ADVANCES IN CELL AGING AND GERONTOLOGY
VOLUME 11

# Mechanisms of Cardiovascular Aging

Tory Hagen
*editor*


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# Mechanisms of Cardiovascular Aging

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ADVANCES IN CELL AGING AND GERONTOLOGY

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# Mechanisms of Cardiovascular Aging

## PREFACE

During the last fifty years there has been a marked increase in mean human lifespan, largely due to the conquering of many pathogen-borne diseases, better prenatal care and improved clinical management of chronic diseases. Aside from accidents and rare inherited disorders, relatively few deaths occur before the age of 65 in developed countries. While we are living longer, an increasing concern is that the quality of life, or healthspan, has not concomitantly increased along with lifespan. Age itself is the leading risk factor for cardiovascular diseases of all types; other chronic diseases such as cancer and senile dementias also markedly increase with age. The mechanisms underlying the aging process as well as that for age-related chronic diseases have been intensely studied; however, significant gaps in knowledge still remain. In particular, little is known about how the aging process affects disease progression and outcome. A case in point is cardiovascular diseases (CVD), which include loss of vasomotor function, athero- and arterio-sclerosis, hypertension, congestive heart failure and stroke. Together these pathologies comprise the leading causes of permanent disability, hospitalization and death for individuals over the age of 65 in the United States. Direct healthcare costs for congestive heart failure alone are currently estimated to exceed 18 billion dollars per annum and future costs will undoubtedly rise along with the aging of the "baby-boom" generation. Thus, there is a critical need to assess both the age-associated causes leading to CVD as well as determine the current state of knowledge on preventative regimens designed to slow or modulate disease progression. Much of the investigation in this important field is focused on the molecular and cellular basis of CVD, and this issue of Advances in Cell Aging and Gerontology provides a timely review of this field.

The book begins with a chapter by Wolk and Somers who eloquently overview both the mechanisms leading to phenotypic manifestations of cardiovascular diseases as well as features of the aging cardiovascular system that may predispose the elderly to risk for CVD. Both genetic and humoral factors associated with cardiac function and vessel compliance are concisely reviewed. This chapter serves as a springboard into others that provide in depth discussions of these topics. The book is divided into three general aspects, which discuss factors that contribute to 1) atherosclerosis; 2) vascular endothelial dysfunction/vessel compliance, and 3) oxidative stress and myocardial decay.

For atherosclerosis, the chapters by Yamashita and Krishnaswamy individually discuss how cholesterol and cytokines affect disease progression, respectively. Other chapters by Drs. Lüscher and Taddei explore endothelial dysfunction and subsequent loss of vasomotor tone. These authors place a particular emphasis on mechanisms contributing to loss of endothelial-derived nitric oxide signaling and its consequences for increased hypertension. The chapter by Fujishima further explores age-related alterations in vessel compliance that contribute to increased hypertension. Finally, Dr. Emily Wilson provides one of the only reviews available on how

aging affects the extracellular matrix and contributes to altered vascular smooth muscle function.

The contribution of oxidants to cardiovascular decay is also prominently featured. Dr. Charles Hoppel and coworkers review the role of mitochondrial decline and cardiovascular disease while Dr. St. Clair examines how superoxide/superoxide dismutase imbalance may significantly contribute to a number of cardiovascular pathologies of aging. Also included is an excellent chapter by Dr. Rifkind summarizing age-related changes in red blood cell physiology.

Additionally, a strength of this book is its discussions summarizing current thought on how diet may modulate cardiovascular decay. The chapter by Marco Cattaneo discusses the evidence that folate modulates homocysteine, thus lowering risk for atherosclerosis. May and Burk also examine how selenium, vitamin C and vitamin E contribute to cardiovascular health. These chapters are further augmented with two additional ones by the editors which review emerging findings suggesting that dietary antioxidants and caloric restriction may effectively slow or prevent disease progression during adult life.

Thus, this book concisely summarizes the current knowledge related to the major aspects contributing to cardiovascular dysfunction in the elderly as well as potential ways of maintaining or improving human cardiovascular healthspan. It is our hope that the information provided will not only act as a review of the current knowledge related to CVD and aging, but will also spur further research designed to improve quality of life in the elderly.

HAGEN
Editor

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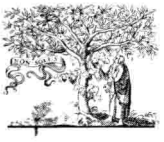

Advances in
Cell Aging and
Gerontology

# Overview of cardiovascular aging

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**Contents**



## Abbreviations

| | |
|---|---|
| PON1 | paraoxonase1 |
| APOE | apolipoprotein E |
| LDL | low-density lipoprotein |

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| | |
|---|---|
| TNFalpha | tumor necrosis factor alpha |
| IGF-I | insulin-like growth factor I |
| REM | rapid eye movement |
| HRV | heart rate variability |
| SERCA | sarcoplasmic reticulum $Ca^{+2}$ ATPase |
| NO | nitric oxide |
| EDHF | endothelium-derived hyperpolarizing factor |

## 1. Aging and the cardiovascular disease burden

Aging is widely conceived as a progressive loss of function, with increasing morbidity and mortality accompanying advancing age. The aging process may be defined by objective quantitative markers, such as functional and cognitive capacities and co-existent diseases. In this context, successful aging is thought of as a state of overall disease-free physical and mental well being. However, qualitative aspects of aging, although not well defined, are an important part of the aging process (von Faber et al., 2001). These markers (such as social contacts, motivations, expectations, the perception of fitness, etc.) reflect adaptation to objectively measured physical limitations inherent to old age. The focus of this overview will be on the mechanisms and characteristics of age-related cardiovascular impairment and the clinical consequences thereof, taking into consideration that cardiovascular aging is not always quantifiable, and is often inferred from surrogates such as reduced exercise tolerance and overt cardiac and vascular disease.

Over the past decades, we have observed a major demographic shift with a dramatic rise in the number and proportion of the elderly population. This trend is likely to continue, with the number of citizens over 65 years of age in the USA projected to be ~70 million by the year 2030 (Population Division, US Census Bureau). These increased numbers will result in a magnified cardiovascular disease burden in the aged population. Over 80% of coronary disease occurs in the elderly, the prevalence rising from 4.5% in 50-year-old men to almost 30% in people in their 70s (Kelly, 1997) (Fig. 1). The incidence of heart failure is 15% in people in their 80s (vs. 1–2% in 40- and 50-year-olds) and that of hypertension is over 30% in the aged population (Kelly, 1997). The morbidity and mortality of cardiovascular diseases in a burgeoning elderly population will impact substantially on health care resources. Hence there is a compelling need to understand better both the mechanisms of cardiovascular aging and the pathophysiological processes underlying cardiovascular diseases in the elderly.

Normal aging is characterized by specific age-related changes in cardiovascular structure and function. These changes may be accelerated by diseases such as hypertension, heart failure, atherosclerosis and diabetes, the prevalence of which are greater in the elderly population. The process of cardiovascular aging is often marked by age-related acute cardiovascular events (such as myocardial infarction or stroke), which further affect the aging process. This overview will focus on the mechanisms and cardiovascular consequences of "normal" aging.

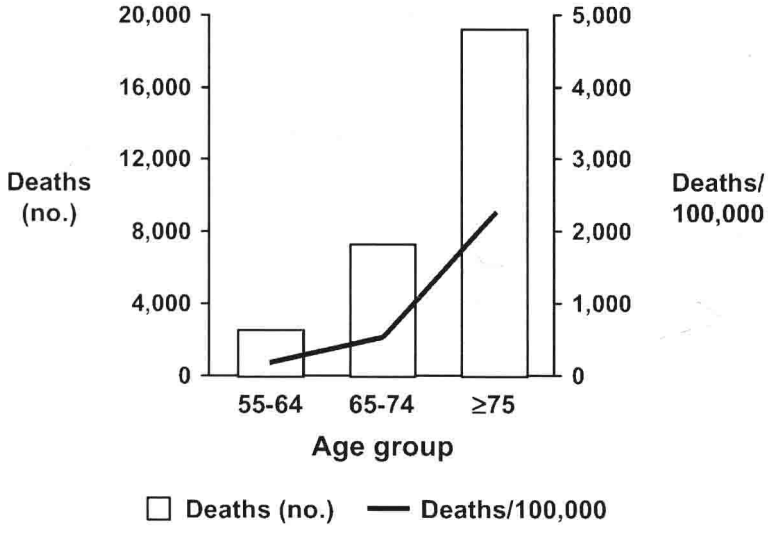


Fig. 1. Total number of deaths and mortality rate from coronary heart disease in various age groups (adapted with permission from Kelly, 1997).

## 2. Mechanisms affecting phenotypic manifestations of cardiovascular aging

The process of cardiovascular aging and the determinants thereof are complex. The phenotype is dynamic and governed by various age-related processes that directly affect cells and tissues of the cardiovascular system. In addition, aging of other non-cardiovascular systems (neuroendocrine, respiratory, etc.) can modify the process of cardiovascular aging and contribute to the overall clinical phenotype (Fig. 2). In this section, we will address the most important influences on the manifestations of cardiovascular aging, ranging from basic genetic and cellular mechanisms to behavioral determinants.

### 2.1. *Genetics*

Longevity is familial. Members of long-lived families tend to live longer. Experimental studies suggest that genes can determine life span, and that longevity is a polygenic trait. Although most studies used relatively simple, invertebrate, short-lived organisms, many human homologs of the longevity genes have been identified or are being sought. Some examples are *age-1*, *daf-2* or *clk* mutations in nematodes (Finch and Tanzi, 1997) or the yeast *RAS2* gene, which encodes a homolog of the mammalian signal transduction protein c-H-ras (Jazwinski, 1998). The common denominator for many mutations associated with a longer life span is increased resistance to stress. Unfortunately, these phenomena are difficult to study because of the complexity of gene–gene and gene–environment interactions during development. Therefore, there is still a large gap between identification of certain molecular or cellular defects and our understanding of their effects on human aging.

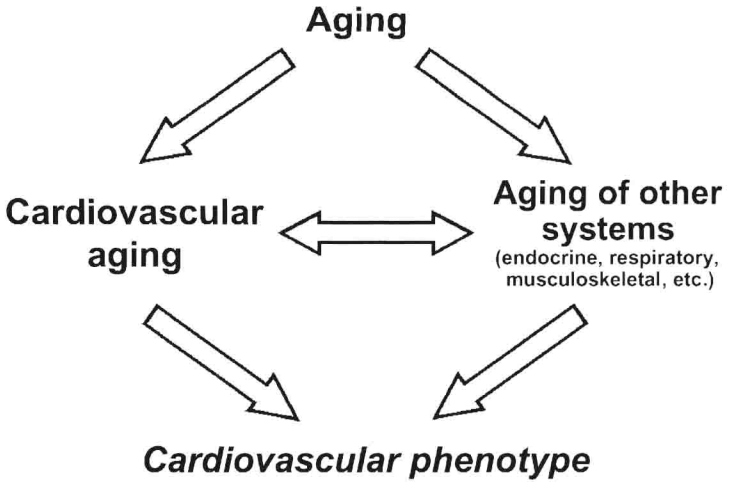


Fig. 2. Interactions between cardiovascular and non-cardiovascular systems in determining the phenotype of the aged cardiovascular system.

Although genetic factors have an influence on the aging process, it has been calculated that the heritability of the human life span is relatively modest, accounting for less than 35% of its variance (Herskind et al., 1996; Finch and Tanzi, 1997). On the other hand, rather than individual longevity genes, certain genetic variants can likely modify the aging process. These gene variants can alter some metabolic pathways, thereby influencing interactions with environmental factors that affect the process of aging. Variation in the serum paraoxonase1 (PON1) gene, the PON1-192 polymorphism, is such an example (Senti et al., 2001). PON1 activity decreases as a function of age only in subjects homozygous for the Q allele. In addition, advancing age increases the risk of myocardial infarction mainly in subjects with the low-activity QQ genotype (Senti et al., 2001).

The French centenarian study of human subjects has attracted great interest (Schachter et al., 1994). In this study, the apoE4 and apoE2 isoforms of the apolipoprotein E (APOE) gene were associated with shorter and longer life span, respectively. Similar results were obtained in a Finnish population (Louhija et al., 1994). The apoE4 allele of APOE is thought to promote premature atherosclerosis, whereas the apoE2 allele has been associated with types III and IV hyperlipidemia. In Italian centenarians, the frequency of apoB with low tandem repeats (apoB-VNTR) was found to be 50% of that in young controls (De Benedictis et al., 1997). Also, the high frequency of the HinfI(+/+) polymorphism of the apo A-IV gene (accompanied by low levels of low-density lipoprotein (LDL) cholesterol and higher concentrations of Lp(a)) has been associated with longevity (Pepe et al., 1998).

De Benedictis et al. (1999) compared mitochondrial DNA population pools between older and younger individuals. The frequency of a particular genotype (the J haplogroup) was higher in centenarians than in younger individuals, suggesting that

mitochondrial DNA inherited variability may play a role in aging and longevity. Also, centenarians appear to have a higher frequency of the 4G allele of the plasminogen activator inhibitor 1 gene (Mannucci et al., 1997), as well as certain alleles of the major histocompatibility complex (Caruso et al., 2000).

### 2.2. *Oxidative stress*

Free radicals and their biology represent one of the most popular theories to explain aging (Bunker, 1992; Muscari et al., 1996). Reactive oxygen species are constantly produced in biological systems as a normal part of aerobic metabolism. The body protects itself against oxidative damage by using various anti-oxidant, free radical scavenger systems (such as superoxide dismutase, catalase, and glutathione). Many reactive oxygen particles escape this defense system to damage critical targets such as DNA. Permanent damage is prevented by a process of constant and efficient repair. Fig. 3 illustrates the fine balance between free radical generating and scavenging systems in human physiology and pathophysiology.

There is evidence to suggest that the aging process is associated with an imbalance between production and removal of free radicals. The increase in oxidative stress may result both from an increase in the generation of free radicals and from a

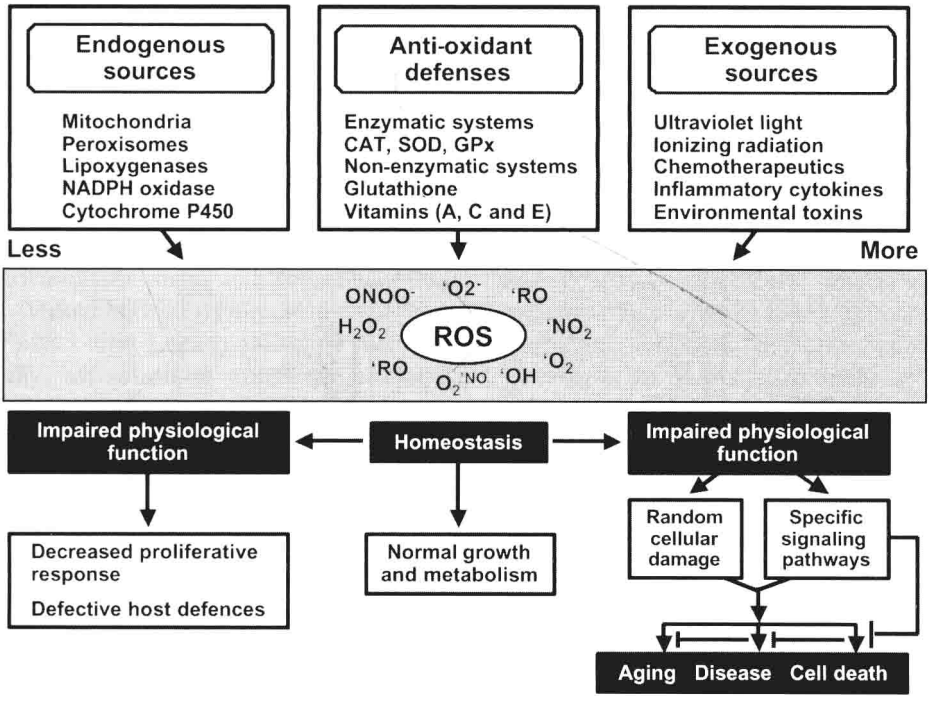


Fig. 3. The sources and biological responses to reactive oxygen species (ROS) (adapted with permission from Finkel and Holbrook, 2000).

decrease in the activity of anti-oxidative enzymes. Both these mechanisms play a role in the process of cardiovascular aging. Age-related mitochondrial damage increases the level of oxidative stress, which in turn further impairs mitochondrial function and, thereby, increases the amount of oxidative stress (a positive feed-back loop) (Cottrell and Turnbull, 2000; Van Remmen and Richardson, 2001). Toxins in the environment (including bacterial and viral infections) may activate a variety of free radical generating systems, leading to tissue damage. These detrimental effects are exacerbated by age-related changes in the immune system and augmented systemic inflammatory responses (Brod, 2000; Saito and Papaconstantinou, 2001).

On the other hand, free radical scavenger enzymes are depleted in the cardiovascular system at an older age. In a recent study in human subjects, the anti-oxidant protection of intracranial arteries (glutathione peroxidase, superoxide dismutase, catalase) markedly decreased with age (Fig. 4), coinciding with a rapid acceleration of atherogenesis in elderly subjects (D'Armiento et al., 2001). In another experimental study, cardiac concentrations of glutathione peroxidase and superoxide dismutase decreased significantly with age in the rat heart (Abete et al., 1999). In addition, older hearts were more susceptible to the detrimental effects of hydrogen peroxide. Taken together, these results suggest that aging hearts are intrinsically more susceptible to free radical-induced damage.

As a consequence of these processes, the amount of oxidative stress increases as an organism ages, allowing progressive cellular damage to occur (Sastre et al., 2000). Most cellular components are known to be susceptible to damage by free radicals. Oxidation of proteins and carbohydrates may result in fragmentation and cross-linking, with a subsequent loss of function (Bunker, 1992). Membrane lipid

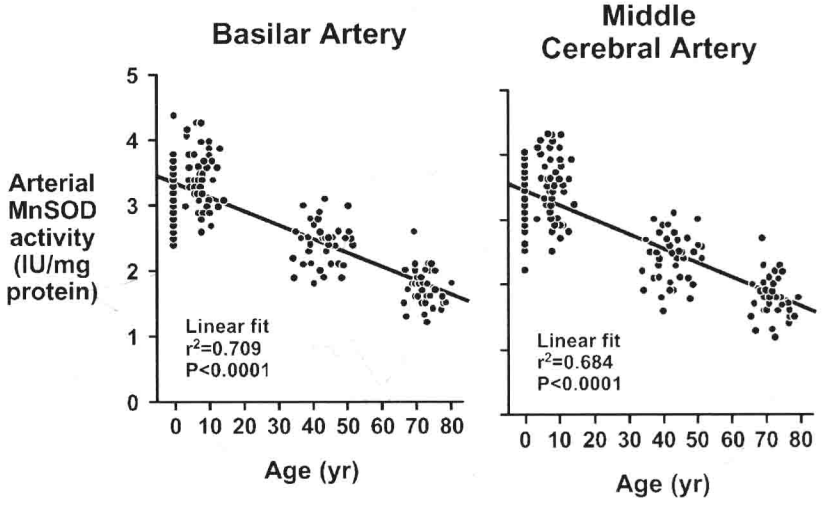


Fig. 4. Activity of the oxygen-radical scavenger manganese superoxide dismutase (Mn-SOD) in the human basilar and middle cerebral arteries (adapted with permission from D'Armiento et al., 2001).

peroxidation may cause a loss of integrity of plasma and intracellular organelle membranes. Free radical-induced DNA cross-linking leads to somatic mutations and the production of defective gene products. Importantly, all these changes are accompanied by an impairment of a variety of cellular repair systems. There is evidence to suggest that species with longer life spans have more efficient repair mechanisms.

An important factor involved in cessation of cell proliferation in normal human cells is the absence of telomerase activity with a consequent erosion of chromosomal telomeres (Bodnar et al., 1998). Oxidative stress increases the rate of telomere shortening (due to single strand DNA breaks) in human fibroblasts, and this effect can be reversed by free radical scavengers (Serra et al., 2000; von Zglinicki et al., 2000). Interestingly, the shorter telomere length has been associated with vascular aging and increased stiffness of large arteries in humans (Chang and Harley, 1995; Benetos et al., 2001). The syndrome of progeria (which accelerates some features of the aging process) is characterized, among other abnormalities, by telomere shortening and premature atherosclerosis (Martin and Oshima, 2000).

It has to be emphasized that, in spite of rapid progress in this area, it is still uncertain whether free radicals influence aging and life span directly or simply play a role in the development of associated cardiovascular diseases. These two processes are likely interrelated.

### 2.3. *Apoptosis*

Apoptosis is a complex and highly regulated process, whereby injured or aging cells are removed from the body. This programmed cell death goes on continuously throughout life and plays an important regulatory role in normal tissue development. Advanced age is associated with dysregulation of apoptosis, with changes in the levels of proteins and other factors that regulate this process (Joaquin and Gollapudi, 2001). This may lead to significant loss of cells in various tissues of the cardiovascular system, with consequent impairment of cardiac and vascular function.

Mitochondrial dysfunction may be an important trigger in age-related apoptosis (Pollack and Leeuwenburgh, 2001; Van Remmen and Richardson, 2001). Specifically, activation of apoptotic mechanisms is caused by mitochondrial oxidative stress, alterations in mitochondrial turnover and a decline in mitochondrial energy production. As discussed above, the amount of oxygen-free radicals and oxidative stress increase with aging.

A number of other factors are also involved in apoptosis. The sympathetic nervous system (noradrenaline), the renin-angiotensin system, cytokines (such as tumor necrosis factor alpha [TNFalpha]), insulin-like growth factor I (IGF-I), calcium overload, etc. may be implicated. Notably, all of these are affected by aging.

### 2.4. *Neuroendocrine aging*

Age-related changes in the neuroendocrine system can indirectly influence cardiovascular physiology as well as the process of aging itself, thereby affecting the

phenotypic features of the aging cardiovascular system (Fig. 2). Some of the most important aspects of this process are addressed below.

Impaired glucose tolerance is common in the aged population. Approximately 40% of individuals aged 65–74 years and 50% of those older than 80 years have impaired glucose tolerance or diabetes mellitus (Lamberts et al., 1997; Perry, 1999). This results from an impairment of insulin secretion by the pancreatic beta cells and from an increase in peripheral insulin resistance. The latter is related to poor diet, physical inactivity, age-related changes in body composition, as well as changes in growth hormone, cortisol, sex hormones and catecholamines (see below). Hyperglycemia leads to aging of the cardiovascular system via increased oxidative stress, potentiated DNA injury and non-enzymatic glycosylation of proteins (Monnier and Cerami, 1981; Fukagawa et al., 1999). In fact, tissue accumulation of glycosylation products occurs with aging even in the absence of hyperglycemia. The role of hyperglycemia in myocardial, microvascular and macrovascular pathology (Duckworth, 2001), and the relationship between insulin resistance and cardiovascular morbidity (Cefalu, 2001; Smiley et al., 2001) are well established.

Growth hormone (and hence IGF-I) secretion decreases with age (Lamberts et al., 1997; Perry, 1999). This decrease has been associated with reduced exercise capacity and increased cardiovascular and cerebrovascular risk, related to increased body fat, hyperlipidemia, structural and functional cardiac abnormalities (e.g. thinning of cardiac walls, reduced diastolic filling), as well as vascular changes (e.g. increased intima/media thickness and more frequent occurrence of atheromatous plaques) (Colao et al., 2001).

The secretion of sex hormones decreases or ceases with age, leading to abrupt menopause in women and more gradual andropause in men. In both sexes, changes in gonadal hormone concentrations affect cardiovascular physiology and confer an increased cardiovascular risk. This increased risk is related to dyslipidemia and atherosclerosis, changes in the regulation of vascular tone (including alterations in central sympathetic neural control) or abnormalities of ventricular relaxation.

Adrenal function is also affected by the aging process. Glucocorticoid secretion and plasma levels increase in older individuals (Van Cauter et al., 1996; Yen and Laughlin, 1998) and may contribute to the cardiovascular effects of aging. Baseline secretion of epinephrine from the adrenal medulla decreases markedly with age. Plasma epinephrine concentrations do not change, however, because of a reduction in epinephrine clearance (Seals and Esler, 2000). Although epinephrine secretion from the adrenal gland is reduced, the release of epinephrine from the heart may be increased (Seals and Esler, 2000).

Plasma norepinephrine (the main neurotransmitter released from post-ganglionic sympathetic nerve endings) also increases with aging (Seals and Esler, 2000). Although norepinephrine measurements in plasma can be affected by age-related changes in catecholamine clearance, measurements of muscle sympathetic nerve activity or tissue catecholamine spillover also confirm that there is an overall increase in the activity of the sympathetic nervous system in the healthy elderly (Fig. 5). This age-related increase in sympathetic activity may be caused by impairment of the arterial or cardiopulmonary baroreflex or by an elevated central sympathetic drive

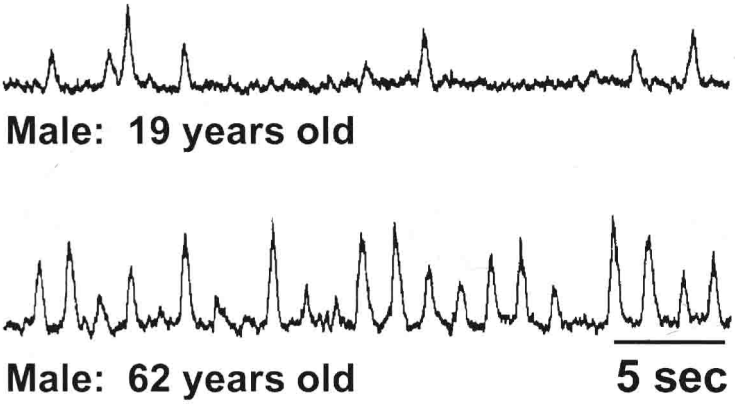


Fig. 5. Effects of age on muscle sympathetic nerve activity (MSNA).

(associated with increased forebrain noradrenergic activity) (Seals and Esler, 2000). Also, it has been suggested that the increase in sympathetic activity may be markedly accelerated during or after menopause (Matsukawa et al., 1998). Interestingly, although baseline serum concentrations of epinephrine and norepinephrine increase with aging, there may be a relative decrease in the release of stimulated catecholamines (Mazzeo et al., 1997; Kerckhoffs et al., 1998).

These autonomic effects of aging are accompanied by changes at the adrenoceptor level. Most notably, elevated catecholamine levels may lead to desensitization and decreased responsiveness of alpha- and beta-adrenoceptors (Kelly and O'Malley, 1984; Jones et al., 2001).

### 2.5. *Dyslipidemia*

Age-related increase in atherosclerosis (see below) may be explained in part by an increase in the plasma concentration of the atherogenic LDLs that occurs with increasing age (Green et al., 1985). The increase in LDL levels in the elderly is accentuated by reduced LDL clearance from the circulation, possibly due to a reduced hepatic LDL receptor expression and enhanced glycosylation of LDLs (Ericsson et al., 1991; Reaven et al., 1999), as well as a number of other factors, including those related to neuroendocrine abnormalities discussed earlier. The increase in LDL cholesterol with age is frequently associated with higher triglyceride levels and insulin resistance. Dyslipidemia is common in elderly people even when they remain active and consume a low fat Mediterranean diet.

Oxidative stress may also relate importantly to atherosclerosis. The oxidized form of LDL may affect endothelial function, alter vasomotor tone and initiate the cascade of atherosclerosis. As discussed, oxidative stress increases with age. Moreover the susceptibility of LDL to oxidation is enhanced in the elderly, with a consequent increase in the accumulation of oxidation products (including oxidized LDL) in the vascular wall (Reaven et al., 1999).