Oxidative Stress and Aging Heart-Diseases

Subjects: Cardiac & Cardiovascular Systems

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Aging can be seen as process characterized by accumulation of oxidative stress induced damage. Oxidative stress derives from different endogenous and exogenous processes, all of which ultimately lead to progressive loss in tissue and organ structure and functions. The oxidative stress theory of aging expresses itself in age-related diseases. Aging is in fact a primary risk factor for many diseases and in particular for cardiovascular diseases and its derived morbidity and mortality. Here we highlight the role of oxidative stress in age-related cardiovascular aging and diseases. We take into consideration the molecular mechanisms, the structural and functional alterations, and the diseases accompanied to the cardiovascular aging process.

Keywords: aging ; oxidative stress ; cardiovascular

1. Behind the scenes of Cardiovascular Aging

1.1. Aging, Oxidative Stress and Cellular Dysfunction

Age-dependent oxidative stress cellular dysfunction is a condition determined by various intrinsic factors. The heart cell, the cardiomyocytes, exert a high aerobic metabolism in order to guarantee their functions. In this scenario cellular metabolism is guaranteed by mitochondrial function[1]. Mitochondria occupy 30% of total cardiomyocyte volume, this guarantees the high energy demands of the heart. Mitochondrial oxidative phosphorylation fueled by catabolism of lipids and carbohydrates is the main source of ATP for heart function. The Krebs cycle is important for ATP generation but its balance and regulation are fundamental for oxidative stress management[2]. Cardiomyocytes aging is one of the main factors leading to cardiovascular diseases. Understanding the processes behind cellular dysfunction in the aging process has led to many findings in relation to mitochondrial dysfunction and its genomic instability and epigenetic regulation[3]. In fact, studies on longevity have highlighted the importance of mitochondria and oxidative stress in the senescence process[4]. As described before, free radicals are generated in different compartments of the cell. However, the main source of free radicals is mitochondria and in particular the electron transport chain located in the inner mitochondrial membrane. The continuous production of free radicals in the mitochondria leads to oxidation of macromolecules and DNA[5]. In particular, during aging nuclear and mitochondrial DNA stability is compromised[6]. Mitochondrial DNA lesions have been shown to carry mutagenic and cytotoxic affects ultimately leading to DNA replication alterations[7][8]. The genomic instability is partially prevented by DNA repair pathways in both mitochondria and nucleus[9]. Despite this DNA damage increases and accumulates during the aging process. Aged mice heart mitochondria have a threefold higher frequency of mitochondrial DNA mutation and deletions[10]. Accumulation of DNA alterations is a driving factor in aging leading to cellular loss of function. Animal models with increased mitochondrial DNA instability mediated by disruption of mitochondrial transcription factor A, showed alteration of mitochondrial morphology leading to higher rates of apoptosis and ultimately to dilated cardiomyopathy[11][12]. An early aging phenotype is characterized by high mitochondrial DNA point mutation as highlighted in mice[13][14]. New animal models have been developed to study the effect of increased mitochondrial DNA deletions in the myocardium. These models have highlighted that mitochondrial DNA dysfunction is not only associated with tissue dysfunction but also with development of premature arrhythmias[15]. Mitochondrial dysfunction and instability contribute to the aging process in other ways as is the case with calcium homeostasis and redox signaling[16][17]. Overall, the aging process and the mitochondrial alterations lead to metabolic changes. Normally up to 90% of cardiac ATP is generated by the use of long-chain fatty acid, only 10% from glucose, lactate, ketone bodies, and amino acids[18][19]. The Randle cycle highlights the substrate selection and interaction. Development of heart disease and aging has been associated with the inversion of metabolic substrate selection[20]. With aging increased glucose metabolism expression, increased glycolytic proteins and the concomitant decline in fatty acid oxidation has shown to be a premature sign of heart failure in younger individuals[21]. As we will mention afterwards, metabolic inversion and heart failure are associated with a reactive hyper-adrenergic state closely linked to impaired glucose metabolism and inevitably to insulin resistance[22].

Another important cellular dysfunction point to address is increased apoptosis during aging[23]. Accumulation of lipofuscin on lysosomes, loss of autophagic management, accumulation of non-functional damaged cell components, in particular mitochondria, leads to activation of the apoptotic pathway[24]. These changes in cardiomyocytes also increase alteration in calcium cellular handling. Calcium plays a crucial role in modulating cardiac function by modulation of myocardial contractility through a complex system of ion channels, ryanodine receptors, and sodium calcium exchangers. On the other hand, myocardial relaxation is mediated by sarcoplasmatic/endoplasmatic reticulum calcium-ATPase (SERCA2a) which seizes calcium to the sarcoplasmic reticulum[25]. The importance of cellular SERCA2a function has been highlighted in oxidative stress and aging. In particular, SERCA2a impairment and consequent increase in calcium stagnation in cytoplasm causes diastolic relaxation impairment. Moreover, animal models by the same mechanism of prolonged cellular contraction showed alterations in myosin heavy chain expression[25]. These changes influence negatively cardiomyocytes contractile and electrical efficiency. Alteration of the contraction and relaxation coupling of cardiomyocytes is at the base of the compensation mechanism that we will describe in the next chapters. In fact, we will see how depletion of cardiomyocytes and inadequate contraction efficiency leads to cardiac hypertrophic remodeling and not only[26].

1.2. Aging in Cardiac Structural and Patho-Physiological Changes

Cardiac structural modifications due to aging bring about various functional and adaptive consequences in heart capacity[27]. Cardiac aging causes fibrosis, left ventricle hypertrophy, diastolic dysfunction, and filling ultimately leading to reduction in cardiac overall compliance and ejection fraction output[28][29]. Gene expression in aging human hearts highlights a shift in cellular capacity. Upregulation of genes for sarcomere and cytoskeletal proteins and downregulation of proteasome components expression reflects the process of myocyte hypertrophy and decreased in protein turnover[30]. This is accompanied by downregulation in Troponin T, SERCA2, and alpha-MHC with a switch towards beta-MHC, with a decrement in contractile efficiency[31]. Mitochondrial disfunction in mice aging cardiomyocytes is an important source of oxidative stress[32]. The inefficiency of aging rat mitochondria is characterized by increase in size, reduction in number of cristae with an overall reduction in ATP production per cell[33]. The high-rate production of reactive oxygen species leads to a vicious cycle[34][35]. In fact, in order to maintain functional demands the aging heart undergoes a process of hypertrophy[36]. This adaptation allows the heart to respond to increase in pressure demand in consequence to vascular stiffness[37]. However, this mechanism fails when heart demands exceed bringing about heart failure[38]. Cardiac hypertrophy in human aging-heart is characterized by increase in cardiomyocyte size with asymmetric left ventricle ventricular wall thickening mainly of the intraventricular septum[39]. These alterations cause alterations in human heart geometry and shape initially granting increase in contractility but on the long run causing oxygen impairment and reduction in contractility[40]. Aging in both mice models and humans is associated with apoptosis and loss of myocytes with a rate of about 45 million per year compensated by increase in single myocyte median volume[41][42]. The overload of the remaining myocytes is an additional reason for compensatory hypertrophy[43]. In addition, the loss of vascular elasticity and the increase in vascular stiffness increases the mechanical load of the aging heart accelerating the way to heart failure[44]. Age-related left ventricle hypertrophy in humans occurs independently of underlining story of hypertension or other causes[45]. Overall, a healthy human aging heart with preserved ejection fraction (EF) shows no change in stroke volume, heart rate, and cardiac output[46]. The main difference is highlight in diastolic function, in fact, the capacity of the ventricle to receive blood results altered by the reduction in ventricle wall elastic compliance[47]. Hemodynamically this can be seen in a reduction in early diastolic filling with an increase in tele systolic filling with an inversion of the E/A parameter and an increase in E/e' better seen in echocardiographic studies[48][49]. This compensatory system present at rest however is not efficacious in case of cardiac demands. The aging-heart in fact compensates the contractile and diastolic function reduction with increase in peak heart rate[50]. Another important age-related alteration in animal model hearts is the calcification of the valves associated with proliferation of fibroblasts and deposition of collagen[51][52]. The cardiac extracellular matrix in the aging heart fills with glycoproteins, proteoglycans, glycosaminoglycans, integrins, and collagen[53][54]. Interesting is the switch from collagen type III to type I, seen in children, young adults, and elderly, which is less distensible and stiffer[55][56]. This also effects negatively the propagation of the electrical signals of the myocytes and of the myofibrillar bundles giving arrhythmias[57][58].

1.3. Aging and Autonomic Nervous System Adaptations

With aging an increasing plasma catecholamine concentrations and sympathetic tone of autonomic nervous system (ANS)[59][60] could impair adaptivity of elderly individuals to the environment[61]. Aging has been implicated in the impairment of alfa and beta-adrenergic receptor sensitivity and vascularresponsiveness[62][63] with a predominance of the alfa tone in muscle vasculature. In fact, in older women we can observe a higher decrease of arterial blood pressure in front of younger ones after an autonomic blockade[64]. Age-related alterations in ANS influence blood pressure, cerebral blood flow, bladder function, and heart rate variability (HRV)[65][66]. HRV is an indicator of arrhythmic complications and a strong predictor of mortality and sudden death[67]. Nocturnal reduction of parasympathetic activity in elderly individuals is

the result of a low vagal hearth control due to the prevalence of the adrenergic tone of SNA. The increase in heart rate combined with the HRV reduction is due to the degeneration of cardiac autonomic function during aging[68] and increases the incidence of cardiovascular events[69] [69]. Active lifestyle is important for the health of the elderly. Intensive physical exercise, increasing muscle mass and fatigue resistance, could minimize autonomic dysfunction in aging with training[70]. A physical training regime could improve adaptations of the autonomic function[71]. Although intensive exercise seems to have benefit for older individuals, there is a need for further studies to realize a regimen of exercise programs. The ANS abnormalities were thought to be a common underlying pathophysiology of CVDs such as hypertension and heart failure[72]. Another issue due to the impairment between the two ANS deregulation is atrial fibrillation, the most common arrhythmia in older people[73]. Denervation of ANS has been shown to be efficient against AF[74]. Patients with AF had reduction in cardiac performance due to the loss of the atrial contraction in ventricular filling.

2. Aging, Oxidative Stress, and Cardiovascular Diseases

As highlighted above, all cells constantly undergo reactions which require transfer of electrons, in order to acquire energy . These complex mechanisms, which occur principally in the mitochondria, require a constant turnover in the oxidative state[75]. The redox reactions and the reactive oxygen species (ROS) generated are highly reactive and are the main source of oxidative stress. The heart's cellular volume is made up for 45% by mitochondria. Oxidative phosphorylation generates radical species, when electrons are lost from mitochondrial complexes I and II, in order to produce adenosine triphosphate (ATP)[76]. The mitochondrial pathway also characterized by formation of NADH and FADH which react with other redox compounds[77]. As cardiomyocytes and endothelial cells age, they produce more ROS. Increased production of ROS leads to functional impairment due to reduction in biological activity of nitric oxide and formation of peroxynitrite, which deactivates several free radical scavengers[78][79]. Another important origin of oxidative stress is aberrant Ca^{2+} reuptake, due to SERCA2 downregulation[80][81]. Constant high concentration of Ca^{2+} levels in the cardiomyocyte's cytosol increases ROS production. As highlighted before the RAAS system also plays an important role in age-related cardiac oxidative stress with direct and indirect involvement of NADPH oxidase complex and of ROS production[82]. Thus age-dependent increase in oxidative damage is the one of the leading causes of CVD (Figure 1)[83].

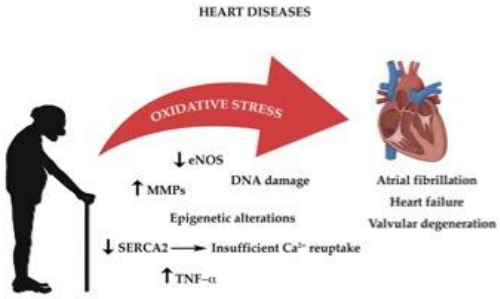

Figure 1. The impact of oxidative stress on age-associated heart diseases

2.1. Atrial Fibrillation

Atrial fibrillation is the most common chronic cardiac rhythm disturbance, it affects 1–2% of the population and the chances of developing this condition increases with age, particularly after age 65[84]. It consists in a rapid heartbeat (tachyarrhythmia) that originates in the upper chambers of the heart, called the atria, preventing them from functioning properly[85]. In such circumstances, the atria are no longer able to expel all the blood, which will remain partially inside the atria with the risk of clot formation][86]. Clot formation due to AF is one the leading causes of cerebrovascular thrombosis[87][88]. In aging the main cause of AF can be found in the hearts structural and functional alteration, as described earlier. Aging itself is the single most important risk factor for AF[89] Among all the previously described alteration, the electrical conduction disturbances, ectopic activity leading to atrial arrhythmogenesis is atrial fibrosis and so dilation[90]. Atrial fibrosis in the human aging heart is associated with excessive accumulation of collagen fibers, in particular type I fibers, and the increase of cross-linking between fibers[91]. Oxidative stress plays an important role in extracellular matrix (ECM) turnover and metabolism. The increase of matrix metalloproteinase (MMP) in human aging hearts with atrial fibrillation has been widely highlighted[92]. Age-related alteration are a summation of structural and electrophysiological remodeling leading to alteration of the mechano-electrical feedback[93]. Overall, this means that the atria are no longer capable of modulating the electric functions of the heart with the induction of mechanical load on the cardiomyocytes[94]. In conclusion, aging is associated with an increase in acute-phase inflammatory cytokines an important stimulus for AF, as it directly increases arrhythmogenicity and calcium homeostasis dysregulation[95][96].

Moreover, as seen in human atrial tissues, ROS and mitochondrial disfunction influence AF due to accumulation of age-related mitochondrial DNA deletion and mutation[97][98]. Oxidative stress and inflammation in aging influence greatly both functional and structural modifications causing electrophysiological remodeling and correlated diseases[99][100].

2.2. Heart Failure

Heart failure (HF) is a complex clinical syndrome defined by the inability of the heart to supply blood in adequate quantities for the body's actual demand or the inability to meet this demand only at ventricular filling pressures above the norm[101]. According to statistics, as the population ages and the number of patients who survive a myocardial infarction increases, the incidence of heart failure continues to rise[102]. If we refer to hemodynamics, heart failure is characterized by reduced contractility of the myocardium measured as ejection fraction (EF), this universally used parameter can actually be not very specific in identifying the cause of cardiac dysfunction. In fact, this condition can be caused by both organic and functional problems. Among the most common causes are myocardial infarction, myocardial ischemia, hypertension, valvulopathies, cardiomyopathies, metabolic diseases, and autoimmune diseases. HF is the most important complication of any heart disease. In the United States of America, it is estimated that in 2006 there were more than 600,000 new cases[103]. In Italy about 5% of the general population (3,000,000 individuals) is affected by overt or asymptomatic HF[104]. Age is a very important risk factor, the incidence remains low in people between 40 and 50 years, while it rises up to 10% in people over 75 years of age[105]. The incidence of this pathology is in rapid increase due to the overall increased survival rate following acute myocardial infarction and to longer life expectancy[106]. Aging (with consequent organ degeneration) causes cardiac efficiency to decrease, amplifying the effect of any pathologies. HF is generally thought to be involved in all those deaths from aging without apparent symptoms. In fact, when cardiac contractility is progressively reduced, whatever the cause, the final effect is hypo-perfusion of the organs vital and in particular of the brain, kidneys, and liver with the progressive functional deterioration[107].

Systolic HF is characterized by the reduced performance of the left ventricle, easily identifiable in patients with a universally adopted echocardiographic parameter such as the ejection fraction (FE), which, however, can vary considerably with the different biomedical imaging methods[108]. The force of contraction of the heart is directly proportional to the conditions of the myocyte, the cell of which the heart muscle is composed: any insult that affects the myocytes is reflected on the compliance of the left ventricle and therefore on the force of contraction (the FE is generally lower than 45%)[109]. Ventricular hypertrophy is one of the adaptation mechanisms of the heart subjected to increased stress that persists for long periods of time; this attempt at correction may be a factor involved in the progression of heart failure[110]. It is certainly not the mechanism that leads to myocardial hypertrophy, it is certain that an increase in systolic wall tension in association with an increase in afterload would cause concentric hypertrophy; on the contrary, an increase in diastolic wall tension in association with an increase in preload would lead to eccentric hypertrophy[111]. In both situations the synthesis of the unit of the myocyte known as sarcomere would be stimulated: in the first case the production of sarcomeres would be stimulated in parallel and in the second in series[111]. Myocytes and their components can be damaged by inflammatory diseases (myocarditis) and by infiltrates (amyloidosis), by toxins or by drugs. The most common mechanism is certainly myocardial ischemia: with the death of myocytes, the myocardium is replaced with fibrous or connective tissue, which have no contractile properties and are similar to scars. These scars can initiate the heart remodeling process, which in turn can lead to heart failure[113]. Heart failure caused by diastolic dysfunction, like systolic dysfunction, may be symptom-free in a compensated patient[114]. What characterizes this alteration is the inability of the left ventricle to adequately relax and this is secondary to the increased stiffness of the ventricular chamber. This attitude of the heart muscle leads to a reduced ventricular filling in diastole, which translates into a reduction in output. The inability to obtain optimal relaxation leads to an increase in end-diastolic pressures, which affect the atria and pulmonary veins[115]. Diastolic dysfunction and systolic dysfunction have many causes in common, most notably older age, high blood pressure, diabetes mellitus, and left ventricular hypertrophy. We can consider separately female sex, diseases of the pericardium and hypertrophic, accumulation and infiltrative cardiomyopathies[116]. Restrictive cardiomyopathy is one of the diseases that most affect diastolic dysfunction. Restrictive cardiomyopathies are characterized by a restrictive filling and a reduced diastolic volume; they are classified into primary and secondary[117].

In the failing aging heart, oxidative stress plays an important role. Both normal aging and pathological aging human hearts show increased levels of ROS[118]. Aging and oxidative stress can be accompanied by other pathological conditions such as diabetes, endothelial dysfunction, atherosclerosis, hypertension, and degenerative diseases increasing the imbalance between ROS production and antioxidant systems[119]. With aging, the compensatory mechanisms do not effectively manage ROS accumulation in mice models. This generates increased oxidation of proteins, lipids, and mitochondrial DNA damage. Electron leak in mitochondria is considered one of the main sources of ROS and adenine nucleotide translocase (ANT) seems to be why[120][121]. ANT oxidative and carbonyl modifications reduce mitochondrial energy output[122][123][124]. The uncoupling of ATP synthesis disrupts the mitochondrial matrix disrupting Ca^{2+} stabilization[125][126]. In fact, failing

senescent mice hearts in conditions of stress, increase by two-fold Ca^{2+} levels, increasing ischemic and reperfusion damage[127]. Progression to heart failure and heart failure itself includes various mechanisms. As seen before, oxidative stress in aging also leads to increased cardiomyocytes apoptosis, ECM remodeling, and altered response to stress all important factors for HF[128]. For all the reasons above, heart failure and aging are synonyms. The aging process and all the changes involved lead to heart failure.

2.3. Valvular Heart Disease

Age is the main driving factor for valvular myxomatous degeneration and valvular sclerosis. Elderly patients have a prevalence of 30–80% of aortic valve sclerosis[129][130]. With age echocardiographic examination in these patients shows an increase in calcification of the aortic valve leaflets and anulus[131][132]. Elderly patients also have concomitant risk factors for rapid progression of valve degeneration such as hypertension, LVH, hyperlipidemia, and kidney failure[133]. Moreover, there is a linear correlation between aortic valve degeneration and atherosclerosis in elderly patients[134]. Valve sclerosis does not have a hemodynamic impact but can evolve into stenosis. Aortic stenosis is characterized by the reduction in the opening of the valve leaflets with consequent increased in pressure gradient between the left ventricle and the aorta[135]. To guarantee the necessity of the increased pressure gradient the heart undergoes myocardial hypertrophy to maintain an adequate systolic function and cardiac output[136]. This mechanism of compensation leads to left ventricle dilatation and deterioration of systolic function on the long run. Another aortic valve degeneration consequence is aortic regurgitation, a situation where the leaflets do not close properly and a backward blood flow in generated. This second condition causes a rapid diastolic filling and eccentric hypertrophy of the heart in order to increase the blood volume output[137]. Same is true for the mitral valve, with aging there is degenerative process involving the annulus and the leaflets[138][139]. In this case ,however, valve regurgitation is more common than stenosis[140]. As for the aortic valve, hypertension, kidney failure, and aortic alterations are risk factors mitral calcification and patients with this such alteration have an increased risk for heart failure, atrial fibrillation, stroke, coronary artery diseases, and overall adverse cardiovascular events and mortality[141]. In humans, mitral valve regurgitation is mainly associated with ischemic heart disease and myxomatous degeneration while mitral stenosis is associated with rheumatic disease[142]. Mitral and aortic valve vices are one of the most common cause of surgery in older population[143]. Interesting are the recent discoveries that associated reduction in telomere length with degenerative valve disease. In particular elderly patients with aortic stenosis had a reduction in leukocyte telomere length[144] Although more research is required to fully understand ROS-induced damage to telomeric DNA, studies suggests that this may be an important factor to take into consideration[145]. Furthermore, even if oxidative stress and telomere shortening in humans still have not been directly correlated, there is a great association with frailty typical of the elderly[146]. Oxidative stress and inflammation play an important role in valvular calcification. The underlining mechanisms are not fully known but local inflammation by hyperlipidemia and diabetes has been shown to be a great promoter of valve and vascular sclerosis[147] . Moreover, human studies have assessed that oxidized lipids seem to be one of the main inflammatory driving factors[148][149][150]. Increased levels of circulating oxidized phospholipid, ox-LDL and of TNF-alpha and inflammatory cells have been highlighted in patients with higher degrease of valvular degeneration[151][152]. High levels of ox-LDL increase the expression of osteogenic factors such as BMP-2, activating TLR expression[153][154]. The vicious cycle of lipid oxidation induces chemokines release and recruitment of monocytes and enhanced expression of ICAM, and MMP, factors leading to reduction NO production[155][156][157][158][159]. In conclusion, valvular heart disease is probably associated to oxidative stress in the aging heart by ROS increase with NO synthase uncoupling mediated mainly by ox-LDL expression of NADPH[160][161].

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