioprotective role in the adult human vasculature. However, the role of angiogenesis is still unresolved whether it plays a central role in the development of atherosclerosis or is responsible for plaque instability. Moreover, recent clinical trials of both proangiogenic and antiangiogenic therapies suggested that inhibition of angiogenesis could be a viable therapeutic strategy for cardiovascular disease.

Conclusion
Undermining oxidative stress and antioxidant therapy could be the keys to managing and combating cardiovascular disorders. Further investigation of genetic variations and dietary patterns, associated with oxidative metabolism, to assist in the elucidation of these interactions involving the pathogenesis of MS, to prevent morbidity and mortality from CVD.

Author Contributions
MF, MAS, KRM and SSK involved in research concept and design, MF and MAS took part in collection and/or assembly of literature and data, MF, MA and KRM involved in data analysis and interpretation, MF, MA and SSK took part in writing the article, and MF, MAS and KRM involved in critical revision of the article. All authors have read and approved the manuscript.

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