Aging and Disease
www.aginganddisease.org
Volume 3, Number 3; 269-279, June 2012

Review

Aging, Metabolic Syndrome and the Heart

Guarner Veronica*, Rubio-Ruiz Maria Esther

Department Of Physiology, Instituto Nacional De Cardiologia "Ignacio Chavez", México.

[Received February 20, 2012; Revised March 10, 2012; Accepted March 11, 2012]

ABSTRACT: Aging is accelerated when metabolic and cardiovascular diseases (CVD) are present and the risk of these diseases increases with age. Many predisposing conditions which increase in prevalence during aging, such as obesity, insulin resistance, inflammation, changes in the activity of the hypothalamus-hypophysis suprarenal axis, stress and hypertension also contribute to increase prevalence of metabolic syndrome (MS) and CVD and will be discussed in this paper. Aging and MS are frequently accompanied by several pathological conditions and some associated phenomena such as increased lipoperoxidation, generation of free radicals, increased peroxidation of nitric oxide (NO) to its toxic species, and others, resulting from oxidative stress which significantly alter the incidence of CVD. The better knowledge of mechanisms linking MS to increased CVD prevalence has led to new predictive measures and to the study of different possible new therapeutic strategies in elderly patients and patients with MS. Preventing and treating MS and CVD would be useful in promoting normal aging.

Key words: Aging; Heart; Metabolic Syndrome; oxidative stress; cardiovascular disease

Aging

Aging is defined as a series of morphological and functional changes which take place over time. The term also refers to the deterioration of the biological functions after an organism has attained its maximum reproductive potential. We do not know yet whether organisms start to grow old from the moment of conception or from maturity, or if aging constitutes a process of evolution or involution [1]. Stress response genes and nutrient sensors regulate energy directed to cell protection, maintenance and longevity; when food is plentiful and stress levels are low, genes support growth and reproduction, in contrast harsh conditions favor a shift in gene activity towards cell protection and maintenance extending lifespan. Important genes in extending lifespan include kinase mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), sirtuins and insulin/insulin like growth factor 1 (IGF-1) signaling. These genes integrate longevity pathways and metabolic signals in a complex interplay in which lifespan appears to be strictly dependent on substrate and energy bioavailability [2].

IGF-1 mediated signaling is determining for longevity. Abnormalities in the insulin signaling pathway generate age-related diseases and increased mortality, whereas the growth hormone (GH)/IGF-1 axis could potentially modulate longevity in many species. Moreover in humans, an age-related decline in IGF-1 levels occurs, and at old age, low IGF-1 levels are associated with frailty, poor nutrition and cognitive decline and an increased risk of death [3,4].

The aging process is altered or accelerated when metabolic and cardiovascular diseases (CVD) are present and the risk of diseases increases with age. Many predisposing conditions which increase in prevalence during aging, such as obesity, insulin resistance, inflammation, changes in the activity of the hypothalamus-hypophysis suprarenal axis, stress and hypertension also contribute to increase prevalence of metabolic syndrome (MS). Aging, the development of insulin resistance and CVD seem to be accelerated in the MS [5-7].

***Correspondence should be addressed to:** Verónica Guarner Ph.D., Departamento de Fisiología, Instituto Nacional de Cardiología "Ignacio Chávez". Juan Badiano 1, Tlalpan México, D.F. 14080, México. E-mail: gualanv@yahoo.com

ISSN: 2152-5250

Aging and metabolic syndrome

MS is a number of criteria reflecting abnormalities in lipid and glucose metabolism. These abnormalities are considered to be a reason for atherosclerosis, CVD and type-2 diabetes mellitus. The prevalence of CVD among patients with diabetes is 3-5 folds higher than in patients without it. MS demonstrates ethnic and gender variants, its frequency depends on the lifestyle and age. MS in an elderly population is a proven risk factor for cardiovascular (CV) morbidity, especially stroke and coronary heart disease (CHD), and mortality. Attention to MS has been attracted in the last decades induced by the obesity epidemic. The adipose tissue and high triglyceride blood levels have been regarded as hallmark of MS. The high prevalence of MS, heart attacks and diabetes in the elderly population makes the evidence of age to be an independent risk factor of the development of metabolic abnormalities [8].

It is generally considered that MS induces precocious aging although the mechanisms that account for this are incompletely known. It is becoming clear that longevity genes might be involved. Experiments with overactivation or disruption of key lifespan determinant pathways, such as silent information regulator sirtuins, p66Shc, and mTOR, lead to development of features of the MS in mice. Additional pathways are involved in linking nutrient availability and longevity, certainly including insulin and IGF-1 signaling, as well as FOXO transcription factors [9].

Pathophysiological abnormalities that contribute to the development of the MS include impaired mitochondrial oxidative phosphorylation and mitochondrial biogenesis, dampened insulin metabolic signaling, endothelial dysfunction, and associated myocardial functional abnormalities. Impaired myocardial mitochondrial biogenesis, fatty acid metabolism, and antioxidant defense mechanisms lead to diminished cardiac substrate flexibility, decreased cardiac energetic efficiency, and diastolic dysfunction. In addition, enhanced activation of the renin-angiotensin-aldosterone system (RAS) and associated increases in oxidative stress can lead to mitochondrial apoptosis and degradation, altered bioenergetics, and accumulation of lipids in the heart. In addition to impairments in metabolic signaling and oxidative stress, genetic and environmental factors, aging, and hyperglycemia all contribute to reduced mitochondrial biogenesis and mitochondrial dysfunction. These mitochondrial abnormalities can predispose a metabolic cardiomyopathy characterized by diastolic dysfunction. Mitochondrial dysfunction and resulting lipid accumulation in skeletal muscle, liver, and pancreas also impede insulin metabolic signaling and glucose metabolism, ultimately leading to a further increase in mitochondrial dysfunction [10].

Free oxygen radicals are involved in a large of number of pathological conditions, including atherosclerosis, alcoholic cradiomyopathy, ischemia-reperfusion injury and ageing. The myocardial cells are an important source of free radicals. When this organ suffers from diminished blood supply to an area as a result of diverse conditions such as a stroke, ischemia produces oxidative stress and structural damage and the affected tissues die due to necrosis. Reperfusion may reverse the lethal process, but often not without taking its toll in the form of injury to the tissues. This is due to calcium re-entry to the cell and this also generates an important amount of free radicals which are linked to alterations in mitochondrial function. There are specific alterations in heart mitochondrial function which occur as a result of ischemia and reperfusion and they involve the electron-transport complexes, ATP concentration, ADP/ATP translocase, permeability transition and uncoupling [11].

In our Institution, we have developed a variant of the sugar induced hypertriglyceridemic and hypertensive rat model described by Reaven [12], which shows characteristics of MS. The pathological condition was induced by adding commercially refined sugar to the animal's drinking water. In previous studies of the model, we found several metabolic and functional alterations such as endothelial dysfunction present in the aorta and mesenteric arteries of the experimental animals. Arteries showed premature aging [13].

When the reperfusion response of these animals was evaluated after 30 minutes of global ischaemia, hearts from MS rats developed lower ventricular pressure (VP) and the conduction rate was higher than in hearts from control rats. The recovery of VP after ischemia was significantly lower in SM than in control hearts. During reperfusion, the incidence of premature beats, ventricular fibrillation and tachycardia in MS hearts was increased. In MS animals, the oxidative processes make a major contribution to the reperfusion injury, suggesting that hypertriglyceridemia and hypertension alter the ability of the myocardium to respond properly under extreme conditions [14,15].

The deleterious association of stress and increased release of free radicals in the MS model has been demonstrated in cardiac ischemia and reperfusion experiments *in vivo*, where the animals recovered from postreperfusion arrhythmias when a free radical scavenger was administered [14]. Male hearts were less efficient than female hearts. When antioxidant defenses were evaluated, in male hearts, superoxide dismutase and catalase activities in MS were significantly lower than in control animals, and both were lower than in MS and

control female hearts [16]. It has also been shown that aging may contribute to reducing the antioxidant capacity at different levels but there is a tendency for females to have a higher antioxidant potential than males [16]. Additionally, metabolic pathways involved in ATP production are diminished in hearts from MS rats when compared to control rats [17]. Preventing and treating MS would be useful in promoting normal aging. Results from the different studies of elderly population-based cohorts provide support for earlier investigations in middle-aged populations to prevent MS components [18].

Heart metabolism during aging in metabolic syndrome

The heart is an omnivore organ, relying on metabolic flexibility, which is compromised by the occurrence of defects in coronary flow reserve, insulin-mediated glucose disposal, and metabolic-mechanical coupling. Obesity, diabetes, and ischemic cardiomyopathy appear as states of high uptake and oxidation of fatty acids that compromise the ability to utilize glucose under stimulated conditions, and lead to misuse of energy and oxygen, disturbing mechanical efficiency. Idiopathic heart failure is a complex disease frequently coexisting with diabetes, insulin resistance and hypertension, in which the end stage of metabolic toxicity manifests as severe mitochondrial disturbance, inability to utilize fatty acids, and ATP depletion. The metabolic cascade outlined may originate in extra-cardiac organs, since fatty acid, glucose levels, and insulin action are mostly controlled by adipose tissue, skeletal muscle and liver, and a broader vision of organ cross-talk may further our understanding of the primary and the adaptive events involved in metabolic heart toxicity [19].

There is compelling evidence that L-Arginine (Arg) regulates interorgan metabolism of energy substrates and the function of multiple organs. Moreover, a growing body of evidence clearly indicates that dietary supplementation or intravenous administration of Arg is beneficial in improving CV, and immune functions, as well as enhancing insulin sensitivity, and maintaining tissue integrity. Additionally, Arg or L-citrulline may provide novel and effective therapies for obesity, diabetes, and MS. Arg is synthesised from glutamine, glutamate, and proline via the intestinal-renal axis in humans and most other mammals. Arg degradation occurs via multiple pathways that are initiated by arginase, nitric-oxide synthase (NOS), Arg: glycine amidinotransferase, and Arg decarboxylase. These pathways produce nitric oxide (NO), polyamines, proline, glutamate, creatine, and agmatine with each having enormous biological importance [20].

The sirtuin (SIRT) family of NAD^+-dependent protein deacetylases and ADP-ribosyltransferases has emerged as exciting targets for CVD management that can impact the CV system both directly and indirectly, the latter by modulating whole body metabolism. Sirtuins link nutrient availability and energy metabolism. Calorie restriction, which increases lifespan and is beneficial in age-related disorders, activates sirtuin. SIRT1-4 regulate the activities of a variety of transcription factors, coregulators, and enzymes that improve metabolic control in adipose tissue, liver, skeletal muscle, and pancreas, particularly during obesity and aging. SIRT1 and 7 can control myocardial development and resist stress- and aging-associated myocardial dysfunction. SIRT1 also promotes vasodilatory and regenerative functions in endothelial and smooth muscle cells of the vascular wall. Given the array of potentially beneficial effects of SIRT activation on cardiovascular health, interest in developing specific SIRT agonists is well-substantiated. Because SIRT activity depends on cellular NAD^+ availability, enzymes involved in NAD^+ biosynthesis, including nicotinamide phosphoribosyltransferase, may also be valuable pharmaceutical targets for managing CVD [21].

Resveratrol might help in the treatment or prevention of obesity and in preventing the aging-related decline in heart function. New SIRT1 activators improve the response to insulin and increase the number and activity of mitochondria in obese mice [22]. Although there is considerable disagreement on the underlying MS pathophysiology, clinical and experimental data support a link between SIRT1 and MS. Interestingly, the only clinical variable related to SIRT1 beyond MS components was age, which is physiologically related to SIRT1 function as a life-span determinant gene [23].

Aging, obesity and cardiovascular disease

Obesity and aging are two overlapping and mounting public health problems. The prevalence of obesity has been related to the increasing prevalence of MS, which is growing progressively even among older age groups. Indeed, insulin resistance observed with aging may be more related to adiposity than aging *per se* [24]. Obesity is linked to an increased production of inflammatory adipokines that may alter insulin sensitivity and muscle mass [25] and is also linked to increased risk of CVD.

Obesity is associated with a clustering of atherogenic risk factors, and when three or more are present it generally signifies an insulin resistance syndrome or MS. This is promoted by weight gain and visceral adiposity. The risk of macrovascular disease is increased before glucose levels reach the diagnostic threshold for "diabetes," and 25% of newly diagnosed

diabetics already have overt CVD. In the Framingham Study, increased risk of CVD was two-fold in men and three-fold in women, eliminating the female advantage over men for all outcomes except stroke. Coronary disease is the most common and lethal sequela, and unrecognized myocardial infarctions are three times more common in diabetic than nondiabetic men. Following a myocardial infarction, diabetes imposes a high rate of recurrence, heart failure, and death, more so in women than men. The risk of CV sequelae in diabetic patients is variable, the majority of events occurring in those with two or more additional risk factors. Because of the variable risk of CVD in either the diabetic or obese person, risk stratification is necessary to determine the hazard of impending CVD. For persons with diabetes or obesity, the chief goal is to avoid the common CV sequelae. Comprehensive care should include not only normalization of the blood sugar, but also weight reduction, dietary fat restriction, strict blood pressure and lipid control, exercise, and avoidance of tobacco. Trial data indicate that preventive measures benefit obese diabetics even more than nondiabetics [26].

Visceral obesity has an important role in the development and progression of aortic stenosis (AS). Calcific AS is a degenerative and unmodifiable process resulting from aging and 'wear and tear' of the aortic valve. There is valvular infiltration by oxidized low-density lipoproteins and the presence of inflammatory cells, along with important tissue remodelling in valves explanted from patients with AS. In addition, visceral obesity has been associated with degenerative changes in bioprosthetic heart valves [27].

Obesity is strongly correlated with insulin resistance, although not all obese patients have insulin resistance, nor does insulin resistance always result in obesity [28]. Obesity leads to insulin resistance through the increased liberation of free fatty acids. Fatty acids interfere with glucose transporter translocation through alterations in protein kinase C λ activity. They also down-regulate insulin receptor substrate 2 (IRS2) and increase the expression of the lipogenic transcription factor SREBP-1c [29].

Fasting insulin is an important indicator of CHD in elderly men. Men (aged 70 to 89 years) with a high fasting insulin level have a higher prevalence of CHD and especially of myocardial infarction. No association between fasting insulin level and hypertension or blood pressure has been observed. Clotting factors, resting heart rate, uric acid, serum albumin, and creatinine may also play a role [30]. Insufficient intracellular fat oxidation is an important contributor to aging-related insulin resistance, while the precise underlying mechanism is unclear. AMPK is an important regulator of intracellular fat oxidation and plays a key role in high-glucose and high-fat induced glucose intolerance [31].

Lipid metabolism is a cornerstone in the development of the commonest important chronic diseases worldwide, such as obesity, CVD, or MS [32]. Among the players identified are regulators such as caveolins and caveolae. Caveolins and caveolae are important in several aspects of the CV biology, including lipid metabolism, vascular contractility, angiogenesis, or the control of cardiac hypertrophy. Caveolae are small plasma membrane invaginations that are observed in terminally differentiated cells. Their most important protein marker is caveolin-1, which plays a key role in the regulation of several cellular signaling pathways and in the regulation of plasma lipoprotein metabolism [33]. Caveolin-1 has also a central role in promoting cellular senescence [34]. This protein also regulates lipoprotein metabolism by controlling plasma levels as well as lipid composition. Among specific protein–protein interactions involving caveolins in cardiac tissue, an association with the endothelial isoform of NOS for its post-translational regulation in endothelial cells and cardiac myocytes, has been found which bears on the enzyme's capacity to modulate NO-dependent endothelial function, angiogenesis, and excitation–contraction coupling [35]. Caveolae also modulate excitation–contraction coupling (ECC) and β-adrenergic stimulation in the adult cardiac myocyte. The interaction of the inhibitory G protein cascade components with caveolin in the caveolae is necessary for effective signalling by this pathway, suggesting that changes in caveolin expression in the adult heart seen during aging and in disease will have consequences for baseline cardiac function and β-adrenergic responsiveness [36].

A good comprehension of the factors that regulate the metabolism of the various lipoproteins such as caveolins and caveolae is a key to understanding the variables associated with the development of CHD, MS and atherosclerosis. Virtually all cell types within the myocardium express caveolae, where cell-specific isoforms of caveolin both maintain the structural organization of these cholesterol-rich of the plasmalemma and serve as scaffolds for the dynamic constitution of ''signalosomes'', or hubs concentrating numerous transmembrane signaling proteins and their effectors [33].

Dyslipidemia, characterized by a high total to high-density lipoprotein cholesterol ratio, is the most predictive lipid profile for coronary disease in the elderly. High triglycerides, accompanied by low high-density lipoprotein (HDL) cholesterol usually signify insulin resistance and more atherogenic, small, dense low-density lipoprotein (LDL). The association between the MS and oxidized LDL and the determination of the

risk for CHD in relation to the MS and levels of oxidized LDL has been studied. MS was associated with higher levels of oxidized LDL not to higher levels of LDL cholesterol. MS which is a risk factor for CHD, is associated with higher levels of circulating oxidized LDL that are associated with a greater disposition to atherothrombotic coronary disease [37].

Fat is a major source of NO stimulated by leptin, an adipocyte hormone. Lipopolysaccharid activates cytokine and inducible NOS (NOS3) production in the cardiovascular system leading to CHD. As fat stores increase, leptin and NO release increases. NO could be responsible for increased CHD as obesity supervenes. Antioxidants, such as melatonin, vitamin C, and vitamin E, probably play important roles in reducing or eliminating the oxidant damage produced by NO [38].

Obesity and age induce a decline in sinoatrial node function in rats which is associated with a structural remodeling of the sinus consisting of an enlargement of the sinus, a hypertrophy of its cells, and a remodeling of the extracellular matrix [39]. In obese women there is an increase in the QTC interval in the electrocardiogram [40]. Patients with dyslypidemia in which fatty acids are increased and insulin sensitivity is decreased, have increased sympathetic activity which leads to electrical instability in the heart, causing ventricular arrythmias and could lead to sudden death [41]. Hyperinsulinemia has been associated to Sick sinus syndrome [42]. In animal models repolarization of the action potential is increased due to increased palmitate which diminishes myocardial contractility [43].

Aging, inflammation, metabolic syndrome and cardiovascular disease

Inflammation is one of the main mechanisms underlying endothelial dysfunction and therefore, it plays an important role in atherosclerosis and other CVD such as hypertension, insulin resistance, dyslipidemias and obesity [44-48]. Inflammation is a key factor in the progressive loss of lean tissue and impaired immune function observed in aging. Low-grade inflammation in adipose tissue contributes to insulin resistance and type-2 diabetes and CVD [49]. This conclusion is predominantly drawn from studies demonstrating associations between elevated (but 'normal range') levels of circulating acute phase inflammatory markers, typified by C-reactive protein (CRP), interleukin-6 and indices of insulin resistance and the development of type-2 diabetes. There is a debate as to whether these associations are independent of body fatness or, rather, an epiphenomenon of central obesity, an important source of inflammatory cytokines [50].

Recent investigations of atherosclerosis have focused on inflammation, providing new insight into mechanisms of the disease. Inflammatory cytokines involved in vascular inflammation stimulate the generation of endothelial adhesion molecules, proteases, and other mediators, which may enter the circulation in soluble form. These primary cytokines also induce production of the messenger cytokine interleukin-6, which stimulates the liver to increase production of acute-phase reactants such as CRP. In addition, platelets and adipose tissue can generate inflammatory mediators relevant to atherothrombosis. Despite the irreplaceable utility of plasma lipid profiles in assessment of atherosclerotic risk, these profiles provide an incomplete picture. The concept of the involvement of inflammation in atherosclerosis has spurred the discovery and adoption of inflammatory biomarkers for CV risk prediction. CRP is currently the best validated inflammatory biomarker; in addition, soluble CD40 ligand, adiponectin, interleukin 18, and matrix metalloproteinase 9 may provide additional information for cardiovascular risk stratification and prediction [51].

Atherosclerosis is a process with inflammatory features and selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity [52]. COX-2 inhibitors appear to alter the balance of vasoactive eicosanoids (prostacyclin and thromboxane) and to suppress the inflammatory mediators implicated in the progression of atherogenesis and ischemic myocardial injury. Neutral, harmful, and beneficial CV effects have all been postulated to result from these changes [53].

In addition to producing more inflammatory cytokines, adipocytes from old mice induce a higher inflammatory response in other cells. Sphingolipid ceramide is higher in old than in young adipocytes. Reducing ceramide levels or inhibiting NF-κB activation decreases cytokine production, whereas the addition of ceramide increases cytokine production in young adipocytes to a level comparable to that seen in old adipocytes, suggesting that ceramide-induced activation of NF-κB plays a key role in inflammation [49].

An elderly immune system becomes more and more predisposed to chronic inflammatory reactions and is less able to respond to acute and massive challenges by new antigens. A young immune system has to cope quickly and efficiently with acute immunological challenges to assure survival and the reaching of reproductive age. Such reaction capability gradually burns out because of lifelong antigenic attrition. Moreover, lifelong antigenic challenges and the increasing antigenic burden determine

a condition of chronic inflammation, with increased lymphocyte activation and proinflammatory cytokines [54].

MS and inflammation intersect with the growing "epidemic" of non-valvular atrial fibrillation (NVAF) with its associated morbidity and mortality along with a number of conditions including aging, thromboembolism, stroke, congestive heart failure and hypertension. Ongoing efforts towards understanding atrial fibrillation are driven, in part, by the concept that atrial fibrillation may in most patients be the consequence of a systemic condition, in which reduced vascular compliance, atherosclerosis, obesity, and inflammation are primary causal factors [55].

Aging, central nervous and stress responses and their influence on metabolic syndrome and cardiovascular disease

Autonomic imbalance, characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system, is associated with various pathological conditions. Over time, excessive energy demands on the system can lead to premature aging and diseases. Therefore, autonomic imbalance may be a final common pathway to increased morbidity and mortality from a host of conditions and diseases, including CVD. Heart rate variability (HRV) may be used to assess autonomic imbalances, diseases and mortality. Parasympathetic activity and HRV have been associated with a wide range of conditions including CVD. Substantial evidence exists to support the notion that decreased HRV precedes the development of a number of risk factors and that lowering risk profiles is associated with increased HRV [56].

Adult aging in humans is associated with marked and sustained increases in sympathetic nervous system (SNS) activity to several peripheral tissues, including the heart, the gut-liver circulation, and skeletal muscle. This chronic activation of the peripheral SNS likely is, at least in part, a primary response of the central nervous system to stimulate thermogenesis to prevent further fat storage in the face of increasing adiposity with aging. However, as has been proposed in obesity hypertension, this tonic activation of the peripheral SNS has a number of adverse secondary CV consequences. These include chronic reductions in leg blood flow and vascular conductance, increased tonic support of arterial blood pressure, reduced limb and systemic alpha-adrenergic vasoconstrictor responsiveness, impaired baroreflex buffering, large conduit artery hypertrophy, and decreased vascular and cardiac responsiveness to beta-adrenergic stimulation. These effects of chronic age-associated SNS activation on the structure and function of the CV system, in turn, may have important implications for the maintenance of physiological function and homeostasis, as well as the risk of developing clinical CV and metabolic diseases in middle-aged and older adults [57].

The autonomic nervous system modulates glucose and fat metabolism through both direct neural effects and hormonal effects. Locally released norepinephrine from sympathetic nerves is likely to increase glucose uptake in skeletal muscle and adipose tissues, independent of insulin, but norepinephrine does not contribute as much as epinephrine to hepatic glucose production. Alterations of central neurotransmission and environmental factors can change the relative contribution of sympathetic outflow to the pancreas, liver, adrenal medulla and adipose tissues, leading to the modulation of glucose and fat metabolism. Recent studies have proposed that leptin, induces the central nervous system to increase sympathetic outflow independently of feeding [29].

Sympathetic nerve fibers innervate white adipose tissue and stimulate lipolysis, leading to the release of glycerol and free fatty acids. There is also a functional parasympathetic innervation and a distinct somatotropy within the parasympathetic nuclei: separate sets of autonomic neurons in the brain stem innervate either the visceral or the subcutaneous fat deposit. Parasympathectomy induces insulin resistance associated with glucose and fatty acid uptake in the fat depot and has selective effects on local hormone synthesis [58,59].

The SNS plays a key role in regulating arterial blood pressure in humans. Sympathetic neural activity (SNA) is tightly linked to blood pressure via the baroreflex for each individual person. However, SNA can vary greatly among individuals and that variability is not related to resting blood pressure; that is, the blood pressure of a person with high SNA can be similar to that of a person with much lower SNA. In healthy normotensive persons, this is related to a set of factors that balance the variability in SNA, including cardiac output and vascular adrenergic responsiveness. CVD can be associated with substantial increases in SNA, as seen for example in patients with hypertension, obstructive sleep apnea, or heart failure. Obesity is also associated with an increase in SNA, but the increase in SNA among patients with obstructive sleep apnea appears to be independent of obesity *per se*. For several disease states, successful treatment is associated with both a decrease in sympathoexcitation and an improvement in prognosis [60].

Studies in experimental rats (WOKW) rats have shown that MS in is associated with impaired coronary function due to altered adrenoceptor sensitivity. The latter may contribute to inappropriately elevated

coronary tone in insulin-resistant subjects, especially when sympathetic activity to the heart is increased [61].

Leptin, in addition to regulating appetite and energy expenditure, also regulates corticotropin function [62]. Weight gain increases feedback to the brain (via hyperleptinemia), which in turn results in hypothalamus-pituitary-adrenal axis (HPA-axis) and SNS overdrive, impaired insulin secretion and insulin resistance [63]. HPA-axis overdrive would account for metabolic abnormalities such as central adiposity, hyperglycemia, dyslipidemia, hypertension and other CVD which are well known clinical aspects of the MS [63].

Stress responsiveness is decreased during aging. The unavoidable chronic overexposure to stressors determines a highly pathogenic sustained activation of the stress–response system, leading to a progressively reduced capacity to recover from stress-induced modifications [54]. Glucocorticoids, the adrenal steroid hormones secreted during stress, may account for this relationship [64].

Stress is a potent modulator of immune function, which in youth can be compensated for by the presence of an optimal immune response. In the elderly the immune response is blunted as a result of the decline in several components of the immune system (immune senescence) and a shifting to a chronic pro-inflammatory status (the so-called 'inflamm-aging' effect) [65]. Aging is accompanied by a greater increase in sympathetic traffic in women than in men, and inflammation (measured via CRP) seems to be more strongly related to the MS in women than in men [66].

Aging and hypertension

Diminished insulin sensitivity is a characteristic feature of various pathological conditions such as the MS, type-2 diabetes and hypertension [67]. There are twice as many hypertensive patients among diabetics than there are among non-diabetics [68].

Patients with essential hypertension are more prone than normotensive subjects to develop diabetes, and this propensity may reflect decreased ability of insulin to promote relaxation and glucose transport in vascular and skeletal muscle tissue [67,69]. Although the of skeletal muscle insulin resistance is multifactorial, there is accumulating evidence that one contributor is overactivity of the RAS [67,69].

Numerous studies focus on comparing the differences in development and aging patterns between hypertensive and normal rats. The contractile responses of vascular smooth muscle to norepinephrine, KCl, 5-hydroxytryptamine, electro-stimulation and calcium-free physiological solution are increased during development and maturity in normal rats. Endothelium-dependent relaxation mediated by acetylcholine as well as isoproterenol, which is mediated by the β-receptor, falls during rat maturation [70].

In an experimental hypertension model in rats, based on a fructose-rich diet, endothelin expression is increased in blood vessels, while NO levels are not modified [71]. In another rat model of hypertension obtained by administering 30% sucrose in the drinking water for 20 weeks, an increased insulin-dependent endothelin response of the vessels has been found [72]. Some characteristics of the aging process in this model have been reported and rats clearly showed premature aging due to the MS [13].

Vascular and associated ventricular stiffness is one of the hallmarks of the aging cardiovascular system. Both an increase in reactive oxygen species production and a decrease in NO bioavailability contribute to the endothelial dysfunction that underlies this vascular stiffness, independent of other age-related vascular pathologies such as atherosclerosis. Arginase, which is expressed in endothelial cells and upregulated in aging blood vessels, competes with NOS for Arg, thus modulating vasoreactivity and attenuating NO signaling. Moreover, arginase inhibition restores endothelial NOS signaling and Arg responsiveness in old rat aorta. Arginase plays a critical role in the pathobiology of age-related endothelial dysfunction [73].

The activation/upregulation of arginase appears to be an important contributor to age-related endothelial dysfunction by a mechanism that involves substrate Arg limitation for NOS 3 and therefore NO synthesis. This leads to impair NO production and contributes to the enhanced production of reactive oxygen species by NOS. Although arginase abundance is increased in vascular aging models, it appears that posttranslational modification by *S*-nitrosylation of the enzyme enhances its activity as well. The *S*-nitrosylation is mediated by the induction of NOS2 in the endothelium. Furthermore, arginase activation contributes to aging-related vascular changes by mechanisms that are not directly related to changes in NO signaling, including polyamine-dependent vascular smooth muscle proliferation and collagen synthesis. Arginase may represent an as yet elusive target for the modification of age-related vascular and ventricular stiffness contributing to cardiovascular morbidity and mortality [74].

Cardiac myocytes contain two constitutive NOS isoforms with distinct spatial locations, which allows for isoform specific regulation. One regulatory mechanism for NOS is substrate Arg bioavailability. Mitochondrial arginase II negatively regulates NOS1 activity, most likely by limiting substrate availability in its microdomain. These findings have implications for therapy in pathophysiologic states such as aging and

heart failure in which myocardial NO signaling is disrupted [74].

NO plays an antiinflammatory role through S-nitrosation of components of NF-κB pathway. There is a regulatory mechanism wherein NF-κB is controlled through arginase dependent regulation of NO levels, which may impact on chronic inflammatory diseases that are accompanied by NF-κB activation and upregulation of arginases [75].

Predictive measures, lifestyle interventions and therapeutics

The better knowledge of mechanisms linking MS to increased CVD prevalence has led to new predictive measures and to the study of different possible new therapeutic strategies in elderly patients and patients with MS. A new predictive measure proposed is evaluating echocardiographic epicardial adipose tissue (EAT) which is becoming a new index of cardiac and visceral obesity. There is a relationship of EAT with coronary artery disease (CAD) risk factors and the extent of coronary atherosclerosis. Waist circumference measurement is not fully reliable in the determination of visceral adipose tissue, especially in elderly individuals. Studies on the reflection of the intra-abdominal fat mass by the EAT mass surrounding the heart have been performed. EAT may reflect the amount of visceral fat, which is associated with insulin resistance and inflammation. The echocardiographic measurement of EAT may provide additional information for assessing CAD risk and predicting the extent and activity of CAD [76].

Therapeutic lifestyle interventions such as changes in diet or phisical exercise have cardioprotective effects through different mechanisms: a heatlhy diet decreases oxidative stress and inflammatory biomarkers and improves endothelial function. Exercise appears to improve endothelial function via several mechanisms, including increased NO production, increased activity and amount of antioxidants, attenuated ROS production, and an apparent reduction in systemic inflammation, possibly related to an increase in myokines resulting from skeletal muscle activation [77].

Despite the strong evidence that ROS are involved in CVD and aging, antioxidant treatments in these pathologies, have failed to demonstrate convincing benefits; although this may be explained by a number of factors such as the use of inefficient antioxidants or suboptimal dosing [78]. Early attempts at antioxidant intervention as a means to delay aging were initiated soon after the free radical theory of aging was proposed, but these pursuits failed to extend life span in most cases. The direct impact of antioxidant enzyme treatment on life span is even less clearly defined in mammalian models. Pharmacological or genetic antioxidant manipulations have had controversial or even contradictory results, since they are trying to manipulate multifactorial phenomena that cannot be explained by a single theory [79].

It is intriguing to note that the cardioprotective effect of some therapeutic measures such as preconditioning is suppressed in some pathological conditions such as aging, obesity hypercholesterolemia, hyperglycemia, hypertension, and cardiac hypertrophy. Ischemic preconditioning consists of brief episodes of ischemia and reperfusion given before prolonged reperfusion. This measure protects the heart from lethal ischemia-reperfusion injury since the abrupt reperfusion to an ischemic myocardium often results in induction of infarction and cardiac dysfunction [80].

Conclusions

The results from the different elderly study populations link the presence of the MS with the development of CVD and functional disability, and further underscore the importance of recognizing and treating its individual components, particularly high blood pressure. Aging and MS are frequently accompanied by several pathological conditions and some associated phenomena such as increased lipoperoxidation, generation of free radicals, increased peroxidation of NO to its toxic species, and others resulting from oxidative stress which significantly alter the incidence of CVD.

References

[1] Guarner V, Carbó R, Rubio ME,Baños de MacCarthy G (2005) Aging of the cardiovascular system. In: Benhagen EF (editor) Hypertension: New research. Nova Biomedical Books.USA. pages: 47-68

[2] Kenyon CJ (2010). The genetics of aging. Nature, 464:504-512.

[3] Rincon M, Rudin E, Barzilai N (2005). The insulin/IGF-1 signaling in mammals and its relevance to human longevity. Exp Gerontol, 40(11):873-877.

[4] Rozing MP, Westendorp RGJ, Frölich M, de Craen AJM, Beekman M, Heijmans BT, Mooijaart SP, Blauw GJ, Slagboom PE, van Heemst D; Leiden Longevity Study (LLS) Group. (2009). Human insulin/IGF-1 and familial longevity at middle age. Aging, 1 (8): 714-722.

[5] Guarner V, Carbó R, Rubio ME, Baños de MacCarthy G (2005). Aging of the cardiovascular system. In: Benhagen EF, editor. Hypertension: New Research. USA: Nova Biomedical Books Publishers, 47- 68.

[6] Baños G, El Hafidi M, Pérez-Torres I, Guarner V (2009). Insulin resistance and the metabolic syndrome. In: Yao EB, editor. Insulin Resistance: New Research. USA: Nova Biomedical Books Publishers, 49-97.

[7] Guarner V, Rubio-Ruiz ME, Perez-Torres I, Baños de McCarthy G (2011). Relation of aging and sex hormones to metabolic syndrome and cardiovascular disease. Exp Gerontol, 46:517-523.

[8] Tereshina EV (2009). Metabolic abnormalities as a basis for age-dependent diseases and aging? State of the art. Adv Gerontol, 22(1):129-38.

[9] Fadini GP, Ceolotto G, Pagnin E, de Kreutzenberg S, Avogaro A (2011). At the crossroads of longevity and metabolism: the metabolic syndrome and lifespan determinant pathways. Aging Cell, 10(1):10-17.

[10] Ren J, Pulakat L, Whaley-Connell A, Sowers JR (2010). Mitochondrial biogenesis in the metabolic syndrome and cardiovascular disease. Mol Med (Berl), 88(10):993-1001.

[11] Baños G, El Hafidi M, Franco M (2000). Oxidative stress and cardiovascular physiopathology. Curr Topics in Pharmacology, 5:1-17

[12] Rubio ME, Baños G, Diaz E, Guarner V (2006). Effect of age on insulin-induced endothelin release and vasoreactivity in hypertriglyceridemic and hypertensive rats. Exp Geront, 41(3):282-288.

[13] Cavajal K, El Hafidi M and Baños G (1999). Myocardial damage due to ischemia and reperfusion in hypertriglyceridemic and hypertensive rats:participation of free radicals and calcium overload. J of hypertens, 17:1607-1616.

[14] Carvajal K, Baños G (2002). Myocardial function and effect of serum in isolated heart from hypertriglyceridemic and hypertensive rats. Clin and Exper Hypertension, 24(4):235-248.

[15] Baños G, Medina-Campos ON, Maldonado PD, Zamora J, Pérez I, Pavón N, Pedraza-Chaverri J (2005). Antioxidant enzymes in hypertensive and hypertriglyceridemic rats: Effect of gender. Clin and Experimental Hypertension, 1:45-57.

[16] Carvajal K, Baños G and Moreno-Sánchez R (2003). Impairment of glucose metabolism and energy transfer in the rat heart. Mol Cell Biochem, 249:157-165.

[17] Denys K, Cankurtaran M, Janssens W, Petrovic M (2009). Metabolic syndrome in the elderly: an overview of the evidence. Acta Clin Belg, 64(1):23-34.

[18] Iozzo P (2010). Metabolic toxicity of the heart: insights from molecular imaging. Nutr Metab Cardiovasc Dis, 20(3):147-56.

[19] Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, Carey Satterfield M, Smith SB, Spencer TE, Yin Y (2009). Arginine metabolism and nutrition in growth, health and disease. Amino Acids, 37(1):153-68.

[20] Borradaile NM, Pickering JG (2009). NAD(+), sirtuins, and cardiovascular disease. Curr Pharm Des, 15(1):110-7.

[21] Alcaín FJ, Villalba JM (2009). Sirtuin activators. Expert Opin Ther Pat, 19(4):403-414.

[22] de Kreutzenberg SV, Ceolotto G, Papparella I, Bortoluzzi A, Semplicini A, Dalla Man C, Cobelli C, Fadini GP, Avogaro A (2010). Downregulation of the longevity-associated protein Sirtuin 1 in insulin resistance and metabolic syndrome: potential biochemical mechanisms. Diabetes, 59(4):1006–1015.

[23] Catalano KJ, Bergman RN, Ader M (2005). Increased susceptibility to insulin resistance associated with abdominal obesity in aging rats. Obes Res, 13(1):11-20.

[24] Dominguez LJ, Barbagallo M (2007). The cardiometabolic syndrome and sarcopenic obesity in older persons. J Cardiometab Syndr, 2(3):183-189.

[25] Wilson PW, Kannel WB (2002). Obesity, diabetes, and risk of cardiovascular disease in the elderly.Am J Geriatr Cardiol, 11(2):119-125.

[26] Mathieu P, Després JP, Pibarot P (2007). The 'valvulo-metabolic' risk in calcific aortic valve disease. Can J Cardiol, 23 (Suppl B):32B-39B.

[27] Crosford R (1999). Insulin resistance, obesity and diabetes: the connection. J Austr College Nutrit Environ Med, 18:3-10.

[28] Unger RH (2003). Lipid overload and overflow: metabolic trauma and the metabolic syndrome. Trends Endocrinol Metab, 14(9):398-403.

[29] Feskens EJ, Kromhout D (1994). Hyperinsulinemia, risk factors, and coronary heart disease. The Zutphen Elderly Study. Arterioscler Thromb, 14(10):1641-1647.

[30] Qiang W, Weiqiang K, Qing Z, Pengju Z, Yi L (2007). Aging impairs insulin-stimulated glucose uptake in rat skeletal muscle via suppressing AMPK alpha. Exp Mol Med, 39(4):535-543.

[31] Garcia-Rios A, Perez-Martinez P, Delgado-Lista J, Lopez-Miranda J, Perez-Jimenez F (2011). Nutrigenetics of the lipoprotein metabolism. Mol Nutr Food Res, 2012 Jan;56(1):171-83.

[32] Frank PG, Pavlides S, Cheung MW, Daumer K, Lisanti MP (2008). Role of caveolin-1 in the regulation of lipoprotein metabolism.Am J Physiol Cell Physiol, 295(1):C242-248.

[33] Volonte D, Zhang K, Lisanti MP, Galbiati F (2002). Expression of caveolin-1 induces premature cellular senescence in primary cultures of murine fibroblasts.Mol Biol Cell, 13(7):2502-2517.

[34] Feron O, Balligand JL (2006). Caveolins and the regulation of endothelial nitric oxide synthase in the heart**.** Cardiovasc Res, 69(4):788-797.

[35] Calaghan S, White E (2006). Caveolae modulate excitation–contraction coupling and h2-adrenergic signalling in adult rat ventricular myocytes. Cardiovasc Res, 69(4):816-824.

[36] Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, Goodpaster B,Harris TB (2004). The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. Diabetes, 53(4):1068-1073.

[37] McCann SM, Mastronardi C, de Laurentiis A, Rettori V (2005). The nitric oxide theory of aging revisited. Ann N Y Acad Sci, 1057:64-84.

[38] Yanni J, Tellez JO, Sutyagin PV, Boyett MR, Dobrzynski H (2010). Structural remodelling of the sinoatrial node in obese old rats. J Mol Cell Cardiol, 48(4):653-662.

[39] Corbi GM, Carbone S, Ziccardi P, Giugliano G, Marfella R, Nappo F, Paolisso G,Esposito K, Giugliano D (2002). FFAs and QT intervals in obese women with

visceral adiposity: effects of sustained weight loss over 1 year. J Clin Endocrinol Metab, 87(5):2080–2083.

[40] Hatem SN, Coulombe A, Balse E (2010). Specificities of atrial electrophysiology: Clues to a better understanding of cardiac function and the mechanisms of arrhythmias. J Mol Cell Cardiol, 48(1):90-95.

[41] Wasada T, Katsumori K, Hasumi S, Kasanuki H, Arii H, Saeki A, Kuroki H, Saito S, Omori Y (1995). Association of sick sinus syndrome with hyperinsulinemia and insulin resistance in patients with non-insulin-dependent diabetes mellitus: report of four cases. Intern Med, 34(12):1174-1177.

[42] Haim TE, Wang W, Flagg TP, Tones MA, Bahinski A, Numann RE, Nichols CG, Nerbonne JM (2010). Palmitate attenuates myocardial contractility through augmentation of repolarizing Kv currents. J Mol Cell Cardiol, 48(2):395-405.

[43] Cyrus T, Sung S, Zhao L, Funk CD, Tang S, Praticò D (2002) Effect of low-dose aspirin on vascular inflammation, plaque stability, and atherogenesis in low-density lipoprotein receptor-deficient mice. Circulation, 106(10):1282-1287.

[44] Das UN (2002). Is metabolic syndrome X an inflammatory condition? Exp Biol Med (Maywood), 227(11):989-997.

[45] Intengan HD, Schiffrin EL (2001). Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. Hypertension, 38(3 Pt 2):581-587.

[46] Lyon CJ, Law RE, Hsueh WA (2003). Minireview: adiposity, inflammation, and atherogenesis. Endocrinology, 144(6):2195-2200.

[47] Shoelson SE, Lee J, Goldfine AB (2006). Inflammation and insulin resistance. J Clin Invest, 116(7):1793-1801.

[48] Wu D, Ren Z, Pae M, Guo W, Cui X, Merrill AH, Meydani SN (2007). Aging up-regulates expression of inflammatory mediators in mouse adipose tissue. J Immunol, 179(7):4829-4839.

[49] Greenfield JR, Campbell LV (2006). Relationship between inflammation, insulin resistance and type 2 diabetes: 'cause or effect'? Curr Diabetes Rev, 2(2):195-211.

[50] Packard RR, Libby P (2008). Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem, 54(1):24-38.

[51] Mukherjee D, Nissen SE, Topol EJ (2001). Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA, 286(8):954-959.

[52] Weir MR, Sperling RS, Reicin A, Gertz BJ (2003). Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. Am Heart J, 146(4):591-604.

[53] De Martinis M, Franceschi C, Monti D, Ginaldi L (2005). Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity. FEBS Lett, 579(10):2035-2039.

[54] Gersh BJ, Tsang TS, Seward JB (2004). The changing epidemiology and natural history of nonvalvular atrial fibrillation: clinical implications.Trans Am Clin Climatol Assoc, 115:149-160.

[55] Thayer JF, Yamamoto SS, Brosschot JF (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol, 141(2):122-131.

[56] Seals DR, Dinenno FA (2004). Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging. Am J Physiol Heart Circ Physiol, 287(5):H1895-905.

[57] Fliers E, Kreier F, Voshol PJ, Havekes LM, Sauerwein HP, Kalsbeek A, Buijs RM, Romijn JA (2003). White adipose tissue: getting nervous. J Neuroendocrinol, 15: 1005-1010.

[58] Krier F, Fliers E, Voshol PJ, Van Eden CG, Havekes LM, Kalsbeek A, Van Heijningen CL, Sluiter AA, Mettenleiter TC, Romijn JA, Sauerwein HP, Buijs RM (2002). Selective parasympathetic innervation of subcutaneous and intra-abdominal fat—functional implications. J Clin Invest, 110:1243-1250.

[59] Charkoudian N, Rabbitts JA (2009). Sympathetic neural mechanisms in human cardiovascular health and disease.Mayo Clin Proc, 84(9):822-830.

[60] Grisk O, Frauendorf T, Schlüter T, Klöting I, Kuttler B, Krebs A, Lüdemann J,Rettig R (2007). Impaired coronary function in Wistar Ottawa Karlsburg W rats-a new model of the metabolic syndrome. Pflugers Arch, 454(6):1011-1021.

[61] Pralong FP, Gaillard RC (2001). Neuroendocrine effects of leptin. Pituitary, 4(1-2):25-32.

[62] Peters A, Schweiger U, Fruhwald-Schultes B, Born J, Fehm HL (2002). The neuroendocrine control of glucose allocation. Exp Clin Endocrinol Diabetes, 110:199-211.

[63] Stein-Behrens BA, Sapolsky RM (1992). Stress, glucocorticoids, and aging. Aging (Milano), 4(3):197-210.

[64] Butcher SK, Lord JM (2004). Stress responses and innate immunity: aging as a contributory factor. Aging Cell, 3(4):151-160.

[65] Kaaja RJ, Pöyhönen-Alho MK (2006). Insulin resistance and sympathetic overactivity in women. J Hypertens, 24(1):131-141.

[66] Sowers RJ (2004). Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol, 286:H1597-H1602.

[67] Michelson RM (2000). Hypertension in the elderly http://pcvc.sminter.com.ar7cvirtual7cvirteng/fgeng/fgc4200i/imichels.htm

[68] Henriksen EJ (2007). Improvement of insulin sensitivity by antagonism of the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol, 293(3): R974-980.

[69] Soltis EE, Newman PS (1992). Ontogeny of vascular smooth muscle responsiveness in the postweaning rat. Dev Pharmacol Ther, 18(1-2):44-54.

[70] Lee DH, Lee JU, Kang DG, Paek YW, Chung DJ, Chung MY (2001). Increased vascular endothelin-1 gene expression with unaltered nitric oxide synthase levels in fructose-induced hypertensive rats. Metabolism, 50(1):74-78.

[71] Nava P, Collados MT, Massó F, Guarner V (1997). Endothelin mediation of insulin and glucose induced

changes in vascular contractility. Hypertension, 30: 825-829.

[72] White AR, Ryoo S, Li C, Champion HC, Steppan J, Wang D, Nyhan D, Shoukas AA, Hare JM, Berkowitz DE (2006). Knockdown of Arginase I Restores NO Signaling in the Vasculature of Old Rats. Hypertension, 47:245-251.

[73] Steppan J, Ryoo S, Schuleri KH, Gregg C, Hasan RK, White AR, Bugaj LJ, Khan m, Santhanam L, Nyhan D, Shoukas AA, Hare JM, Berkowitz DE (2006). Arginase modulates myocardial contractility by a nitric oxide synthase 1-dependent mechanism. Proc Natl Acad Sci U S A, 103(12):4759-4764.

[74] Ckless K, van der Vliet A, Janssen-Heininger Y (2007). Oxidative-Nitrosative Stress and Post-Translational Protein Modifications: Implicationsto Lung Structure-Function Relations. Arginase Modulates NF-kB Activity via a Nitric Oxide–Dependent Mechanism. Am J Respir Cell Mol Biol, 36(6):645-653

[75] Karadag B, Ozulu B, Ozturk FY, Oztekin E, Sener N, Altuntas Y (2011). Comparison of epicardial adipose tissue (EAT) thickness and anthropometric measurements in metabolic syndrome (MS) cases above and under the age of 65. Arch Gerontol Geriatr, 52(2):e79-84.

[76] Bronas, UG and Dengel, DR (2010). Influence of Vascular Oxidative Stress and inflammation on the development and progression of atherosclerosis. Am J Lifestyle Medicine, 4(6):521- 534.

[77] Levonen AL, Vähäkangas E, Koponen JK and Ylä-Herttuala S (2008). Antioxidant Gene Therapy for Cardiovascular Disease: Current Status and Future Perspectives. Circulation, 117:2142-2150.

[78] Kregel KC and Zhang HJ (2007). An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. Am J Physiol Regul Integr Comp Physiol, 292:R18–R36.

[79] Balakumar P, Singh H, Singh M, Anand-Srivastava MB (2009). The impairment of preconditioning-mediated cardioprotection in pathological conditions. Pharmacol Res, 60(1):18-23.