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Age-Related Changes in the Cardiovascular System

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INTRODUCTION

According to the US Census Bureau, the proportion of people in the United States over the age of 65 years is increasing. Current estimates indicate that approximately 30 to 35 million people are 65 years of age or older. In the year 2030, it is estimated that there will be approximately 55 to 60 million people in this age category. This aspect of our population has an important impact on the understanding of cardiovascular disease (CVD) because it is known that advancing age confers the major risk. The incidence and prevalence of CVD increases dramatically with advancing age in both men and women.

Aging is a complicated event, and most individuals consider the process a loss in general function that impairs ability. Epidemiological studies have demonstrated that the process of aging is the major risk factor

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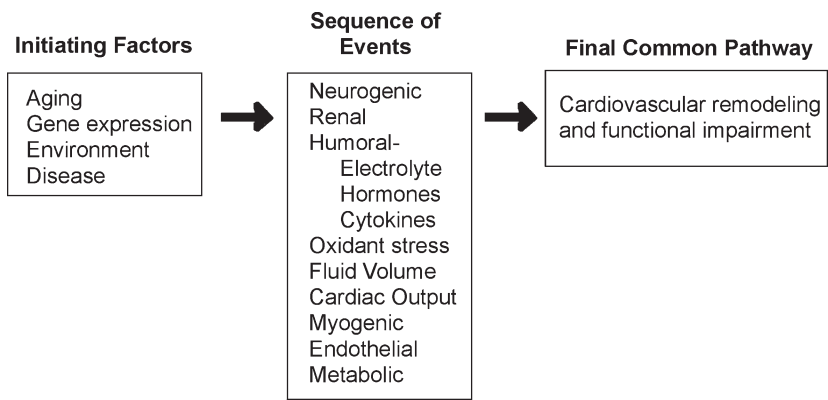


Fig. 1. Mechanisms of cardiovascular changes in aging. Aging is an independent risk factor for cardiovascular disease. The effects of aging are diverse and can be identified at the molecular, cellular, tissue, organ, and system levels as contributing to the altered function of the intact organism. The effects of aging act with other variables (initiating factors), such as gene expression, environment, and disease, to alter various organ systems. With respect to cardiovascular remodeling and impaired function in older individuals (final common pathway), it is known that the changes are modulated by other systems in the body (sequence of events).

for cardiovascular impairment (Fig. 1). The reason for this dominance is that aging occurs while an individual is responding to various stressors by changing patterns of gene expression (genetic traits) on a background of environmental factors and disease states.

The effects of aging are diverse and can be identified at the molecular, cellular, tissue, organ, and system levels as contributing to the altered function of the intact organism. With respect to the cardiovascular system (Fig. 1), it is known that the changes that occur with age are modulated by other systems in the body. For example, functional changes in the autonomic nervous system during aging affect the overall function of the cardiovascular system owing to the fact that the latter is controlled in large part by the former. Another example is that changes in the endocrine system can have an important impact on cardiovascular function. Testosterone levels decrease with age, and it is known that this hormone alters the distribution of contractile proteins in the heart. It should also be recognized that age-related changes in the cardiovascular system differ in male and female subjects.

This brief review summarizes several aspects of cardiovascular aging. The goal is to separate those changes in the heart and vasculature associated with aging in healthy individuals from those associated with disease

processes. Clearly, it is nearly impossible to dissociate all the components of aging from those that are characteristic of disease processes. Aging of the cardiovascular system is the platform from which CVDs are launched. Thus, the reader is directed to other reviews of these topics for a more complete treatment of the subject (*see refs. 1–16*). Other chapters within this volume also address adaptive and pathological changes in the cardiovascular system brought on by disease.

AGE-RELATED CHANGES IN VASCULAR FUNCTION

Increased Wall Thickening and Arterial Stiffening

Extensive evidence has demonstrated that wall thickening and dilation are the major structural changes that occur in the large elastic arteries during aging (Fig. 2; *see refs. 1, 4, 7, and 14* for review). The wall thickening involves both the tunica intima and the tunica media. As a consequence of this remodeling, there is a reduction in arterial compliance with an increase in vessel stiffness. Increased pulse wave velocity reflects this vascular stiffening because it is determined by the intrinsic stress/strain relationship of the vascular wall and by the mean arterial pressure.

Factors that contribute to the increased wall thickening and stiffening in aging include increased collagen, reduced elastin, and calcification. The amount of extracellular matrix increases and becomes particularly rich in glucosaminoglycans. These changes should not be considered “atherosclerotic” even though the factors are associated with this disease process (*17*). Age-dependent thickening of the arteries occurs in the absence of atherosclerosis and with aging in nonhuman primates and rodents. Thus, aging of the arteries is likely an adaptive mechanism to maintain conditions of blood flow and wall tension.

When the large arteries become stiffer, there is an increase in systolic arterial pressure, a decrease in diastolic pressure, and a widening of the pulse pressure (*see ref. 1* for review). This pattern of changes in the vasculature with respect to indices of blood pressure is much different from that seen in hypertension, for which there is an increase in total peripheral resistance. An increase in total peripheral resistance tends to increase both systolic and arterial pressure to a similar degree.

Endothelial Dysfunction

A portion of the stiffening of large arteries during the aging process can be attributed to a reduction in endothelial function, which normally opposes contraction of the underlying vascular smooth muscle (*5,18–23*). The principle finding is that with aging there is a reduction in the

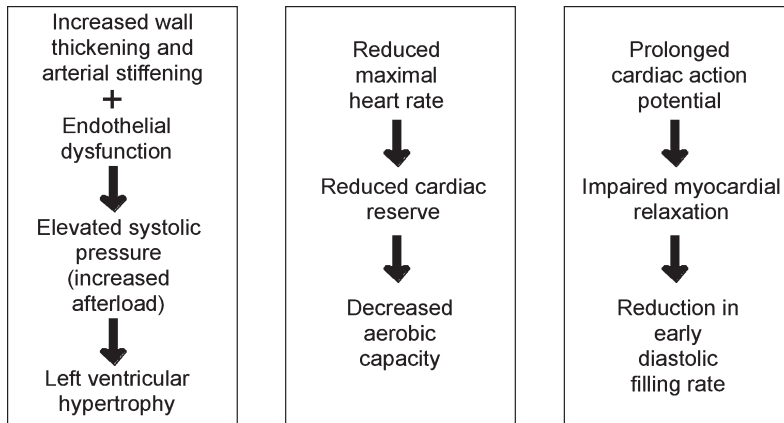


Fig. 2. Age-related changes in the cardiovascular system. The major age-related changes in the cardiovascular system are (a) arterial stiffening; (b) endothelial dysfunction, which promotes vasoconstriction; (c) elevated systolic blood pressure and increased pulse pressure; (d) increased left ventricular wall thickness; (e) reduced early diastolic filling of the ventricles; (f) impaired cardiac reserve; (g) alterations in heart rate rhythm; (h) prolonged cardiac action potential; and (i) a decline in renal function that contributes to improper maintenance of extracellular fluid volume and composition. These age-associated changes in cardiovascular function contribute to morbidity and mortality brought about by various disease states (i.e., hypertension, atherosclerosis, heart failure, etc.).

amount of nitric oxide (NO) produced by the endothelial cells. NO is produced from L-arginine by endothelial nitric oxide synthase (eNOS). This enzyme is constitutively active and regulated by the intracellular concentration of calcium (Ca^{2+}). eNOS is inhibited competitively by analogs of L-arginine such as *N* ω -nitro-L-arginine. Asymmetric dimethylarginine, an endogenous inhibitor of eNOS, is increased in older individuals and may therefore serve as an additional mechanism to lower NO production by the endothelium (19).

In addition to a reduction in the production of NO by the endothelial cells, it has been demonstrated that the bioavailability of NO is reduced with aging (5). This reduction is thought to be mainly the result of an increase in oxidative stress during aging. Presumably, superoxide anion quenches endothelium-derived NO through a chemical reaction to form peroxynitrite (5,15,22). Thus, vasoconstriction is promoted because the dilator activity of NO is removed. However, this is not the only mechanism by which superoxide acts because it is known to cause contraction of vascular smooth muscle in the absence of the endothelium or in the presence of inhibitors of nitric oxide synthase.

Once produced, endothelium-derived NO diffuses to the smooth muscle cells. NO binds to smooth muscle cell-soluble guanylate cyclase, leading to an increase in cyclic guanosine 3'5' monophosphate (cGMP) and the subsequent activation of cGMP-dependent protein kinase. NO/cGMP/cGMP-dependent protein kinase signaling has been proposed to decrease intracellular Ca^{2+} concentration via the inhibition of L-type Ca^{2+} channels and the activation of sarcoplasmic reticulum Ca^{2+} -ATPases, as well as induce cellular hyperpolarization through the activation of membrane K^{+} channels. NO has other actions, such as activation of ribosyl transferases and nitration of proteins, which could also contribute to inhibitory effects and vasodilation. Reductions in many of the components of these NO-dependent cell-signaling pathways have been observed in the vasculature of aging animals and humans.

The barrier function of the endothelium also changes during the aging process (5). Compared to vessels of young animals, the permeability of the endothelium is increased in older animals.

AGE-RELATED CHANGES IN CARDIAC FUNCTION

Heart Rate and Cardiac Output

Resting heart rate does not change dramatically with age (*see* ref. 2 for review). In the supine position at rest, heart rate in older men does not differ from that in younger men. In changing from the supine to the sitting position, heart rate increases; the magnitude of this change is somewhat less in older men.

During exercise, the maximal heart rate attainable is lower in older individuals than in younger individuals. This inability to raise the heart rate to high levels during exercise is reflected in lower cardiac output reserve in older subjects and contributes to declining aerobic capacity in advancing age. Other factors that contribute to the reduction in aerobic capacity in older individuals include the following: (a) an increase in body fat, (b) a reduction in muscle mass, and (c) impaired oxygen extraction.

It should also be noted that a considerable portion of the diminished hemodynamic response during vigorous exercise is related to the inability of the sympathetic nervous system to provide adequate modulation of cardiac output. As noted by Lakatta and Sollott (4), the reduced β -adrenergic modulation of cardiac function is one of the best-characterized changes that occur in the cardiovascular system during aging, and it has been characterized at the molecular, cellular, organ, and system levels with integration into the intact organism.

The variability in heart rate (beat-to-beat fluctuation) declines during aging (*see refs. 2 and 14 for review*). This alteration in heart rhythm is a reflection of dysregulation of the autonomic nervous system commonly found in older individuals. Based on the accumulated evidence, it is widely believed that the dramatic change in cardiac function attributable to altered heart rhythm places the aging population at increased risk of morbidity and mortality.

Left Ventricular Wall Function

The stiffening of arteries during aging affects cardiac structure and function (*see refs. 2 and 14 for review*). As noted in the section “Increased Wall Thickening and Arterial Stiffening,” systolic blood pressure increases with age. This increase in afterload contributes to a moderate increase in left ventricular mass observed in many individuals between the third and ninth decades of life. A large portion of this hypertrophy is caused by an enlargement of cardiac myocytes because of the addition of sarcomeres. There is a decrease in myocyte number in the aging myocardium, but the mechanism for this myocyte loss is unclear (24).

Left ventricular filling during the early phase of diastole slows after the age of 20 years, and by the 80 years of age, the rate is approximately 50% of its peak value observed in early life (*see refs. 2 and 14 for review*). Accumulation of fibrous material in the left ventricle and slowing in Ca^{2+} activation from the preceding systole are possible mechanisms contributing to this reduced early diastolic filling rate. Regardless, adequate filling of the left ventricle occurs in late diastole because of an increase in atrial contraction. Thus, the atria are often hypertrophied in older individuals because of this augmented atrial contraction. Left ventricular systolic function is preserved during aging.

Myocardial Contraction

Contraction of the cardiac myocyte is initiated by an action potential that causes an increase in intracellular Ca^{2+} concentration to activate interaction between contractile proteins. The activator Ca^{2+} comes from several sources, including a transmembrane flux of the cation and a release from storage sites inside the cell (sarcoplasmic reticulum). During relaxation of the cardiac myocyte, the intracellular concentration of Ca^{2+} is reduced by pumping it back into the sarcoplasmic reticulum and by extrusion from the cell (sodium–calcium exchange, plasma membrane Ca^{2+} ATPase).

Excitation–contraction coupling in the cardiac myocyte changes during aging (2,25–28). The action potential becomes prolonged, and the cytosolic Ca^{2+} transient after excitation is increased, leading to pro-

longed contraction. The prolonged action potential is caused by slower inactivation of L-type Ca^{2+} current and reduction in outwardly directed potassium currents (26,27). The prolonged Ca^{2+} transient is caused partly by a reduction in uptake of the cation by the sarcoplasmic reticulum (2). There is also an increase in the transcripts for the sodium–calcium exchanger, which serves to extrude calcium from the cell. These age-associated changes in Ca^{2+} movements impair myocardial relaxation and contribute to the aforementioned reduction in early diastolic filling rate characterizing the aging heart.

KIDNEY FUNCTION AND THE CONTROL OF EXTRACELLULAR FLUID VOLUME IN AGING

Normal aging is accompanied by alterations in many aspects of renal morphology and function in both humans and animals (29–32). Whereas the prevalence of declining renal function in aging is recognized, the mechanisms responsible for the decline remain obscure and highly controversial. Renal mass decreases by 20 to 25% between the ages of 30 and 80 years (30). Glomerular filtration rate declines by approximately 10% each decade after 30 years of age and is accompanied by an increase in renal vascular resistance and a decrease in glomerular number. The decline in glomerular filtration rate and glomerular number stimulates a compensatory increase in the size of the remaining glomeruli (30,31, 33,34). Age-related sclerosis of the remaining glomeruli, thickening of basement membrane, accumulation of extracellular matrix, expansion of the glomerular mesangium, and alteration of tubular epithelial transporters are also commonly reported (35). These factors contribute to an overall decline in glomerular filtration rate and impairment of tubular reabsorptive function that compromises the ability of the kidneys to maintain proper extracellular fluid volume and composition. This progressive loss of renal functional reserve develops over decades and may be unnoticed until the subject is faced with significant cardiovascular or extracellular fluid challenge (31). The addition of other cardiovascular risk factors, such as salt sensitivity, hypertension, and diabetes, accelerates the loss of functioning nephrons and increases the susceptibility of elderly individuals to end-stage renal injury (36).

Regulation of glomerular perfusion, glomerular capillary pressure, medullary blood flow, and renal hemodynamics all occur through adjustments in renal microvascular resistance (37). Resistance changes are controlled by intrinsic mechanisms such as autoregulation and locally released autocrine and paracrine factors as well as through extrinsic mechanisms, which include sympathetic nerves or circulating vasoac-

tive agents (37). In normal kidneys, locally produced NO, adenosine, prostaglandins, endothelin, angiotensin II, and myriad tubular and endothelial factors combine to modulate intrarenal vascular function. Studies have shown that the influence of these regulatory systems on renal vascular function is reduced in aged subjects, possibly exposing glomeruli to inappropriately high blood pressures and promoting glomerular and vascular inflammation and sclerosis (38,39). Thus, age-related impairment of renal vascular control can account for some of the reduction in glomerular number and glomerular filtration rate known to define the senescent kidney.

Kidney-related volume and electrolyte disturbances also represent a significant clinical challenge in elderly individuals (30,31,40). The genesis of such disturbances remains poorly understood, but includes both renal tubular and neurological mechanisms. Renal tubular function is reduced in elderly subjects, leading to a reduced ability to excrete a sodium or an acid load and a compromised ability to maintain potassium balance. As the excretory capacity of the kidney declines, the ability of the kidney to eliminate drug metabolites also declines. Accordingly, therapeutic regimens need to be adjusted to account for reduced renal clearance to prevent drug toxicity or overdose (35).

Paradoxically, the aged kidney also exhibits reduced urinary-concentrating ability, leading to polyuria and reduced ability to conserve filtered sodium (30,31,40). This is coupled with a reduced thirst sensation, leading to overall volume contraction and susceptibility to hyponatremia, hyperkalemia, and acidosis. Thus, cardiovascular management of elderly individuals can be complicated by conditions of volume and electrolyte overload or volume and electrolyte deficit. Diagnosis and treatment of such conditions certainly require consideration of both renal and cardiovascular issues to correct clinical and physiological abnormalities safely in elderly patients.

ETIOLOGY OF AGING IN THE CARDIOVASCULAR SYSTEM

The mechanistic explanation for aging of the cardiovascular system is an area of intense study. Most investigators believe that aging is the result of cumulative damage brought on by a variety of insults. Oxidative stress, nonenzymatic glycation, and changes in gene expression influence aging of the cardiovascular system (2,5,41,42). Thus, it is often stated that aging of the cardiovascular system resembles the morphological and biochemical changes seen in inflammation. This is reasonable because the two processes share many common features, such as alterations in reactive oxygen species and cytokine expression.

Many of the changes in the aging cardiovascular system are not fixed. Indeed, endurance training has a beneficial effect on maximum oxygen consumption, diastolic filling, myocardial relaxation, and vascular stiffening (43–45).

SUMMARY

This brief review provides an overview of the major age-related changes in the cardiovascular system. These changes include the following:

- arterial stiffening
- endothelial dysfunction promoting vasoconstriction
- elevated systolic blood pressure and increased pulse pressure
- increased left ventricular wall thickness
- reduced early diastolic filling
- impaired cardiac reserve
- alterations in heart rate rhythm
- prolonged cardiac action potential
- a decline in renal function that contributes to improper maintenance of extracellular fluid volume and composition.

These age-associated changes in cardiovascular function precede clinical disease (hypertension, stroke, atherosclerosis, etc.).

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REFERENCES

1. Lakatta EG, Levy D. Arterial and cardiac imaging: major shareholders in cardiovascular disease enterprises. Part I: Aging arteries: A “set up” for vascular disease. *Circulation* 2003;107:139–146.
2. Lakatta EG, Levy D. Arterial and cardiac imaging: major shareholders in cardiovascular disease enterprises. Part II: The aging heart in health: links to heart disease. *Circulation* 2003;107:346–354.
3. Lakatta EG. Arterial and cardiac imaging: major shareholders in cardiovascular disease enterprises. Part III: cellular and molecular clues to heart and arterial aging. *Circulation* 2003;107:490–497.
4. Lakatta EG, Sollott SJ. Perspectives on mammalian cardiovascular aging: humans to molecules. *Comp Biochem Physiol A Mol Integr Physiol* 2002;132:699–721.
5. Yu BP, Chung HY. Oxidative stress and vascular aging. *Diabetes Res Clin Pract* 2001;54(suppl 2):S73–S80.
6. Isoyama S. Age-related changes before and after imposition of hemodynamic stress in the mammalian heart. *Life Sci* 1996;58:1601–1614.
7. Ferrari AU. Modifications of the cardiovascular system with aging. *Am J Geriatr Cardiol* 2002;11:30–33.

8. Pugh KG, Wei JY. Clinical implications of physiological changes in the aging heart. *Drugs Aging* 2001;18:263–276.
9. Lakatta EG. Cardiovascular aging research: the next horizons. *J Am Geriatr Soc* 1999;47:613–625.
10. Franklin SS, Gustin W 4th, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997;96:308–315.
11. Aviv A. Salt consumption, reactive oxygen species and cardiovascular aging: a hypothetical link. *J Hypertens* 2002;20:555–559.
12. Kass DA. Age-related changes in ventricular-arterial coupling: pathophysiologic implications. *Heart Fail Rev* 2002;7:51–62.
13. Schutzer WE, Mader SL. Age-related changes in vascular adrenergic signaling: clinical and mechanistic implications. *Ageing Res Rev* 2003;2:169–90.
14. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. *Physiol Rev* 1993;73:413–467.
15. Matz RL, Schott C, Stoclet JC, Andriantsitohaina R. Age-related endothelial dysfunction with respect to nitric oxide, endothelium-derived hyperpolarizing factor and cyclooxygenase products. *Physiol Res* 2000;49:11–18.
16. Lundberg MS, Crow MT. Age-related changes in the signaling and function of vascular smooth muscle cells. *Exp Gerontol* 1999;34:549–557.
17. Homma S, Hirose N, Ishida H, Ishii T, Araki G. Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. *Stroke* 2001;32:830–835.
18. Asai K, Kudej RK, Shen YT, et al. Peripheral vascular endothelial dysfunction and apoptosis in old monkeys. *Arterioscler Thromb Vasc Biol* 2000;20:1493–1499.
19. Challah M, Nadaud S, Philippe M, et al. Circulating and cellular markers of endothelial dysfunction with aging in rats. *Am J Physiol* 1997;273 (4Pt 2):H1941–H1948.
20. Cernadas MR, Sanchez de Miguel L, Garcia-Duran M, et al. Expression of constitutive and inducible nitric oxide synthases in the vascular wall of young and aging rats. *Circ Res* 1998;83:279–286.
21. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *J Am Coll Cardiol* 1994;24:471–476.
22. van der Loo B, Labugger R, Skepper JN, et al. Enhanced peroxynitrite formation is associated with vascular aging. *J Exp Med* 2000;192:1731–1744.
23. Chen J, Brodsky SV, Goligorsky DM, Hampel DJ, Li H, Gross SS, Goligorsky MS. Glycated collagen I induces premature senescence-like phenotypic changes in endothelial cells. *Circ Res* 2002;90:1290–1298.
24. Anversa P, Palackal T, Sonnenblick EH, Olivetti G, Meggs LG, Capasso JM. Myocyte cell loss and myocyte cellular hyperplasia in the hypertrophied aging rat heart. *Circ Res* 1990;67:871–885.
25. Orchard CH, Lakatta EG. Intracellular calcium transients and developed tensions in rat heart muscle. A mechanism for the negative interval-strength relationship. *J Gen Physiol* 1985;86:637–651.
26. Josephson IR, Guia A, Stern MD, Lakatta EG. Alterations in properties of L-type Ca channels in aging rat heart. *J Mol Cell Cardiol* 2002;34:297–308.
27. Walker KE, Lakatta EG, Houser SR. Age associated changes in membrane currents in rat ventricular myocytes. *Cardiovasc Res* 1993;27:1968–1977.
28. Janczewski AM, Spurgeon HA, Lakatta EG. Action potential prolongation in cardiac myocytes of old rats is an adaptation to sustain youthful intracellular Ca²⁺ regulation. *J Mol Cell Cardiol* 2002;34:641–648.

29. Baylis C, Corman B. The aging kidney: insights from experimental studies. *J Am Soc Nephrol* 1998;9:699–709.
30. Beck LH. Changes in renal function with aging. *Clin Geriatr Med* 1998;14:199–209.
31. Beck LH. The aging kidney: defending the delicate balance of fluid and electrolytes. *Geriatrics* 2000;55:26–32.
32. Herrera AH, Davidson RA. Renovascular disease in older adults. *Clin Geriatr Med* 1998;14:237–254.
33. Fliser D, Ritz E. Relationship between hypertension and renal function and its therapeutic implications in the elderly. *Gerontology* 1998;44:123–131.
34. Hill GS, Heudes D, Bariety J. Morphometric study of arterioles and glomeruli in the aging kidney suggests focal loss of autoregulation. *Kidney Int* 2003;63:1027–1036.
35. Muhlberg W, Platt D. Age-dependent changes of the kidneys: pharmacological implications. *Gerontology* 1999;45:243–253.
36. Ruilope LM. Prevalence of renal disease in elderly hypertensive patients with cardiovascular problems. *Coron Artery Dis* 1997;4:483–488.
37. Navar LG, Inscho EW, Majid SA, Imig JD, Harrison-Bernard LM, Mitchell KD. Paracrine regulation of the renal microcirculation. *Physiol Rev* 1996;76:425–536.
38. Ungar A, Castellani S, Di Serio C, et al. Changes in renal autacoids and hemodynamics associated with aging and isolated systolic hypertension. *Prostaglandins Other Lipid Mediat* 2000;62:117–133.
39. Drew B, Leeuwenburgh C. Aging and the role of reactive nitrogen species. *Ann NY Acad Sci* 2002;959:66–81.
40. Stout NR, Kenny RA, Baylis PH. A review of water balance in ageing in health and disease. *Gerontology* 1999;45:61–66.
41. Lucas D, Szweda LI. Cardiac reperfusion injury: aging, lipid peroxidation and mitochondrial dysfunction. *Proc Natl Acad Sci USA* 1998;95:510–514.
42. Barja G. Endogenous oxidative stress: relationship to aging, longevity and caloric restriction. *Ageing Res Rev* 2002;1:397–411.
43. Brenner DA, Apstein CS, Saupe KW. Exercise training attenuates age-associated diastolic dysfunction in rats. *Circulation* 2001;104:221–226.
44. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* 1993;88:1456–1462.
45. Tanaka H, DeSousa CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. *Arterioscler Thromb Vasc Biol* 1998;18:127–132.



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