Clinical Aspects of Aging Physiology
Fundamentals of Geriatrics
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Learning Objectives

Demonstrate understanding of:

1. The context of healthcare for older Americans in the 21st Century
2. The clinically relevant biological changes of pure aging in humans
3. The complexity of interrelationships among pure aging, risk factors and disease
4. How these organ changes influence presentation, clinical course and response to treatment of disease
Who Are the Elders of America?

- They are us; dying is going out of style
- The front edge of the post-WWII (1946-64) birth cohort (the “Baby Boomers”) began to turn 65 January 1, 2011; >2.5 M/year – already >45 M
- Nearly 80 million born; >77 M alive - most will survive well beyond 65
- Best educated, wealthiest Americans ever
- Grew up in 1960s healthcare; saw their grandparents’ and parents’ lives made better by Medicare and Medicaid
Population Aging

- Average life expectancy (ALE) at birth in ancient Rome for a citizen was ~25 years; 35 years in England during the American Revolution.

- In 1900 America, 48: 50 for ♂, 47 for ♀; in 2015, 81 and 76, respectively – 1900 years for 1st 25-year gain in ALE, <100 years for the next.

- For Americans reaching adulthood in 2016, ALE is 85+ for women and 80 for men.

- Maximum life span increase, though slower than increase in ALE, has not slowed since 1950s.
U.S. Lags Other Countries: Mortality Amenable to Health Care

*Countries’ age-standardized death rates before age 75; including ischemic heart disease, diabetes, stroke, and bacterial infections (WHO and CDC mortality data)

Nolte E, McKee M. Variations in Amenable Mortality - Trends in 16 High-Income Nations,” Health Policy, online 9/12/11
We Outspend the World on Healthcare

Legend for Figures 1.1 through 1.4

1. Australia 10. Greece 19. Poland
7. Finland 16. South Korea 25. United Kingdom
8. France 17. Netherlands
9. Germany 18. New Zealand
26. United States

Data source: OECD
Life expectancy for older women
(stratified by functional disability and co-morbidities)


Life expectancy for older men
(stratified by functional disability and Co-morbidities)
Ten Themes of Aging

1. Pure Aging – What happens if you survive, no matter how well you live your life (e.g., diet, habits, exercise) – changes in all organs (kidney, heart, lung et al.) - inevitable and irreversible, if truly aging, as opposed to disease – presbyopia, LV stiffness, decreased $C_{CR}$

2. Restricted capacity in organs to maintain homeostasis under stress, leading to rapid decompensation of “weak link” systems (CNS, CV, renal) – delirium complicating pneumonia, falling when jostled in the mall

4. Disease in elders is often modified (presentation, clinical course, response to treatment, outcomes) beyond the syndromes by pure aging effects – SDH more frequent with less trauma, afebrile pneumonia, painless AMI

5. Pure aging effect is misinterpreted as disease – slow information retrieval or presbycusis called dementia

6. Disease misinterpreted as pure aging effect – obvious dementia symptoms called “old age,” falls ignored
Ten Themes of Aging

7. Medication Hazards – pure aging and common diseases greatly increase the risks for adverse drug effects; most often manifest as CNS or CV toxicity

8. Multiple Pathology – Interactions of multiple diseases accelerate potential for harm

9. Diseases Special in Aging – Common only in elders; all clinicians must know – DCHF, HTN, AF, AD

10. Aging is not as important as we once thought
Every organ changes in a characteristic pattern if the effects are due only to aging

- Inevitable
- Irreversible
- Variable within and among individuals
- Usually decremental
- Linear
- Plasticity (organ reserve)
- Surviving
Skin (Dermatology)

- Decline with age in:
  - Provitamin D3 production by keratinocytes
  - Dermal thickness and vascularity
  - Melanocytes in skin
  - Eccrine glands
  - Proliferative potential of keratinocytes

- Increase with age in:
  - Wrinkles, but sun and tobacco smoke > age
  - Proliferative lesions (!)
Immune Changes of Human Aging

- B cells - # unchanged, but decreased antibody production & clonal expansion; ↑auto-antibodies (but less autoimmune disease)
- T cells
  + Thymic involution (hormones); DTH, cytotoxicity, proliferative response all ↓
  + Cytokines – IL-2 ↓
- NK cells - # ↑, normal function
Weight increases to mid-60s in ♂, 70s in ♀

- BMI and TBW decline in old age; BMI underestimates obesity in elders (↑FM, ↓FFM)
- Estimation of energy needs based on body weight: 25 to 30 kcal/kg/day; BMR does NOT change with age
- Controversy on obesity and mortality, but
  - Definite association of co-morbidity and disability in obese elders; if co-existing sarcopenia, major declines in function
  - Weight loss sparing muscle is beneficial
Mechanism of Insulin Resistance

- Glucose intolerance = insulin resistance (IR); detectable in all, and 30% with mostly type 2 DM
- Insulin molecule identical in healthy elders, IR elders and type 2 DM; receptor numbers and binding affinity of receptors (liver, muscle) for insulin unchanged with age
- Insulin-signaling defect limits mobilization of glucose transporters needed for insulin-mediated glucose uptake and metabolism in muscle and fat – post-receptor binding events
- Pure aging doesn’t necessarily = harmless
Diabetes Prevention Program (DPP)

![Graph showing cumulative incidence of diabetes over years for Placebo, Metformin, and Lifestyle interventions.](image-url)
Pulmonary Changes of Aging

- ↓Elasticity (↑stiffness), ↓alveolar exchange area
- Shallow alveolar sacs, ↓ airway size, ↓ chest wall compliance, intercostal muscle atrophy, ↓ 25% diaphragm strength
- ↓Arterial PaO₂ through mid-life, but then constant (~80 mmHg) > age 65
- ↑V/Q mismatch, ↓FVC, FEV1 (30 ml/yr > age 30)
- ↓Vital capacity (-21), ↑TLC (+3), ↑FRC (+9), ↑RV (+20)
- ↓Maximum breathing capacity
- A-V O₂ difference – conflicting data
- Decreased survival probability with pneumonia
<table>
<thead>
<tr>
<th>Structure or Function</th>
<th>Age-Related Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocytes</td>
<td>↓ number, ↑ size; ↑ fibrocytes</td>
</tr>
<tr>
<td>LV Stiffness</td>
<td>↑ (↓ compliance)</td>
</tr>
<tr>
<td>LV Wall Thickness</td>
<td>↑</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>↑</td>
</tr>
<tr>
<td>Left Atrium</td>
<td>↑</td>
</tr>
<tr>
<td>LV Diastolic Passive Filling</td>
<td>↓ (atrial contraction more important)</td>
</tr>
<tr>
<td>Maximum Heart Rate</td>
<td>↓</td>
</tr>
<tr>
<td>Maximum Cardiac Output</td>
<td>↓</td>
</tr>
<tr>
<td>Vo₂ MAX</td>
<td>↓</td>
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<tr>
<td>Vasodilatation with exercise</td>
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</tbody>
</table>
Common Clinically Important Pure Aging Cardiovascular Changes in Older Persons

- Decreased cardiovascular reserve (fatigue, CHF)
- Increased stiffness of LV (HFPEF)
- Rise in systolic BP (HTN, stroke)
- Decreased baroreflex sensitivity (syncope)
- Autonomic dysfunction (syncope)
- Sinus node atrophy and dysfunction (syncope)
- Increase in fibrinogen, & factors V, VIII, IX (thrombosis)
- Valvular sclerosis and calcification (aortic stenosis)
Age Changes in Blood Pressure

Widening pulse pressure with age

Source: J Gerontol Med Sci 1997;52:M177-83
Cumulative Fatal and Non-Fatal Stroke Rate Per 100 Volunteers

Impact of Treating HTN in Subjects Over Age 80 Years

21%↓

Placebo group

P=0.02

Active-treatment group

No. at Risk
Placebo group 1912 1492 814 379 202
Active-treatment group 1933 1565 877 420 231

Follow-up (yr)

Impact of Treating HTN in Subjects Over Age 80 Years

Impact of Treating HTN in Subjects Over Age 80 Years

Death from Any Cause by Lowering BP to 120

B  Death from Any Cause

Hazard ratio with intensive treatment, 0.73 (95% CI, 0.60–0.90)

Cumulative Hazard

0.0 0.2 0.4 0.6 0.8 1.0

0.00 0.02 0.04 0.06 0.08 0.10

Years

No. at Risk
Standard treatment 4683 4528 4383 2998 789
Intensive treatment 4678 4516 4390 3016 807

Primary CVD Outcome* in SPRINT >75 Years by Baseline Frailty Status

Exclusions: DM, Stroke or CHF history, SBP < 110 after 1 minute of standing

* Composite of nonfatal AMI, ACS, nonfatal stroke, nonfatal CHF, death from CV causes

Williamson JD et al. JAMA. Published online May 19, 2016. doi:10.1001/jama.2016.7050
Primary CVD Outcome* in SPRINT >75 Years by Baseline Frailty Status

Exclusions: DM, Stroke or CHF history, SBP < 110 after 1 minute of standing

*Composite of nonfatal AMI, ACS, nonfatal stroke, nonfatal CHF, death from CV causes
Elevated BP is tightly associated with stroke and other bad CV outcomes; BP reduction has reduced morbidity, mortality and functional loss in multiple trials.

But elders with poor functional status are at high risk for adverse effects of anti-hypertensive drugs, and the worse the function, the greater the risk.

Increased adverse effects and the shortened life expectancy for elders with the worst function argue for avoiding treatment.

Observational studies have shown increased mortality and complications in low-functioning elders treated with BP-lowering medications.
Summary of Treatment for HFpEF

- Diuretics, but only 2 days
- \(\beta\)-blockade – no clear benefit
- ACE Inhibition, ARB – no reduction in mortality in multiple studies, but fewer hospitalizations; candesartan most potent
- Aldosterone inhibition – negative for now
- Digoxin – a long story
- Calcium channel blockade?

Mortality > Age 65 for Normal Diastolic Function, vs Mild, Moderate or Severe Diastolic Dysfunction

18% women, 15% men
47% women, 49% men
30% women, 15% men

US Prevalence of AF by Age and Gender

2012 = >2.3 million
2050 = ~5.6 million

Go AS et al. JAMA 2001;285:2370-2375
Atrial Fibrillation (AF)

- Commonest arrhythmia in adults; ↑ with age
- Associated with other conditions
  - Cardiac - CHF (↑mortality), HTN, RHD
  - Non-cardiac – stress (hyperthyroid), acute illness (PNA, any), drug (EtOH)
- ↑ Physiologic burden to old heart - slowing of diastolic filling 2° LV stiffness → greater dependence on atrial contraction for filling
- Embolic stroke - clot in poorly contracting LAA
- Rhythm control doesn’t reduce mortality in CHF; rate control does (Roy et al. NEJM. 2008;358:2667-77)
4X increase in age-adjusted incidence and prevalence of AF; Risk of AF doubled with each decade of age; Risk factor shift to more effect of obesity and diabetes. Nonetheless, 74% ↓ stroke rate 1998–2007 vs. 1958–67, & 25% ↓ in mortality

Aging of Gastrointestinal Organs

- GI complaints very common in elders
- 35%-40% of adults > 60 patients (~50 million) present with GI symptoms annually
- GERD and constipation are the most common diagnoses, but many complaints go undiagnosed
- Small bowel shows only minor alteration in motility (dysrhythmia), no effect in absorption
- Colon function unchanged in pure aging
Aging of GI Organs – Hepatic Function

- Clearance ↓ - decline in blood flow with age
- Metabolism
  - Phase I – cytochrome microsomal enzyme-mediated deoxidation, hydroxylation and phosphorylation all decline (e.g., H2 blockers, long-acting benzodiazepines, theophylline)
  - Phase II - conjugation (glucuronidation, sulfation), acetylation little Δ (lorazepam)
  - Smoking stimulates mono-oxygenase enzymes, ↑clearance of theophylline - ↓therapeutic efficacy

Plasma and tissue levels usually increased, and demand dose reduction, esp. for phase I agents
GI Aging – Taste, Smell, Swallowing

- Taste bud numbers, sweet unchanged; ↓ salt detection; bitter exaggerated; volume, quality of saliva ↓ - impact often is less interest in food, worsened by common diseases (saliva flow, periodontal) and medications

- Smell - olfactory bulb atrophy, ↓ central processing → ↓ perception, ↓ interest in food – common diseases (AD, PD) → severe loss

- Abnormal transfer of food bolus from oral cavity to pharynx in ~ 60% of >65 without dysphagia

- Delayed elevation of larynx, ↓ clearance from pharynx → aspiration risk
Renal Changes of Aging

Kidney is classic biologic model of decline with aging (1 longitudinal study→ no change age 40 to 80 in 30%, 5-10% severe decline [not replicated])

- Renal weight, volume ↓20-30% by age 80; most loss is cortical, not medullary
- Increased percentage of sclerotic glomeruli, focal GS and 2° A-V shunts bypass sclerosed glomeruli
- BM thickening, atrophic tubules, mesangial sclerosis
- Number of glomeruli ↓30-50% by 80; glomeruli left hypertrophy, ↑IG pressure and hyperfiltration GS
Age-related glomerulo-sclerosis (right) – replacement of normal cellularity (left) with matrix, and adherence to Bowman’s capsule
Renal Function Changes with Age

- Increased % sclerotic glomeruli, in spite of ↑blood flow to remaining glomeruli results in:
  - Overall decline in function
  - Renal blood flow ↓ 10%/decade
  - ↓Response to salt or water load
  - ↓Renal tubular secretion
  - Glomerular filtration rate ↓ 1 ml/min/yr>40

Creatinine clearance ↓ in step with GFR; imperative to calculate $C_{CR}$ in elders
Age-related Structural Brain Changes

- Enlarged Subdural space predisposes to SDH
- Narrower gyri
- Wider sulci
- Enlarged ventricles
Pure Aging by Neurologic Exam

- ↓ arm swing, ↑ tone - ↓ Dopamine neurons
- ↓ DTRs in feet
- ↓ Gag reflex
- ↓ Ability to prevent postural sway
- ↓ Ability to prevent orthostatic hypotension
- ↓ Baroreflex sensitivity
- ↓ Hand- and foot-tapping speed
- Restricted upward gaze
Pure Aging Changes in Memory

- Most memory functions change little with pure aging – mild decrease in attention; elders more easily distracted, so avoid competing tasks
- Processing speed (reaction, retrieval, timed tasks, perceptual), free recall, multi-tasking all decline with age
- Retrieval of names, persons especially, and objects often transiently lost
Obligatory Memory Changes of Aging

- Sensory memory - earliest stage (visual, auditory, tactile) - unstable, rapid decay; no age-related change
- Primary (short-term) memory - rehearsal transfers sensory to short term memory - no loss with age
- Long term (secondary) - hours, days, years
  - Semantic memory – facts, meanings - no Δ
  - Procedural – biking, music, knots - no Δ
  - Episodic – events, time, place - ↓
<table>
<thead>
<tr>
<th>Modifiable Risk Factors in Dementia</th>
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<tbody>
<tr>
<td><strong>For</strong></td>
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<tr>
<td>● Hypertension</td>
</tr>
<tr>
<td>● Obesity</td>
</tr>
<tr>
<td>● Diabetes</td>
</tr>
<tr>
<td>● Inactivity</td>
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<tr>
<td>● Smoking</td>
</tr>
<tr>
<td>● Depression</td>
</tr>
<tr>
<td>● Low education</td>
</tr>
<tr>
<td><strong>Against</strong></td>
</tr>
<tr>
<td>● Absence of box 1</td>
</tr>
<tr>
<td>● High education</td>
</tr>
<tr>
<td>● Cognitive engagement</td>
</tr>
<tr>
<td>● Physical activity</td>
</tr>
<tr>
<td>● Mediterranean diet</td>
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<tr>
<td>● High social supports</td>
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</tbody>
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Declines in Special Senses

- Vision - ↓ accommodation (presbyopia), low-contrast acuity, glare tolerance, adaptation, color discrimination, attentional visual field all decline, due to changes in the eye peripherally and in central processing

- Hearing - Neural, conductive and sensory losses (presbycusis); primarily high tones (consonants) – 50% clinically significant
Strength and Balance

- Major confounders are disuse and disease
- Muscle mass, strength ↓; modifiable by training – at best ~15% ↓ by 80; fast twitch type 2 ↓↓
- Sarcopenia (>50% ↓) common, NOT pure aging
- Strength, cerebellar integrity, hearing and vision all play a role in balance
- Vestibular portion of 8th CN – degeneration of otoconia (otolith granules) – multiple diseases, 8th N sensitivity to drugs are confounders
- Single stance, eyes closed a powerful discriminator
Urinary Tract Aging
(↑risks for UI, but does not cause)

- Detrusor overactivity
- Benign prostatic hyperplasia
- More urine output later in the day
- Atrophic vaginitis and urethritis
- Increased post-void residual urine
- Decreased ability to postpone voiding
- Decreased total bladder capacity
- Decreased detrusor contractility
Bone Changes with Age

- Balance of bone resorption and new bone formation disrupted – drop in formation, resorption unchanged
- BMD declines with age in 🗣️ and 🗣️
  - In 🗣️ loss begins in late 30s, abruptly accelerates with menopause
  - 🗣️ begin gradually 40s-50s, continue inexorably; exacerbated by hypogonadism
- Osteoblasts↓, osteoclasts↑, fat↑
- Osteoporosis risk ↑↑ - major determinant is peak bone mass – public health issue
Gynecological Aging

- External genitalia - labial thinning, wrinkling, pallor, dryness; gray hair; clitoris enlarges
- Breast atrophy, fibrous thickening
- Vagina - atrophy, friability, shortening, shrinkage, decreased secretions (pH up); ↓ rugae, squamous maturation; mucosa thins
- Cervix shrinks, os obscured; uterus small
- Ovaries should not be palpable 10 years PM
- Urethra - functional length, closing pressure ↓, mucosa atrophies
Male Urogenital Aging

- External genitalia - scrotal thinning, pallor, graying and thinning of pubic hair
- Mild gynecomastia
- Benign prostatic hyperplasia
- Urethra - closing pressure diminished
- Mild changes in semen (volume, more abnormal spermatozoa, less motility); men are fertile lifelong
- Erectile changes - duration, firmness, frequency; longer refractory period
What Doesn’t Change With Age?

- Fasting blood sugar
- Electrolyte composition of the blood, pH
- Hemoglobin & Hematocrit
- Leukocyte and platelet counts
- Number of teeth
- Cardiac output (at rest and moderate exercise)
- Levels of most hormones (insulin, cortisol, thyroxin, testosterone, parathormone; not estrogen)
- Cognitive function