Physiology of Aging

An overview of the changes in physiology one experiences in later life as they age.

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Objectives

- *Cardiovascular System*
- *Respiratory System*
- *Hematology*
- *Immunology*
- *Musculoskeletal*
- *Renal and Urinary Tract*
- *Nervous System*
- *Brain and Cognition*

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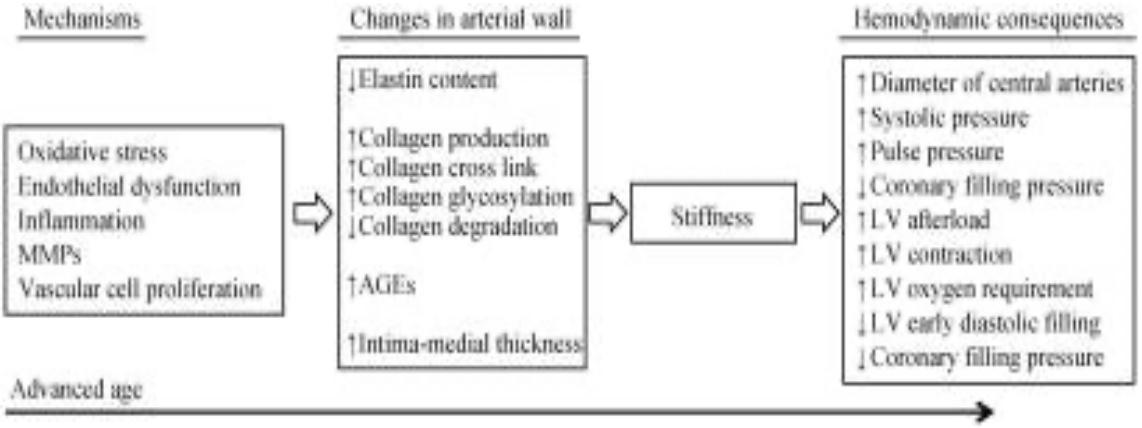
Cardiovascular System

INTRODUCTION

Cardiovascular disease increases with age. This may be due to prolonged exposure to risk factors such as hypertension, smoking and dyslipidemia. However, normal aging changes are defined through studies of people without hypertension and clinical cardiovascular disease. There is increasing evidence that the normal aging process causes changes in the structure and function of the heart and vasculature, independent of risk factors (1).

SUMMARY OF MOLECULAR MECHANISMS LEADING TO ARTERIAL STIFFNESS



AGEs: advanced glycation end products; LV: left ventricular; MMPs: matrix metalloproteases.

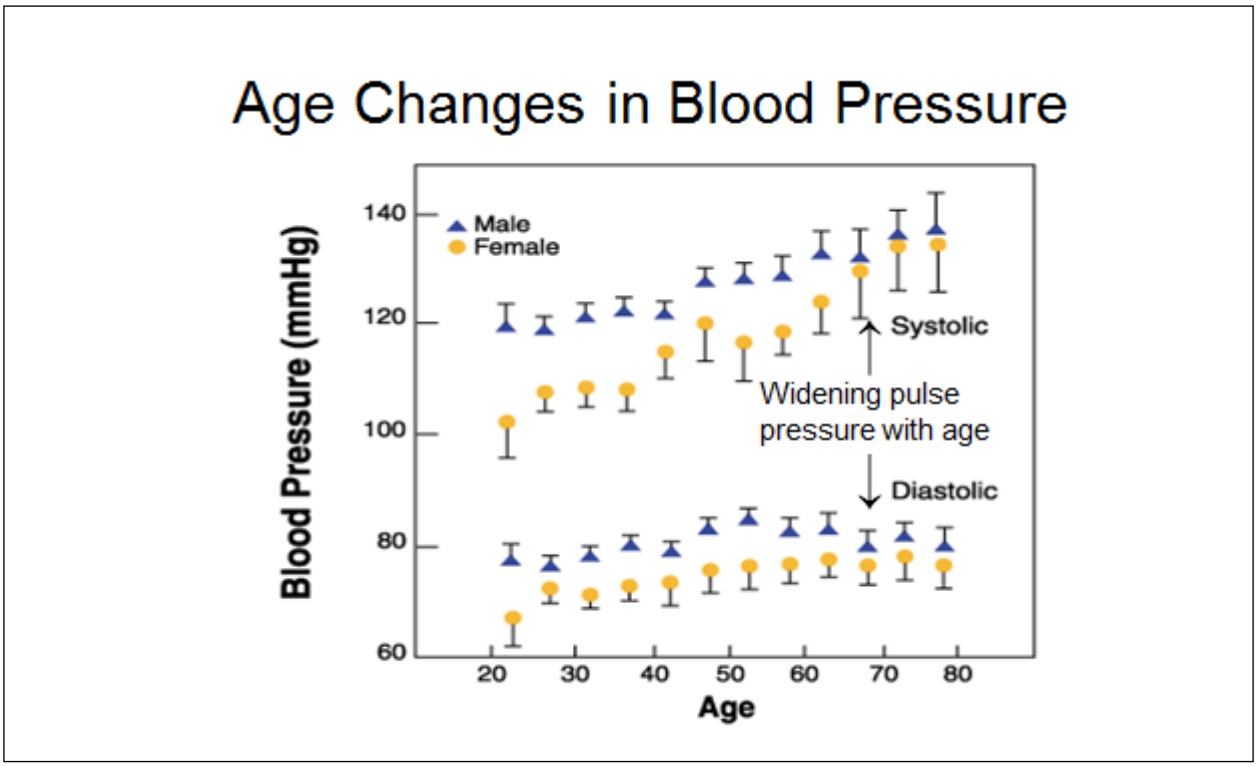
Older adults have reduced maximal function and less reserve capacity for stressful condition as compared with younger people. This is due to a combination of changes resulting in endothelial dysfunction, ↑ arterial stiffness, ↑ left ventricular (LV) stiffness, altered mechanism of left ventricle and arterial function due to ↑ stiffness, reduced baroreflex and autonomic reflexes, and degenerative changes of the conduction system (3).

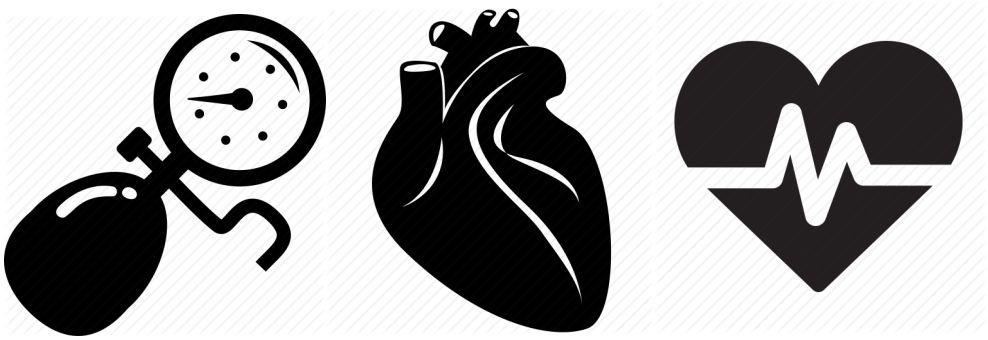
	STRUCTURAL CHANGES	FUNCTIONAL IMPLICATIONS

VASCULAR STRUCTURE	• Remodeling begins with microscopic changes in the vessel wall structure that are present even in early adulthood and increase with aging (2)
	  ○ ↑ reactive oxygen species (ROS) content, inflammatory changes, ↓ nitric oxide availability and endothelial dysfunction, producing a reversed stiffness gradient along the arterial branches
	  ○ Significant risk factor for atherosclerosis
	• Dilation of the centrally located, large elastic arteries → ↑ lumen size, length and wall thickness (mainly in intimal layer, rather than media) (2)
	  ○ ↑ collagen content and cross-linking → stiffening of subendothelium, more central artery than periphery (3)
	  ○ Calcification of media
	  ○ Because the aorta is fixed at both of its ends, length ↑ leads to tortuousity, ectasia and a shift in position to the right. Often seen on chest x-rays in the elderly
	  ○ Elastin content of vessel walls ↓ leading to fraying and fragmentation of elastin, potentially due to inappropriate activation of matrix metalloproteinases
	• Endothelium dependent relaxation is usually mediated by nitric oxide. With age, however, the endothelium's ability to produce nitric oxide is reduced at every level of the vasculature (3).
	  ○ Most likely due to less effective acetylcholine activity
	  ○ Also possible role of reduced levels of nitric oxide synthase and production of oxygen free radicals in aging cells (1)
		• ↓ response to blood flow caused by structural changes, ↑ the overall pulse wave velocity
		  ○ Associated with hypertension and other adverse cardiovascular events (1)
		• Stiffness of central arteries → lack of expansion with each contraction → stroke volume is transmitted in systole → systolic blood pressure ↑
		• ↑ arterial stiffness also causes small intravascular volume changes to produce large changes in blood pressure
		• Elastic recoil does not dissipate in diastole and therefore diastolic pressure ↓ → ↑ pulse pressure
		  ○ Widened pulse pressure is harmful to end organs and ↑ risk for kidney, heart disease, dementia and overall mortality (3)
		• ↓ endothelial production of nitric oxide leads to ↓ smooth muscle control → impaired blood vessel relaxation

	STRUCTURAL CHANGES	FUNCTIONAL IMPLICATIONS

HEART	• ↑ in fat deposition at the outer epicardial and pericardial level
	• Calcium deposition ↑ in certain areas
	• The atria size dilated with ↑ volume
	• Left ventricular wall thickness ↑
	• Coronary arteries more dilated and collaterals may also ↑ in number and size
	• Greater deposition of amyloid after age 90 but not commonly before 60; may also contribute to LV stiffness
	• Collagen and collagen cross-linking with adjacent fibers also increase by almost two-fold; can lead to interstitial fibrosis
	• Fatty infiltration and fibrosis → atrial septum thickens and less mobile with respiration (1)
	• ↓ elastin
	• ↑ fibroblasts, ↓ active heart cells
	• Sinoatrial node cells (normally act as the heart pacemaker) ↓ in number
	  ○ A-V node seems to have lesser cellular losses by comparison
	  ○ Remaining cardiac myocytes bigger and ↑ size variability → ↑ mechanical burden on heart.
	• Cardiac valves have ↑ collagen deposition degeneration, lipid accumulation and focal dystrophic calcification in the leaflets and annuli → higher circumference, annular dilatation
		• ↑ myocardial stiffness
		• ↓ ventricular compliance → impaired passive left ventricle filling (1)
		  ○ Left atrial dilation and hypertrophy.
		  ▪ More forceful atrial contraction helps late diastolic filling and compensates for reduced early filling of the ventricle due to its impaired relaxation
		  ▪ Atrial dilation generally does ↑ risk of fibrillation and other arrhythmias (4)
		  ○ Active filling from atrial contraction in late diastole can contribute up to 70% of LV end diastolic volume (3)
		  ▪ Loss of this atrial contraction due to conditions e.g. atrial fibrillation → ↓↓ diastolic volume and predispose to diastolic heart failure in the elderly
		• Cardiac valves may have trivial amount of valvular regurgitation
		• May be ↓ parasympathetic nervous system input and ↓ response to autonomic stimulation → ↓ heart rate variability; correlated with ↓ in physiologic reserve (2, 4).





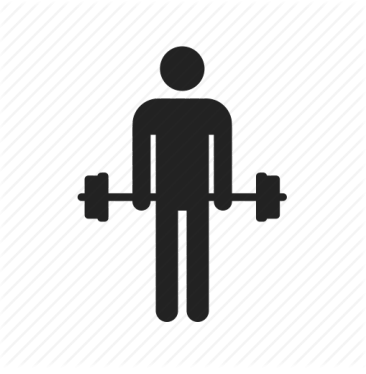
GENERALLY UNCHANGED IN NORMAL AGING

- Left ventricular systolic function, heart's ability to contract
- Stroke volume (volume of blood pumped from the ventricle with each beat) generally same or slightly higher
- Left ventricular ejection fraction (LVEF = ratio of the stroke volume to the volume of blood left in the ventricle at the end of diastole) (1).
- Resting heart rate, mediated by parasympethic nervous system (vs. intrinsic heart rate, related to sinus node function, ↓ by 5-6 beats/minute with each decade of age) (1)

THE AGING HEART WITH EXERCISE

- Diastolic function, particularly with exercise, is significantly impaired with age → up to 50% decrease in the rate of left ventricular filling in early diastole. Likely due to:
    - ↑ ventricular stiffness, ↓compliance and impaired passive filling of the ventricle.
    - Changes in myocyte function due to impaired uptake of intracellular calcium.
    - Greater vascular stiffness, higher mechanical load and prolonged time to contraction.
- When older persons change position from supine to seated, ability to ↑ heart rate is less, possibly related to sympathetic nervous system effects
- ↑ level of body fat, ↓ muscle mass and ↓ oxygen extraction → ↓ in aerobic capacity
- Maximum amount of oxygen that can be used during exercise, VO2max, starts ↓ing progressively in early adulthood independent of gender and body size.
    - Most likely due to ↓ maximum heart rate (↓ sensitivity to beta-adrenergic sympathetic stimulation, ↑ parasympathetic vagal tone, ↓ number of sinoatrial nodal pacemaker cells, ↓ sensitivity to catecholamines) → ↓ ardiac output + ↓ stroke volume (3, 4)
    - However, because there is an ↑ amount of blood in the ventricle at the end of diastole, there is a ↑ stretch on the heart → stronger contraction by the Frank Starling principle which helps to mitigate the changes in cardiovascular function.
    - Endurance and aerobic exercise can partially overcome the age-related changes in VO2max, arterial stiffness and cardiac output
        - Does not affect ↓ in maximum heart rate during exercise
    - Exercise can also protect against development of cardiovascular disease, such as myocardial ischemia, in older adults (1, 4)





CARDIOVASCULAR SYSTEM: ESSENTIAL POINTS

Cardiac Structural Changes

- ↑ LV wall thickness, ↓ LV chamber size
- ↑ Atrial size
- Cardiac valves have ↑ collagen deposition degeneration, lipid accumulation and focal dystrophic calcification in the leaflets and annuli □ higher circumference, annular dilatation

Cardiac Histologic Changes

- ↓ Cardiomyocyte number (↑ apoptosis, necrosis)
- ↑ Myocyte size (hypertrophy)
- ↑ Lipid deposits
- ↑ Collagen and fibrosis in myocardium

Vascular Structural Changes

- ↑ Vascular intimal thickening
- ↑ Vascular stiffness

Molecular Changes

- Altered calcium handling
- ↓ Beta-adrenergic responsiveness

Functional Implications

- ↑ Afterload
- Diastolic dysfunction
- ↓ Contractility
- ↓ Maximum heart rate

REFERENCES

1. Howlett SE. Effects of aging on the cardiovascular system. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th ed. New York: WB Saunders; 2010. 91-96 p.
2. Kitzman, DW, Taffet G. Effects of aging on cardiovascular structure and function. In: Halter, JB, Ouslander JG, Tinetti ME, et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6th ed. New York: McGraw Hill; 2009. 883-95 p.
3. Dai X, Hummel SL, Salazar JB, Taffet GE, Zieman S, Schwartz JB. Cardiovascular physiology in the older adults. J Geriatr Cardiol. 2015 May; 12(3):196-201 p.
4. Oxenham H, Sharpe N. Cardiovascular aging and heart failure. Eur J Heart Fail. 2003 Aug; 5(4):427-34 p.
5. Pearson JD1, Morrell CH, Brant LJ, Landis PK, Fleg JL. Age-associated changes in blood pressure in a longitudinal study of healthy men and women. J Gerontol A Biol Sci Med Sci. 1997 May; 52(3): M177-83.
6. ACGME and American Geriatrics Society. Educational Resources on Aging. POGOe - Portal of Geriatrics Online Education; 2013 Available from: https://www.pogoe.org/productid/20141.

Respiratory System

Respirology Changes with Age

Although age causes changes in lung function, there is also a significant contribution from the accumulation of environmental exposures. Direct smoke and also second-hand passive smoke exposure is very influential. Oxidants produced from cigarette fumes and other airway inflammation causes, lead to decline of lung function over time. There may be an effect of critical early life periods that determine peak lung function and subsequent lung function in adult and elderly lungs. If peak lung function reserve is not achieved, there may be a trajectory of decline that causes symptomatic lung dysfunction in mid or later life. Factors in early life that are influential in determining whether peak function reserve is achieved include premature birth, asthma, environmental exposure, nutrition and respiratory infection. Environmental pollution, nutrition, respiratory infection and physical activity may also be factors in accelerated age-related decline in lung function (1).

LUNGS

Structural Changes (1,2)

1) Parenchymal change →↓ elastic recoil

- Alveoli and alveolar ducts enlarge → alveolar surface area ↓ as much as 20%
- ↓ surface area → ↓ surface tension forces → small airways collapse during expiration (↑ during infection or respiratory compromises due to overall reserve being lower)
- ↓ glandular epithelial cells →↓ production of mucus and impaired respiratory defense from infectious organisms

2) Stiffening of the lung or reduced chest wall compliance

- Loss of intervertebral disc space, ossification of costal cartilages and calcification of rib articulatory surfaces
- Osteoporosis causing kyphosis and ↑ anterior-posterior chest diameter →10% ↓ in forced vital capacity (FVC) with vertebral collapse (3)

3) Weakened respiratory muscles

- ↓ number of type IIa fibers (fast-fatigue resistant) → impairs strength and endurance
- ↓ intercostal muscle strength → ↑ load on the diaphragm → ↑ breathlessness
- Disease states: e.g. COPD, CHF, malnutrition contribute to altered muscle structure and functioning
- Physical deconditioning, sarcopenia, hormone imbalance and vitamin D deficiency will amplify age-related structural lung changes as body is less able to adapt to structural limitations

Functional Changes (1)

- Elastic recoil of lung tissue ↓ → lungs easier to expand during a deep breath → ↑ total lung capacity (TLC)
    - BUT because chest wall stiffer →.maximal inspiratory effort cannot produce a higher lung volume even though the lungs more easily expandable → TLC **stable** with aging
- ↓ lung elastic recoil → ↑ residual volume (RV), functional residual capacity (FRC) and ratio of residual volume to total lung capacity (RV/TLC)
    - Premature airways closure and ↑ chest wall stiffness
- If RV/TLC is abnormally high, called "hyperinflation," which can be seen in both asthma and COPD
- Vital capacity (VC) ↓ with age because TLC remains the same while RV ↑ (1,2)
- Sleep disordered breathing more common
    - ↑ upper airway resistance and ↓ respiratory effort to overcome it

SPIROMETRY

- Shape of the Flow-Volume (F-V) curve becomes more curvilinear
    - Decreased expiratory flows at low lung volumes due to smaller mean diameters of the small airways (1)
- Approximately one-third liter of FEV_1 lost with each decade and, because it ↓ more than FVC, the ratio of FEV_1/FVC also ↓ with age, approximately 0.2%/year (more quickly in females)
- Many other factors that cause FEV_1 ↓with age (2):
    - Smoking, COPD or asthma
    - Barriers to taking a deep breath e.g. obesity, malnutrition, heart disease and chest wall deformities
- Diaphragm strength ↓ with age (2)
    - Mean maximal inspiratory pressure (MIP) in an 85 year old is about 30% lower than a 65 year old person of same gender.
    - low MIP can → low FVC
- Maximal oxygen uptake, VO2max, ↓
    - ↓ cardiac output and respiratory factors, including ventilation perfusion mismatch
    - Regular exercise can reduce this effect to some extent (2)
- ↑ airway reactivity, with lower thresholds for bronchospasm (3)
- Absolute value of diffusing capacity for carbon monoxide (DLCO) varies with height, age, gender and race (2)
    - After the age of 40, the DLCO ↓ about 5%/decade, even in healthy persons
    - Structural changes, V/Q mismatch, ↓ in pulmonary capillary blood volume and capillary density

PULMONARY IMMUNE SYSTEM

↑ susceptibility to pathogens with age (1):

- Mucosal barrier of the lung worn down
- Decreased mucociliary clearance
- Impaired chemotaxis and phagocytosis, ↓ superoxide production and ↓ bactericidal neutrophil function (3)
- Dendritic cells and natural killer cells less effective
- Hyperinflammatory environment (even in healthy elderly) with ↑ circulating proinflammatory cytokines and anti-inflammatory mediators

REFERENCES

1. Davies GA, Bolton CE. Age-Related Changes in the Respiratory System. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th ed. New York: WB Saunders; 2010. p.97-100.
2. Enright PL. Aging of the Respiratory System. In: Halter JB, Ouslander JG, Tinetti ME *et al.*, editors. Hazzard's Geriatric Medicine and Gerontology. 6th ed. New York: McGraw Hill; 2009. p. 983-98.
3. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging. 2006;1(3):253-60.

Haematology

INTRODUCTION

In healthy aging, there are only **minor changes in the hematologic system**. Significant qualitative deficiencies in blood cell function are more likely result of age-associated chronic disease than aging alone (1).

However, with age there is a (3):
- Gradual decrease in bone marrow cellularity,
- Increased risk of myeloproliferative diseases and anemia
- Decline in adaptive immunity

IMPORTANT CONSIDERATIONS

UNCHANGED (2,3):
- Red-cell life span
- Iron turnover
- Blood volume

Bone marrow mass ↓
Fat in bone marrow ↑

↓Functional response (2,3)

Compensatory response to phlebotomy, hypoxia and other insults is **delayed and not strong** (2,3).

Total circulating white blood cells **UNCHANGED**, but function of various cell types ↓
- ↑ tendency for clonal expansion → ↑ likelihood of developing hematologic malignancies (1, 2)
- ↓ immune cell function is most consistent change (3)

INCREASED
myelotoxicity (chemotherapy) risk (2)

Number of platelets **UNCHANGED**, BUT:
- ↑ platelet responsiveness to thrombotic stimulators, which leads to small ↓ in bleeding time.

Generally a “procoagulant” state (2,3) which may be more clinically significant when there is also underlying atherosclerotic vascular disease (3).

- Fibrinogen, factor V, factor VII, factor VIII, factor IX, high molecular weight kininogen and prekallikrein ↑ (2, 3)
- May be related to low-grade inflammation (2, 3)

D-dimers ↑ 2x without evidence of thrombosis (2,3)

Significant ↑ Plasminogen activator inhibitor-1 (major inhibitor of fibrinolysis/clot breakdown) leads to **increased** risk for deep vein thrombosis (2, 3)

HEMATOLOGY AND AGING: ESSENTIAL POINTS

In healthy aging, there are only **minor changes** in the hematologic system. This includes:

- Gradual decrease in bone marrow cellularity
- Increased risk of myeloproliferative diseases and anemia
- Decline in adaptive immunity

There is generally a more “procoagulant” state, which may be more clinically significant when there is also underlying atherosclerotic vascular disease.

REFERENCES

1. Kanapuru B and Ershler WB. Blood Disorders in the Elderly. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7 th Ed. New York: WB Saunders; 2010. pp 775-790.

2. Taffet GE. Normal aging. In: UpToDate, Schmader KE (Ed), UpToDate, Waltham, MA. (Accessed on November 28, 2015).

3. Ershler WB and Dan L. Longo DL. Hematology in Older Persons. In: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT. In: Williams Hematology, 8 th Ed. 2010, by The McGraw-Hill Companies pp. 149-164.

4. Kanapuru B and Ershler WB. Blood Disorders in the Elderly. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th Ed. New York: WB Saunders; 2010. pp775-790.

5. Taffet GE. Normal aging. In: UpToDate, Schmader KE (Ed), UpToDate, Waltham, MA. (Accessed on November 28, 2015).

6. Ershler WB and Dan L. Longo DL. Hematology in Older Persons. In: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT. In: Williams Hematology, 8 th Ed. 2010, by The McGraw-Hill Companies pp. 149-164.

Immunology

INTRODUCTION

The process of the immune system aging and becoming impaired in its defensive abilities is known as immuno-senescence. There are changes seen in both innate and adaptive immunity, although the adaptive immune response shows much more profound changes with aging (Moro- García, Alonso-Arias, López-Larrea, 2013). In general, older people are also more likely to have conditions or diseases that lead to impaired immunity. This may complicate the assessment of the impact that aging has on immune function (Tummala, Taub and Ershler, 2010).

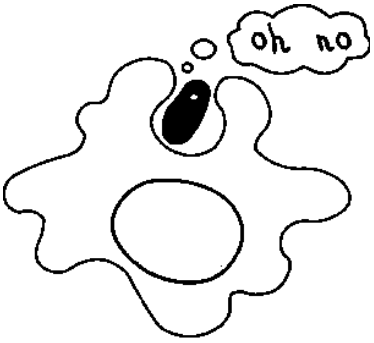
IMPORTANT CONSIDERATIONS

SPECIFIC HOST DEFENSE

In the cellular immune system, there are no age-specific significant changes in the total number of peripheral blood cells, including lymphocytes, monocytes, NK cells, or polymorphonuclear leukocytes. Generally B- and T-lymphocyte numbers remain the same with age. There is a proportional change in the ratio of helper to suppressor cells (T4/T8). There is also an increase in memory cells, those that express the CD45 surface marker, with age (Moro-García et al., 2013).

CUTANEOUS IMMUNE SYSTEM

There is a specialized immune system found in the skin consisting of lymphocytes and antigen-presenting cells. Langerhans cells, found in the epidermis and useful for capturing antigens entering the body through the skin, are decreased in number and function with age. Keratinocytes are also affected by age. They produce less IL-1 and more of the antagonist of the IL-1 receptor. As a result, local inflammation and activation of innate immune responses are reduced at infection sites. In addition to these changes, the changes in morphology and structure of aged skin causes an increase in skin infection (Weinberger et al., 2009).



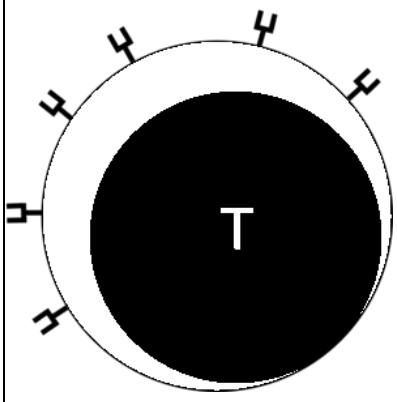
PHAGOCYTOSIS

Elderly individuals maintain the number and overall phagocytic capacity. However, neutrophil functions such as endothelial adherence and granule secretory behaviour, are reduced in aging. Also, significantly fewer neutrophils have been found to arrive at skin abrasion sites. The expression of Toll-like receptors (TLRs) and GM-CSF receptors are not decreased, however, ligation of these receptors results in altered signal transduction. These alterations may be the cause of dysfunctional neutrophils and decreased response to stimuli such as infection with gram positive bacteria (Tummala et al., 2010).

Macrophage activation is also altered with age potentially due to reduced gamma interferon signal from T lymphocytes. There is a decrease in the number of macrophage precursors and macrophages in the bone marrow. There may also be altered signal transduction causing impaired cytokine production after TLR stimulation. In addition, there is lessened expression of MHC class II molecules both in humans and in mice with resulting decreased antigen recognition and processing by these antigen presenting cells. This reduced antigen process leads to lower quantities of activated T cells locally and fewer signals at the site of infection (Tummala et al., 2010).

Antigen-presenting dendritic cells (DC) may be altered in function with aging. The elderly have been found to have a decrease in number and migration of Langerhans cells in skin though function for antigen presentation is still sufficient. DCs from “frail” elderly, however, seem to have reduced expression of costimulatory molecules, secrete decreased amounts of interleukin-12 (IL-12) and stimulate a less strong T-cell proliferative response in comparison to the non-“frail” elderly (Tummala et al., 2010.

Complement activity and neutrophil function have not been found to decrease with age.
However, natural killer (NK) cells become impaired in responding to cytokines causing decreased ability to kill target cells and to synthesize cytokines and chemokines (Tummala et al.,2010).



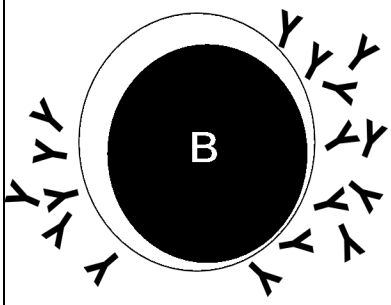
QUALITATIVE CHANGES IN T-CELL FUNCTION

The thymus atrophies due to a decrease in serum hormones with age and therefore, its function also declines. There are changes in thymic dependent immunity-adaptive T-cellimmunity. There is a notable decrease in naïve lymphocytes, which causes loss of adaptive immune function with age. Moreover, aged naïve CD4+ T cells proliferate less and produce less IL-2 in response to antigenic stimulation. Memory CD4 T-cells with age, as compared withnaïve, increase in number, live long and are relatively competent. However, they have beenfound to respond less well to antigens over time with impaired proliferation and cytokine secretion (Moro-García et al., 2013).

Cell surface receptor expression changes significantly with aging. CD28-CD8+ T cells make up the majority of circulating CD8+ cells in older people. These are relatively inactive and have reduced proliferative response to T cell antigen receptor (TCR) cross-linking, although capacity for cytotoxicity remains intact. There is a loss of CD28 expression but a gain of expression of stimulatory NK cell receptors in CD28-CD8+ memory T cells that enables their effector function as a compensation for impaired proliferation (Moro-García et al., 2013;Tummala et al., 2010).

Naïve CD8+ T cells are reduced with some oligoclonal expansion of CD8+ T cells. This may occur to control a latent viral infection or to fill available T-cell space due to decreased thymus production. When the clonal expansion reaches a certain threshold, the diversity of T-cell repertoire is reduced and the ability to protect against new infections is compromised. Clonal expansion of CD28-CD8+ T cells is associated with increased infections and failed response to vaccines in the elderly (Moro-García et al., 2013). Due to the combined effects of thymic tissue loss, repeated antigenic exposure and alteration in susceptibility to apoptosis, the thymic and lymphoid tissue in older persons holds mainly nonresponsive memory CD8+ CD28- CD T cells and causes faulty cell mediated immunity (Tummala et al., 2010).

T-cell lymphokine production and regulation, particularly IL-2, is reduced with age. There is also a dramatic decline in the proliferative ability of T lymphocytes to nonspecific mitogens. Although the number and affinity of mitogen receptors on T lymphocytes do not change, the number of T lymphocytes capable of dividing in response to mitogen exposure is reduced and activated T cells do not have as many divisions (Weinberger et al., 2009; Tummala et al., 2010).



QUALITATIVE CHANGES IN B-CELL FUNCTION

In the humoral immune system, the number of peripheral blood B cells is not changed with age. However there is a decline in antibody production after vaccination due to reduced antigen-specific B-cell expansion and differentiation which results in low titres of antigen-specific IgG. Evidence suggests a mild to moderate increase in total serum immunoglobulin IgG and IgA levels with no change in IgM levels (Tummala et al., 2010).

Both the primary and secondary immune responses to vaccination are impaired. With age, there is usually a lower and later peak in antibody titres and more rapid declines in titres after immunization. Serum autoantibodies may be organ-specific. For example, antiparietal cell, antithyroglobulin and antineuronal antibodies. Circulating immune complexes and organ-nonspecific autoantibodies, such as those to rheumatoid factors, are also increased with age. There may also be an association of vascular insults and disease with autoantibodies, such as antiphospholipid antibodies (Weinberger et al., 2009).

There is also a decreased production of early progenitor B cells resulting in low output of new naïve B cells with clonal expansion of antigen-experienced B cells which forms a limited repertoire in immunoglobulin production in B cells. This leads to reduced generation of antigen-specific IgG titres. The antibodies produced by older B cells are usually of low affinity due to reduced class switching and somatic recombination in the variable region of the immunoglobulin gene that is necessary for antibody production and diversity (Tummala et al., 2010).

IMMUNOLOGY AND AGING ESSENTIAL POINTS

Immunosenescence = The process of the immune system aging and becoming impaired in its defensive abilities

Adaptive immune response shows more profound changes:

- Humoral Immunity: ↓ Number of B cells precursors and peripheral B cells (3)
- Cellular Immunity:
    - Involution of thymus gland (2, 3)
    - Number of naive T cells exiting thymus significantly ↓ with progressive age
    - Overall ↓ in T cell function (including IL-2 production), number and diversity (1, 3, 4)
    - After 65yrs, profound ↓ in T cell receptor diversity (critical for protection from new, e.g. viral infections)
    - ↓ Ability of T cells to mount immune response against new antigens (3)
    - ↓ Numbers of CD4 T cells
    - ↓ Ability of T cells to help B cells proliferate and produce antibodies (3)
    - After age 50, ↓ T regulatory cells (maintain homeostasis, limit autoimmune responses, modulate inflammatory responses to infectious agents and tumors)
    - ↑ incidence of autoimmunity and malignancy (3)

The most significant changes of the innate immune system are with macrophages:

- Significant ↓ in bone marrow precursors with aging (2, 3)
- ↓ IFN-gamma signal from T lymphocytes
    - altered macrophage activation (2)
- Possible ↓ nitric oxide and reactive oxygen production
    - ↓ macrophage activity
    - longer duration of infection by extracellular bacteria + delayed wound healing (3)

REFERENCES

1. Moro-García MA, Alonso-Arias R, López-Larrea C. When Aging Reaches CD4+ T-Cells: Phenotypic and Functional Changes. Front Immunol. 2013 May 10;4:107.

2. Tummala MK, Taub DD, Ershler WB. Clinical Immunology: Immune Senescence and the Acquired Immune Deficiency of Aging. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7 th Edition. New York: WB Saunders; 2010: 82-90.

3. Azar A, Ballas ZK. Immune function in older adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 21, 2015).

4. Weinberger B, Weiskopf D, Grubeck-Loebenstein B, Immunology and Aging. In: Halter JB, Ouslander JG, Tinetti ME et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6th Edition. New York: McGraw Hill; 2009: 23-36.

5. Hall KE. Effect of aging on gastrointestinal function. In: Halter JB, Ouslander JG, Tinetti ME et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6th Edition. New York: McGraw Hill; 2009. pp.1059-1064.

Musculoskeletal

INTRODUCTION

Musculoskeletal health declines with age. Regenerative cells (e.g. osteoblasts and chrondrocytes) are reduced. There is also a change in structural proteins (e.g. collagen and elastin) with a build up of degraded molecules in muscloskeletal tissue matrices. Levels of trophic hormones, growth factors and cytokines are all decreased and lead to delayed healing and repair (1, 2, 3).

IMPORTANT CONSIDERATIONS

Musculoskeletal problems are a frequent source of pain and disability in the elderly.

- Aging causes changes in muscle, bone, cartilage and soft tissue that lead to **osteoporosis** and **osteoarthritis** (OA), reduction in joint range of motion and difficulty initiating movement (1)

- There is an age-related increased prevalence of common musculoskletal conditions that begin at young ages and cause increasing pain and disability (e.g. seronegative spondyloarthropathies: ankylosing spondylitis, reactive arthritis, psoriatic arthritis) (1)

- There is a greater incidence of rheumatologic conditions such as polymyalgia rheumatica, Paget's bone disease and crystalline arthropathies (1)

OVERVIEW OF MAJOR CHANGES

	STRUCTURAL CHANGES	FUNCTIONAL IMPLICATIONS
MUSCLE	Sarcopenia = age-related loss of muscle mass and strength (2) • In women, related to ↓ levels of estrogen and vitamin D levels (1) • In men related to ↓testosterone and physical performance (1) • ↓levels of growth hormone and IGF-1 may also contribute (1) Muscle mass ↓ in relation to body weight by ~30-50% (2) • Generally, loss from legs more than from arms • Type I slow-twitch fibers less affected than fast-twitch Muscle quality ↓due to presence of more fat and connective tissue into old muscle (2)	Loss of muscle leads to (2): • Age-related insulin resistance • Changes in body composition and distribution volumes for water soluble drugs Strength shows ↓↓in part due to loss in muscle mass (2) • Grip strength ↓ (2) • Lower extremity strength ↓relatively faster than upper extremity (2) • Activity may decrease rate of ↓but will not prevent it altogether (2) Muscle more easily fatigued (2). Healing of injured muscle slower and often not complete (2)

BONE	• Progressive ↓ in osteoblast number and activity
	• Osteoclast activity generally unchanged (2) (though ↑ in postmenopausal women (1))
	• Loss of mineral in both cortical, or peripheral skeleton, and trabecular (axial skeleton) bone types (1,2)
	• ↓Bone mass is ~ 0.5%/year (2)
	  ○ Weight-bearing cortical bones lose material from endosteal surface (2)
	  ○ E.g. in femur: cortex thins and fat fills most of marrow cavities (1, 2)
	• Pro-inflammatory environment enhances loss of bone (1,2)
		• Probability of fracture and after fracture, rate of repair slower (1,2)
		• Overall strength of bone also significantly ↓ (1)
		  ○ Build-up of microfractures within bone tissue (1)
		• In women, compounded changes of menopause (loss of estrogen) on bone mass and function (1,2)
		• Vitamin D deficiency more common and hastens loss of bone (2)
		• ↓Weight bearing activity contributes to negative calcium balance and loss of bone mineral (1,2)

SOFT TISSUES	• ↓Collagen production →	• ↓Ligament elasticity → communication between joints and tissues compromised (1,3)
SOFT TISSUES	• Connective tissue less resistant to calcium crystal formation →	• ↑Crystalline arthropathies (1)
SOFT TISSUES	• Intervertebral discs of spine: ○ ↓Diameter of nucleus pulposus and hydrostatic pressure within the region →	• Greater compressive stress in outer fibrous ring, annulus fibrosus (1,3)

REFERENCES

1. Gregson CL. Bone and Joint Aging. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7 th Edition. New York: WB Saunders; 2010: pp. 117-122.

2. Taffet GE. Normal aging. In: UpToDate, Schmader KE (Ed), UpToDate, Waltham, MA. (Accessed on November 21, 2015).

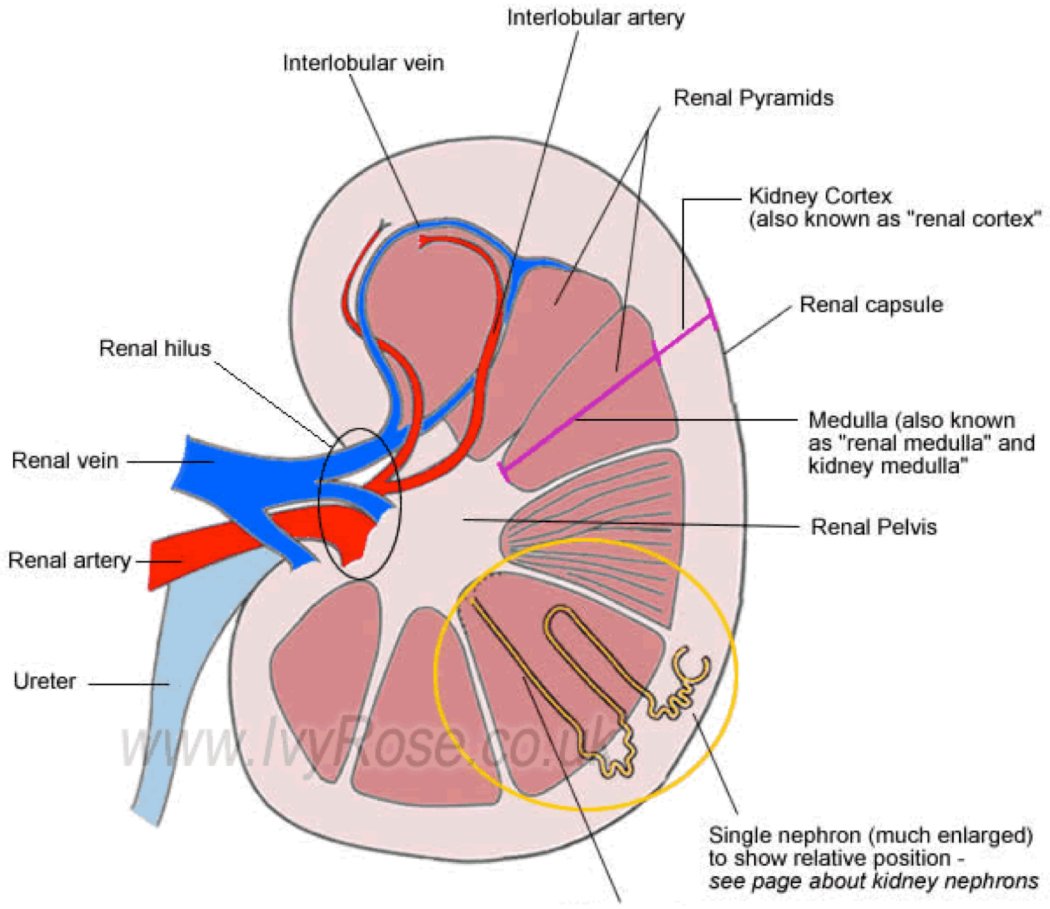
3. Loeser RF, Delbono O. Aging of the Muscles and Joints. In: Halter, JB, Ouslander JG, Tinetti ME, et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6 th Edition. New York: McGraw Hill; 2009. pp. 1355-68.

Renal and Urinary Tract

INTRODUCTION

Urine storage and release is a result of renal output, lower urinary tract biomechanical and sensorimotor function, central processing abilities, and mobility (1). Upper urinary tract includes the kidneys and ureters. Overall, there are individual variations of renal function with age that are affected by factors such as underlying genetics, gonadal hormonal levels, diet, and smoking (1)

DIAGRAM OF KIDNEY AND URETERS



KIDNEY STRUCTURAL CHANGES

- Renal mass progressively ↓ with age
  - renal cortex affected more than medulla (2); largest reduction in number and size of nephrons (1)
  - ↑ interstitial spaces between tubules and ↑ interstitial connective tissue (1)
- ↑ Granular and pitting appearance likely due to vascular changes (1,2)
- Tubular atrophy, ↓ number, volume, length and ↑ diverticula → simple cysts (2)
- ↑ Glomeruli sclerosis → filtering regions are less effective (1,2)
- The number of visual glomeruli declines parallel to weight changes (2)
- Intrarenal vascular changes: arterial sclerosis is the main feature (2)
  - Renal Cortex most changed (modest change in medulla):
    - Hyalinization and collapse of the glomerular tufts, loss of luminal space, decreased blood flow overall (1)
  - Hyperfiltration theory (1):

Non-sclerosed glomeruli enlarge and hyperfilter → ↑ capillary blood flow through the remaining glomeruli → ↑ in intracapillary pressure (sheer stress) → local endothelial destruction + glomerular damage → progressive glomerulosclerosis.

KIDNEY FUNCTIONAL CHANGES (HEMODYNAMIC)

Hemodynamic changes:

- Glomerular filtration rate (GFR) declines about 8.0 mL/min per 1.73 m^2/decade starting in 40s, for ~67% of people (1, 3)
  - Does not necessarily correlate with increased serum creatinine as there is age-related muscle mass reduction → net decline in creatinine production with age (1)
  - Serum creatinine levels generally overestimate GFR with age, particularly women and underweight, severely frail (1)
  - However, high creatinine level above normal range, fairly reliable, indicative of underlying pathology (1)
- Progressive ↓ in renal blood flow, ~10%/decade (1, 3)
  - Renal medulla maintains perfusion but cortical perfusion may ↓ (1)
  - Renin and angiotensin (RA) levels significantly ↓ and ability of RA system to respond to various stimuli also ↓ (1)
- Due to greater number of sclerotic glomeruli and inability to increase renal plasma flow→ renal functional reserve ↓ (3)
- ↑ likelihood of aging kidney to develop acute kidney injury and progress to end-stage renal disease, particularly in the setting of comorbid cardiovascular disease (3)

KIDNEY FUNCTIONAL CHANGES (TUBULES)

Tubules:

- Tubular function ↓ with age (1, 3)
  - Ability to handle water, sodium, potassium and other electrolytes ↓ (1,3)
  - Total body potassium ↓ along with muscle mass loss; however ↓ aldosterone (which ↑ excretion of potassium in distal tubule) predisposes to hyperkalemia (3)
  - Sodium exchange and salt resorption in the ascending loop of Henle ↓
    - ↓ serum aldosterone secretion and ↓ response to aldosterone and angiotension II (1)
    - Impaired capacity to respond to sodium load, elderly have develop extracellular volume expansion when sodium intake increased (3)
    - When other comorbidities are present, e.g. cardiovascular diseases, even moderate volume expansion may lead to severe conditions e.g. pulmonary edema (3)
  - Impaired renal concentrating and diluting ability (3)
  - Under normal conditions, older patients maintain acid-base balance but when acid load increased, their ability to ↑ acid excretion is ↓ (3)

LOWER URINARY TRACT (BLADDER AND OUTLET)

In the lower urinary tract, aging may be associated with an increased prevalence of multiple bothersome symptoms and dysfunction. There are underlying age-related changes in tissue properties and sensorimotor function. However, the structural changes are complicated by other age-related physiologic changes, comorbidities, functional impairment and the effect of medications (1,4).

OVERALL, aging has been associated with:

- ↑ Volume at first desire to void (1)
- ↓ Bladder capacity, voiding volumes and flow rates (1)
- Impaired detrusor contractility and sphincter function, which may be associated with sarcopenia (1)
- ↑ Nighttime urine production(4)
- In women, urethral changes related to withdrawal of estrogen (1):
  - Functional length and closing pressures ↓
  - Mucosa atrophies and therefore, less effective barrier from bacterial contamination

RENAL AND URINARY TRACT CHANGES WITH AGE: **ESSENTIAL** POINTS

KIDNEY STRUCTURAL CHANGES

- Renal mass ↓
- ↑ Glomeruli sclerosis → filtering regions are less effective
- Intrarenal vascular changes: arterial sclerosis causes decreased blood flow, particularly in the renal cortex

KIDNEY FUNCTIONAL CHANGES

- ↓ GFR for majority
- Functional reserve ↓ → ↑Likelihood of aging kidney to develop acute kidney injury and progress to end-stage renal disease, particularly in the setting of comorbid cardiovascular disease
- Tubular function ↓ in ability to handle water, sodium, potassium and other electrolytes
- ↓ Aldosterone predisposes to:
    - ↑ Risk of hyperkalemia
    - Sodium exchange and salt resorption ↓
    - Impaired ability to respond to sodium load
- Impaired renal concentrating and diluting ability

LOWER URINARY TRACT: BLADDER AND OUTLET

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REFERENCES

1. Smith, P. and Kuchel, G. Aging of the Urinary Tract. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th Edition. New York: WB Saunders; 2010: 111-116.

2. Esposito C, Dal Canton A. Functional changes in the aging kidney. J Nephrol. 2010 Sep-Oct; 23 Suppl 15:S41-5.

3. Pannarale G, Carbone R, Del Mastro G, Gallo C, Gattullo V, Natalicchio L, Navarra A, Tedesco A. The aging kidney: structural changes. J Nephrol. 2010 Sep-Oct;23 Suppl 15:S37-40.

4. Tannenbaum, C. Chapter 10 Keeping Dry: Managing Urinary Incontinence. In: Holroyd-Leduc J, Reddy M, editors. Evidence-Based Geriatric Medicine: A Practical Clinical Guide. Oxford: Blackwell Publishing Ltd; 2012: p. 124-139.

Nervous System

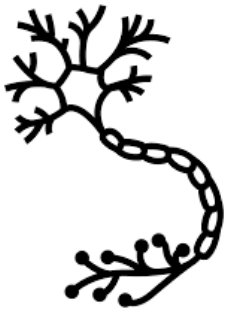
OVERVIEW OF MAJOR CHANGES

AUTONOMIC CARDIOVASCULAR CONTROL

- Baroreflex sensitivity ↓ progressively due to both vascular and neural changes
- ↓ Reciprocal heart rate changes produced by changes in arterial pressure ("cardiovagal baroreflex gain")
- ↓ Parasympathetic/vagal
- ↓ Cardiac vagal innervation

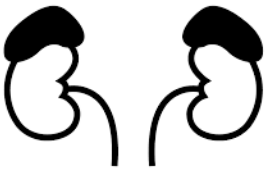
BLOOD PRESSURE CHANGES

- β -adrenergic responses to norepinephrine blunted
  - ↓ β1 responses → Impaired cardio-acceleration and ↓ cardiac contractility
  - ↓ β2 responses →↑ Vascular tone because α1 vasoconstriction ability unchanged
- The combination of age-related vascular stiffening and ↓ β-adrenergic function →↓ Arterial baroreflex sensitivity
- ↑ Risk for orthostatic hypotension due to ↓ postural cardio-acceleration and ↓ baroreflex gain
- Blood pressure maintained by ↑ peripheral vascular tone, despite ↓ cardio-acceleration
  - Due to high dependence on vascular resistance, dehydration and vasodilator medications are at ↑ risk for hypotension and syncope



SYSTEMIC SYMPATHETIC FUNCTION

- ↑ Central sympathetic outflow → ↑ Levels of plasma norepinephrine but ↓ norepinephrine clearance
- Adrenaline secretion from the adrenal medulla ↓↓ and adrenaline release in response to acute stress ↓ in older men.
    - β -adrenergic responses to norepinephrine ↓ likely due to β -adrenergic receptor down-regulation



NEUROENDOCRINE CHANGES

- Plasma renin and aldosterone levels ↓
- Atrial natriuretic peptide ↑ 5-9x
- The vasopressin response to hypotension may also be ↓
- Therefore, sodium and water conservation challenging and volume depletion more common →↑ syncope risk

REFERENCES

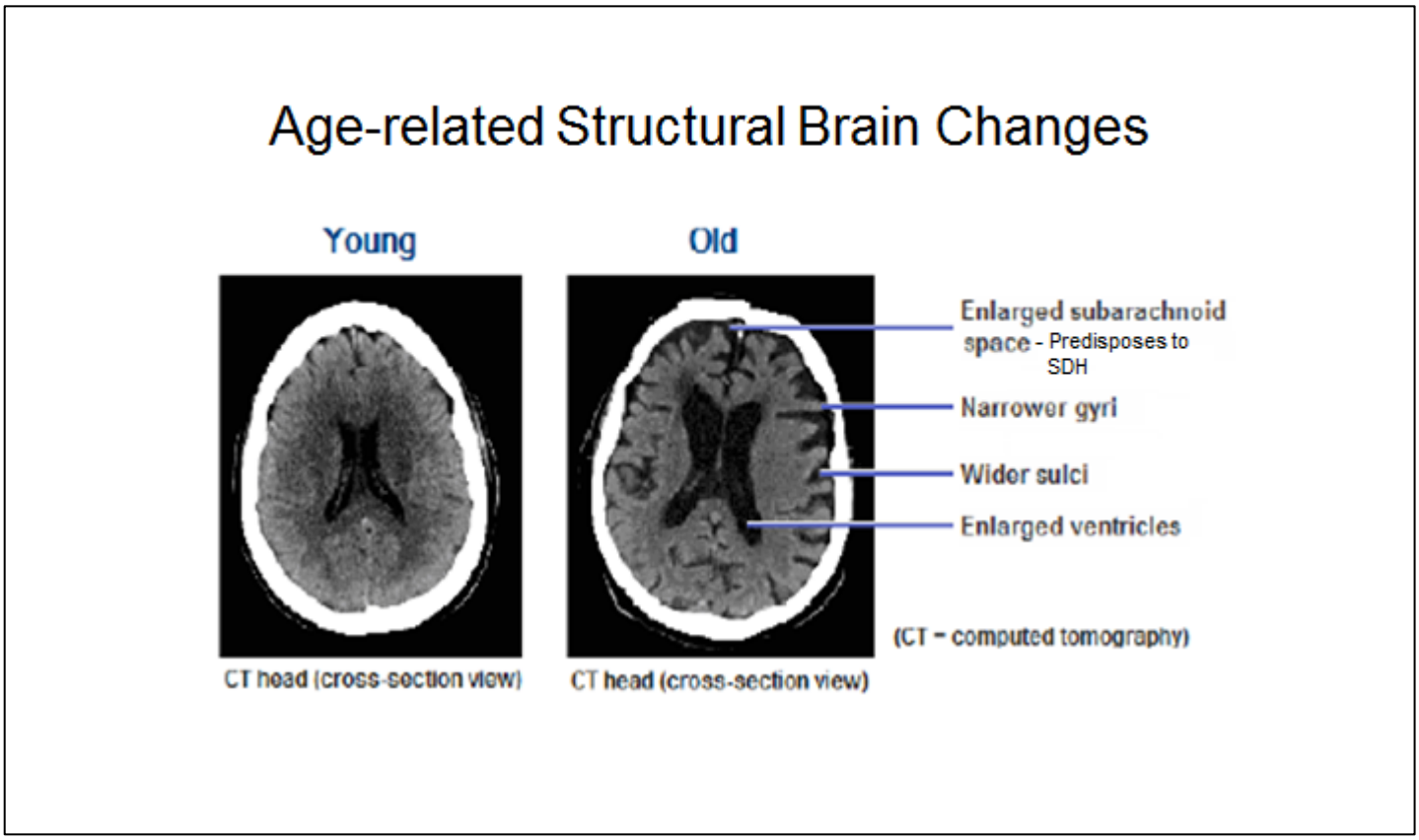
1. Kaufmann H, Biaggioni I. Disorders of the Autonomic Nervous System. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7 th Edition. New York: WB Saunders; 2010: pp. 498-510.

Brain and Cognition

STRUCTURAL BRAIN CHANGES

As the brain ages, it decreases in mass at a rate of about 1% per year after age 60, with more loss in white matter than grey matter. Age-related neuronal loss occurs predominantly in the largest neurons located in the cerebellum and cerebral cortex (9) whereas the hypothalamus, pons, and medulla do not show the same changes. (8)

Cerebral atrophy entails narrowing of gyri and widening of sulci and the subarachnoid space. This is more pronounced in the presence of neurodegenerative disorders. (1) Although neurons both continue to form new synapses and regenerate throughout the life span, the overall rate of loss is greater than gains (8)



NEUROTRANSMITTER CHANGES

In addition to structural changes, there are also alterations of neurotransmitter levels:

- ↑ Monamine oxidase (MAO) levels
- ↓ Dopamine (and binding sites),
- ↓ norepinephrine
- slight ↓ in GABA levels

CEREBROVASCULAR CHANGES

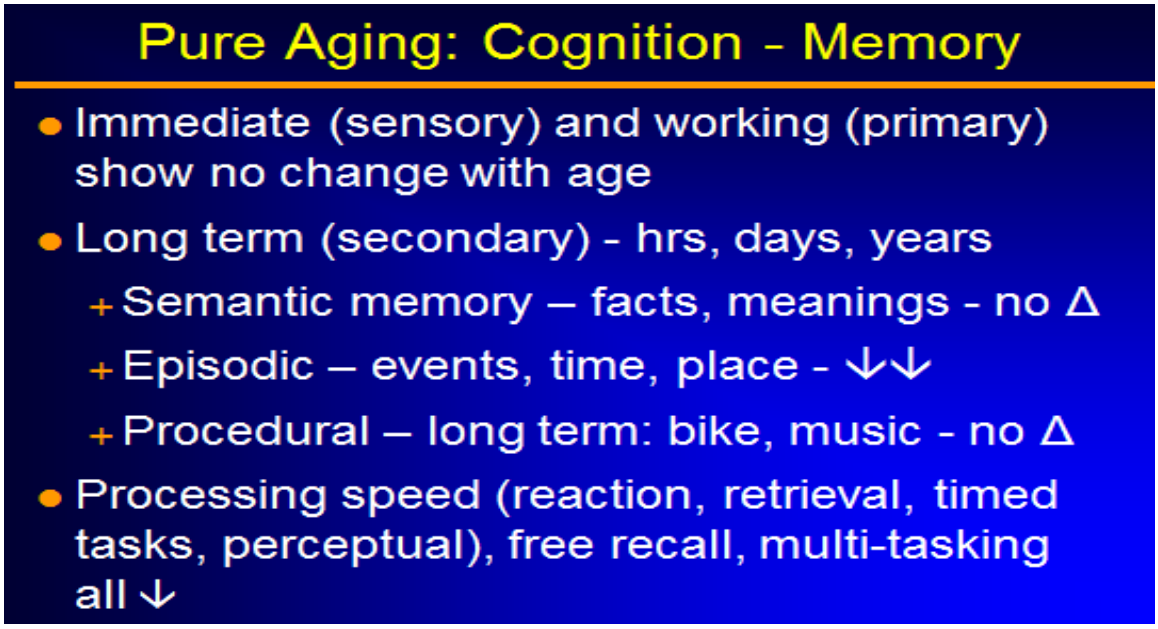
- Vessels that supply blood to the brain are vulnerable to age-related atherosclerosis and arteriosclerosis → more susceptible to occlusion or rupture (stroke)
- Age-dependent cerebral vascular changes strongly linked to heart disease and hypertension
  - Apolipoprotein E polymorphisms linked to ↑ risk of both atherosclerosis and Alzheimers disease (AD), with the apolipoprotein E4 ↑ing risk
- ↓ cerebral blood flow (about 20% from age 30 to 70) → ↓ cerebral metabolic rate for oxygen and glucose use
  - Mechanisms similar to elsewhere in the body including:
    - oxidative damage to vascular endothelial cells
    - inflammatory response in which macrophages could penetrate the blood–brain barrier
- Important transport functions of cells (e.g. endothelial, astrocytes) comprising the blood-brain barrier may also be impaired
- During normal aging, and much more in AD, β-amyloid (Aβ) forms insoluble aggregates (plaques) in the brain parenchyma and vasculature
  - Aβ = 40- to 42-amino-acid peptide that arises from a much larger membrane-spanning β-amyloid precursor protein (APP)

COGNITION

There are individual variations in cognitive abilities with aging. There are also a variety of confounding factors in ascertaining cognitive abilities including depression and delirium (4).

- **↓ processing speed, cognitive flexibility, visuospatial perception, working memory and divided attention (5)**
- ↑ distractability (6)
- Memory deficits generally related to the storage of long-term episodic memories (6)
- Fluid intelligence, ability to learn and use new information to solve abstract problems, and speed of performance on structured tasks decreases gradually (7)
- Performance on tasks of executive function mildly ↓ (6)
    - May be due to ↓ in executive function itself or in the processing speed required to complete these types of tasks (5,6)
- Generally stable areas of cognition with age (5,6):
    - Delayed memory, particularly visual memory
    - General language or verbal abilities remain stable with age
    - Knowledge base, including general information about the world, continually expands with age
    - Ability to learn new information (7)
    - Retention of new encoded information, access to remotely learned information, procedural memory, practical problem solving, experiential knowledge and vocabulary (7)

EFFECT OF AGING ON COGNITION AND MEMORY



MENTAL STATUS EXAMINATION

The frequency of cognitive disorders greatly increases with age. A comprehensive mental status examination consists of cognitive, functional and behavioural domains using performance and informant measures. It also includes observation of the patient's level of arousal or alertness, appearance, emotion, behavior, movements, and speech. Cognition includes attention, memory, language, visuospatial and executive abilities. It is important to note that performance on structured testing can be influenced by age, handedness, education, and sociocultural background (3).

Examples of such examinations include the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCa) often administrated in a clinician's office space or by bedside. Although these are quick and reliable ways to estimate severity and progression of cognitive impairment, they cannot be solely used to diagnose a disease. A full Mental Status Examination can be done in cases where cognition must be more comprehensively assessed.

REFERENCES

1. Misiaszek BC. Geriatric Medicine Survival Handbook 2009
2. Mattson MP. Human Brain: Cellular and Neurochemical Aspects of the Aging Human Brain. In: Halter, JB, Ouslander JG, Tinetti ME, et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6th Edition. New York: McGraw Hill; 2009. p. 739-750.
3. Kaufmann H, Biaggioni I. Disorders of the Autonomic Nervous System. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th Edition. New York: WB Saunders; 2010: p. 498-510.
4. Galvin JE. Mental Status and Neurological Examination in Older Adults. In: Halter, JB, Ouslander JG, Tinetti ME, et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6th Edition. New York: McGraw Hill; 2009. p. 153-169.
5. Craft S, Cholerton B, and Reger M. Cognitive Changes Associated with Normal and Pathological Aging. In: Halter, JB, Ouslander JG, Tinetti ME, et al., editors. Hazzard's Geriatric Medicine and Gerontology. 6th Edition. New York: McGraw Hill; 2009. p. 751-765.
6. Martin J, Gorenstein M. Normal cognitive aging. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th Edition. New York: WB Saunders; 2010: p. 170-177.
7. Taranweh R, Galvin E. Neurologic Signs in the Elderly. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th Edition. New York: WB Saunders; 2010: p. 101-105.
8. ACGME and American Geriatrics Society. Educational Resources on Aging. POGOe - Portal of Geriatrics Online Education; 2013 Available from: https://www.pogoe.org/productid/20141.