

Cardiovascular Risk in Relation to Age and Gender

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ABSTRACT

The aging and elderly populations are particularly susceptible to cardiovascular disease. Age is an independent risk factor for cardiovascular disease (CVD) in adults, but these risks are compounded by additional factors, including frailty, obesity, and diabetes. These factors are known to complicate and enhance cardiac risk factors that are associated with the onset of advanced age. Sex is another potential risk factor in aging adults, given
Keywords: Cardiovascular, hormone, gender.

that older females are reported to be at a greater risk for CVD than age-matched men. However, in both men and women, the risks associated with CVD increase with age, and these correspond to an overall decline in sex hormones, primarily of estrogen and testosterone. Despite this, hormone replacement therapies are largely shown to not improve outcomes in older patients and may also increase the risks of cardiac events in older adults.

INTRODUCTION

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels.[1] CVD includes coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack).[2] Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, abnormal heart rhythms, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis. Cardiovascular diseases (CVDs) are important causes of worldwide preventable morbidity and mortality [1, 2]. CVDs have become a leading cause of mortality and morbidity in developing countries and rates are expected to rise further over the next few decades [3]. Age dominates risk factors for cardiovascular disease (CVD) [3]. Indeed, the advent of contemporary treatments for acute coronary syndromes and stroke have

helped to extend life expectancy [3]. Although an enormous success from an individual perspective, the resultant demographic shift presents one of the greatest challenges for the social and health care systems worldwide. The population over 65 years of age will double from 12% in 2010 to 22% in 2040 [3]. Indeed, by 2020, the number of people 60 years of age and older will surpass the number of children below 5 years of age. The pace of population aging around the world is increasing dramatically, particularly in low- and middle-income countries (e.g., Chile, China, Iran, and Russia). Although aging presents an array of disorders, CVD carries the greatest burden for the older population, their care givers, and health systems [5]. Coronary heart disease (CHD) associates strongly with age, and is the leading cause of death in Europe and the United States [6]. The prevalence of CVD increases in people >65 years of age,

especially in those >80 years of age, and will increase by ~10% over the next 20 years [6]. From 2010 to 2030, an additional 27 million people will have hypertension, 8 million will have CHD, 4 million will have stroke, and 3 million will have heart failure due to the rapid accumulation of elders [7]. Increased CVD prevalence also interplays with frailty, a condition of increased vulnerability to stressors. A meta-analysis that included 54,250 elderly patients associated CVD with an odds ratio (OR) of 2.7 to 4.1 for prevalent frailty and an OR of 1.5 for incident frailty in those without frailty at baseline [8]. Current projections predict an increase in expenditures for CHD and heart failure of ~200% over the next 20 years, with stroke expected to contribute the largest relative increase in annual medical costs of 238% [8]. These considerations highlight the urgency of understanding why age contributes crucially to the development of CVD in order to enable us to cope with the aging of the population. This review provides clinical and experimental evidence to support the established link between aging and CVD.

Pathophysiology of CVD In Aged Adults

Functional changes in aging adults hearts have been characterized, which include reports of diastolic and systolic dysfunction, and also electrical dysfunction, including the development of arrhythmias [9]. Collectively, both functional and electrical defects result in a high prevalence of heart failure, atrial fibrillation, and other CVDs, in aging patients [9]. The high prevalence of CVD in this population has been linked to a number of factors, including increased oxidative stress, inflammation, apoptosis and overall myocardial deterioration, and degeneration [10]. An increase in the production of reactive oxygen species (ROS) is known to occur with the onset of

advanced age [10], and is linked to persistent inflammation and progression to chronic disease status, as in CVD [11]. Increased production of proinflammatory markers is a hallmark of aged hearts, including high levels of interleukin-6 (IL-6), tumor necrosis factor- α (TNF α), and CRP (C-reactive protein) [11]. Production of inflammatory factors and other mediators contribute to cardiac remodeling, including significant extracellular matrix (ECM) remodeling, which is caused by impaired ECM turnover [12]. Dysregulation in matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) expression levels are frequently linked to increased collagen deposition and the development of cardiac hypertrophy and fibrosis in aged hearts [13]. Fibrosis and hypertrophy are both significant structural changes that lead to eventual cardiac dysfunction in aging patients [13]. Fibrosis, due to impaired ECM turnover, has been shown to develop in the atria of aging patients, which also results in atrial fibrillation in many of these patients [12]. Oxidative stress, including the production of excess ROS that occurs with cardiac aging, will also lead to mitochondrial dysfunction [9]. Cardiac aerobic metabolism is greatly dependent on mitochondrial production of ATP; thus, the loss of mitochondrial function plays a major role in the development of cardiac dysfunction in aging adults [13]. It has been reported that mitochondrial DNA is particularly susceptible to oxidative damage, since it lacks protective histones, and is in close proximity to ROS production during electron transport [14]. ROS production has also been shown to impair the efficiency of mitochondrial respiration, which also contributes to the cardiac aging process via augmented ROS production [14]. Mitochondrial oxidative stress has also been shown to result in

impaired calcium signaling via dysregulation in the type 2 ryanodine receptor (RyR2) [15]. RyR2, a calcium ion channel, is primarily responsible for the release of calcium from the sarcoplasmic reticulum, allowing for muscle contraction [15]. Decreased activity of sarcoplasmic reticulum Ca²⁺ ATPase pump (SERCA) has also been observed with age [16]. Generation of biologically active lipid mediators may also result in response to age-related inflammation. Mitochondrial dysfunction due to increased ROS has been reported to result in production of lipid oxidation, which has been linked to the development of atherosclerosis [17]. Although impaired lipid metabolism via mitochondrial dysfunction is known to occur with age, however, this process is still not completely understood. One experimental study in mice reported that diets enriched with omega-6 in older aged mice leads to chronic low-grade inflammation and impaired oxidative-redox balance, resulting in electrocardiographic disturbances [18]. Collectively, age-related oxidative stress results in significant cellular and structural changes, and these eventually lead to impaired cardiac functionality and development of CVD.

The Prevalence of Aging Adults Admitted to Critical Care

Risks associated with age present an inimitable difficulty with regards to medical treatment, especially with respect to critical and intensive care treatments. Given that the prevalence of health complications increases with advanced age, it is no surprise that the average age of patients admitted to the ICU is approximately 60 years [19]. However, advanced age has been reported to be associated with increased mortality in ICU patients, even after controlling for preexisting morbidities [20]. Thus,

advanced age is a risk for mortality in ICU patients, regardless of treatment intensity [21]. While age is an independent risk factor for mortality in ICU patients, the presence of health conditions and diseases are known to significantly augment the risk of mortality in these patients [22]. Thus, a higher prevalence of CVD in elderly ICU patients has been reported, including higher rates of heart failure, arrhythmia, and valvular heart disease [23]. High mortality rates due to CVD in critically ill patients have even resulted in the implementation of specialized health units for cardiac patients, referred to as coronary care units (CCU), or more recently, cardiovascular intensive care units (CICU) [24]. Another risk for aging adult ICU patients is the use of mechanical ventilation. The average age of ventilated patients in the ICU is ~60 years [25]. Importantly, both age and length of ventilation are associated with mortality in ICU patients [25]. Advanced age is also an important factor associated with an increased risk of failed extubation. Studies demonstrate that approximately 35% of elderly patients are reintubated within 48 to 72h after extubation [26]. Ventilation with high levels of supplemental oxygen presents another potential risk for elderly patients. Supplemental oxygen is frequently implemented for the treatment of hypoxia, in order to improve arterial oxygen levels in critically ill patients [27]. However, high oxygen exposure (hyperoxia) has been also shown to induce oxidative stress due to increased production of ROS, which results in significant lung injury [28]. Additionally, hyperoxia is known to induce hemodynamic changes, including the appearance of decreased heart rate, stroke volume, and cardiac output in patients [29]. Of critical concern,

hyperoxia in critically ill patients is also strongly associated with increased risks for poor outcome and high mortality rates [30]. Reports suggest that cardiac patients may be at a greater risk for worsened outcomes with supplemental oxygen exposure.

Management and Treatment of CVD in Older Adults

While age is shown to be independently associated with inflammation and a risk for CVD, health behaviors may also complicate these factors. Health behaviors that are commonly linked with poor outcomes in CVD patients include inactivity, poor nutrition, and smoking [31]. The AHA reported that these health behaviors, in addition to poor sleep behavior, are all associated with higher risk for development of CVD [6]. Self-management of these health behaviors, under the direction of medical care specialists, have shown promise in CVD patients. Thus, lifestyle modifications are a key to promoting better health in aging adults, and are a fundamental approach to reducing cardiovascular risk in adults [32]. Examples of lifestyle changes that have been directly linked to decreased risk of CVD include maintenance of a healthy weight, avoidance of tobacco products, and regular exercise [32]. Diet supplementation with inorganic nitrate has demonstrated beneficial effects on vascular function in older adults, via improvements in endothelial function. Thus, inorganic nitrates may also reduce vascular stiffness, and thus the risk of atherosclerosis [33]. Enhanced endothelial function and vascular flexibility, following mineral nitrate supplementation, has been shown to lead to an overall reduction in systolic pressure, particularly in older adults with mild hypertension. Endothelial function may also be improved by the addition of dietary antioxidants [33]. Vitamin C,

vitamin E, polyphenols, and carotenoids have all been shown to reduce oxidative stress, and thereby may provide a protective effect against CVD [33]. Antioxidants are reported to work primarily by reducing the production of ROS, typically associated with advancing age, which may help to avoid initiation of the inflammatory cascade [34]. Excess ROS results in oxidation of lipoprotein (LDL), which is also shown to result in the development of CVD. Reduction of ROS by antioxidants prevents the uptake of oxidized LDL into macrophages, avoiding their conversion into foam cells, and further prevents these from adhering to the endothelium, which would otherwise result in the development of atherosclerotic lesions. The use of antioxidants has also been shown to prevent the release of destructive inflammatory cytokines, which play a crucial role in the activation of the inflammatory cascade. Physical inactivity has been reported to be a major cause of chronic illnesses, such as CVD. Regarding the benefit of physical activity, walking has been reported to aid older men in the management of coronary heart disease. Additionally, regular walking activity may increase longevity by decreasing the risk of CVD and other age-related diseases [35]. Additionally, exercise has been shown to be particularly beneficial to aging adults, by protecting against age-related adverse systemic and cellular effects of aging, and by reducing cellular senescence [36]. Additionally, exercise is reported to improve endothelial function in older adults, but with certain differences in males and females. Specifically, endurance exercises are more consistently associated with improved endothelial function in males than in postmenopausal women, due to their lack of estrogen, and subsequently increased oxidative stress. Telemedicine and

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telemonitoring has also gained exposure for its potential to prevent and/or gauge risk factors associated with CVD. Studies show that self-management via mobile and telehealth technologies can improve outcomes in patients with hypertension, such as the use of mobile blood pressure monitoring. Unfortunately, elderly adults show low participation in these technologies. In addition to lifestyle changes, statins, a class of lipid-lowering drugs, are typically implemented as a primary measure to prevent CVD. Statins have been reported to reduce total cholesterol in older adults [37]. Statin use has been shown to result in a 31% decrease in low-density lipoprotein (LDL) cholesterol, and a 14% increase in high-density lipoprotein (HDL) cholesterol, in older adult patients. Statins are associated with decreased all-cause mortality and cardiovascular events in older individuals without an established CVD diagnosis. Overall, statins lower the risk of MI and stroke in older adults. Administration of statins in older adults with diagnosed CVD is reported to result in a 14% decrease in triglyceride levels. Moreover, in one study statins were found to decrease the risk of MI by 39.4% in older adults, as compared with those treated by a placebo [38]. Furthermore, statin treatment has also led to a 23.8% decreased risk of stroke as compared with a placebo [39]. Although statins are the primary medications for atherosclerosis patients, this class of medications is responsible for muscular dysfunctions, myopathy, rhabdomyolysis, and elevated creatinine kinase levels. Thus, the risks of this medication in older adults must be carefully examined when considering its overall benefit. Additionally, while statins have been reported to reduce cardiac mortality in patients after MI, one study reported lower rates of reduction for women as compared with men. However,

a recent study has published findings which demonstrate that women are less likely to participate in recommended statin therapy after their first MI, as compared with men, which may partially account for diminished mortality reduction for women after MI [40].

Molecular Features of Age-Related CVD Telomeres and cellular senescence

Accumulation of senescent cells within the vascular wall and heart can contribute to structural and functional decline of the CV system with age [41]. Considerable evidence implicates telomere shortening in cellular senescence. Telomeres consist of repetitive nucleotide sequences (TTAGGG) at the ends of mammalian chromosomes, that preserve chromosome stability and integrity by preventing deterioration or fusion with neighboring chromosomes [23]. Each cell division shortens telomeric DNA until, at a critical length, the cells lose capping function at the chromosomal ends, activating DNA damage checkpoints, cell senescence, and eventually apoptosis. Telomere shortening has particular relevance in the setting of CVD. Leukocyte telomere length (LTL) associates significantly with vascular cell senescence, aortic valve stenosis, CV risk factors (i.e., hypertension, type 2 diabetes, obesity, and smoking), and risk of atherothrombotic events. However, the causality of these associations remains uncertain [24]. Patients with clinical and subclinical features of atherosclerosis display reduced LTL compared with healthy controls, even after adjustment for relevant confounders, such as age, sex, and race. In a recent case-control study, individuals with shorter LTL had a higher presence of ischemic (OR: 1.37; 95% confidence interval [CI]: 1.06 to 1.77) and hemorrhagic stroke (OR: 1.48; 95% CI: 1.08 to 2.02) as compared with the highest tertile of telomere length [12].

Moreover, patients with reduced LTL had a significantly increased risk for both incident plaque (hazard ratio: 1.49; 95% CI: 1.09 to 2.03) and plaque progression (hazard ratio: 1.61; 95% CI: 1.26 to 2.07) [1]. A recent meta-analysis, including prospective and retrospective studies on the association between LTL and CHD (43,725 participants of whom 8,400 had CVD), revealed that patients with the shortest LTL had a higher relative risk (RR) for CHD (RR: 1.54; 95% CI: 1.30 to 1.83) and cerebrovascular disease (RR: 1.42; 95% CI: 1.11 to 1.81) [38]. Critical aspects associated with cellular senescence include age-dependent defects of adrenergic signaling and calcium handling. Plasma levels of norepinephrine significantly increase with age, as the result of reduced plasma clearance and increased spillover from the tissues. A reduction of the catecholamine reuptake transporter localized in sympathetic nerve terminals also contributes to elevated catecholamine concentrations with aging. Together, these alterations progressively impair adrenergic responsiveness, resulting in β -adrenergic desensitization. This phenomenon ultimately reduces the number, affinity, and internalization of β -adrenergic receptors (namely the β_1 -adrenergic receptor subtype), coupled with abnormalities in membrane adenylate cyclase activity or cellular production of cyclic adenosine monophosphate [21]. Such defects of autonomic modulation favor chronotropic incompetence and reduced inotropic reserve of the LV, thus affecting exercise tolerance. Reduction of calcium reuptake by the myocardial sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2a) is another key feature of cardiomyocyte aging, yielding impaired early diastolic LV filling and a compensatory increase in atrial contraction [34]. Calcium transient

amplitude decreases gradually with age, being 3.2-fold smaller in myocytes from patients ≥ 75 years of age than in those younger than 55 years of age. An age-related delay in propagation of the calcium transient from the sarcolemma to the cell center may also occur [27]. Moreover, aged myocytes have reduced SERCA2 expression, limiting the amount of releasable sarcoplasmic reticulum calcium, as well as calcium release-induced ICa calcium channel inactivation. These changes dampen mechanical efficiency and electrophysiological properties, and increase the risk of arrhythmias (i.e., atrial fibrillation) in the older population [17].

Mitochondrial oxidative stress

Mitochondrial overproduction of ROS likely contributes to cellular senescence [12]. This process ultimately leads to formation of the highly reactive products O₂⁻ or H₂O₂, whose accumulation and diffusion fosters senescence, DNA mutations, inflammation, and multiple cell death pathways [19]. The mitochondrial adaptor p66Shc gained increasing attention due to its pivotal role in ROS generation and cellular apoptosis. Cells lacking the p66Shc gene have reduced intracellular free radicals, and mice lacking p66Shc exposed to high oxidative stress have diminished systemic and intracellular ROS. Additionally, genetic deletion of p66Shc in the mouse extended lifespan by 30%. Age-dependent alteration of p66Shc signaling profoundly affects CV homeostasis. Indeed, deletion of p66Shc in mice protects from systemic and cerebral age-dependent endothelial dysfunction by virtue of decreased ROS production and conserved NO bioavailability [13]. Our own recent work also underscored the relevance of this gene in the pathogenesis of stroke. In fact, p66Shc-deficient mice display decreased ROS production in the brain,

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and have reduced stroke size following ischemia-reperfusion brain injury. We further demonstrated that even post-ischemic in vivo silencing of p66Shc prevents ischemia-reperfusion brain injury in mice, mainly through preservation of blood-brain barrier integrity. The observation that p66Shc expression increases significantly in stroke patients and correlates with neurological deficits supports the clinical relevance of these experimental findings. Expression of p66Shc also increases in peripheral blood mononuclear cells (PBMCs) of patients with acute coronary syndrome and type 2 diabetes. The activation of this protein by several CV risk factors, such as hyperglycemia, oxidized low-density lipoprotein, smoking, and hypertension, further supports its contribution to clinical CVD. Taken together, experimental and clinical data strongly indicate p66Shc as a potential therapeutic target in the setting of age-related CVD [10]. The Activated Protein-1 (AP-1) transcription factor JunD has emerged as a mediator of oxidative stress in aging. Dimeric complexes from 3 main families of DNA-binding proteins (Jun, Fos, and ATF/CREB) assemble to form AP-1 transcription factors with activities that depend critically on their specific components and the cellular microenvironment [12]. JunD regulates cell growth and survival, and protects cells against oxidative stress by modulating genes involved in antioxidant defense and ROS production [4]. We recently reported that JunD falls during aging both in the mouse aorta and in PBMCs from old as compared with young, healthy humans. Young mice lacking JunD display premature endothelial dysfunction and vascular senescence similar to aged wild-type mice. Aortas from JunD^{-/-} mice have augmentation of the aging markers p53 and p16INK4a,

reduced telomerase activity, and mitochondrial DNA damage. By contrast, in vivo overexpression of JunD rescues vascular aging features in old mice [30]. Mechanistic experiments revealed that age-associated reductions in JunD cause an imbalance between oxidant (NADPH oxidase) and scavenger enzymes (namely, manganese superoxide dismutase and aldehyde dehydrogenase 2), leading to early redox changes, mitochondrial dysfunction, and vascular senescence [32]. In accord with our findings, lack of JunD promotes pressure overload-induced apoptosis of myocytes, hypertrophic growth, and angiogenesis in the heart. Ongoing screening of chemical libraries aim to identify compounds capable of restoring JunD activity in the vasculature and the heart [15]. The family of nicotinamide adenine dinucleotide-dependent proteins termed sirtuins have an established role in human aging [40]. A recent study found that endogenous SIRT1 expression in VSMCs correlated inversely with donor age. Age-related loss of SIRT1 correlated with functional deficits, diminished stress response, reduced capacity for migration/proliferation, and increased senescence. Moreover, activation of SIRT1 may promote preservation of endothelial cell function during aging. Hypercholesterolemic mice with endothelial-specific SIRT1 overexpression or those exposed chronically to a SIRT1 activator exhibit attenuated atherogenesis, whereas reduced SIRT1 activity results in greater foam cell formation and atherosclerosis. The observation that immunosuppressant drugs (i.e., sirolimus and everolimus) cause endothelial senescence via SIRT1 inhibition supports these results. SIRT1 blockade also impairs eNOS functionality, whereas its activation improves endothelial NO availability [24]. Moreover,

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microRNA-217, an endogenous SIRT1 inhibitor, triggers endothelial senescence by suppressing SIRT1-dependent eNOS functionality. Recent work identified SIRT1 as a master regulator of p66Shc transcription, controlling acetylation of histone H3 bound to the p66Shc promoter. Impaired SIRT1 activity also favors acetylation of NF- κ B p65, leading to its nuclear translocation and transcription of inflammatory genes, as described earlier [23]. Moreover, SIRT1 represses detrimental pathways of arterial aging, such as Forkhead box O (FOXO) 1, 3, and 4, thus preventing DNA damage, cell cycle arrest, and oxidative stress [16]. SIRT1 deacetylates LKB1, leading to activation of the final effector enzyme 5' adenosine monophosphate-activated protein kinase, a central energy regulator involved in glucose homeostasis, maintenance of cellular adenosine triphosphate levels, and endothelial integrity via regulation of eNOS activity and autophagy [20].

Genomic instability

Accumulation of genetic damage through the course of life likely contributes importantly to aging (Central Illustration). Genome alterations fall into 3 main categories: 1) chemical damage to genomic DNA; 2) mutations (e.g., addition, deletion, or substitution of bits of genetic code); and 3) epigenetic alterations, which modify gene activity without affecting DNA sequence. To cope with genetic lesions, organisms have evolved highly proficient DNA repair systems that can, in most cases, restore the correct base pair sequence. Defects in DNA repair nonetheless occur, and can contribute to cellular senescence and organ dysfunction. Genomic instability particularly affects the CV system. Hutchinson-Gilford progeria syndrome, characterized by massive nuclear DNA damage, associates with premature atherosclerosis and CVD, which lead to

fatal MI or stroke by an average age of 13 years. Similarly, mice with genomic instability resulting from defective nucleotide excision repair genes ERCC1 and XPD recapitulate aging features, such as endothelial cell senescence, vascular stiffness, and hypertension, at a very young age. CV aging in this setting results mostly from eNOS and sirtuin deregulation, as well as augmented NADPH oxidase [35]. Beyond genetic diseases, a growing body of evidence indicates that sporadic genomic mutations accumulated across the lifetime represent a major underpinning of CVD. Several studies have shown the presence of DNA damage in both circulating cells of patients with atherosclerosis and in the plaques themselves. PBMCs from patients with CHD have chromosomal damage and mitochondrial DNA deletions that correlate with disease severity [25]. Similarly, data from the AortaGen Consortium showed that genetic variation in the nucleotide excision repair components (namely, a single-nucleotide polymorphism [rs2029298] in the promoter region of the DNA damage-binding protein 2 [DDB2] gene) associated strongly with carotid-femoral pulse wave velocity. Genomic instability in senescent VSMCs increases phosphodiesterase type 1 (PDE1) expression, with subsequent impairment of NO/cyclic guanosine monophosphate signaling and endothelial dysfunction. Human genetic studies consistently reveal significant associations of PDE1A single-nucleotide polymorphisms with diastolic blood pressure and carotid intima-media thickness [23]. Overall, extensive evidence shows that genomic damage accompanies CV aging. With age, humans can accumulate somatic mutations that give rise to hematopoietic clones associated not only with myelodysplastic syndromes

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and hematologic malignancies, but surprisingly, even more strongly with CV risk [1]. Future research in this area should unveil new interventions aimed at preserving genome stability to alleviate age-related CVD.

Chromatin modifications

Although many studies have focused on the genes that influence aging, nongenomic regulation of aging has gained increasing attention. Growing evidence suggests that epigenetic modifications can derail transcriptional programs implicated in oxidative stress, inflammation, angiogenesis, and cellular metabolism, thus fostering maladaptive pathways and features of vascular aging (Central Illustration). Epigenetic modifications acquired during life appear durable and relatively stable, thus providing a molecular framework through which the environment interacts with the genome to alter gene expression. Indeed, epigenetic modifications caused by environmental stimuli can be inherited, thus contributing to early senescent traits and CVD in young adults [18]. Chromatin modifications include DNA methylation and post-translational histone modifications (Central Illustration). DNA methylation, which involves the addition of a methyl group to DNA nucleotides, represses gene transcription by affecting chromatin accessibility to the transcriptional machinery. DNA methylation progressively decreases with age in mice and humans, whereas the rate of demethylation associates inversely with age.

Clinical Aspects of CVD in Elderly Patients

A number of age-related conditions present particular challenges to the clinical care of our cardiovascular (CV) patients. The accumulation of elderly individuals in our population underscores

the growing importance of CV aging to practitioners [33].

Systolic hypertension and widened pulse pressure

With aging, the aorta stiffens due to increased collagen and decreased elastin. Augmented transforming growth factor (TGF)- β activity favors the accumulation of collagen in the aortic wall. The activity of various elastases, including matrix metalloproteinases (MMPs), such as MMP-9 and MMP-12, as well as overexpression of the cysteine proteinases cathepsins S, K, and L, and the serine proteinase neutrophil elastase, elaborated by inflammatory cells, can all contribute to depletion of elastin [37]. These alterations in the aorta's extracellular matrix contribute importantly to its loss of distensibility. This increased stiffness raises reflected waves and elevates systolic pressure. Yet diastolic pressure tends to decline with age. As aortic pulse wave velocity increases, pulse pressure rises. Indeed, pulse pressure is an independent risk factor for CV events. Isolated systolic hypertension accounts for the majority of uncontrolled hypertension in Americans over 50 years of age. The fall in diastolic pressure decreases the drive for coronary perfusion that occurs primarily during diastole, favoring the development of myocardial ischemia. The increased systolic pressure with age increases left ventricular (LV) afterload, a major determinant of myocardial oxygen requirements. Chronic exposure to increased systolic pressure leads to LV hypertrophy, causing a further rise in myocardial oxygen demand. Mediators, such as TGF- β , angiotensin II, and the mineralocorticoid aldosterone, contribute mechanistically to hypertrophy and fibrosis in the pressure-overloaded LV. Thus, the systolic hypertension and decreased diastolic pressure associated

with aging yield a “perfect storm” of decreased oxygen supply in the face of augmented oxygen demand. As coronary atherosclerosis also advances with age, this additional limitation to oxygen supply often compounds the increased oxygen demand typically encountered in the aging CV system. In addition to altered large artery function, chronic hypertension promotes remodeling of the myocardial microvasculature [30]. Thickening of the tunica media of myocardial arterioles can further impede LV perfusion and impair vasomotion. These consequences of the increased systolic and decreased diastolic pressure that typically accompany aging conspire to cause myocardial ischemia. The regulation of arteriolar remodeling in the myocardium subjected to increased systolic and decreased diastolic pressure likely involves the same pathways implicated in generation of aortic stiffness. We lack sufficient understanding of the primary age-related triggers for these pathophysiological processes that contribute enormously to CV complications in the aging population [16]. Fortunately, some interventions can improve outcomes in patients with isolated systolic hypertension. The SHEP (Systolic Hypertension in the Elderly), Syst-Eur (Systolic Hypertension in Europe), Syst-China (Systolic

Hypertension in China), and other studies offer a rich database affirming the ability of pharmacological treatment of individuals in their 60s or 70s to reduce substantially stroke and total mortality, with lesser benefit for ischemic cardiac events [16]. Avoiding excessive sodium intake may provide an additional, nonpharmacological intervention for control of hypertension in older individuals [18]. Some have raised concerns regarding the safety of aggressive lowering of blood pressure in elderly patients, particularly those with concomitant coronary artery disease. Indeed, a J-shaped curve relating CV outcomes to blood pressure may pertain to this population. Yet the HYVET (Hypertension in the Very Elderly Trial) and SPRINT (Systolic Blood Pressure Intervention Trial) studies confirmed the relative safety and efficacy of antihypertensive treatment in the older population, although recent data suggest maintaining diastolic pressure above 70 mm Hg in those with established coronary artery disease. Clinicians should tailor the aggressiveness of antihypertensive treatment of geriatric patients on an individualized basis, depending on the status of the coronary arteries, frailty, the integrity of autonomic function, and other variables [13].

CONCLUSION

Cardiovascular disease (CVD) is a major health concern in the aging population. While age is an independent risk factor for CVD, other additional risk factors that are closely associated with advanced age, have been shown to compound these risks, including frailty, obesity, and diabetes. CVD risk factors are becoming

increasing common in our rural communities. Of all the cardiovascular risk factors commonly assessed, hypertension and obesity are commoner in the rural community. The consequences of these risk factors in the face of low awareness call for greater public health awareness campaigns.

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