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Oxidatively Modified Biomolecules: An Early Biomarker for Acute Coronary Artery Disease

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1. Introduction

Cardiovascular disease is the worldwide major cause of mortality and morbidity. The 2009 annual report from World Health Organization **(**WHO**)** highlighted the mortality rate prediction of the population worldwide that, in 2030, cardiovascular disease will become the major cause of deaths, and the mortality rate will higher than other infectious diseases such as HIV, Tuberculosis, malaria infection (World Heatlh Organization ,2009). Moreover, this report also mentioned that, among cardiovascular diseases, ischemic heart disease and cerebrovascular disease, which were reported as top 2 cause of mortality in 2004, are expected to still be the major cause of death in next 20 years (World Heatlh Organization ,2009). Coronary artery disease is a sequence of pathophysiologic processes in coronary arteries, myocardial ischemia and infarction (Wudkowska et al.2010). Therefore, the early diagnostic of myocardial ischemia and infarction, will lead to the rapid and more effective of medical intervention, and safe the patients' life. The standard diagnosis of coronary artery disease focuses on clinical assessment such as history of chest pain associated with electrocardiogram (ECG) changes, and elevation of cardiac specific-biochemical markers (Maneewong K. et al.2011).

Determination of serum or plasma level of cardiac specific-biochemical markers is one of the most essential and effective way for diagnosing myocardial ischemia/infarction. The ideal cardiac markers should have high specificity, high sensitivity, rapidly released after the onset of the symptoms, abundant in cardiac tissue but less in other tissues, long half life in blood circulation, and capable of representing the prognosis and estimating the infarct size.

It has been known that coronary artery disease, especially myocardial ischemia and ischemia-reperfusion injury is the phenomenon that related to an oxidative stress (Buja2005), which is an imbalance and inadequate production of reactive oxygen species (ROS), subsequently resulted in biochemical modifications of major principle biomolecules such as proteins, lipids, and nucleic acids (Valko et al.2007;Sbarouni et al.2008a;Sbarouni et al.2008b;Sbarouni et al.2008c;le-Donne et al.2003a;le-Donne et al.2003c). Some oxidatively modified biomolecules such as Ischemia Modified Albumin or IMA, has been approved by US Food and drug Administration (FDA) and used as a rule-out marker for acute myocardial ischemia (Apple et al.2005;Bar-Or et al.2000;Sbarouni et al.2008c;Sbarouni et

al.2008a;Sbarouni et al.2008b;Van et al.2010). In addition, many of oxidatively modified biomolecules have been reported to correlate with the severity of coronary artery disease and possibly used as a marker for myocardial ischemia (Apple et al.2005;Bar-Or et al.2001c; Bar-Or et al.2000;le-Donne et al.2003b;Berlett & Stadtman1997;Kiyici et al.2010;Turedi et al.2010; Melanson & Tanasijevic2005;Van et al.2010;Shen et al.2010;Pantazopoulos et al.2009; Bhagavan et al.2003;Santalo et al.2003;Sinha et al.2003;Mutlu-Turkoglu et al.2005;Mocatta et al.2007; Beal2002;Docherty2010;Wudkowska et al.2010;Charpentier et al.2010;Maneewong K. et al.2011; Sbarouni et al.2008a; Sbarouni et al.2008b;Sbarouni et al.2008c;le-Donne et al.2003a; le-Donne et al.2003d).

In this chapter, studies of oxidatively modified biomolecules such as proteins, lipids, and nucleic acids, related to coronary artery diseases will be discussed. Moreover, clinical usefulness of determining these oxidatively modified biomolecules as a biomarker for coronary artery disease will also be addressed.

2. Oxidative stress

The term oxidative stress has been commonly mentioned or explained the underline pathophysiological mechanism of some diseases during the last thirty years (Hensley et al.2000). Oxidative stress is referred to an inadequate of free radicals generation and/or insufficient removal of the radicals by antioxidants, radical scavengers. Free radicals can also be defined as atoms or molecules containing one or more unpaired electrons on an open shell configuration (Lushchak2011), which generate the highly reactivity properties of the molecules. There are 2 major types of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS).

2.1 Reactive Oxygen Species

Reactive oxygen species (ROS) are generated from oxygen metabolism include superoxide anion ($O_2{}^{\bullet-}$), peroxyl ($RO{}^{\bullet}_2$), hydroperoxyl ($HRO_2{}^{\bullet-}$), and hydroxyl radical ($^{\bullet}OH$). In addition, ROS can also be non-radical species such as hydrogen peroxide (H_2O_2) and hydrochlorous acid (HOCl). ROS can be generated from regular metabolic processes or from external sources such as X-ray exposure, air pollutants, cigarette smoking, and etc. The primary source of intracellular free radicals generated by the addition of one oxygen electron, which is resulted in superoxide ($O_2{}^{\bullet-}$) (equation 1).

$$O2 + e- \longrightarrow O_2{}^{\bullet-} \tag{1}$$

Intracellular mechanism to balance the generation of superoxide is achieved by specific enzyme called superoxide dismutase (SOD), which catalyze the changing of superoxide to oxygen and hydrogen peroxide (H_2O_2) (equation 2).

$$\overset{\text{SOD}}{2\,O_2{}^{\bullet-} + 2H^+ \longrightarrow O_2 + H_2O_2} \tag{2}$$
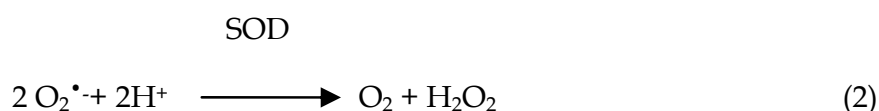
This hydrogen peroxide (H_2O_2) that is generated from equation 2 has a property of being an oxidizing agent and serve as a major source of $^{\bullet}OH$, which is one of the very harmful reactive oxygen species to the cell. According to hydrogen peroxide is non-radical and weak
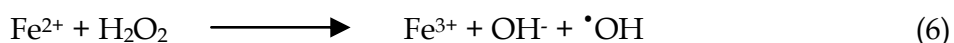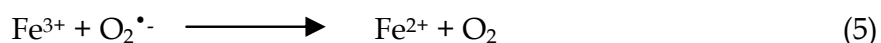
polar, it can penetrate through the lipid bilayer of cell membrane or mitochondrial membrane, and destroy some biological molecules such as proteins, lipids, and nucleic acids. Cellular balancing mechanism for H_2O_2 is the enzyme catalase, which convert two molecules of H_2O_2 to oxygen and water (equation 3)

$$2\,H_2O_2 \xrightarrow{\text{(Catalase)}} 2H_2O + O_2 \tag{3}$$
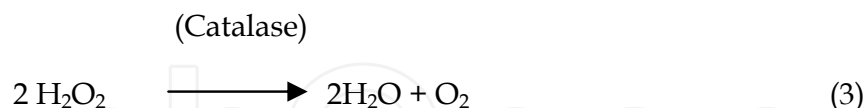
Another alternative mechanism generating ROS in the cell is the Haber-Weiss reaction, which is a chemical catalysis of superoxide and hydrogen peroxide by ferric ion (Fe^{3+}) to generate hydroxyl radical ($^{\bullet}OH$) (equation 4)

$$O_2^{\bullet-} + H_2O_2 + O_2 \xrightarrow{Fe^{3+}/CU^{2+}} OH^- + {}^{\bullet}OH \tag{4}$$
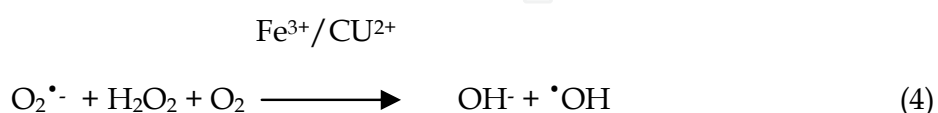
In addition, superoxide can reduce ferric ion to form ferrous ion (equation 5), the reaction called "Fenton reaction". The production of ferrous ion in first Fenton reaction can react with H_2O_2 in the second reaction and result in OH^- and $^{\bullet}OH$ generation (equation 6).

$$Fe^{3+} + O_2^{\bullet-} \longrightarrow Fe^{2+} + O_2 \tag{5}$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + {}^{\bullet}OH \tag{6}$$

2.2 Reactive Nitrogen Species

Reactive nitrogen species (RNS) are generated from the reaction of nitric oxide (NO), which is enzymatically generated by nitric oxide synthetase (NOS). The NOS oxidized the amino acid L-arginine or L-citrulline. The member of RNS include nitric oxide (NO) and nitrogen dioxide ($NO^{\bullet}_2$), as well as non radicals nitrogen species e.g. peroxynitrite ($ONOO^-$), nitrousoxide (HNO_2), and alkyl peroxynitrates (RONOO). Among these RNS molecules, $^{\bullet}NO$, and $ONOO^-$ are the most investigated species, which have significant impact in cardiovascular complication (Kumar et al.2010).

2.3 Antioxidants

Antioxidants are either endogenous or exogenous compounds that prevent the generation of harmful free radicals, reduce the generated radicals, inactivate their harmful reactivity, and thereby block the chain reactions of these oxidants. The primary or chain breaking antioxidants so called "scavenger" which is neutralize the free radicals by donating one of their own electrons (Kumar et al.2010). The secondary or preventative antioxidants work by sequestration of transition metal ions or removal the peroxides by catalase and glutathione peroxidase. The tertiary antioxidants defense is the repairing of damaged molecules, in attempt to avoid the accumulative damages (Kumar et al.2010).

3. The oxidative modification of biomolecules

Reactive oxygen species readily attack a variety of important biomolecules, including carbohydrates, proteins, lipids, and nucleic acids. Interaction between ROS and these

biomolecules resulted in biochemical modifications, which alter the functions as well as the properties of these biomolecules (Figure 1).
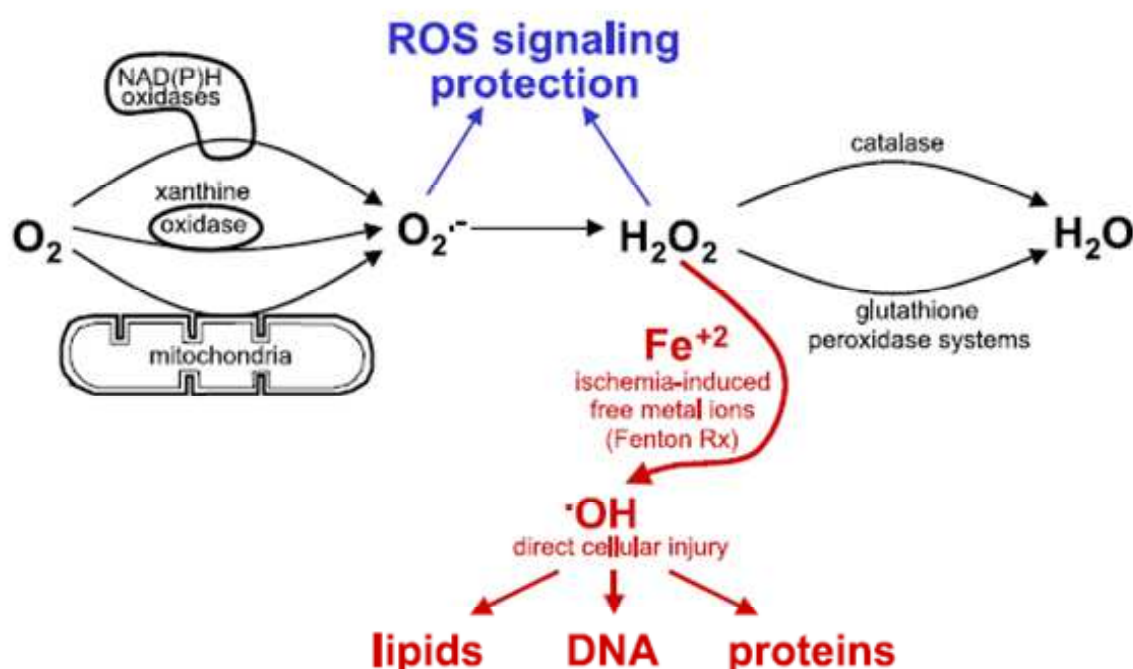

Fig. 1. Oxidative modification of biomolecules (Becker2004). In normal physiological conditions, superoxide and hydrogen peroxide are generated. Generation of intracellular ROS may activate the intracellular signaling pathways for cardiac protection, for example in ischemic preconditioning. The generated hydrogen peroxide, especially in myocardial ischemia, reacts with ferrous ion in Fenton reaction, which results in hydroxyl radicals. Over production of the hydroxyl radical causes oxidative modification of biomolecules, such as lipids, proteins, and nucleic acids.

3.1 Proteins

It has become manifested that proteins are also concerned as a target of free radical destruction. The mechanism involved in the oxidation modification of proteins is thought to occur at the monomeric level of amino acids, especially cysteine, tyrosine, phenylalanine, tryptophan, histidine, and methionine. The process of proteins oxidation creates new functional groups such as hydroxyl groups and carbonyl groups. These added up new functional groups can be generated by different mechanisms and can also indicate the degree of oxidative modification. The outcomes of the oxidative modification of proteins cause proteins fragmentation, cross-linking and unfolding, which may activate or hinder proteolytic and proteasome-mediated turnover. The biomarkers of oxidatively modified proteins include protein carbonyl, ischemia-modified albumin, and etc. Ischemia modified albumin (IMA) and protein carbonyl (PC) are oxidatively modified proteins found in many oxidative related disorders such as myocardial ischemia, renal ischemia, (Apple et al.2005;Pantke et al.1999;Bar-Or et al.2000;Kiyici et al.2010;Turedi et al.2010;Melanson & Tanasijevic2005). According to this, many studies suggested the ability of these two oxidatively modified proteins as the early biomarkers for diagnosis of coronary artery disease.

3.2 Lipids

Lipids are the basic biomolecules found throughout the cells, such as phospholipids component of the cell membrane. Therefore, lipids can be one of an oxidative modification targets, similar to proteins. Oxidative modification of lipids are the chain reactions, lead to the degradation of lipids or so-called "lipid peroxidation", which mediated by free radicals abstract electrons from lipid molecules such as aldehyde group e.g. Malonaldehyde (MDA). Polyunsaturated fatty acids are more sensitive to the lipid peroxidation according to these lipids contain multiple double bonds in between methylene- CH_2- groups that easily react with reactive hydrogen atoms (Lu et al.2010). The reactions of oxidative modified lipids consist of three major steps including; the initiation step, where is a fatty acid radicals are produced. The propagation is the direct reaction with oxygen molecules produced peroxyl fatty acid radials that react with another free fatty acid producing a different fatty acid radical and lipid peroxide or a cyclic peroxide and termination. The destruction of lipid molecules by lipid peroxidation can cause membrane permeability alteration, loss in fluidity, decreasing in electrical resistance, change in phospholipids bilayer membrane disruption, membrane-bound enzyme malfunction and loose of integrity ionic gradient, disruption or activation of enzyme function, and cellular injury (Ayres1984). Biomarkers of lipid peroxidation include malonaldehyde, F2-Isoprostanes, and etc.

3.3 Nucleic acid

Nucleic acid is one of the basic biomolecules that play many essential roles in the cell. The nucleic acids-DNA and RNA- are the principal informational molecules of the living cells. During aging processes, free radicals such as $^\bullet$OH can be generated and can bind to DNA molecules. Association and reaction of free radical to DNA can lead to DNA bases damaging, both purines and pyrimidines, and result in DNA strand break (Valavanidis et al.2009). Alteration of purines and pyrimidines play a significant role in large variety of pathological stages such as cancer (Kasai1997). Biomarkers of oxidative modified nucleic acid include 8-hydroxy-2'-deoxyguanosine, 8-nitroguanin, and etc.

4. Oxidatively modified biomolecules as cardiac markers for coronary artery disease

4.1 Ischemia modified albumin

Generation of reactive oxygen species resulted in the modification of proteins, which introduce new functional groups such as hydroxyl groups and carbonyl groups (le-Donne et al.2003b;Berlett & Stadtman1997). Among these proteins, ischemia-modified albumin (IMA) was reported as an early biomarker in many pathological disorders (Kiyici et al.2010;Montagnana et al.2006;Abboud et al.2007;Gunduz et al.2009;Sharma et al.2007).

Ischemia Modified Albumin (IMA) is serum albumin that modified at the N-terminal portion, especially at aspartate-alanine-histidine-lysine sequences, by oxidative stress generated during ischemia (Bar-Or et al.2001b). This modification reduced the ability of albumin to bind with metal ions such as cobalt, copper, and nickel (Bar-Or et al.2001a) (Figure 2). The ischemic mechanism initiated with the insufficiency of oxygen supply during ischemia, which caused cardiomyocytes cellular anaerobic metabolism. Within a few seconds after occlusion of a major coronary artery tissue oxygen content decreases and

mitochondrial oxidative metabolism becomes inhibited. At this point, a compensatory increase in anaerobic glycolysis for ATP production leads to accumulation of hydrogen ions and lactate, resulting in intracellular acidosis and inhibition of glycolysis (Reimer & Ideker1987). An aerobic glycolysis cannot provide sufficient ATP to meet the demand of myocardium. The depletion of ATP also causes the interruption of cellular ion-pumps and calcium influx to the cells. The excess intracellular calcium activates calcium-dependent proteases such as calpain, calmodulin, generates $O_2^{\bullet-}$ and converts to H_2O_2. Blood consist of transition metals such as copper and iron, which can interact with $O_2^{\bullet-}$ and H_2O_2 and form the strong oxidant $^{\bullet}OH$, which lead to cellular destruction. Proteins, predominantly albumin, are damaged by free radicals especially at amino terminus (N-terminus), resulting in the albumin N-terminal derivatives. Human serum albumin, a major protein in circulation, consists of 585 amino acid residues with half life in circulation approximately 19 days. The metal binding properties of albumin depend on the three dimensional structure binding sites, which are distributed over the molecule (Bar-Or et al.2001b;Takahashi et al.1987). The modification of albumin during ischemia is independent on cell death, and can be an early biomarker for such an early stage of ischemia.
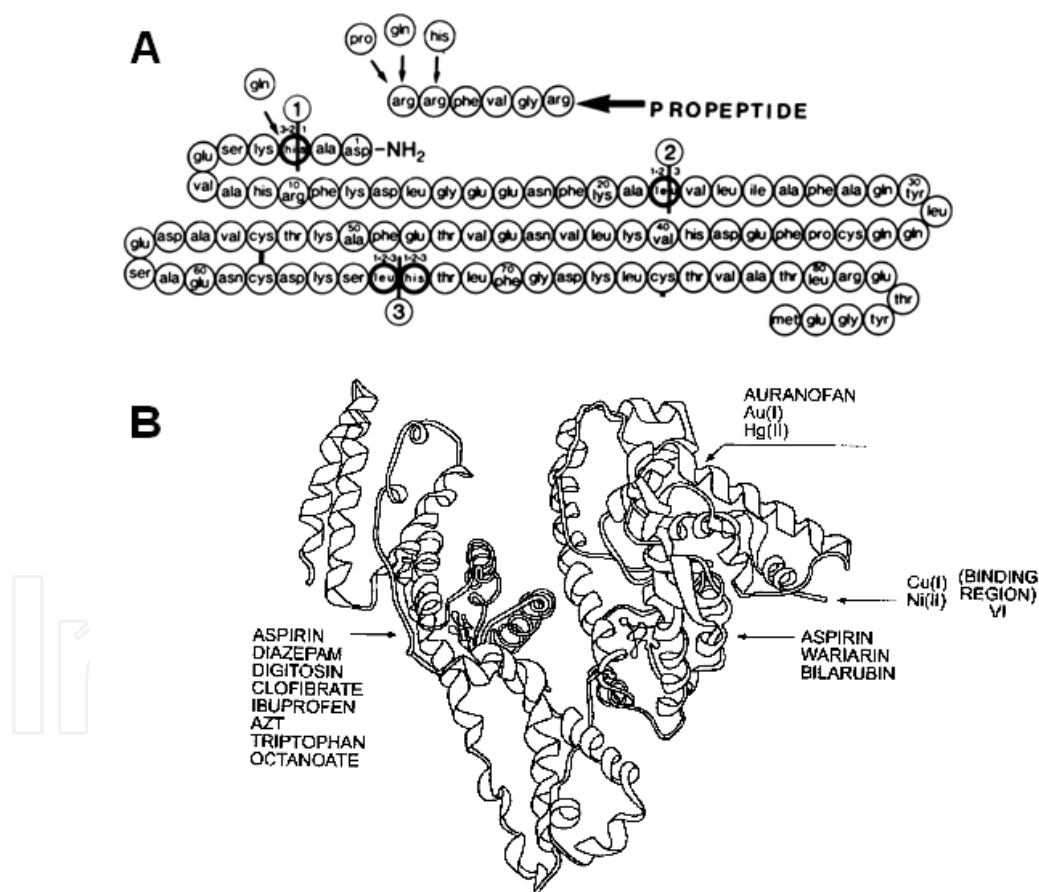

Fig. 2. The amino acid sequences (A) and molecular structure of albumin (B). This figure is modified from figure3 of Takahashi et al. (Takahashi et al.1987). Proteins albumin is oxidatively modified at NH_2 terminal of albumin.

Determination of serum or plasma IMA can be performed by Albumin Cobalt Binding (ACB) method. In 2003, US Food and drug Administration (FDA) approved that ACB

method is the diagnostic test for acute myocardial infarction (Van et al.2010). The principle of ACB method is based on the principle of free radicals, which is generated during ischemia, alters the metal ions binding capacity of serum albumin (Sbarouni et al.2008a) (Figure 3). The test is currently called IMA test instead of the ACB test. It has been reported that IMA test could be used for screening the patients with chest pain, who suspected AMI, at the emergency department, excluded patients from the other causes of chest pain (Bar-Or et al.2000). Many studies show that IMA levels increased in patients with acute coronary syndrome and also elevated in myocardial ischemia (Sbarouni et al.2008a). The analytical sensitivity of the test is 13 u/ml, with 98% recovery (Sbarouni et al.2008a). Moreover, there were reports mentioned of non-interfering effect from bilirubin, hemoglobin, cholesterol, total proteins, and number of cardiac drugs (Govender et al.2008). It was also reported that no biological variation of IMA regarding race and gender (Govender et al.2008).

According to the ability to detect IMA as a result of ischemia, the event of reduce oxygen supply prior to cardiomyocytes necrosis, make IMA test good enough to be an earlier cardiac marker (Sbarouni et al.2008a). It was reported that the serum IMA level increased and can be detected within 6-10 minutes after ischemia and returned back to baseline within 6 hours (Bhagavan et al.2003). This could be an advantage of IMA, in comparison to the other conventional cardiac markers such as cardiac troponin and CK-MB, which are necrotic marker and could not be detected until 4-6 hours after onset of chest pain/ischemia (Wu et al.1999). Determination of IMA has been used triage patient who suspected from cardiac ischemia. Low level of serum IMA, would estimate low risk for a cardiac ischemic event and make a rapid consideration to exclude or discharge patient. Low level of serum IMA perhaps indirectly predicts the low level of cardiac troponin (Sbarouni et al.2008a). So, it can make a clear distinct when the negative results from IMA, troponin, and ECG can exclude the patients from ACS (Bhagavan et al.2003). The assay method can be easily and rapidly performed by spectrophotometric method. It has been shown that IMA test has high method sensitivity more than troponin as it gave positive results in 84% of patient who suspect ACS while cardiac troponin could detect only 42% (Takhshid et al.2010). Combination with triple tests including ECG, IMA, and cardiac troponin could increase the negative predictive value for ACS to 96% (Takhshid et al.2010). Furthermore, IMA test might reduce in the number of diagnostic tests such as determination of serum high sensitivity C-reactive proteins (hsCRP), NT-proBNP elevation, and cTnT release (Kazanis et al.2009), invasive imaging, which have high cost (Keating et al.2006).

However, it seems like IMA test lack of specificity. High serum IMA level can also be detected in other diseases such as cancer, acute infections, end renal disease, and liver cirrhosis, (Kazanis et al.2009). Therefore, the negative results from cTnT test and IMA allow more confident to exclude the patients, who suspected AMI. However, a positive IMA alone still need further investigation. Moreover, it has been reported that serum IMA level can also be elevated in plasma from healthy subjects, 24-48 hours after exercise (Kim et al.2008). Therefore, utilization of IMA test as cardiac marker for coronary artery disease need to be further investigated to ensure the value of the test.

4.2 Proteins carbonyl

The carbonyl (CO) groups in proteins compose of aldehyde and ketone groups. Proteins Carbonyl groups (PC) is a product of oxidative modification on amino acid residues,

especially proline, arginine, lysine, and threonine from free radicals reactions, forming protein carbonyl groups [53]. In addition, protein carbonyl groups can be generated from an indirect mechanism of the hydroxyl radical-mediated oxidation of lipids (Figure 4). The product of lipid peroxidation, which will be described latter in this chapter, can diffuse across cell membrane, allowing the reactive aldehyde-containing lipids, which will covalently modified proteins in the cell (Grimsrud et al.2008). Proteins oxidation changes proteins functions by changing in pattern of proteins folding, which is important for their activity, decrease catalytic activity of enzyme, and finally breakdown of proteins by proteases (Almroth et al.2009). The cleavage of proteins may occur by either the amidation pathway or by oxidation of glutamyl side chain. Redox cycling cation such as Fe^{2+} or Cu^{2+} can bind to cation binding location on proteins. Free radical attack by H_2O_2 or $O_2^{\bullet-}$ can transform side chain of amine groups into carbonyls.
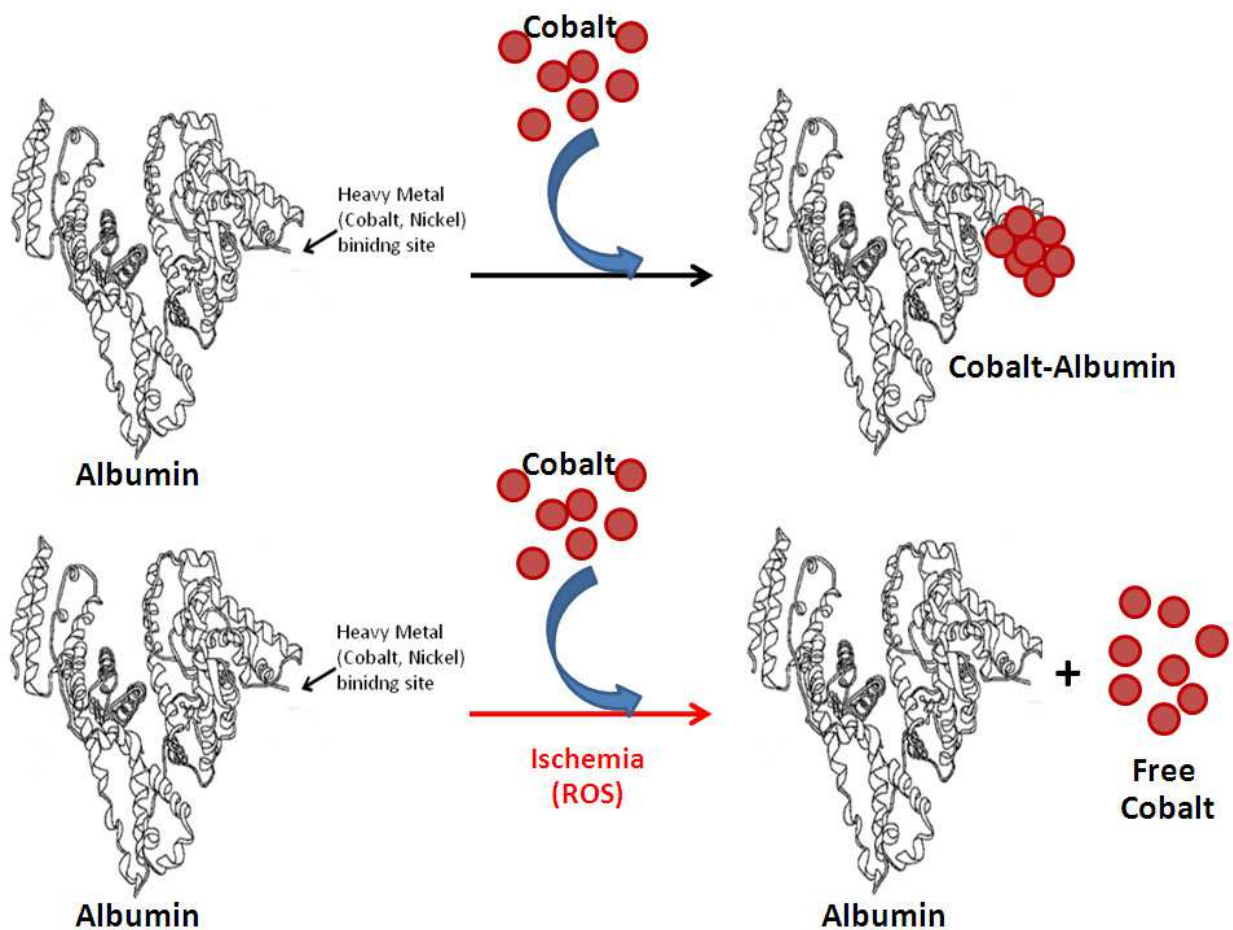

Fig. 3. Principle of Albumin cobalt binding (ACB) assay. In physiological conditions, albumin capable of binding with metal ions such as cobalt, copper, and nickel, at amino terminal end of the protein. During ischemia, N-terminal portion of albumin, especially at aspartate-alanine-histidine-lysine sequences, is modified and result in the reduction in albumin-metal ions binding ability.

Laboratory measurement of PC can be performed by variety of methods, for example, spectrophotometric assay, HPLC, ELISA, and immnunoblotting (le-Donne et al.2003a;le-

Donne et al.2003b;le-Donne et al.2006). Spectrophotometric assay for PC can be perform by 2,4-dinitrophenylhydrazine (DNPH spectrophotometric method), which based on the formation of a stable dinitrophenyl (DNP) hydrazone reacts in acidic pH solution. Spectrophotometric DNPH assay showed high sensitivity detection of carbonyl content level in purified proteins (le-Donne et al.2003b;Levine et al.1994). This method does not require any expensive or specialized equipments. It has been shown that the serum level of PC increased rapidly in blood stream and still remained at least 24 hours (Mutlu-Turkoglu et al.2005). Mutlu-Turkoglu *et al.* demonstrated that serum PC level increased in coronary artery disease, atherosclerotic lesion in human, and during ischemia-reperfusion (Mutlu-Turkoglu et al.2005). As it has also been reported that PC can be generated following the onset of myocardial infarction (Paton et al.2010) suggested the diagnostic value of PC and may be used as biomarker for coronary artery disease. The stability of this assay remained in hours and days, whereas lipid oxidation products can be removed within minutes (Mutlu-Turkoglu et al.2005). In AMI, serum PC level was significantly increased when compared with normal control (Paton et al.2010). Diagnosed value of PC in human can also be used in environmental studies, monitoring in subjects who exposed to the bunker oil (Almroth et al.2009). Although PC has been proven as a sensitive marker, but it was shown to has less specificity, similar to IMA. The increasing in serum level of PC can be detected in other human diseases such as Alzheimer' disease, cataract genesis, chronic hepatitis, diabetics, cigarette smoker, and after doing exercise (Mutlu-Turkoglu et al.2005). According to the time consuming and proteins precipitation is required in spectrophotometric method, this technique is inappropriate to determine the PC level in large number of clinical samples. Therefore, other techniques, for example ELISA, were developed. Recently, the findings from our study demonstrated that PC could be an early marker for myocardial ischemia. Serum PC level in non-ST elevation myocardial infarction (NSTEMI) was significantly higher than that in ST elevation myocardial infarction (STEMI) and healthy controls, suggesting that PC is an early marker. Moreover, combinatorial determination of PC with IMA helps to improve the diagnostic power of these two markers (Maneewong et al.2011).

4.3 8-hydroxy-2'-deoxyguanosine

As mentioned in the previous section, free radicals can attack DNA and cause molecular structural alterations of DNA and result in DNA strand break. The interaction of $^{\bullet}$OH with the nucleobases of DNA, such as guanine, form the C8-hydroxyguanine (8-OHGua) or its nucleoside form deoxyguanosine (8-hydroxy-2'-deoxyguanine) or so called 8-OH-dG. The 8-OH-dG can be further oxidized and produced 8-oxo-7,8-dihydro-2'-deoxyguanine or 8-oxodG (Valavanidis et al.2009) (Figure 4). Although the other nucleic acids in DNA molecules can react with $^{\bullet}$OH in the same manner, the 8-oxodG is the major form of oxidative modified nucleic acids in DNA, and known as a potential biomarker of carcinogenesis (Kasai1997). These days, the 8-OHdG can be a biomarker of oxidative stress, aging and cancer. This molecule can be measured and analyzed using high sensitivity by high performance liquid chromatography (HPLC), gas-chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry- mass spectrometry (LC-MS-MS), immunohistochemical methods, and single cell electrophoresis (Griffiths et al.2002;Halliwell & Whiteman2004;Collins et al.2004). There are many reports that the elevation of 8-OHdG related to some pathological disorders, for example, urinary 8-OHdG has been established as a marker to evaluate oxidative stress in carcinogenic exposure, environment pollutants

and cigarette smoking (Kiyosawa et al.1990;Asami et al.1996). Elevation of 8-OHdG has been found in the plasma and myocardium of the patients with heart failure (Kono et al.2006). Recently, Himmetoglu *et al.* reported that the plasma level of 8-OHdG increased in patients with myocardial infarction and the level of this molecule decreased after reperfusion therapy in patients with MI, suggested that 8-OHdG could possibly be biomarker for monitoring or determining the prognosis of the patients (Himmetoglu et al.2009). In addition, Nagayoshi *et al* demonstrated that the urinary levels of 8-OHdG were significantly higher in cardiac patients when assessed the serial alteration of oxidative stress of patients with AMI (Nagayoshi et al.2005).
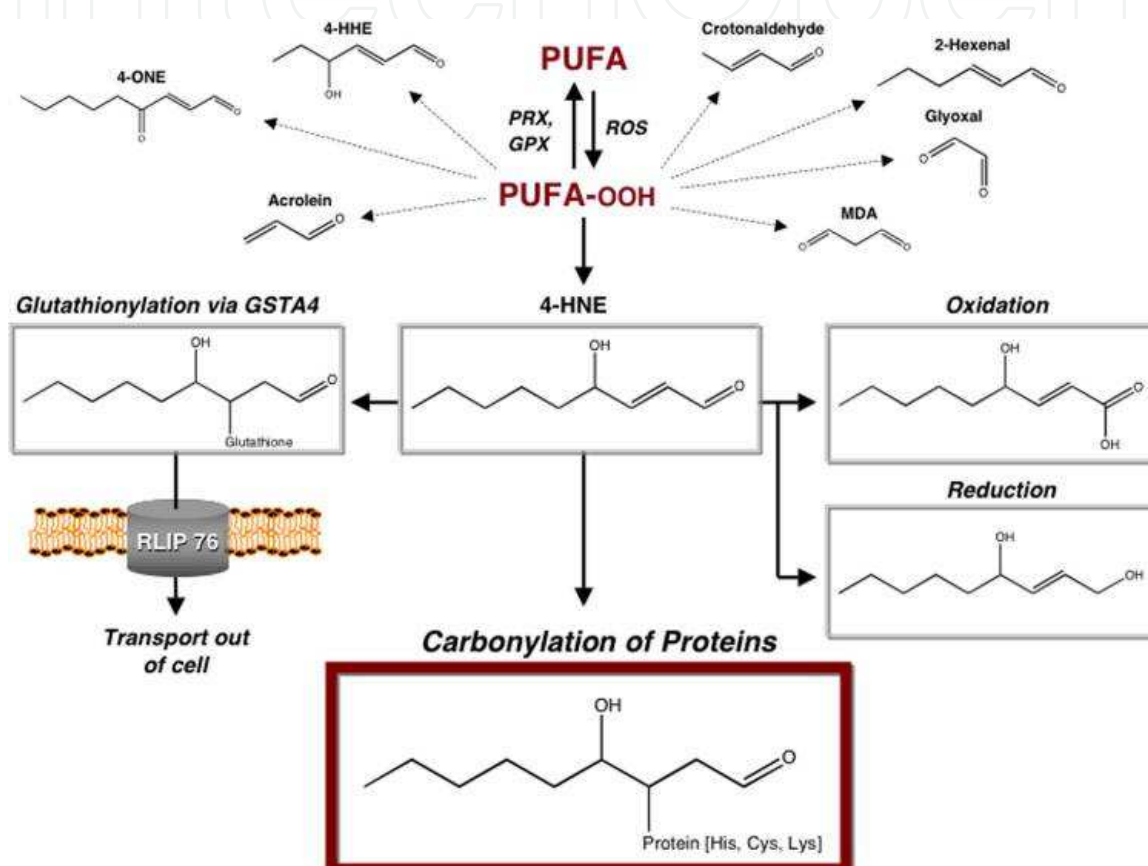

Fig. 4. Mechanism of ROS stimulates lipids peroxidation induced proteins carbonylation (Grimsrud et al.2008). Proteins carbonylation can be induced by the oxidative modification of polyunsaturated fatty acids (PUFA), which then undergo to lipid peroxidation reaction generating products such as α,β-unsaturated aldehyde 4-HNE. These molecules act as electrophiles in the covalently modification of proteins via non-enzymatic addition reactions.

It is known that reactive nitrogen species or RNS such as nitric oxide (NO) and peroxynitrite (ONOO-) can modify the molecular structure of DNA (Ohshima et al.2006). The 8-nitroguanine is the example of nucleic acid in DNA, which can be oxidatively modified by RNS. There is overwhelm data showed that 8-nitroguanine is undetectable in normal tissues, which indicating that this molecule may be a candidate as a biomarker for DNA damage induced by RNS (Akaike et al.2003;Ma et al.2004;Horiike et al.2005;Pinlaor et al.2004). Several techniques have been developed for determining 8-nitroguanine in clinical

samples, for example, HPLC with electrochemical detection, HPLC with a UV detector, GC-MS, and immunohistochemistry (Halliwell & Whiteman2004;Ohshima et al.2006;Sawa et al.2006). Many studies showed that 8-nitroguanine increased in inflammation, carcinogenesis, and cigarette smoke (Hiraku2010). However, there are no any evidence of the increasing in 8-nitoguanine in coronary heart diseases. Therefore, further investigation of 8-nitoguanine in coronary heart diseases is still need to be further investigated.

4.4 MDA

One of the most frequently used biomarkers indicating lipid peroxidation is plasma concentration of malondialdehyde (MDA). This molecule is one of the end products of lipid peroxidation in the cell membrane or in low-density lipoproteins (LDL) (Ogino & Wang2007). Quantification of plasma MDA level can be performed by thiobarbituric acid (TBA) test (Nielsen et al.1997). TBA-reactive substances (TBARS) formed in plasma, urine, or tissue samples that need to be calibrated by sample pretreatment procedure, which forms a red adduct with 2 molecules of TBA (MDA-TBA2). The adducted compounds are separated by an HPLC method, which originally described by Wong $et.$ $al.$(Wong et al.1987) and Carbonneau $et.$ $al.$ (Carbonneau et al.1991). The GC-MS method has been used to analyze the plasma MDA as well (Yeo et al.1994). It has been reported that the plasma from patients with coronary artery disease also had higher level of MDA than the healthy subjects, suggested that MDA could be one of the candidate biomarkers for coronary artery disease (Rajesh et al.2011;Rao & Kiran2011;Mogadam et al.2008;Pasupathi et al.2009). A recent report also suggested that serum levels of TBARS, which was determined by reverse-phase HPLC and spectrophotometric method, were a good predictive marker in patients with stable coronary artery disease (Walter et al.2004).

4.5 F_2-Isoprostanes

Isoprostanes are a complex family of compounds generated from arachidonic acid via a free radical's catalyzed mechanism. This compound was firstly discovered in 1990 by Morrow $et.$ $al.$ who discovered prostaglandin-F_2-like compounds, and termed this newly discovered compound as F_2-isoprostanes (Morrow et al.1990). The F_2 -isoprostanes can be generated by the oxidative induced peroxidation of arachidonic acid (Figure 5).

Determination of F_2-isoprostanes is similar to other techniques measuring the products from lipid peroxidation including GC-MS, which might be associated with an immunoaffinity extraction, GC-tandem MS, and LC-tandem MS (Halliwell2000). Although these techniques have high specificity, the budget cost of these techniques is the impediment of their routine use (Milne et al.2005). Determination of 15- F_{2t}-IsoP in urine samples, by radioimmunoassay, has been validated and easier alternative to GC-MS. In addition, the new technique is developed, for example enzyme-immunoassay for detecting F_2-isoprostanes (Milne et al.2005).

F_2-isoprostanes can be measured in varieties of clinical samples, for example urine, plasma, bronchoalveolar lavage fluid, bile, cerebrospinal, seminal and pericardial fluids (Iuliano et al.2001;Lindsay et al.1999;Delanty et al.1997;Cipollone et al.2000;Reilly et al.1997). In addition, F_2-isoprostanes can be detected in normal tissues, including umbilical cords (Chu et al.2003). The level of F_2-isoprostanes increased in cigarette smoking, similar to other oxidative modified molecules, which is known that the increasing in smoking can cause the

oxidative stress (Reilly et al.1996;Morrow et al.1995). The measurement of isoprostanes in biological fluids has prompted clinical investigations on the pathophysiological role of lipid peroxidation in cardiovascular diseases. In coronary artery disease, the quantified isoprostanes was mostly in 15- F_{2t}-IsoP and 5- F_{2t}-IsoP, which can be measured in urine samples (Haschke et al.2007). The urinary level of 15- F_{2t}-IsoP and 5- F_{2t}-IsoP was found to increase in, unstable angina, reperfusion following myocardial infarction and cardiopulmonary bypass, coronary angioplasty (Sakamoto et al.2002). These findings suggested that isoprostane could be biomarker for coronary artery disease.
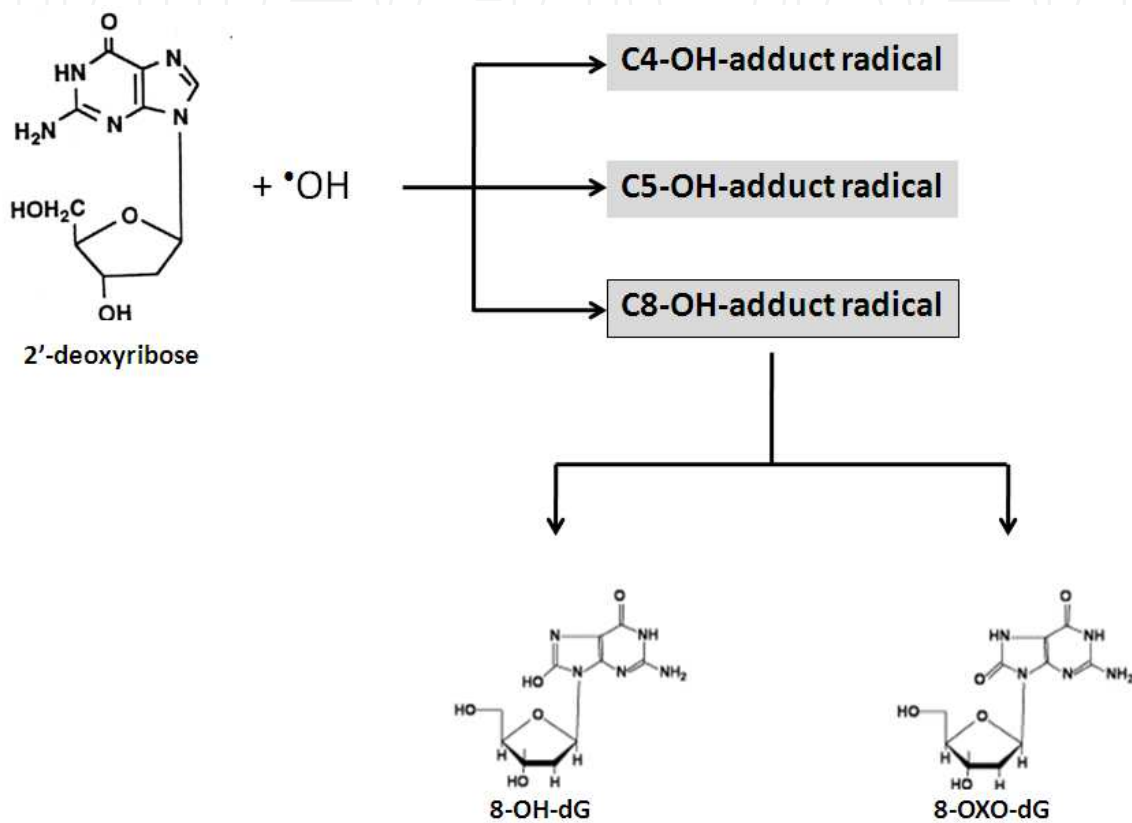

Fig. 5. The Chemical reaction of 2'-deoxyguanosine with hydroxyl radicals. The Oxidative modification reactions of 2'-doxyguanosine cause by hydroxyl radicals. This radical adducts are oxidized to 8-hydroxy-2'-deoxyguanosine (8-OHdG), or it tautomer 8-oxo-7-hydro-2'-deoxyguanosine (8-oxodG).

4.6 Advanced Glycation End-Produces (AGEs)

Advanced glycation end-produces (AGEs) are products of non-enzymatic glycation of proteins by reducing sugars (Zieman & Kass2004). AGEs was firstly discovered in early of 1900s by Louis Camille Mailard by the non-enzymatic chemical reaction between reducing sugars and amino groups on proteins to form protein-protein crosslink and complex yellow-brown pigments (Zieman & Kass2004). The Maillard reaction occurs when the reducing sugars, such as glucose, react with an amine groups, result in the formation of an unstable Shift bases (Figure 6). The produced unstable Shift bases that transform to an Amadori product, which can further rearrange to form advanced glycation endproducts (AGEs) capable of crosslinking proteins (Figure 7, 8).
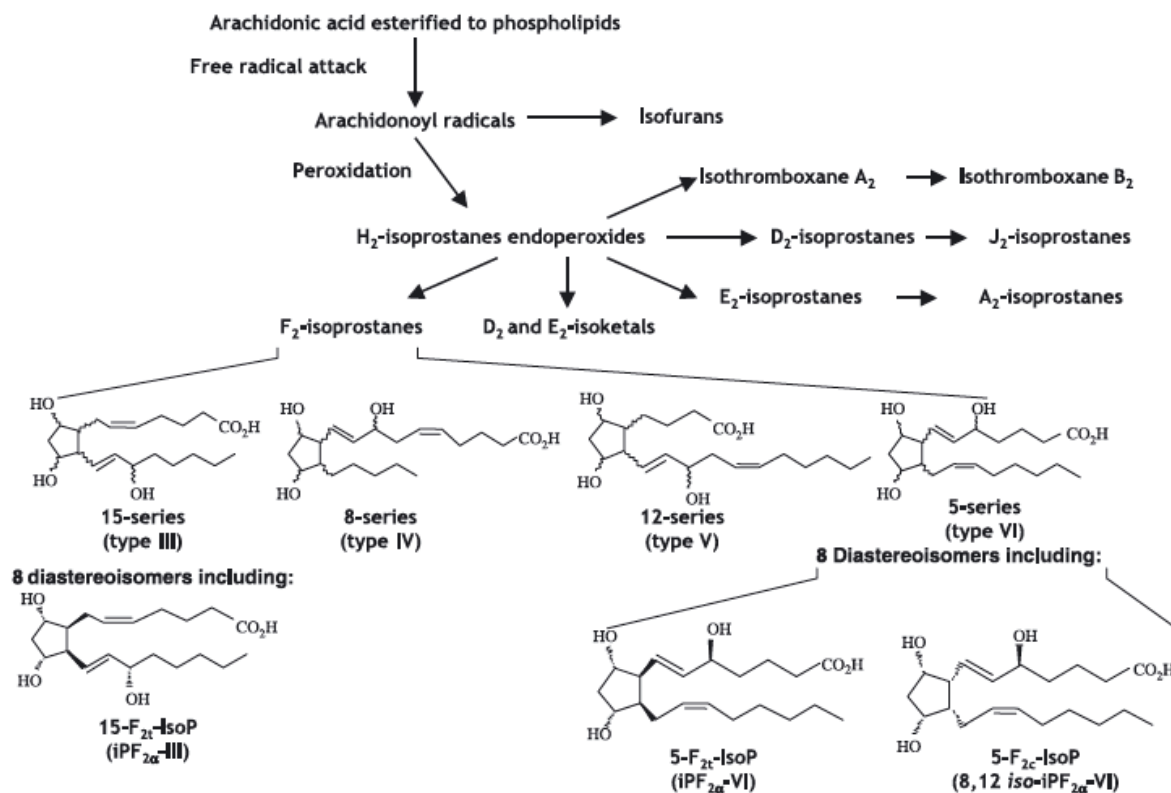
Fig. 6. Metabolic pathways of isoprostane (Cracowski & Durand2006). Free radicals interact with arachidonic acid produce arachidonyl radicals; these molecules were continue to the lipids peroxidation reaction and generated four types of prostaglandin-H₂-like compounds, which subsequently reduced to be 4 prostaglandin F2α.
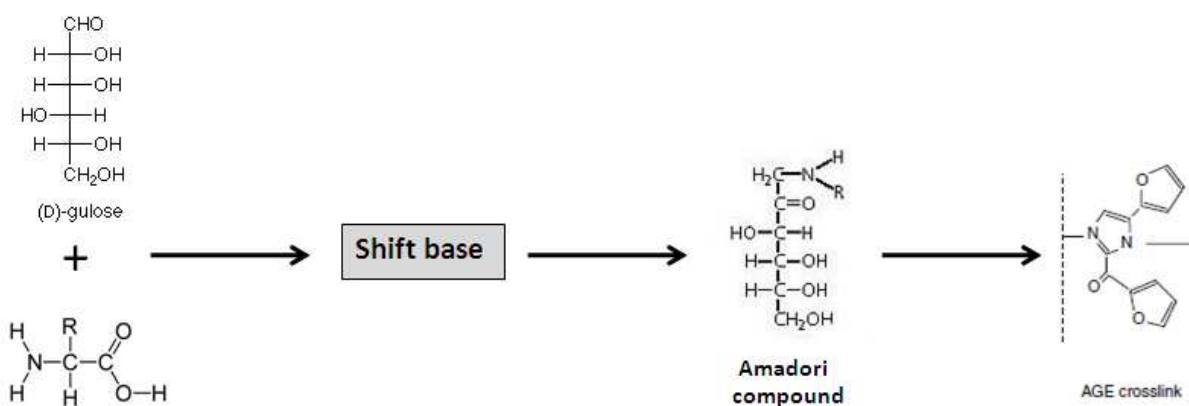

Fig. 7. The Maillard reaction is chemical reaction between a reducing sugar, such as glucose, and amino acid groups. The outcome from this reaction is the formation of unstable Schiff bases that can transform to an Amadori products, which can rearrange to form advanced glycation endproducts (AGEs) (Zieman & Kass2004).
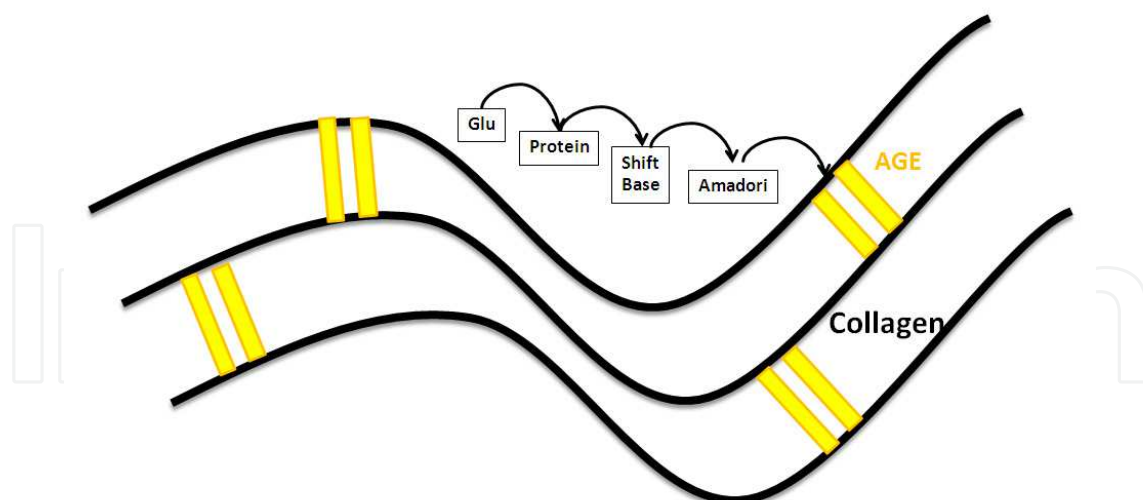
Fig. 8. The formation of collagen-collagen-AGEs crosslinking, this figure was modified from Zieman et. al. AGEs from the Maillard reaction can accelerate enzymatically crosslinking reaction of collagens strands (Zieman & Kass2004).

It has been known that AGEs play important role in the pathogenesis of diabetic vascular complications, as they lead to an abnormal leakage of proteins from the circulation and a progressive constriction of the luminal area of vessel (Brownlee et al.1988;Makita et al.1991;Ono et al.1998). Moreover, AGEs have been recognized as factors in the pathogenesis of other diabetic complications, such as nephropathy and retinopathy (Makita et al.1991;Ono et al.1998). In addition, the level of serum concentration of AGEs was associated with severity of coronary arthrosclerosis and development of this pathology in type 2 diabetic patients (Kiuchi et al.2001). Interestingly, it has been reported that the serum level of AGEs were elevated and correlated significantly with oxidized LDL, especially in diabetic patients (Lopes-Virella et al.2011). A recent evidence of 18-year study showed that the serum level of AGEs could predict the mortality from cardiovascular disease and coronary heart disease in non-diabetic women (Kilhovd et al.2005).

Determination of AGEs is similar to other techniques, used in determining other oxidative modified biomarkers, such as HPLC, GC-MS, ELISA, and immunochemistry (Ogino & Wang2007). The accuracy and reproducibility of these techniques have not been well examined according to lack of universally established unit of measurement, for comparing study findings from different laboratories (Ogino & Wang2007). Furthermore, AGEs has been reported to increase in cigarette smoking, similar to the findings found in other biomarkers (Nicholl & Bucala1998).

5. Early cardiac biomarkers for diagnostic acute coronary syndrome

The biochemical markers have been routinely used to assess myocardial damage, especially in patients suspected with ACS. World health organization criteria, formulated in 1979, have classically diagnosed in ACS patients if the patient present two (probable) or three (definite) diagnostic criteria of acute coronary syndrome. The criteria including clinical history of ischemic type chest pain lasting for more than 20 minutes, changes in serial ECG tracings, and elevation of serum cardiac biomarkers. Patients with ACS are subdivided into the

following 2 major categories based on the results from electrocardiogram (ECG) including those whose ECG show ST-elevation that is diagnostic of acute ST-elevation myocardial infarction (STEMI) and those who present other patterns of ECG change, but not categorized in STEMI, called non- ST elevation ACS (NSTEACS). The latter include unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) (Morrow et al.2007;Wiviott & Braunwald2004). The ECG in NSTEMI can be interpreted in the way that the artery is only partially blocked, or only transiently occlusive, and results in coronary ischemia without the appearance of ST-segment elevation. The ECG is the most readily available tool for diagnosing STEMI. However, the limitation of ECG is usually occur in acute chest pain, according to the low sensitivity of the baseline ECG, which is only 60% (Panteghini2002). Undetectable of ST-elevation of ECG lead to delay in final diagnosis and affect treatment and clinical outcome. Therefore, determination of high sensitivity, specificity and early ischemic biomarker is useful for diagnosis of acute myocardial ischemia, particularly in NSTEMI patients. There are many types of conventional cardiac biomarkers such as creatine kinase- MB isoenzyme (CK-MB), cardiac troponin I or T (cTnI, cTnT). These conventional cardiac markers are known to release in blood circulation as a result of cellular necrosis, not early enough to detect the early phase of myocardial ischemia that may not excess the reference range of biochemical markers of myocardial necrosis. Determination of plasma/serum cardiac biomarkers in patients, who has arrived hospital after the onset of symptoms, may not be detected. Therefore, screening method, for measuring the early cardiac biomarkers that actually reflect the early phase of cellular injury, is extremely useful. The more rapid diagnosis, the more effective intervention and treatment, the less cost for hospital stay, secondary prevention and reduce effective budget for screening test to exclude myocardial infarction patients (Figure 9)

Creatine kinase (CK) is an enzyme responsible for transferring a phosphate group from ATP to creatine. The molecular weight of this enzyme is approximately 80,000 dalton. It is composed of M and/or B subunits build up at least 3 isoenzymes including CK-BB, CK-MB, and CK-MM or CK-1, CK-2 and CK-3, respectively. Moreover, there are one more isoenzymes that have been reported e.g. mitochondrial isoenzyme. CK-2 or CK-MB is sometime called the cardiac isoenzyme as it is predominant isoenzyme in myocardium, whereas there is only 2-5% in skeletal muscle. CK-MB can be found in large amount of infarcted myocardium and can rise up in the circulation within 3-6 hours after ischemia, peaks in 10-48 hours, and returns to normal within 72 hours (Wu et al.1999). However, an elevated serum CK-MB may occur in people with severe skeletal muscle damage (such as in muscular dystrophy, accident) and renal disease (Green et al.1986). In such cases, the ratio of CK-MB per total CK, or CK index, is very helpful. If the index is under 4%, a non-myocardial source of high CK-MB should be concerned. One of the limitations of determining serum CK-MB is undetectable of minimal myocardial injury, late rise in the setting of AMI.

Cardiac Troponin is a useful cardiac marker, localized in myofibrils. Troponin consists of 3 subunits including inhibitory subunit (cTnI), calcium binding subunit (cTnC), and tropomyosin binding subunit (cTnT). The troponin complex is located on the thin filaments of the contractile muscles and regulates the calcium mediated interaction of myocardial myosin and actin filaments. The specificity, sensitivity, and reliability of troponin assay for diagnosed myocardial necrosis make cardiac troponin be an ideal cardiac marker. In addition, the minimal concentration in serum cardiac troponin, from healthy people without

cardiac disease, cannot be detected (Adams, III et al.1993). Among those 3 forms of cardiac troponin, troponin C cannot be used as cardiac marker according to non-specific expression in various tissues, not only the heart (Adams, III et al.1993). Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are 2 forms that normally used as cardiac marker. It has been known that, after myocardial ischemia, elevated cTnT last for 10 days to 2 weeks. The advantages of cTnT include highly sensitive for detecting MI, cTnT level may also help to risk stratify afterward, qualitative test run in 10 minutes. In contrast, the disadvantage of using cTnT assays as cardiac markers due to non specificity of cTnT, which can be found in unstable angina, chronic renal failure (Wood et al.2003). The cTnI is also being an ideal marker for ACS, according to high sensitivity and specificity of this marker in AMI. However, these two markers could not counted as the early marker, as it need increase around 6 hours after ischemia, until the level of cTnT is significantly higher than normal level.

The oxidatively modified markers such as PC and IMA have been proven as potential cardiac marker for diagnosis of ACS. However, determining of oxidative modified markers is not specific for myocardial ischemia. For example, it has been reported that the plasma level of IMA can be increased in cerebral, gastrointestinal intestinal and skeletal muscular ischemia as well as myocardial ischemia (Matthews et al.1990;Siegel et al.1995). Therefore, it is recommended that the interpretation of a positive IMA finding should be combined with other clinical indices (Shen et al.2010). Recently, our study showed the usefulness of determining serum IMA and PC content level to identify acute myocardial infarction, particularly in STEMI. The level of both serum IMA and PC content were significantly higher in STEMI compared to healthy control and determination of serum IMA level in combination of serum PC content level improved test performance (Kumphune et al.2010). However, the results from our recent study reported that diagnosis of NSTEMI was not improved by combination of serum IMA and PC level, in contrast, individual determination of serum PC content showed a good area under ROC curve and high PPV for NSTEMI diagnosis (Maneewong et al.2011). Charpentier *et. al.* also demonstrated in a large cohort study of patients admitted to an emergency department for chest pain that IMA did not provide valuable information for ACS diagnosis (Charpentier et al.2010). The possible explanation is NSTEMI patients did not have major myocardial necrosis, unlike in patients with STEMI. Therefore, the minor myocardial damage possibly has less degree of ROS mediated proteins oxidation.

Another limitation of using oxidative modified biomarkers is the interpretation in elder patients. It has been reported that oxidative modified forms of proteins were accumulated during aging (Berlett & Stadtman1997). For example, increases in proteins carbonyls occur in rat hepatocytes, drosophila, brain, and kidney of mice and in brain tissue of gerbils (Beal2002). In humans proteins carbonyls increase with age in brain, muscle, and human eye lens (Beal2002). The carbonyl content of human fibroblasts also increases as a function of age of the donor (Beal2002).

There are some reports determining other oxidative modified molecules, such as 8-OH-dG, isoprostane, and AGEs, in ACS. However, those reports were indicated only the incidences of elevated markers in ACS, but not the efficiency of the test. Therefore, determination of analytical method efficiency of those markers is challenge and need to be further investigated.
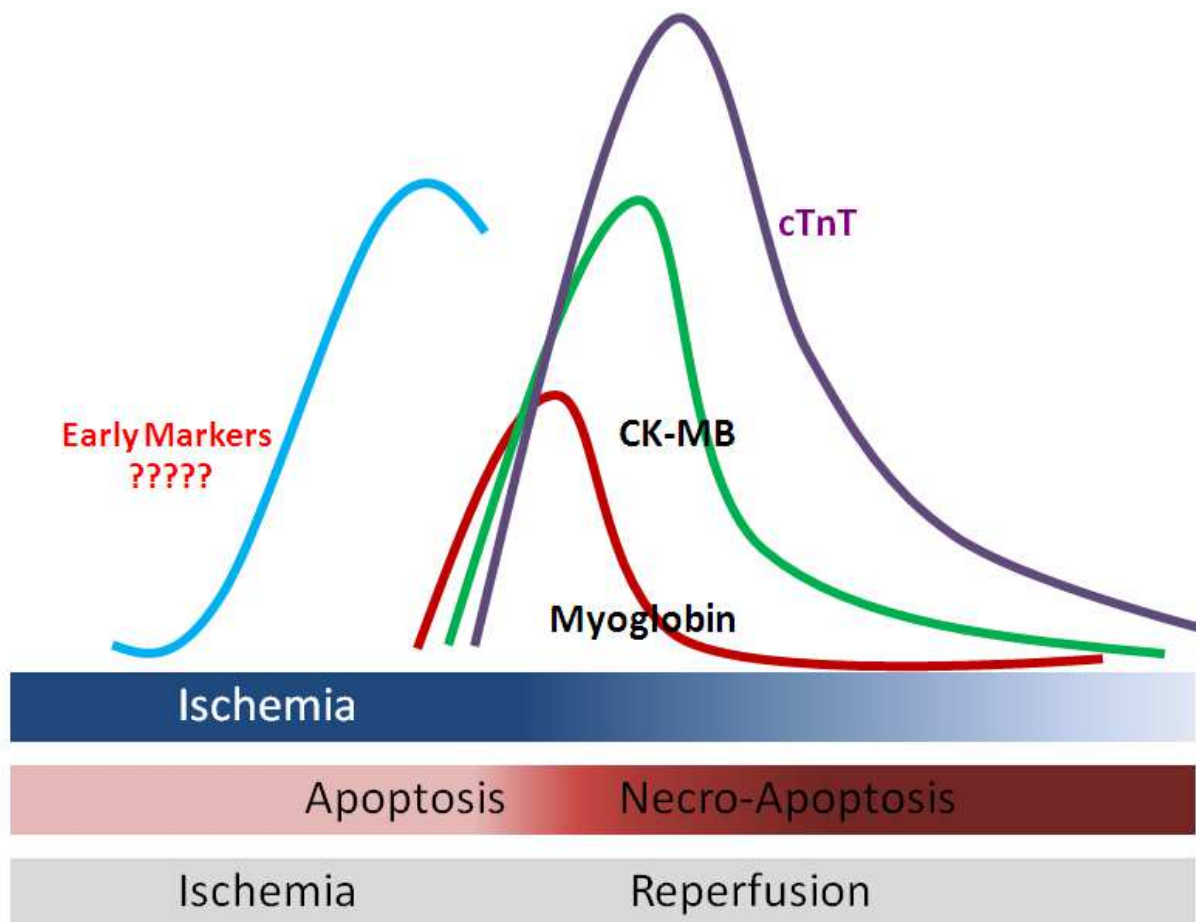
Fig. 9. The kinetics curve of conventional biomarkers. The rise and fall pattern of conventional cardiac biomarkers such as myoglobin, CK-MB, and cTnT. These markers release to circulation many hours after the onset of chest pain, post ischemia. Novel early markers, probably oxidatively modified markers, which release into blood stream, right after the onset of ischemia, will helpful.

6. Conclusion

Early cardiac biomarkers are essential for diagnosis of acute coronary syndrome. Conventional markers might not early enough to detect the early phase of cellular injury according to ischemia. Many oxidatively modified biomolecules were studied and known to have potential as cardiac markers. Further intensive investigation of these cardiac markers, especially the diagnostic power, is very helpful and can be used in real clinical investigation of coronary artery disease.

7. Acknowledgement

8. References

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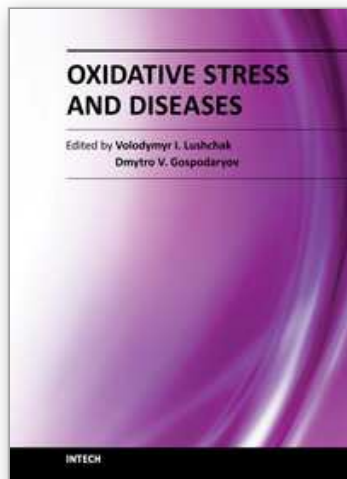
Oxidative Stress and Diseases

Edited by Dr. Volodymyr Lushchak

The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

How to reference

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Sarawut Kumphune (2012). Oxidatively Modified Biomolecules: An Early Biomarker for Acute Coronary Artery Disease, Oxidative Stress and Diseases, Dr. Volodymyr Lushchak (Ed.), ISBN: 978-953-51-0552-7, InTech, Available from: http://www.intechopen.com/books/oxidative-stress-and-diseases/oxidative-modified-biomolecules-an-early-biomarker-for-acute-coronary-artery-disease

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