Cardiovascular Aging
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Disclosures for Richard W. Besdine, MD

- I have no financial relationship with a commercial entity producing health-care related products and/or services
- I have a deep and abiding passion for improving health and healthcare for older persons, and will do almost anything to achieve the goal
Learning Objectives

Be able to demonstrate understanding of:

- The changes resulting from pure aging in the cardiovascular system
- The effects of these changes on cardiovascular function in healthy elders
- The effects of interactions between these changes of aging and the most common cardiovascular diseases on the clinical manifestations and management of these diseases in elders
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
Understanding Cardiovascular Aging

- As in all organs, CV disease manifestations and pathophysiology in elders are driven by interactions of these diseases with pure aging changes in structure and function of heart and vasculature.

- High prevalence of CV disease in elders complicates defining pure aging; e.g., HTN, CHD.

- Aging changes are defined in studies of subjects without HTN and free of clinical CV disease, who have normal resting and exercise ECGs.

- But physical activity, dietary, smoking and other habits, and BP levels defining HTN add complexity.
Prevalence of CVD by Age and Gender among Americans

Men
Women

Men:
- 20-24: 5.5%
- 25-34: 10.4%
- 35-44: 17.4%
- 45-54: 34.2%
- 55-64: 51.0%
- 65-74: 65.2%
- 75+: 79.0%

Women:
- 20-24: 4.6%
- 25-34: 4.2%
- 35-44: 13.6%
- 45-54: 28.9%
- 55-64: 48.1%
- 65-74: 65.2%
- 75+: 70.7%
# Cardiovascular Admissions

## Number of Admissions (000)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total</th>
<th>Age &gt;65 (13%)</th>
<th>Age &gt;75 (6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>675</td>
<td>401 (59.4%)</td>
<td>216 (32.0%)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>1280</td>
<td>685 (53.5%)</td>
<td>293 (22.9%)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>483</td>
<td>308 (63.8%)</td>
<td>184 (38.1%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>701</td>
<td>560 (79.9%)</td>
<td>378 (53.9%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>812</td>
<td>609 (75.0%)</td>
<td>388 (47.8%)</td>
</tr>
</tbody>
</table>
Reduction in Deaths from CHD 1980-2000

From 10 peer-reviewed studies

% CHD Death Decrease from Rx and Risk Reduction

- United States, 1968–76: 40% Treatments, 54% Risk factors, 6% Unexplained
- New Zealand, 1974–81: 40% Treatments, 60% Risk factors
- The Netherlands, 1978–85: 46% Treatments, 44% Risk factors, 10% Unexplained
- United States, 1980–90: 43% Treatments, 50% Risk factors, 7% Unexplained
- IMPACT Scotland, 1975–94: 35% Treatments, 55% Risk factors, 10% Unexplained
- IMPACT New Zealand, 1982–93: 35% Treatments, 60% Risk factors, 5% Unexplained
- IMPACT England and Wales, 1981–2000: 38% Treatments, 52% Risk factors, 10% Unexplained
- IMPACT United States, 1980–2000 (our study): 47% Treatments, 44% Risk factors, 9% Unexplained
- Finland, 1972–92: 24% Treatments, 76% Risk factors
- IMPACT Finland, 1982–97: 23% Treatments, 53% Risk factors, 24% Unexplained

The Aging Heart

<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>
</tr>
<tr>
<td>Vasodilatation with exercise</td>
<td>↓</td>
</tr>
</tbody>
</table>

Common Clinically Important Pure Aging Cardiovascular Changes in Older Persons

- Decreased cardiovascular reserve
- Increased stiffness of LV
- Rise in systolic BP
- Decreased baroreflex sensitivity
- Autonomic dysfunction
- Sinus node atrophy and dysfunction
- Increase in fibrinogen, & factors V, VIII, IX
- Valvular sclerosis and calcification
Intrinsic cardiac effects and ↑ peripheral resistance contribute to declines in VO₂ Max.
Early in diastole, failure of LV relaxation reduces passive filling phase

Thus more filling must be generated by atrial contraction, occurring late in diastole

Accordingly, rapid heart rates that shorten diastole can compromise cardiac output

And any interference with atrial contraction (e.g., AF) further reduces diastolic filling

Active filling also impaired – Ca^{++} handling

Neubauer S. NEJM. 2007;356:1140-51
Diastolic Filling Changes With Age

• Implications of cardio-acceleration
Arterial Changes with Aging

- ↑ Vascular stiffness indices; pulse wave velocity
- ↑ pulsatile load (↑ systolic and pulse pressures)
- Decrease and fragmentation of elastin
- Calcification of media, ↑ vessel diameter
- ↑ collagen & collagen cross-linking
- ↑ Intimal-medial thickness
- ↓ Endothelial peptide function
- ↓ NO production
Age Changes in Blood Pressure

Widening pulse pressure with age

Rates of Awareness, Rx & Control of HTN

2010 Update
67 M HTN
46% Controlled
54% Uncontrolled
Of Uncontrolled:
40% Unaware
16% Aware, no Rx
44% Aware, Rx

Chobanian AV. NEJM 2009;361:878-87
Aging-Related Changes Increase Risk for Cardiovascular Diseases

- LV stiffness $\rightarrow$ diastolic heart failure
- BP and PP $\Delta$s $\rightarrow$ HTN, Stroke
- Atherosclerosis $\rightarrow$ Coronary heart disease
- Autonomic dysfunction, Baroreflex blunting $\rightarrow$ Syncope
- Sinus node ischemia, Apoptosis $\rightarrow$ AF
- Autonomic dysregulation $\rightarrow$ Ventricular ectopy
Hypertension (HTN)

- SBP↑ with age; continuous risk - no age adjustment
- ↑ peripheral vascular stiffness and resistance are physiologic hallmarks of HTN in older persons
  - ↑ BP variability, sympathetic tone
  - Impaired vasodilatation
  - ↓ NO from vascular endothelium
  - ↓ Vasodilatation by β-adrenergic stimulation
  - ↑ Vasoconstriction by α-adrenergic stimulation
- Age-related ↓ in renal function predisposes to HTN
HTN Treatment Issues in Elders

- SHEP randomized ~5000 persons ≥60 (SBP ≥160 to treatment or not (thiazide 12.5, 25; atenolol 25, 50) and followed 5 years for total strokes (primary) and CV morbidity/mortality, all mortality, and QOL
- Reduced strokes 36% (RR=0.64, P=0.0003; absolute benefit of 30/1000 over 5 years) and CV events 32% (55/1000 over 5 years)
- Behavioral interventions work (↓EtOH, weight, salt, tobacco; ↑exercise)
- Systolic and diastolic HTN should be treated in elders

SHEP Cooperative Research Group. JAMA. 1991;265:3255-64
Average Systolic and Diastolic Blood Pressure During SHEP Trial

Blood Pressure, mm Hg

Follow-up, mo

Placebo

Treatment

Placebo

Treatment

Cumulative Fatal and Non-Fatal Stroke Rate Per 100 Volunteers

SHEP Cooperative Research Group. JAMA. 1991;265:3255-64
SHEP results were definitive, but nearly 20 years later, still uncertainty about very old with HTN.

Optimal BP target not defined >80; observational data suggested HTN treatment → ↑mortality.

But recent data document efficacy: ~2000 > 80 (mean 83+) BP >160 (173/91) randomized to indapamide, perindopril as needed, or placebo, followed ~ 2 yrs, target 150/80 – mean reduction of 15 mm – fewer adverse events in treated group.

Dosing caution - postural hypotension, electrolyte abnormalities, drug interactions.

Impact of Treating HTN in Subjects Over Age 80 Years

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Impact of Treating HTN in Subjects Over Age 80 Years
Prognosis after Acute MI by Age

Circulation 1996;94:1826-33
HF with Preserved Ejection Fraction

- HFPEF, but major problem is diastole
- Increase in fibrous tissue and in size of cardiac myocytes results in LVH and stiffening, and increases risk for HFPEF
- Superimposed hypertension markedly increases diastolic stiffness via production of left ventricular hypertrophy, and produces congestive heart failure with preserved systolic function (EF > 50%) – majority of CHF in older persons is diastolic, not systolic

# Prevalence of Pre-clinical Systolic and Diastolic Dysfunction (Random Community Sample)

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Participants</th>
<th>Ejection Fraction, %</th>
<th>Diastolic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤40</td>
<td>≤50</td>
</tr>
<tr>
<td>General Adult Population (≥45 y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1991</td>
<td>1.1 (0.7-1.7)</td>
<td>4.9 (4.0-6.0)</td>
</tr>
<tr>
<td>Men</td>
<td>952</td>
<td>2.0 (1.2-3.1)</td>
<td>7.9 (6.3-9.8)</td>
</tr>
<tr>
<td>Women</td>
<td>1039</td>
<td>0.3 (0.1-0.8)</td>
<td>2.2 (1.4-3.3)</td>
</tr>
<tr>
<td>High-Risk Population (Age ≥65 y and Hypertension or Coronary Artery Disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>396</td>
<td>2.8 (1.4-4.9)</td>
<td>10.9 (8.0-14.4)</td>
</tr>
<tr>
<td>Men</td>
<td>196</td>
<td>5.1 (2.5-9.2)</td>
<td>16.8 (11.9-22.8)</td>
</tr>
<tr>
<td>Women</td>
<td>200</td>
<td>0.5 (0.0-2.8)</td>
<td>5.0 (2.4-9.0)</td>
</tr>
</tbody>
</table>

*Preclinical denotes no previous validated congestive heart failure diagnosis. Ejection fraction was assessed by 2-D visual method.*

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

- Normal: 18% women, 15% men
- Mild: 47% women, 49% men
- Moderate or Severe: 30% women, 15% men

Rx of CHF with Preserved Ejection Fraction

- Diuretics, but only 2 days
- ß-blockade – no clear benefit
- ACE Inhibition, ARB – no reduction in mortality in multiple studies, but fewer hospitalizations; candesartan most potent
- Aldosterone inhibition (spironolactone, eplerenone [less gynecomastia]) – pending
- Digoxin – a long story
- Calcium channel blockade?

Studied in DIG Trial in HFPEF cohort (Ancillary) as part of DIG; ~ 1000 ambulatory pts on ACEI & diuretic randomized to dig, followed for 37 months

NO significant benefit to HF hospitalization (HFH), HF mortality or CV mortality, BUT

Magnitude of dig-associated reduction in HFH (HR 0.79) similar to benefit in systolic failure (HR 0.72), with 7-fold more patients

Also, 75% of HFPEF pts had class I-II symptoms

No further dig trials underway

Ahmed A. Circulation. 2006;114:397-403
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Physicians should control ventricular rate in patients with atrial fibrillation.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Physicians should use diuretics to control pulmonary congestion and peripheral edema.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Physicians might recommend coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.</td>
<td>Iita</td>
<td>C</td>
</tr>
<tr>
<td>Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>The use of digitalis to minimize symptoms of heart failure might be considered.</td>
<td>Iib</td>
<td>C</td>
</tr>
</tbody>
</table>

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)
Atrial Fibrillation (AF) Among Elders

- Most of those at highest risk are old, but reluctance to use VKA in elders – 1/3 of eligible
  - Many co-morbid conditions
  - Many medications, diet, adherence, testing
  - Falls are frequent
  - Intracranial hemorrhage is frightening, disabling and lethal
- Data are persuasive on risk-benefit, but…
- Use of VKA declines as AF patients get >80
Morbidity of Atrial Fibrillation

- AF increases stroke risk 5- to 6-fold, and increases embolism risk 18-fold
- The age boom of this century ensures many more fibrillators over the coming decades
- AHA estimates that 20% of the nearly 800,000 strokes (140,000 deaths) annually are secondary to AF – 3rd leading cause of death
- Of patients with AF who are not treated with anticoagulants, 35% will have a stroke at some point in their lifetimes
Anticoagulation Risks for Elders

- Extreme old age
- Multiple coexisting conditions
- Multiple medications
- Renal impairment – universal with aging
- Hepatic detoxification impairment
- Medication errors
- Frequent falls
- Cerebral amyloid angiopathy
## Risk Stratification; e.g., CHADS$_2$

<table>
<thead>
<tr>
<th>Risk Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHF</strong></td>
<td>(C) 1</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>(H) 1</td>
</tr>
<tr>
<td><strong>Age &gt;75 yr</strong></td>
<td>(A) 1</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>(D) 1</td>
</tr>
<tr>
<td><strong>Stroke or TIA</strong></td>
<td>(S) 2</td>
</tr>
</tbody>
</table>

Gage et al. JAMA 2001;285:2864
# CHADS<sub>2</sub> Risk Score

<table>
<thead>
<tr>
<th>Patients (N=1733)</th>
<th>Score</th>
<th>Stroke Rate (%/yr, adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>27%</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>30%</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>19%</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>13%</td>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>4%</td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Gage et al. JAMA 2001;285:2864
Stop Anticoagulation if Patient Remains in NSR? NO!

Why not?

1. Follow-up must be assiduous because AF is highly likely to recur, even when anti-arrhythmic drugs are at therapeutic levels.
2. Recurrence of AF often asymptomatic - most patients who have symptomatic AF also have asymptomatic AF by Holter.
3. First sign of recurrence can be a stroke.
Net Clinical Benefit of Warfarin, by Age & CHADS2 Score

Dabigitran Concerns

- FDA approved a 75 mg dose without data on benefit – based only on predicted pharmaco-kinetics related to renal function
- Dose response associations with age, sex, CHF, weight, Hgb; use of PPIs, amiodarone, verapamil (fatal GI bleed)
- Only 1/3 of those on it got it approved use (AF)
- Abundant case reports of fatal and near-fatal bleeding, mostly in elderly patients
- >80% cleared as creatinine, so must adjust for decline in creatinine clearance with age
- 30% increase in AMI or ACS

Radecki RP. Ann Int Med. 2012; 157:2-4