The Heart Break of Advancing Age

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Aging is the major risk factor for the quintessential diseases in our society.

Atherosclerosis

Hypertension

↓

Myocardial Infarction

Stroke

Heart Failure

Do We Know Why?

TODAY'S MENU

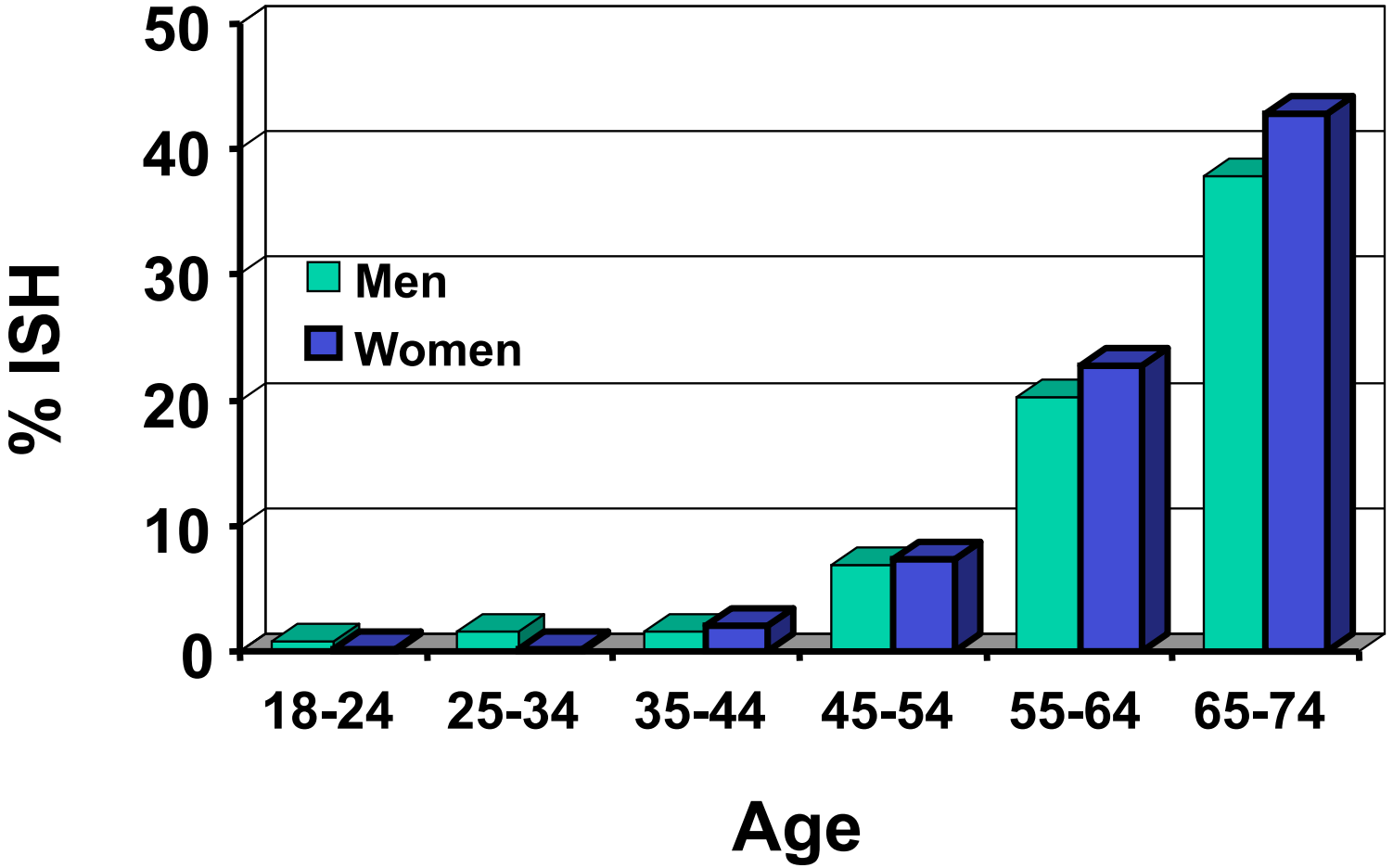
ARTERIAL AGING

- Age is the major Risk Factor for Arterial Disease
- Arterial Aging in Apparently Healthy Humans
- Risky Components of Arterial Aging at the Clinical Level
- Risky Components of Arterial Aging under the Microscope
- Retardation or Prevention of Arterial Aging

CARDIAC AGING

- LV - Arterial Coupling

Prevalence of ISH

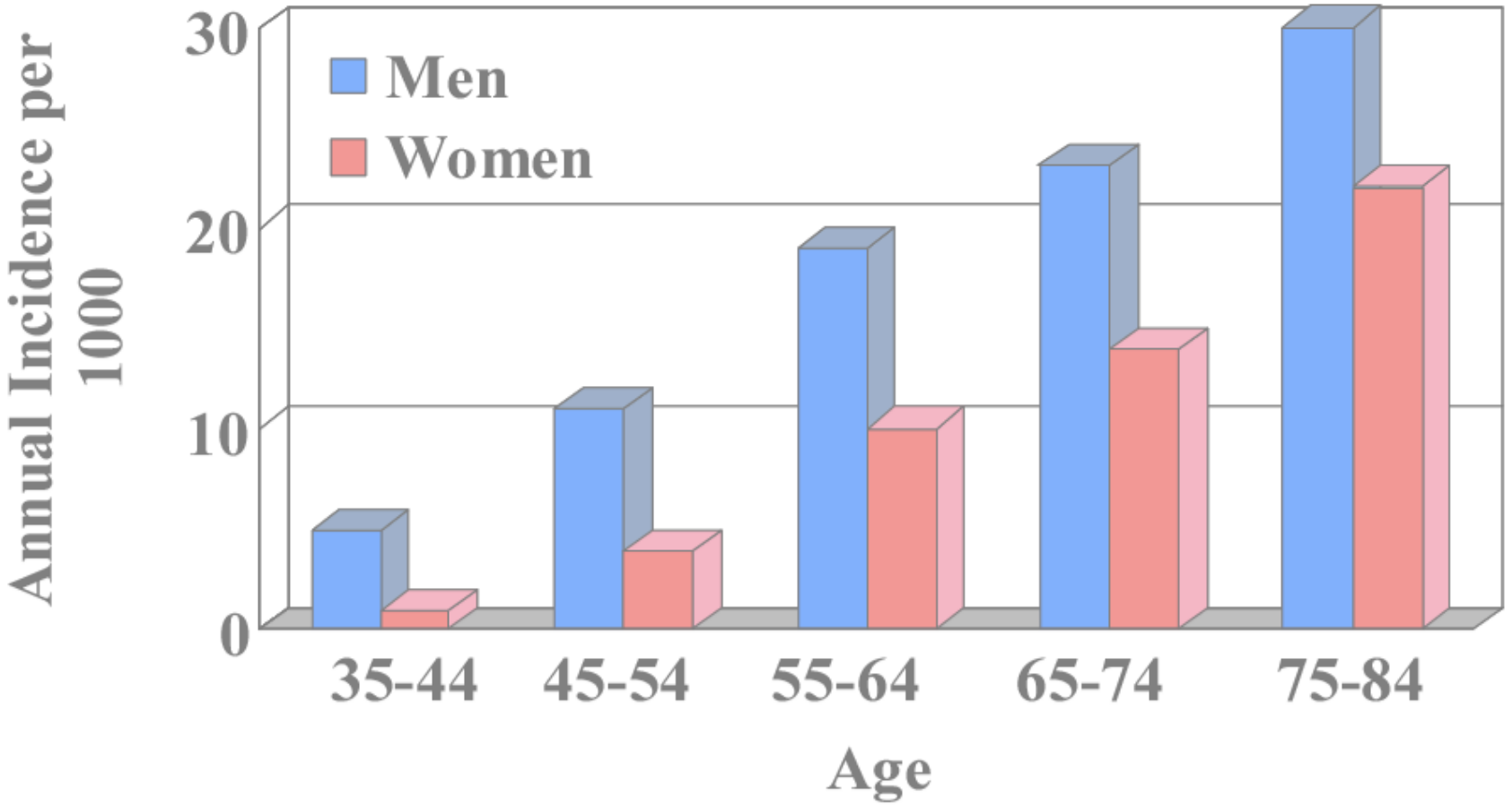


Based on NHANES III Survey

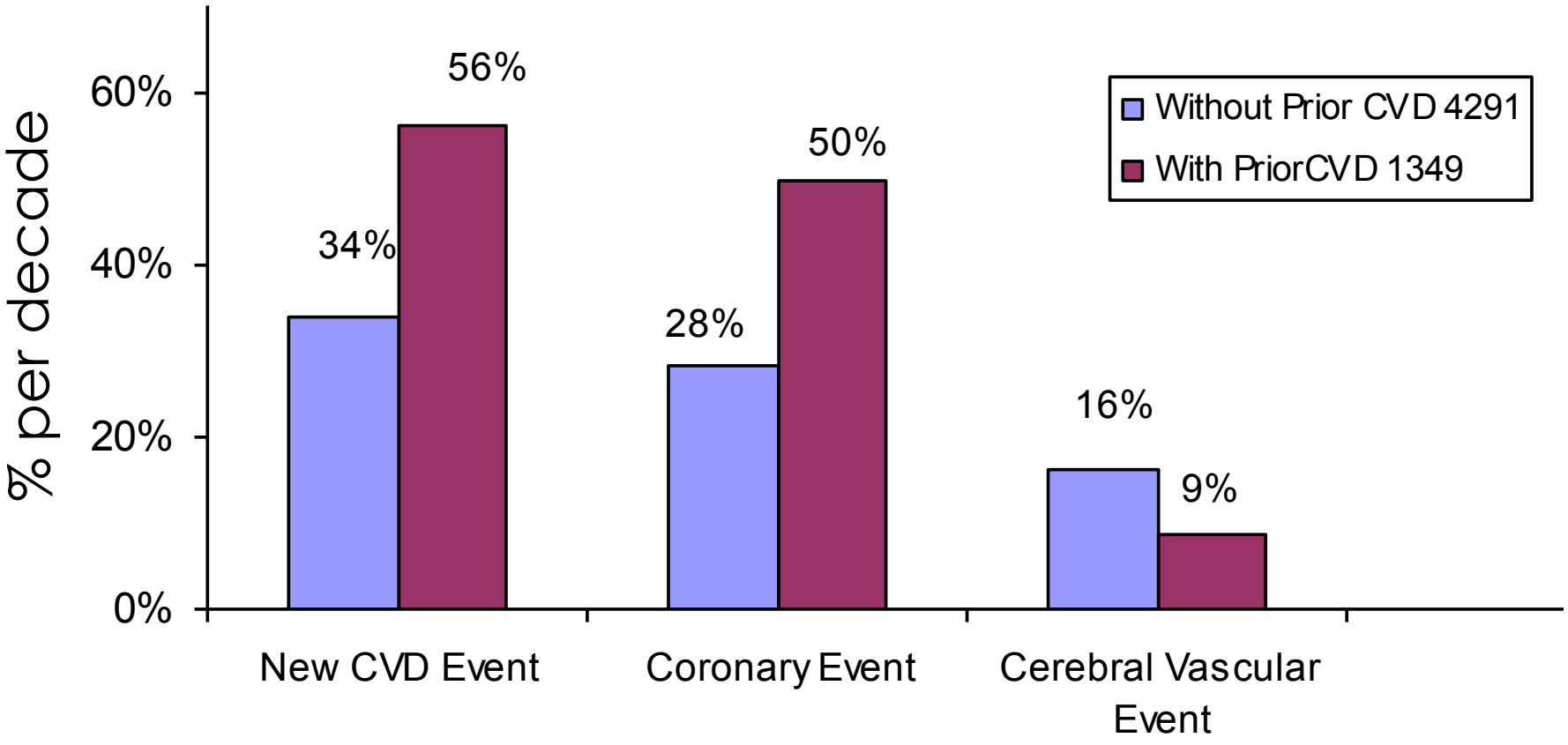
Joffres, *AJH* 2001;14:1099

Incidence of CHD by Age and Sex

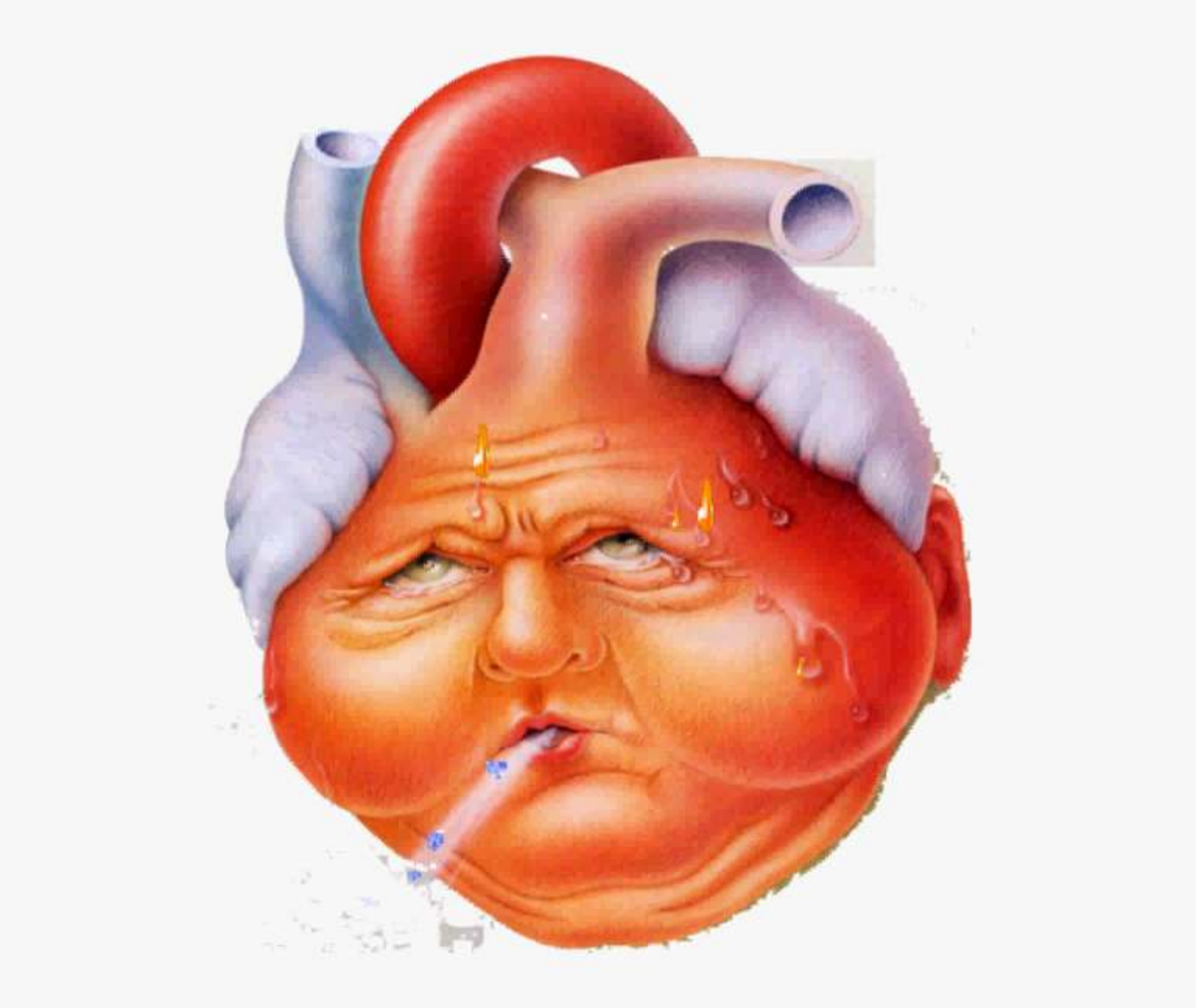
(Framingham)



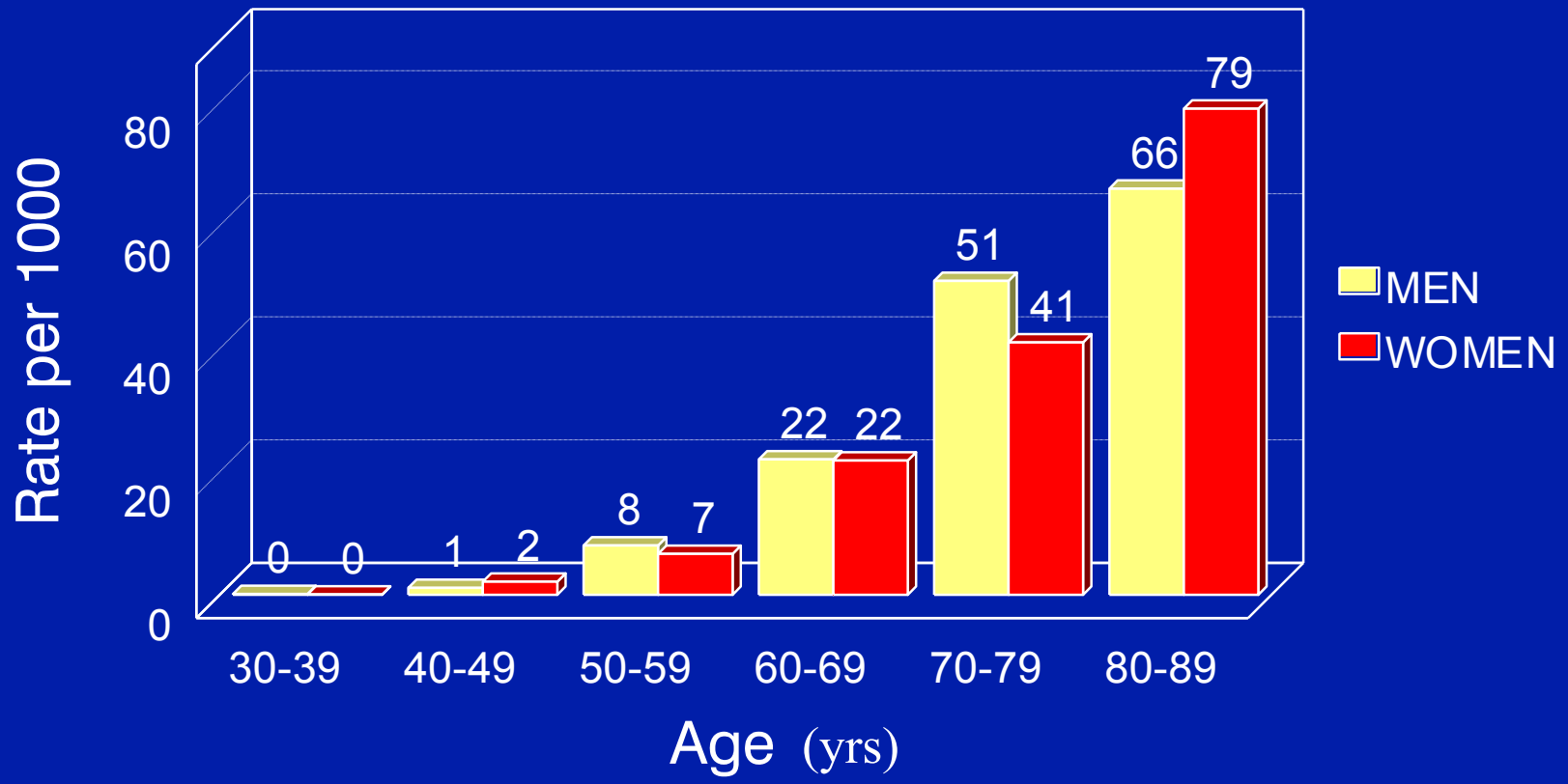
New CVD Events Over a Decade of Follow-Up Cardiovascular Health Study (>65 yrs of age)



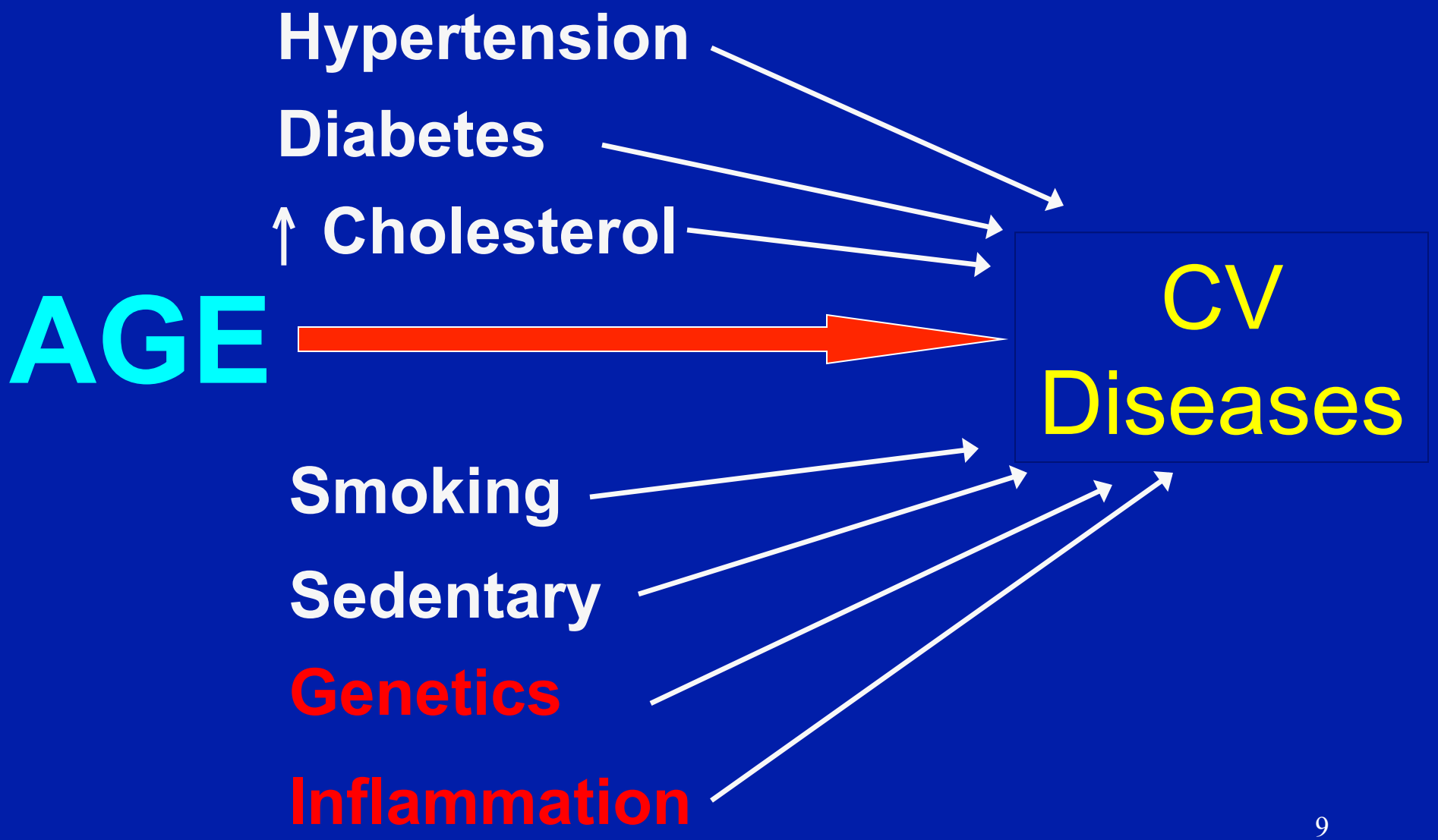
Chronic Heart Failure



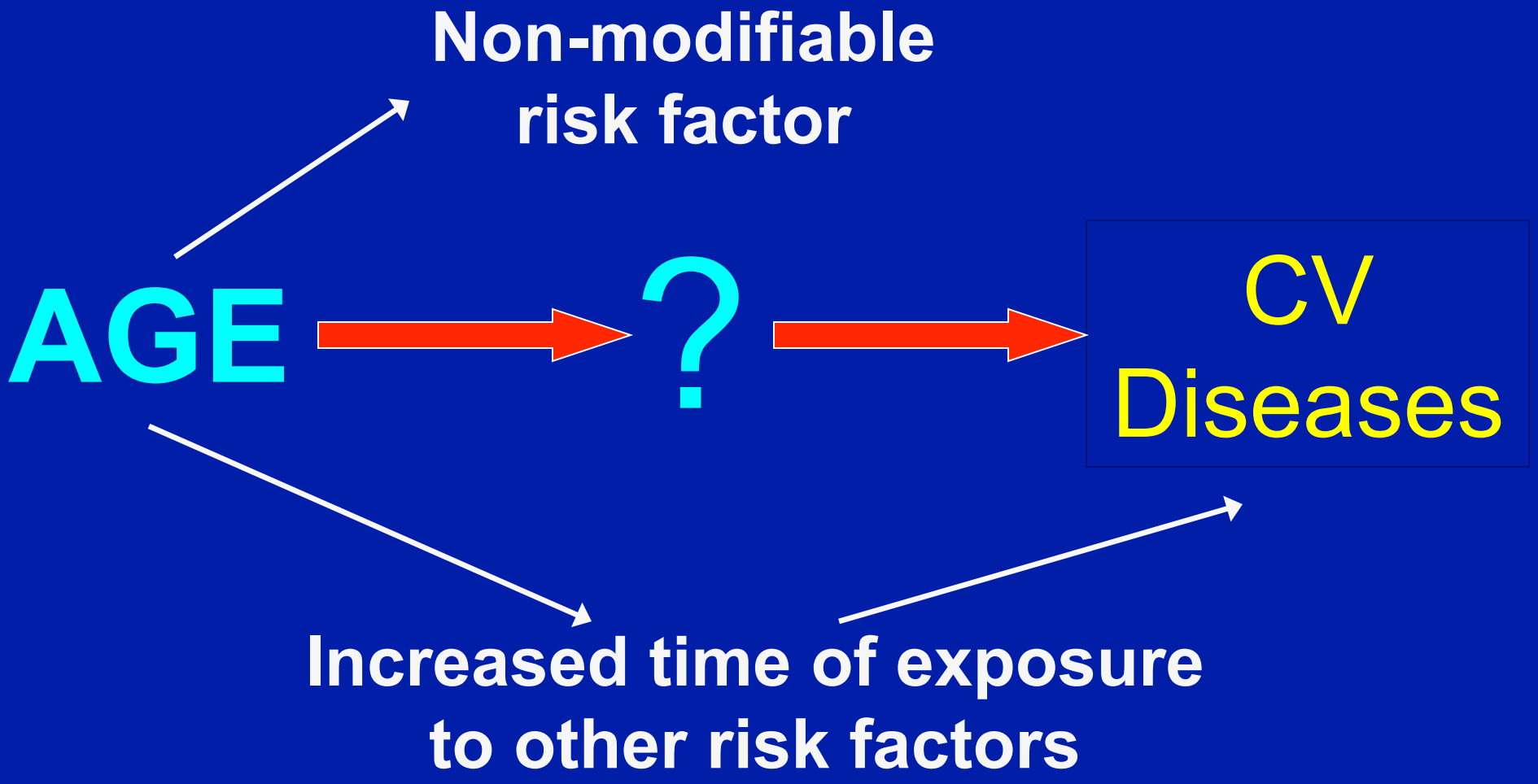
Prevalence of Heart Failure by Age (Framingham)



Age is the Dominant CV Risk Factor



What are the Risky Aspects of Aging?



Understanding why arterial aging is a dominant risk factor for arterial diseases

- **Need to define arterial aging sans clinical disease**
- **Need to understand mechanisms of arterial aging sans clinical disease**

TODAY'S MENU

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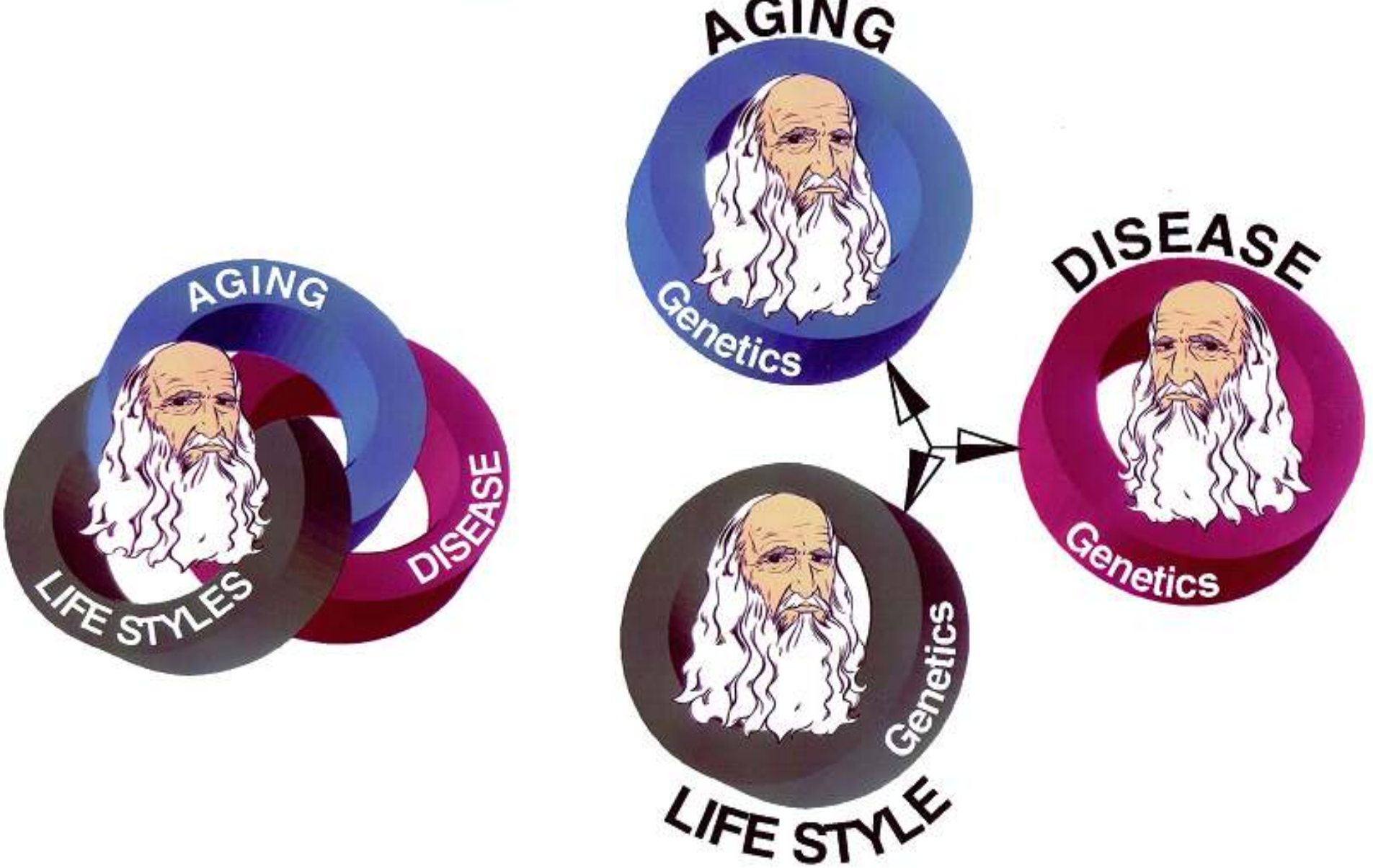
CARDIAC AGING

- LV - Arterial Coupling

The BLSA

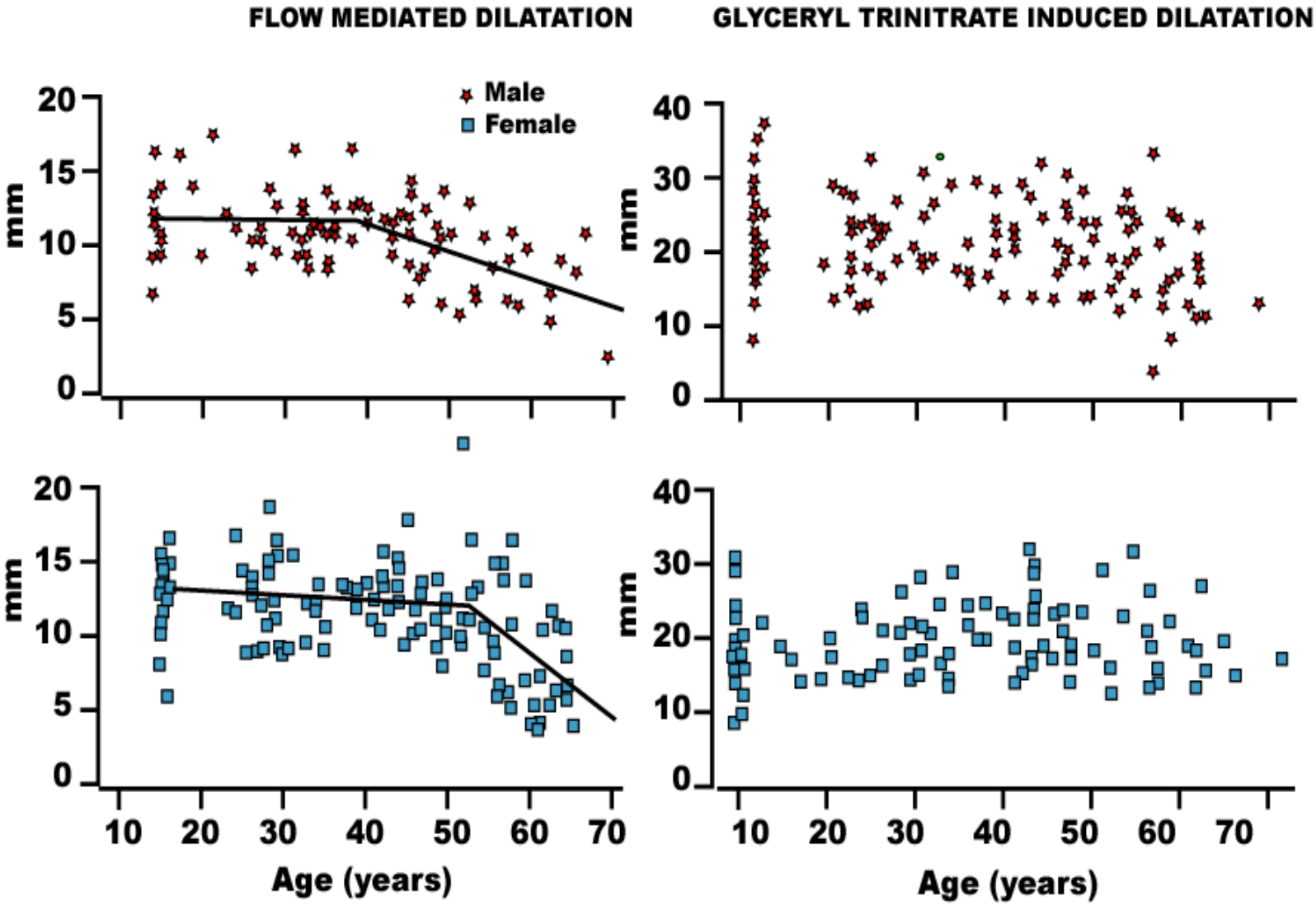

AGING
Genetics
DISEASE
Genetics
Genetics
LIFE STYLE
AGING
DISEASE
LIFE STYLES

Arterial Aging Without a Textbook Clinical Disease Diagnosis

Age-Associated Changes in Central Arterial Structure and Function During "Normative Aging"

- ↑ Intimal-Medial Thickness
- ↑ Collagen Content
- ↓ Elastin (frayed)
- ↑ Lumen Size
- ↓ Endothelial Function
- ↑ Stiffness
- ↑ Systolic Pressure
- ↑ Pulse Pressure

Endothelial Function vs Age

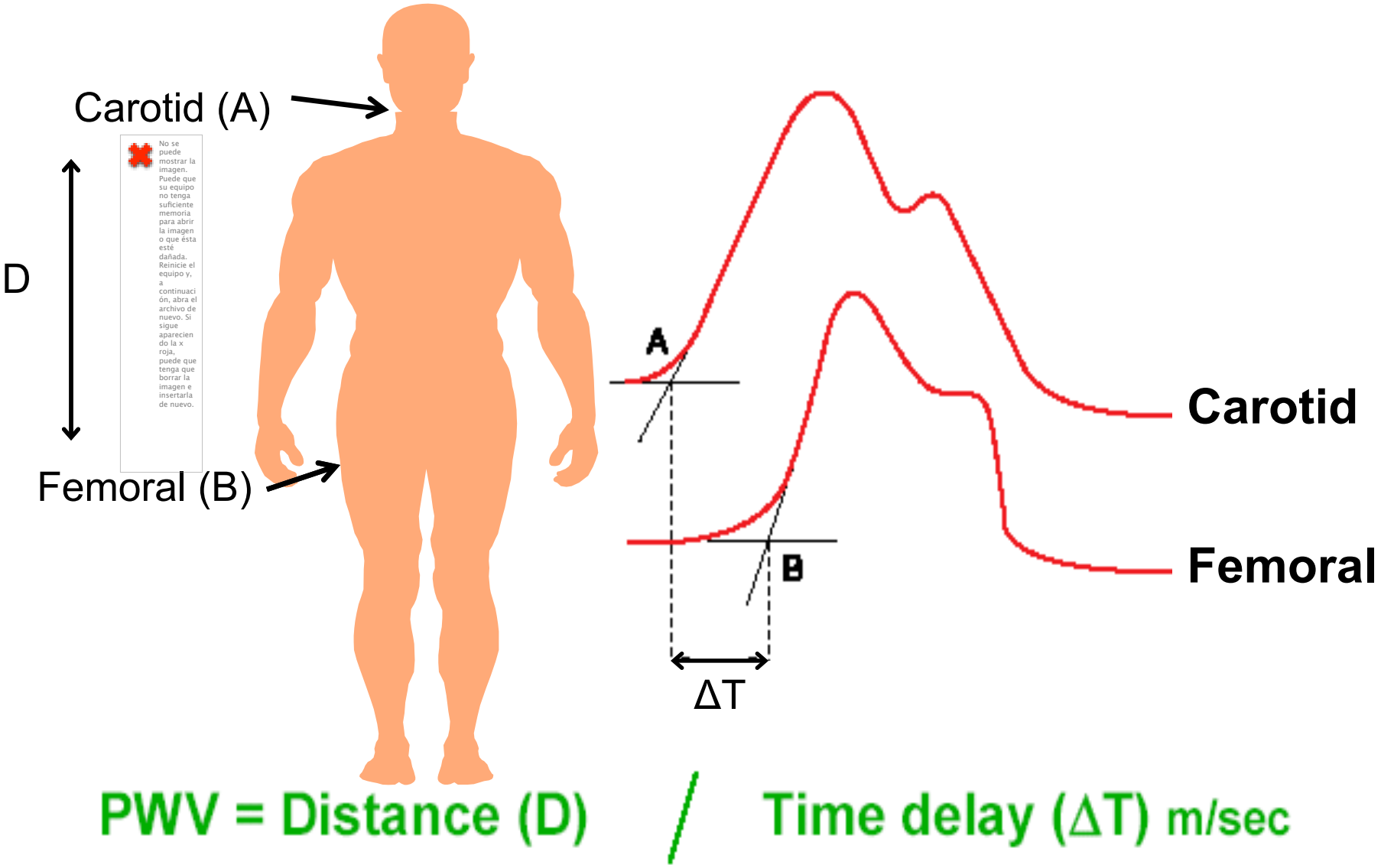


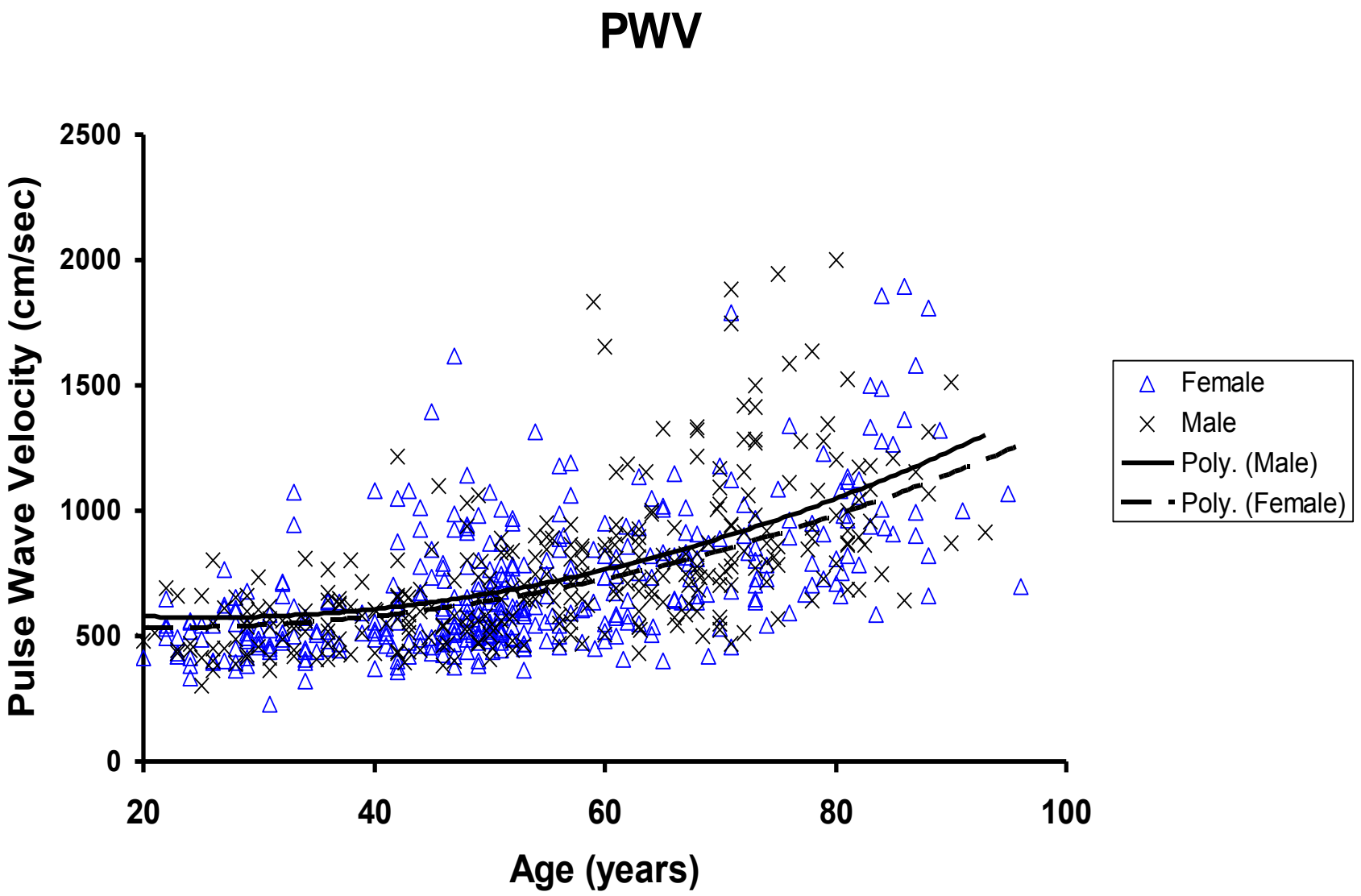
J Am Coll Cardiol 1994:24:471-476

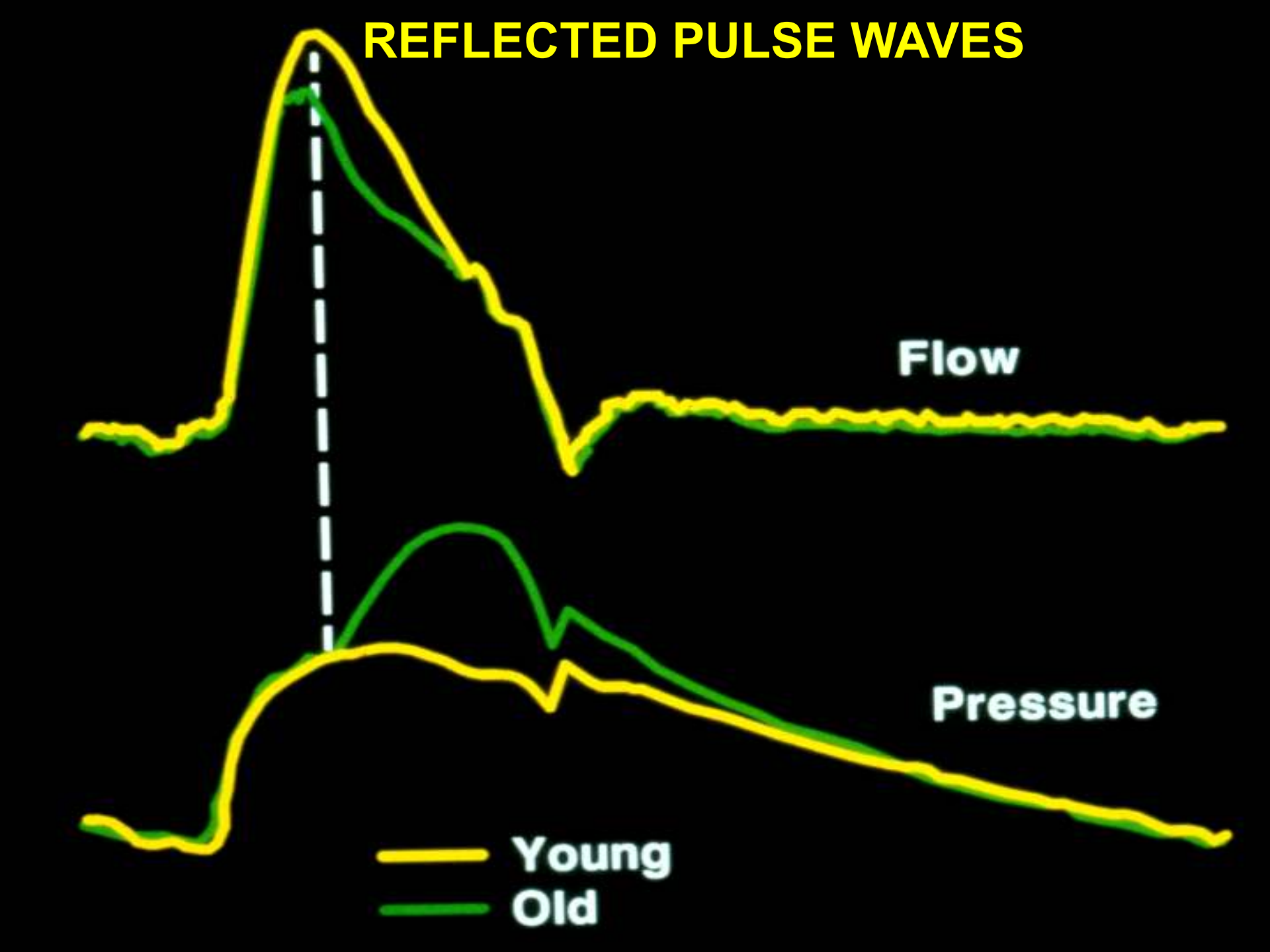
Pulse Wave Velocity

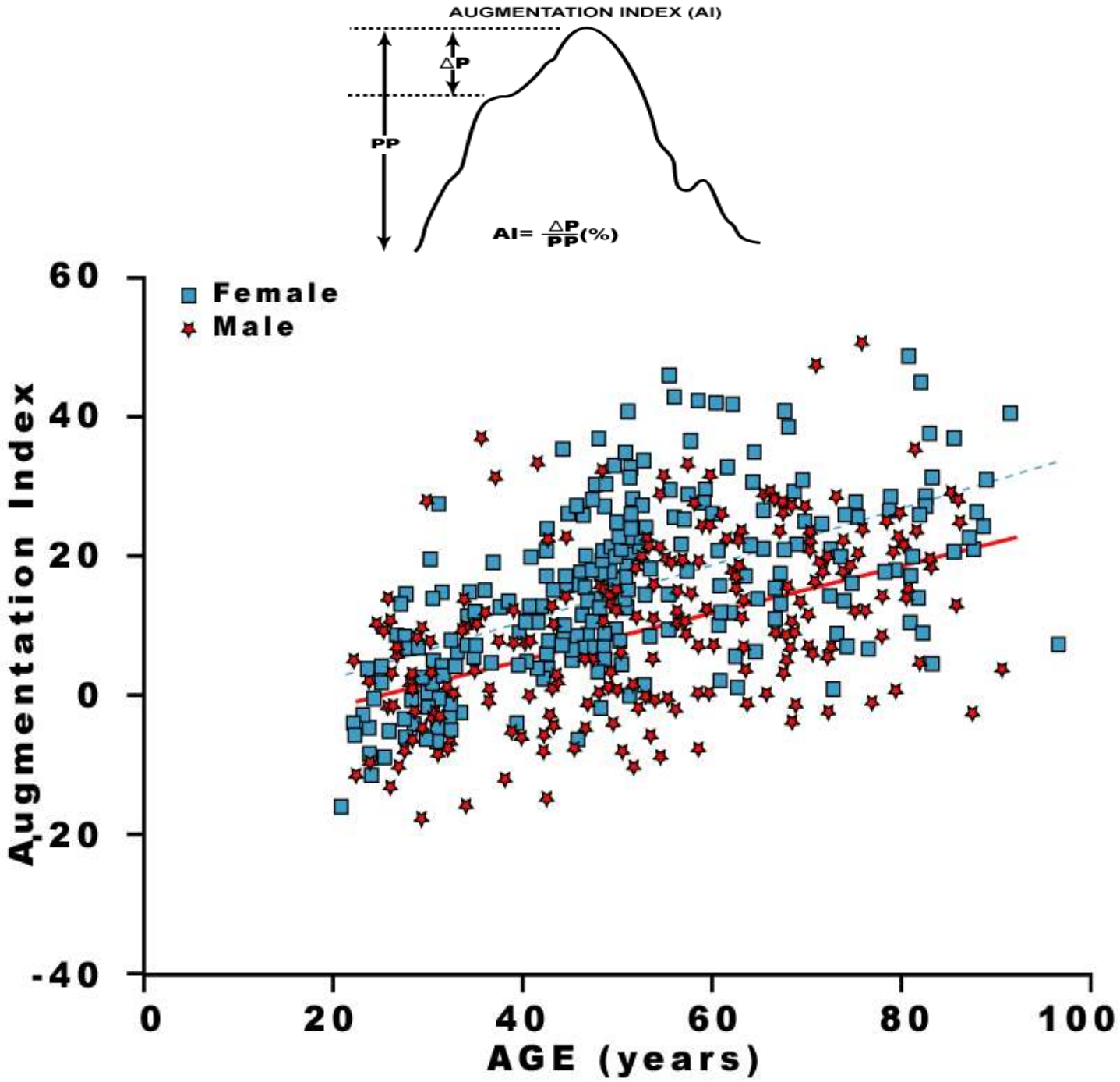
- Pulse wave is generated with each systolic contraction of the LV
- Pulse wave distends the arterial tree as it propagates centrifugally
- Velocity of this pulse wave is related to the stiffness of the arterial wall

Assessment of Pulse Wave Velocity

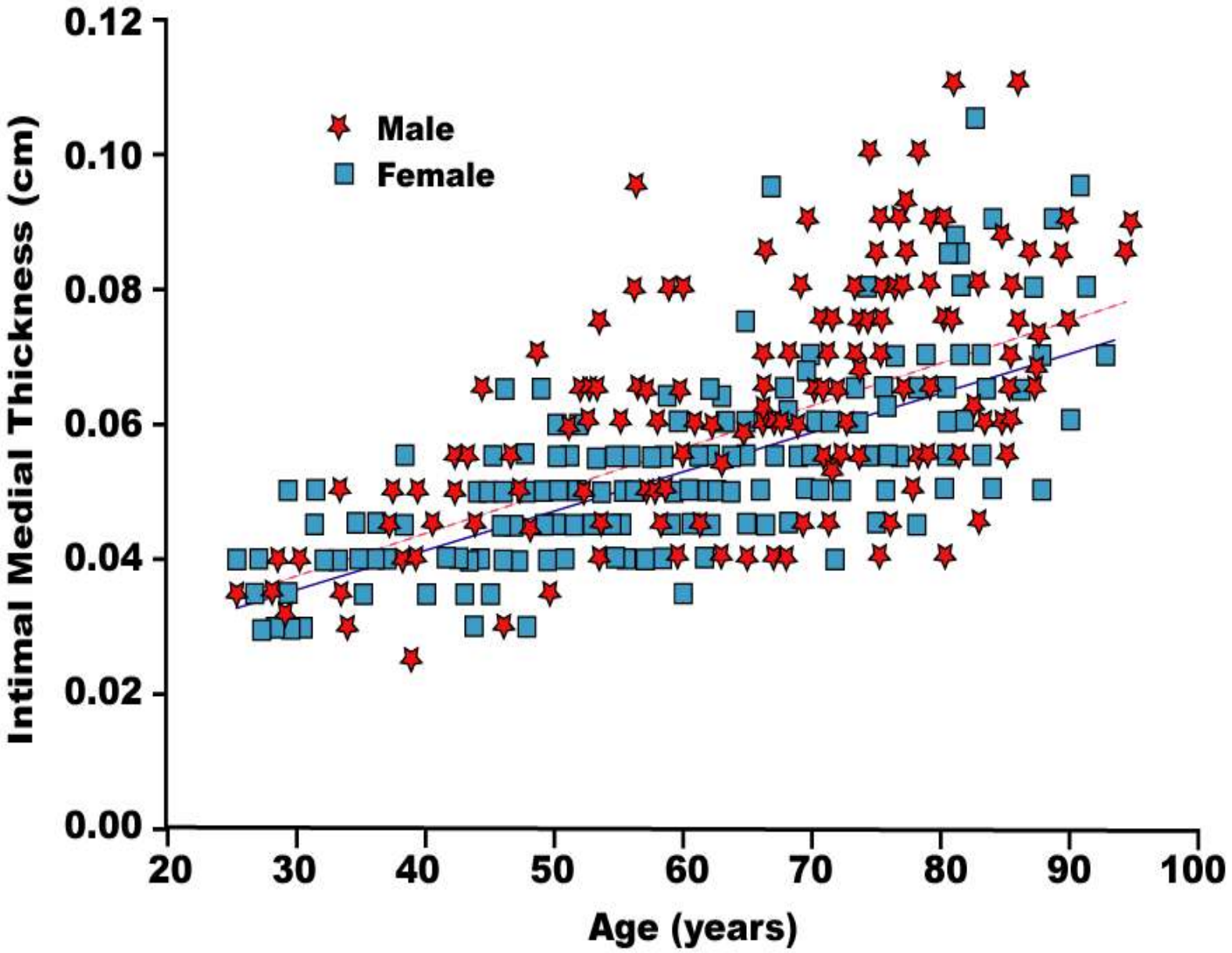



PWV
Pulse Wave Velocity (cm/sec)
2500
2000
1500
1000
500
0
20
40
60
80
100
Age (years)
Female
Male
Poly. (Male)
Poly. (Female)


REFLECTED PULSE WAVES
Flow
Pressure
Young
Old


AUGMENTATION INDEX (AI)
ΔP
PP
AI= ΔP/PP(%)
Female
Male
Augmentation Index
60
40
20
0
-20
-40
0
20
40
60
80
100
AGE (years)

Intimal Medial Thickness



Do We Know Which of These Age-Associated Arterial ChangesWhat Are The "Risky" Ones?

TODAY'S MENU

ARTERIAL AGING

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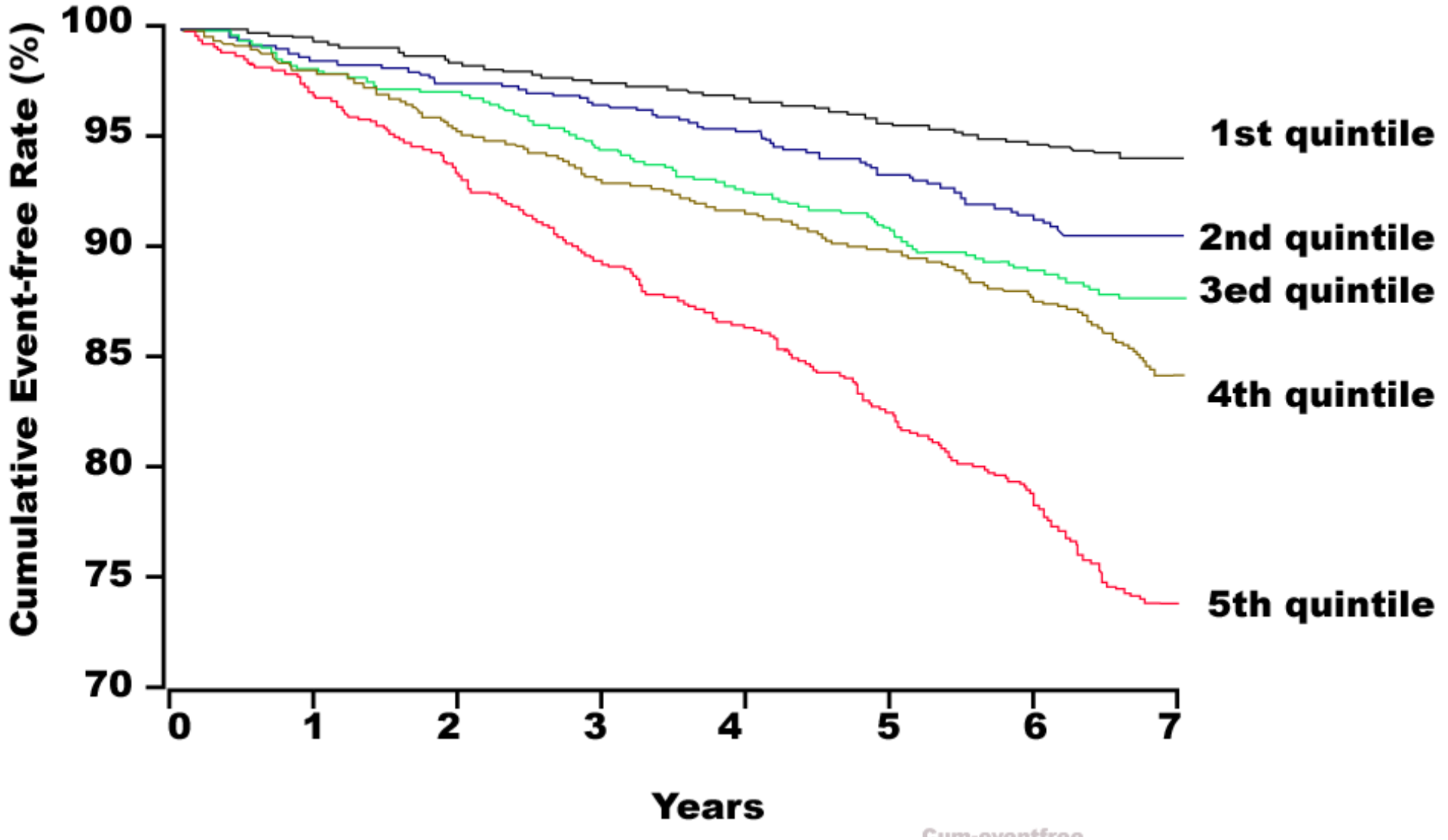
CARDIAC AGING

- LV - Arterial Coupling

Documented Risky Components of Arterial Aging

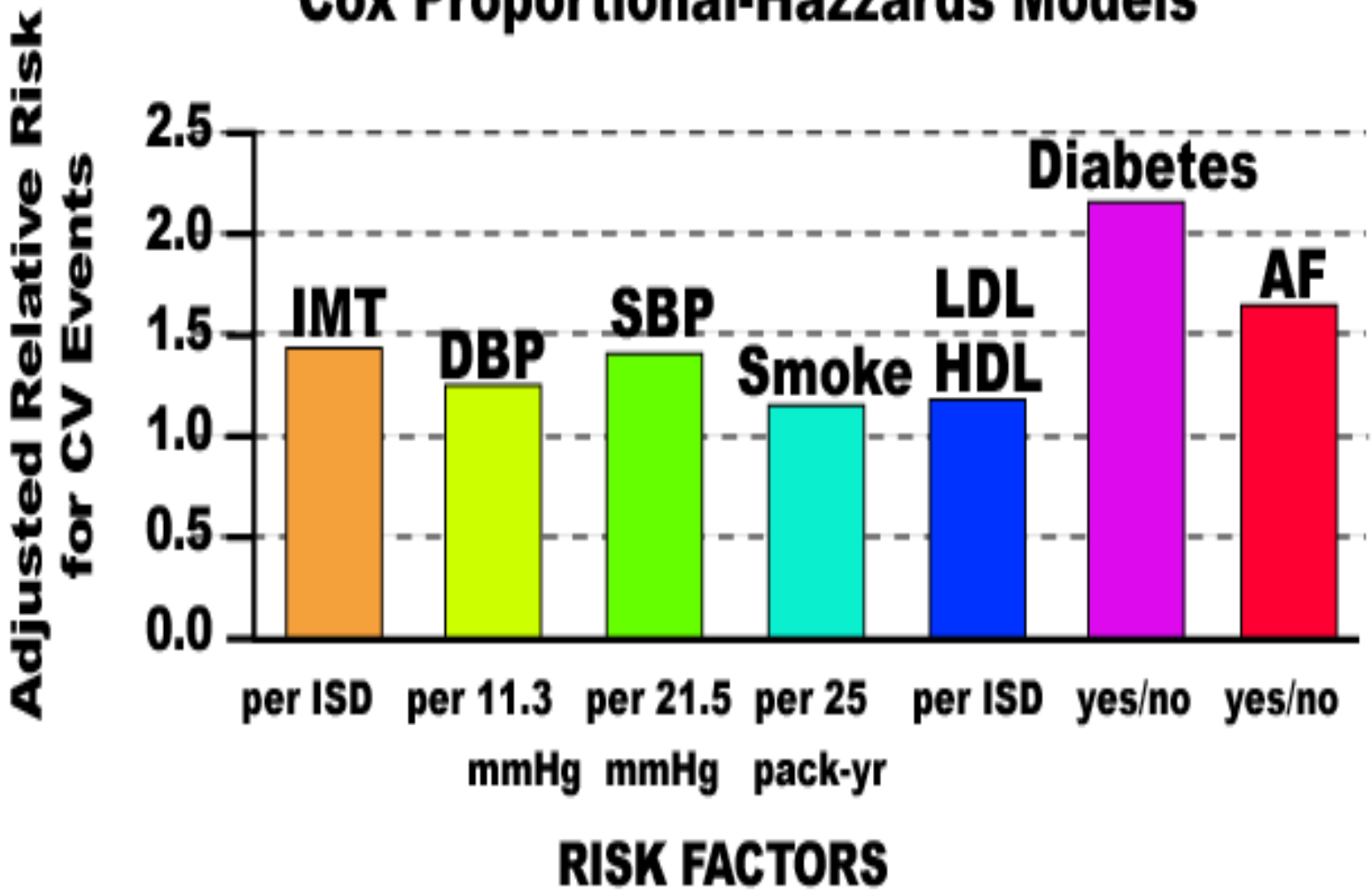
- Pulse Wave Velocity
- Intimal-Medial Thickness
- Endothelial Dysfunction
- Augmentation Index
- Pulse Pressure

Cumulative Event-Free Rates for Myocardial Infarction or Stroke According to Quintile of Combined Intima-Media Thickness



N Engl J Med 1999:340:14-22

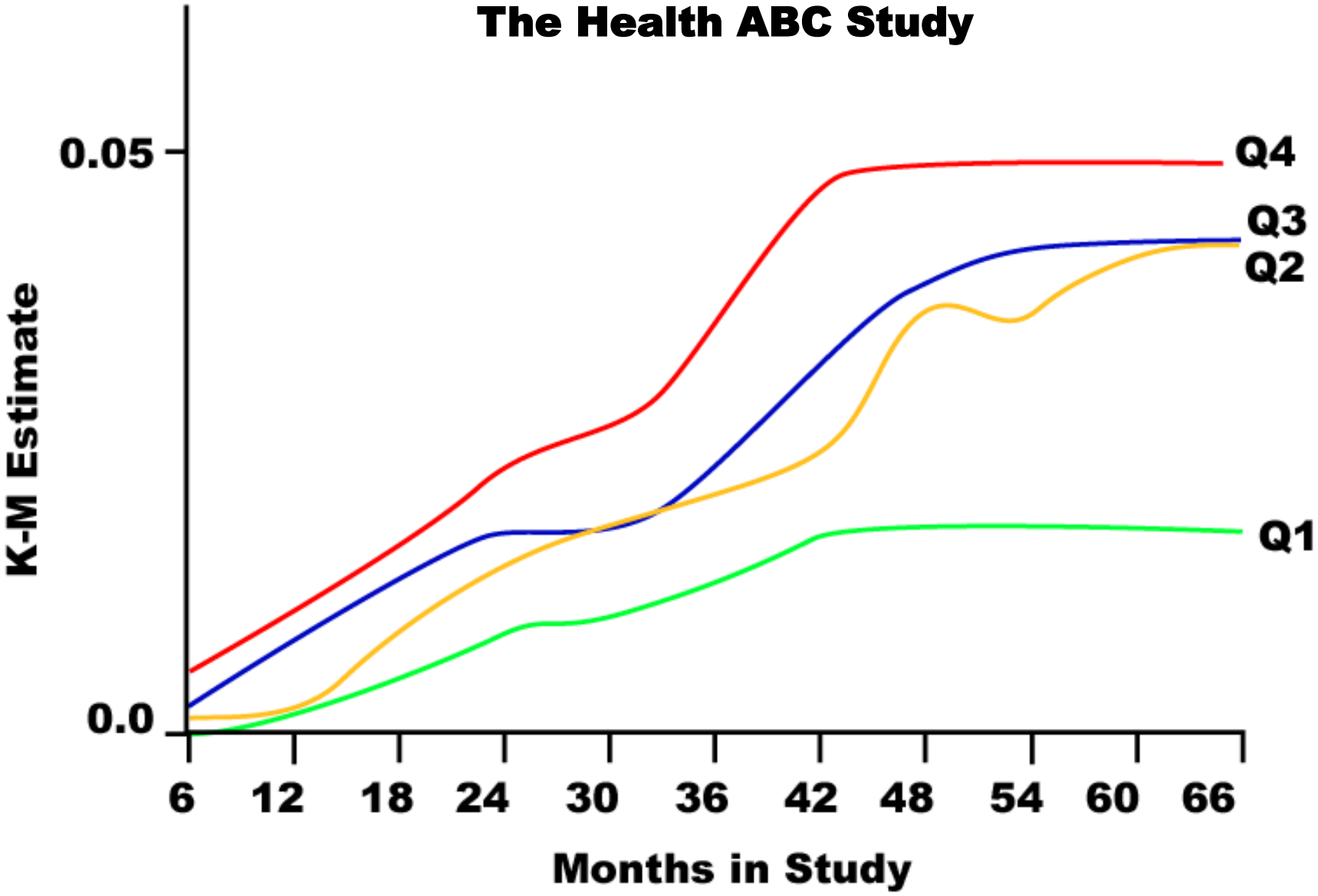
Age and Sex Adjusted Risk Factors for Combined Event of Stroke or Myocardial Infarction in Cox Proportional-Hazzards Models



N Engl J Med 1999:340:14-22

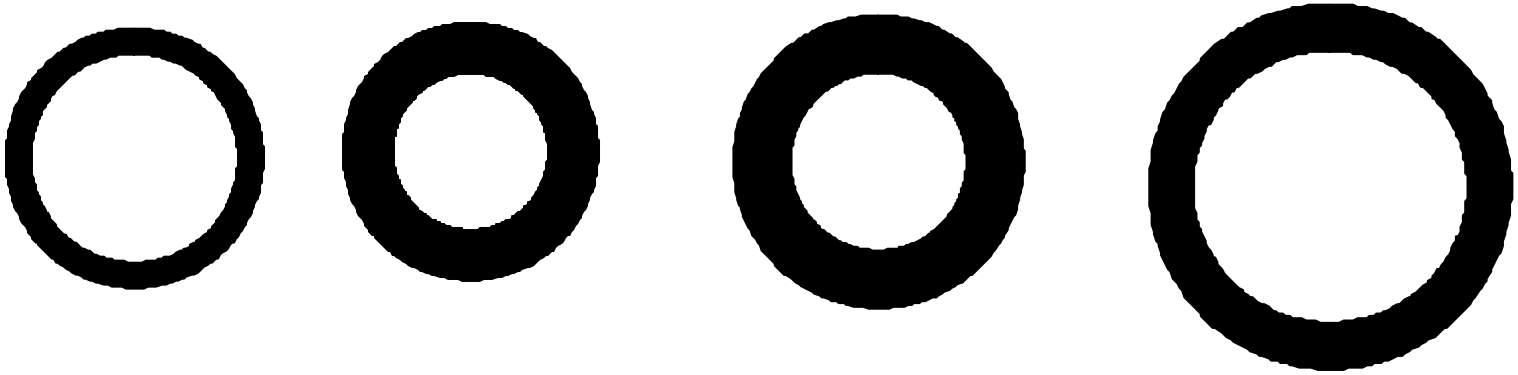
Pulse Wave Velocity Predicts CV Mortality

The Health ABC Study



The Spectrum of Arterial Remodeling

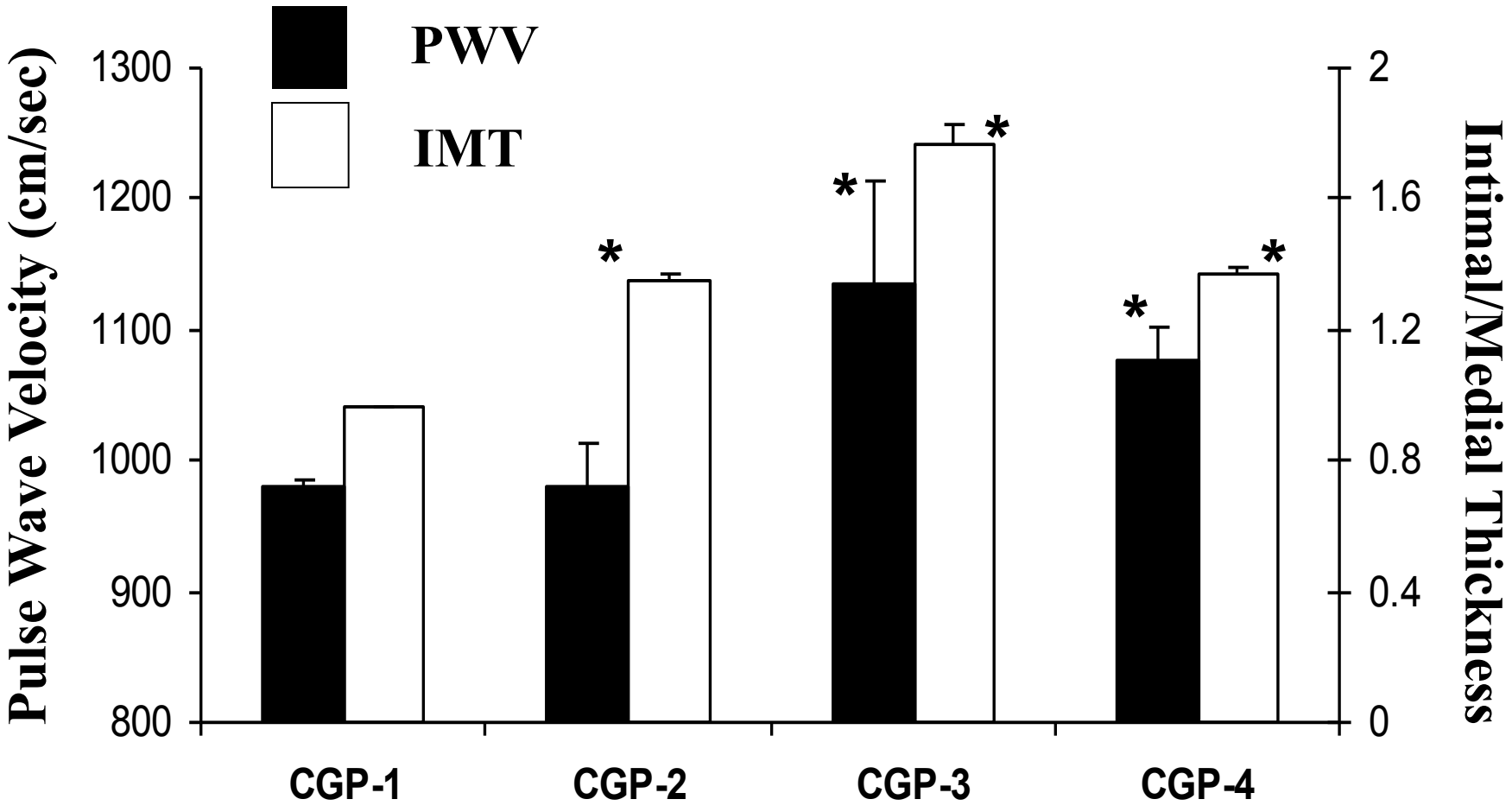
Carotid Geometric Phenotypes*



CGP-1 CGP-2 CGP-3 CGP-4

CGP1 (normal): normal W/L and VM;
CGP2 (remodeling): ↑ W/L and normal VM;
CGP3 (hypertrophy): ↑ W/L and ↑ VM;
CGP4 (hypty + dilation): normal W/L and ↑ VM.

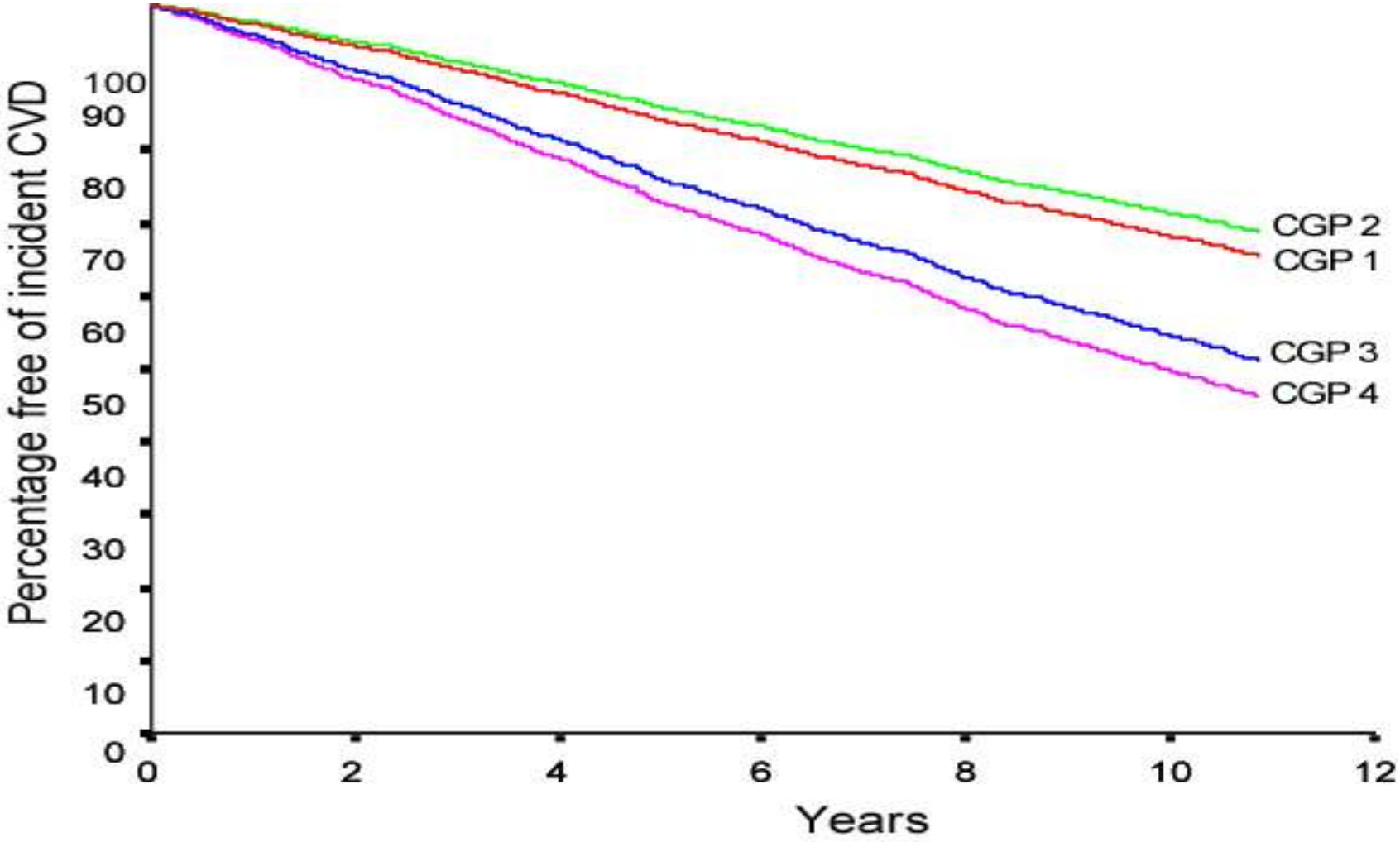
Pulse Wave Velocity
Cardiovascular Health Study



*** p< .05 vs. CGP1**

Cardiovascular Health Study

Unadjusted Incident CVD-free survival according to CGP*



CGP:*

Based on the age- and sex- specific 75th percentile for W/L and VM of the 1524 elderly normotensive free of prevalent CVD participants in the Cardiovascular Health Study

Aging blood vessels are fertile soil in which the seeds of vascular disease flourish!

What do we know about cellular and molecular mechanisms of the risky aspects of arterial aging?

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CARDIAC AGING

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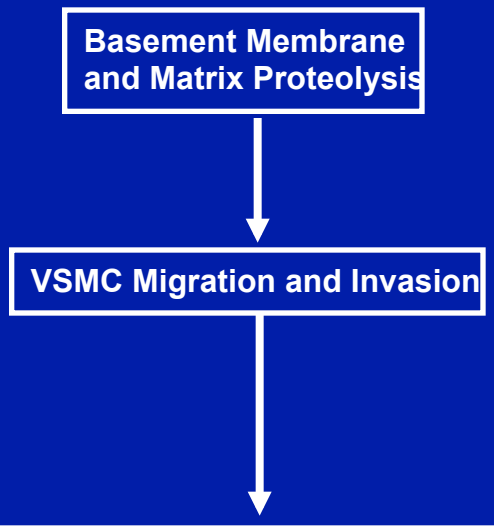
Aging and Diseases of Large Arteries

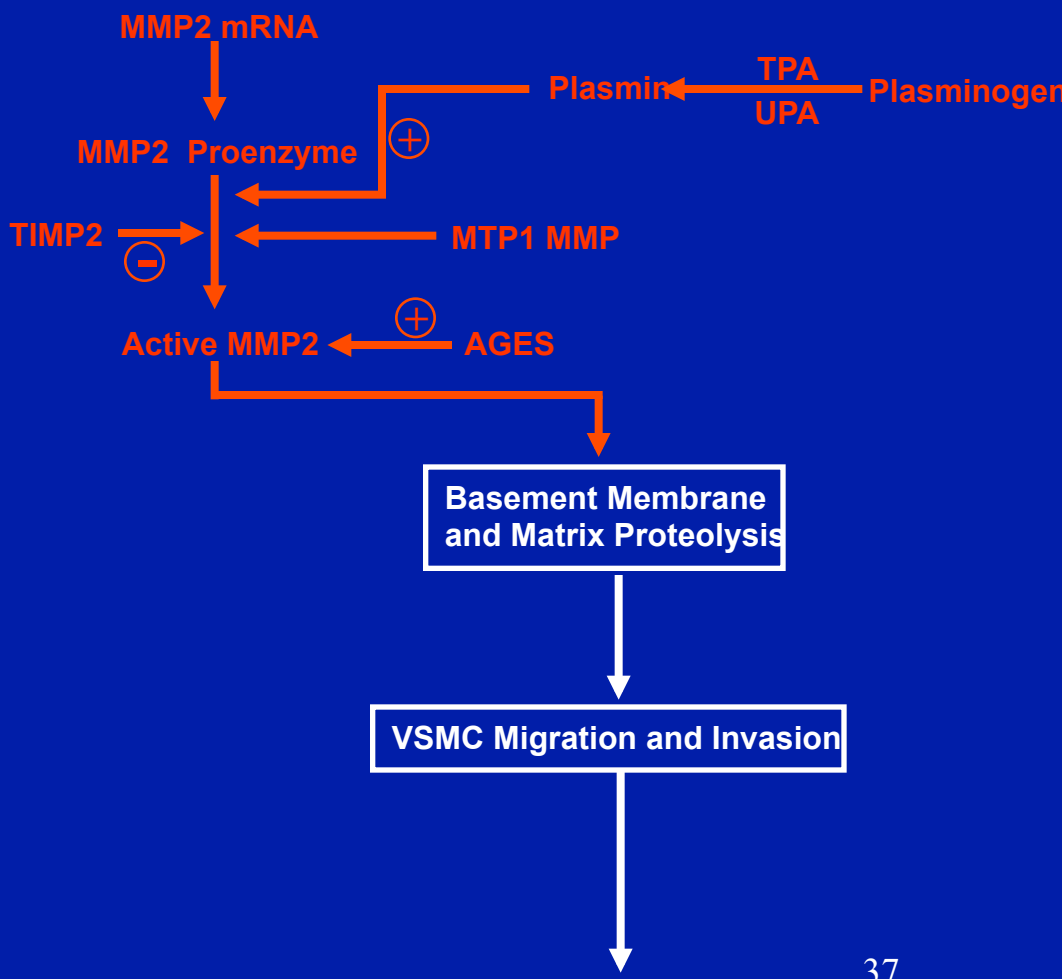
	Humans (>65 yrs)	Monkeys (15-20 yrs)	Rats (24-30 mos)
Lumenal dilation	+	+	+
↑Stiffness	+	+	+
Endothelial dysfunction	+	+	+
Diffuse Intimal Thickening	+	+	+
VSMC	+	+	+
Macrophages	+	-	-
Matrix	+	+	+
MMP dysregulation	+	+	+
MCP-1/CCR2	+	+	+
TGFB	?	+	+
ICAM	?	?	+
Local ANGII-ACE	+	+	+
Lipid involvement	-	-	-
Hypertension	(±)	-	-
Atherosclerosis	(±)	-	-

AGE ASSOCIATED REMODELING OF LARGE ARTERIES



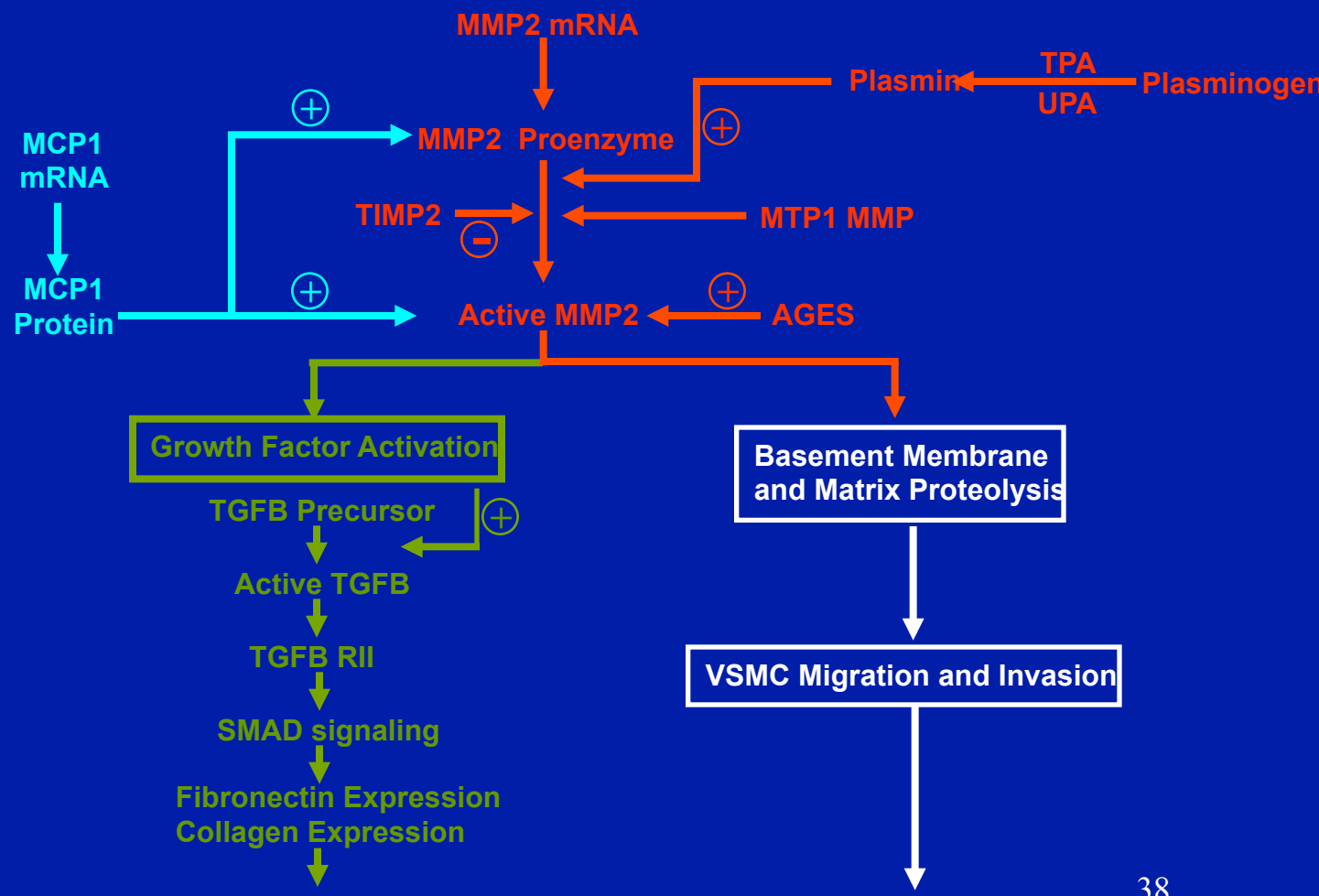
ARTERIAL DILITATION; INTIMAL-MEDIAL THICKENING; STIFFENING

AGE ASSOCIATED REMODELING OF LARGE ARTERIES



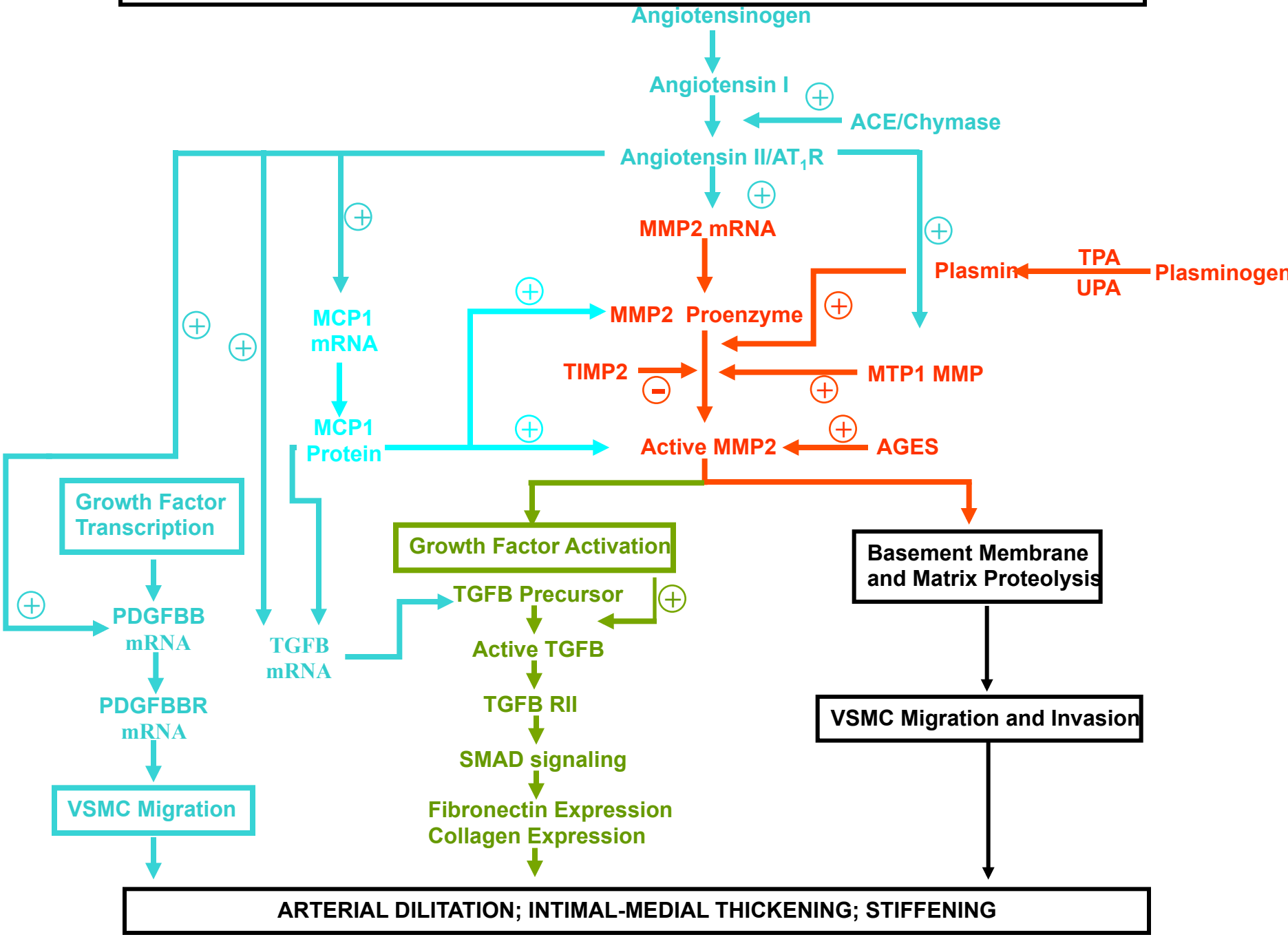
ARTERIAL DILITATION; INTIMAL-MEDIAL THICKENING; STIFFENING

AGE ASSOCIATED REMODELING OF LARGE ARTERIES

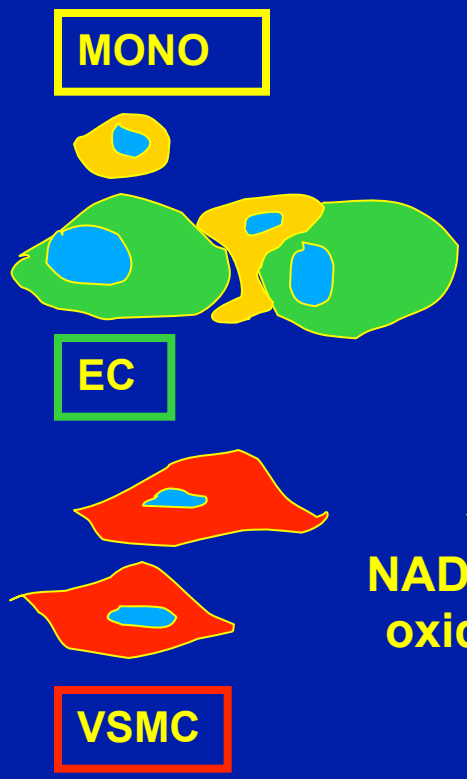


ARTERIAL DILITATION; INTIMAL-MEDIAL THICKENING; STIFFENING

AGE ASSOCIATED REMODELING OF LARGE ARTERIES



RENIN-ANGIOTENSIN SYSTEM IN THE VASCULAR BIOLOGY OF AGING



Catecholamines → Angiotensin I ← SHEAR STRESS + CIRCUMFERENTIAL WALL STRESS

ACE

ANGIOTENSIN II

AT_1R

NF-kB

NAD(P)H oxidase | ICAM | TGFβ1 | MCP-1 | ProMMP-2

$ONOO^-$ ← $NO^- + O_2^-$

H_2O_2

TGFβRII

CCR2

MT1MMP

Plasmin

TIMP-2

AGE's

Active MMP-2

AGE-ASSOCIATED ARTERIAL REMODELING

Cellular and Molecular mechanisms of risky aspects of arterial aging, are in fact, those that have been implicated in experimental atherosclerosis or hypertension in younger animals.

Arterial Remodeling with Aging, Hypertension and Atherosclerosis

	Aging					
	Humans >65 yrs	Monkeys 15-20 yrs	Rats 24-30 mo	Rabbits 3-6 yrs	Hypertension	Atherosclerosis
Lumenal dilation	+	+	+	+	?	?
↑ Stiffness	+	+	+	+	+	+
Endothelial dysfunction	+	+	+	+	+	+
Diffuse Intimal Thickening	+	+	+	+	+	+
Lipid involvement	-	-	-	-	±	+
↑ VSMC number	+	+	+	+	+	+
Macrophages	+	-	-	-	+	+
T-cell	+	-	-	-	+	+
↑ Matrix	+	+	+	+	+	+
↑ Local ANGII-ACE	+	+	+	+	+	+
MMP dysregulation	+	+	+	?	+	+
↑ MCP-1/CCR2	+	+	+	+	+	+
↑ ICAM	?	?	+	?	+	+
↑ TGFB	?	+	+	?	+	+
↑ NADPH Oxidase	?	?	+	?	+	+
↓ VEGF	+	?	?	+	+	+
↓ Nitric Oxide Bioavailability	?	?	+	+	+	+
HYPERTENSION	±	±	±	±	+	±
ATHEROSCLEROSIS	±	-	-	-	±	+

? Information unknown

If arterial aging is a risk factor for vascular disease, then arterial aging, per se, is a target for treatment and prevention !

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CARDIAC AGING

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Can Age-Associated Arterial Changes be Prevented or Delayed?

YES!

Potential Treatment/Prevention
Life Style
Pharma

- Life Style Modification (Exercise ↓ NaCl intake)
- Currently Available Drugs
  (ACEI, ARBS, SNP, L-arginine)
- Novel Drugs
  - Cross-Link Breakers (Primates, Dogs, Rats)
  - Elastase Inhibition
- Hormonal Rx in & Post Menopause
- Reduced Caloric Intake (Rats, Primates)

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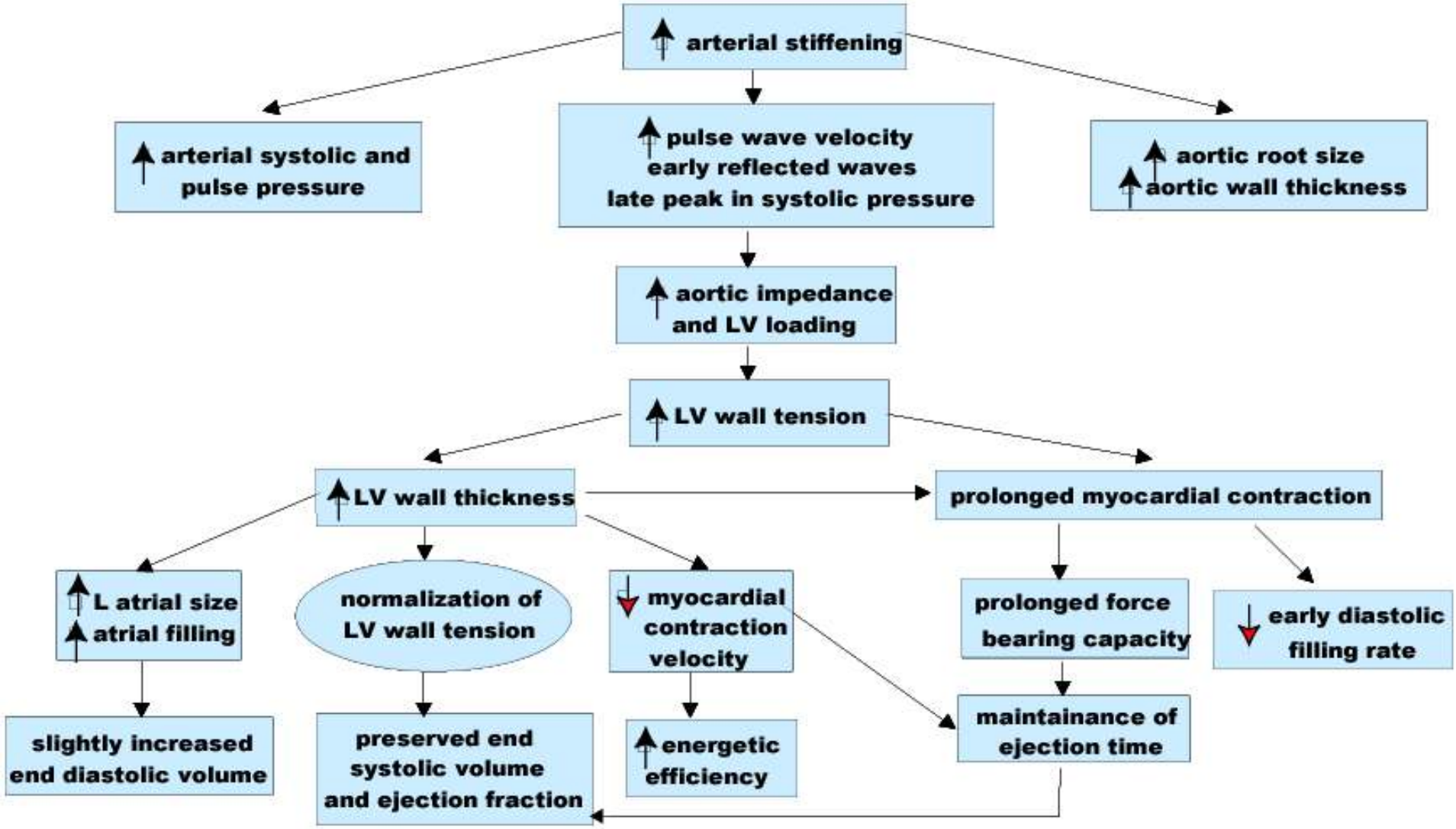
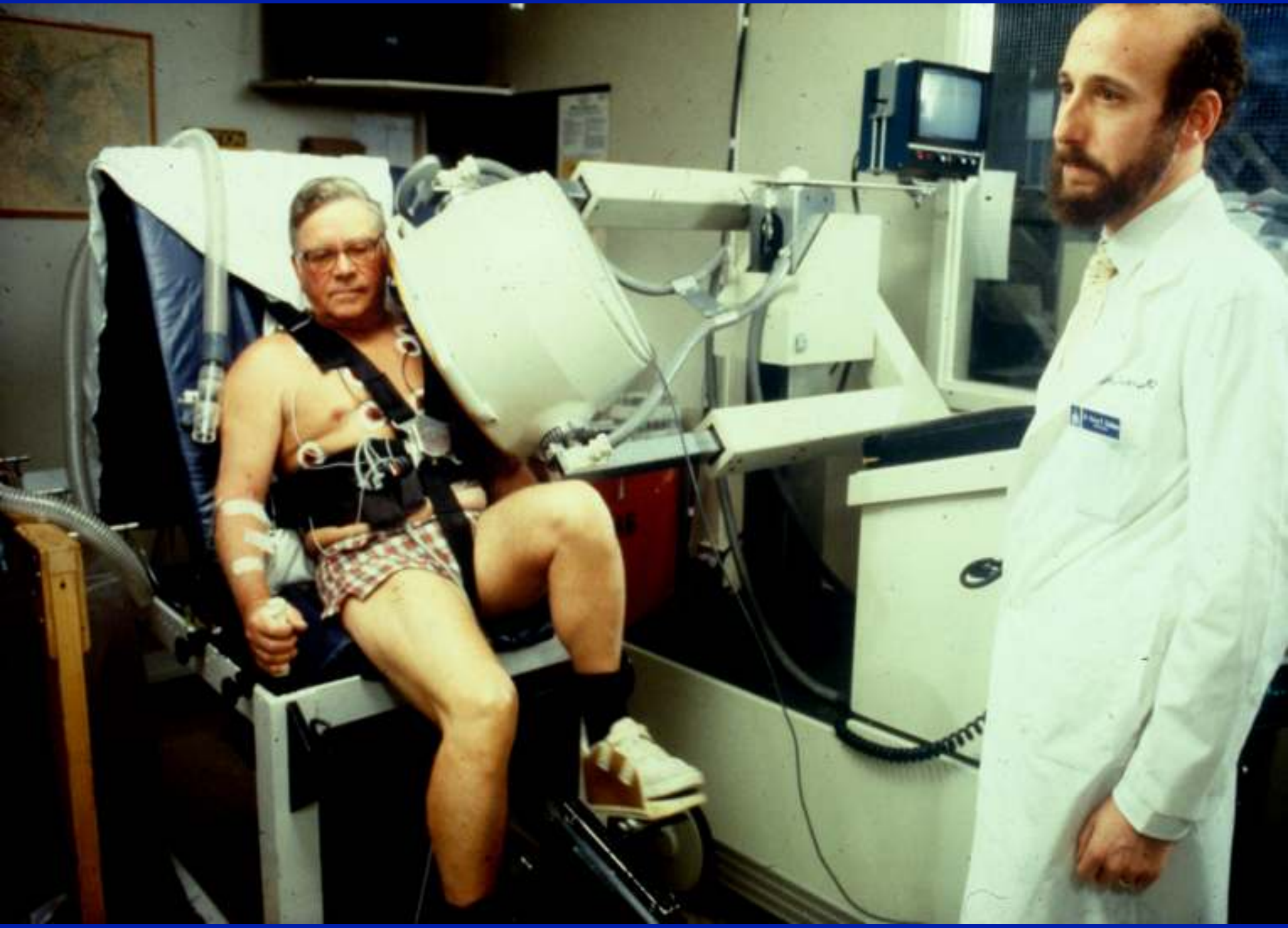
Cardiac Aging Without a Textbook Clinical Disease Diagnosis

Age Associated Changes in Resting Cardiovascular Structure/Function
In the Absence of a Textbook Clinical Diagnosis



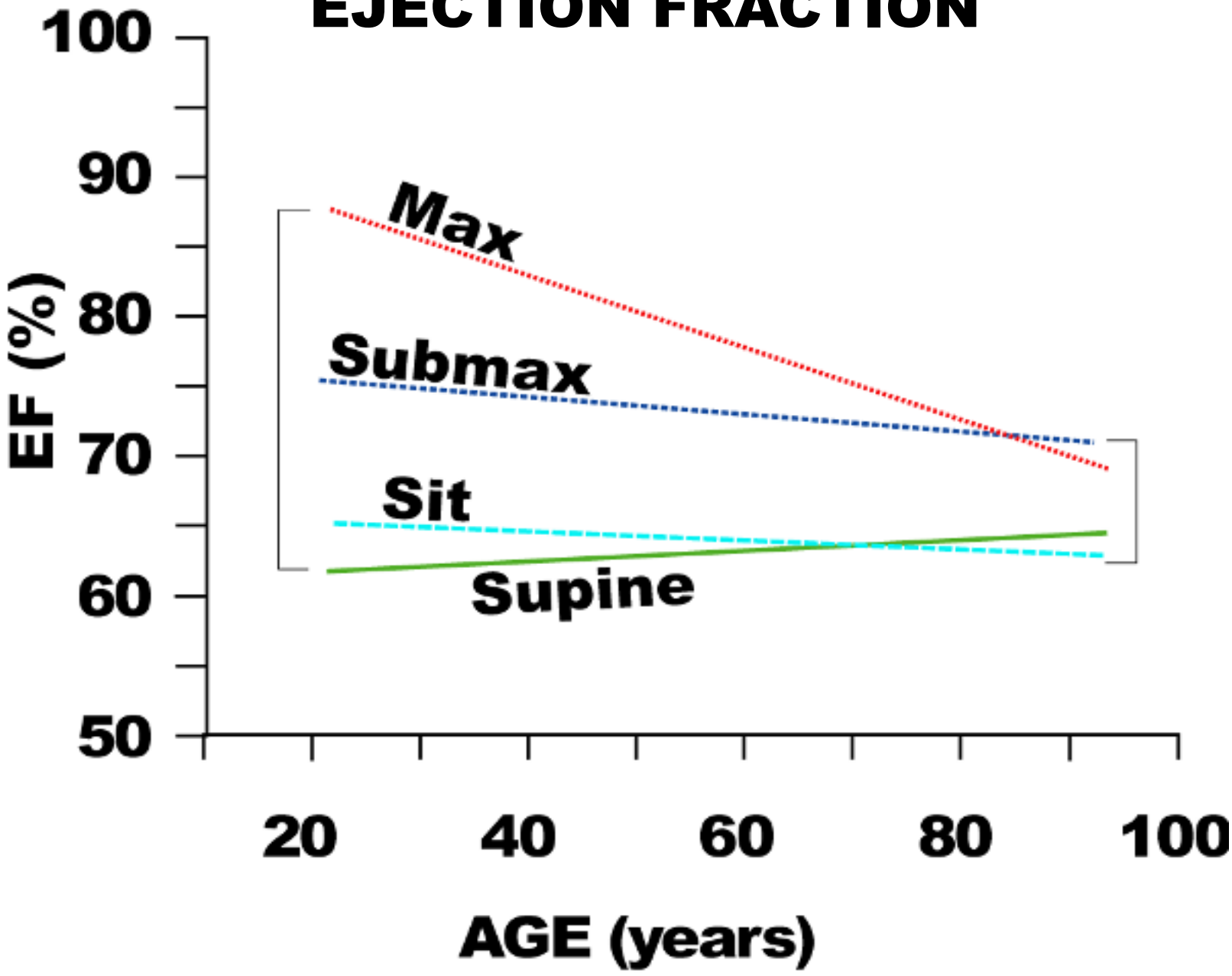
Cardiovascular Reserve

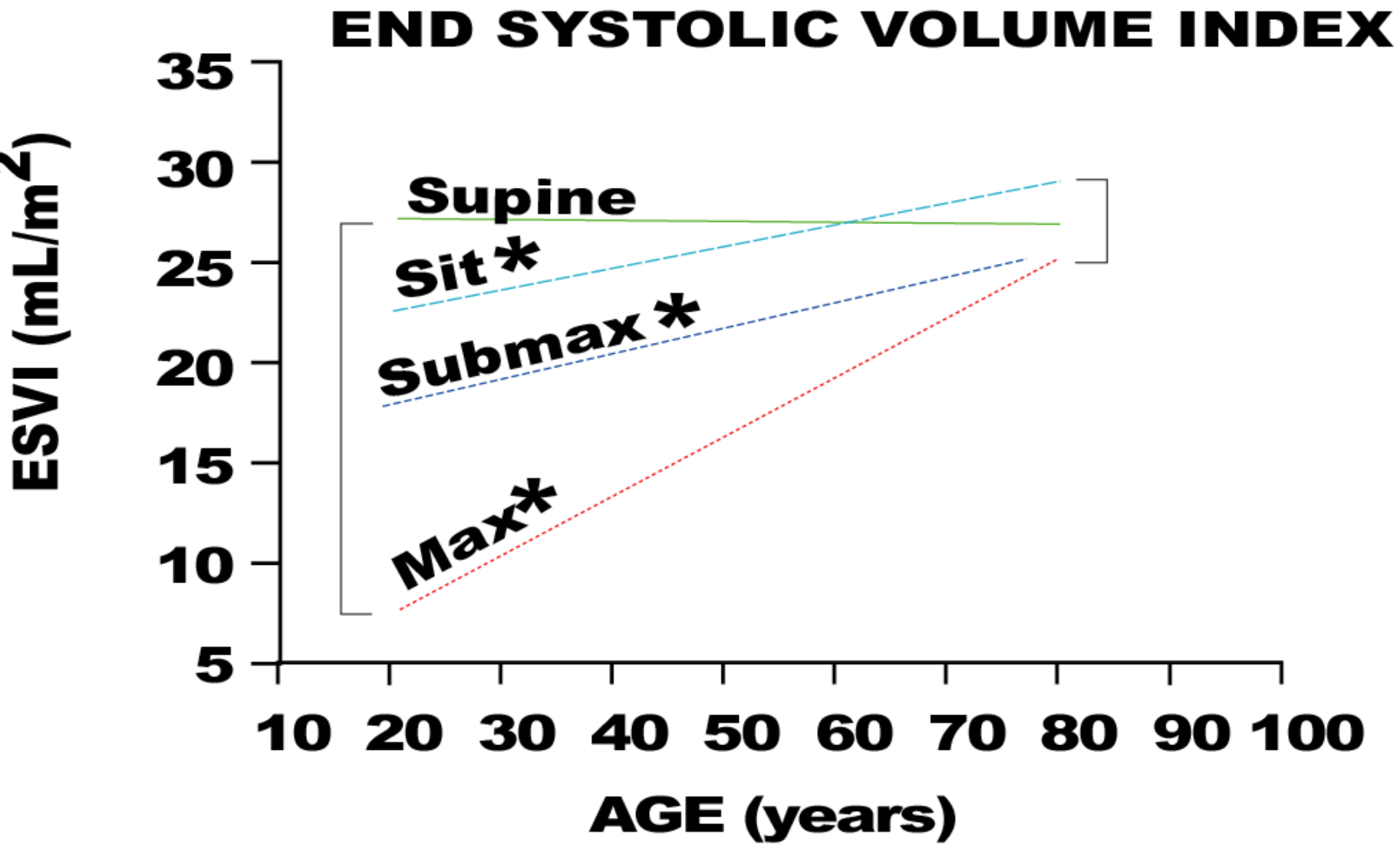
Heart pumps more blood as blood shifts from the venous to arterial circulation



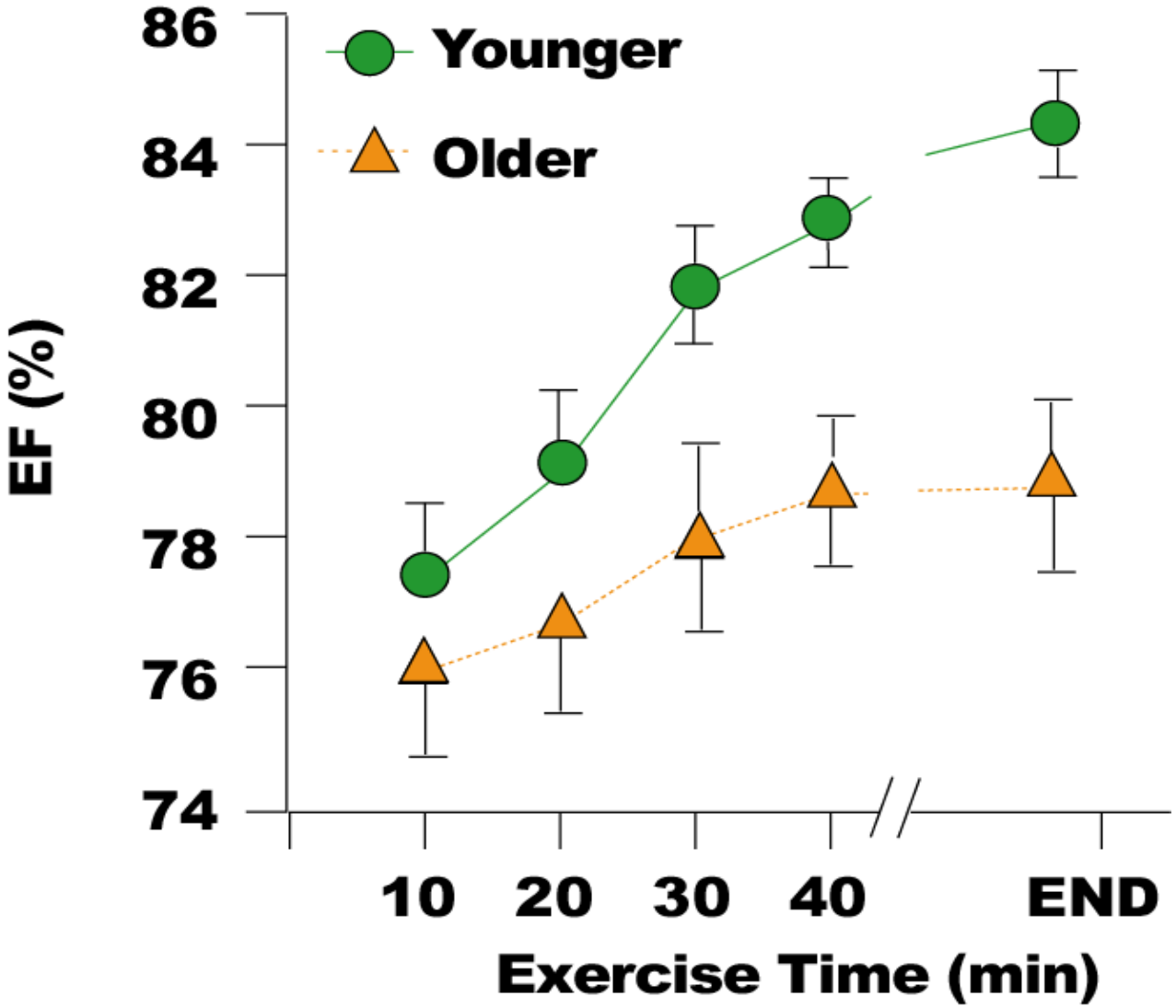
Basal EF is Not Altered By Aging in Carefully Screened, Sedentary Community Dwelling Persons, and Averages 65%. But EF Reserve is Compromised and on Average Maximal EF Declines with Aging.

EJECTION FRACTION



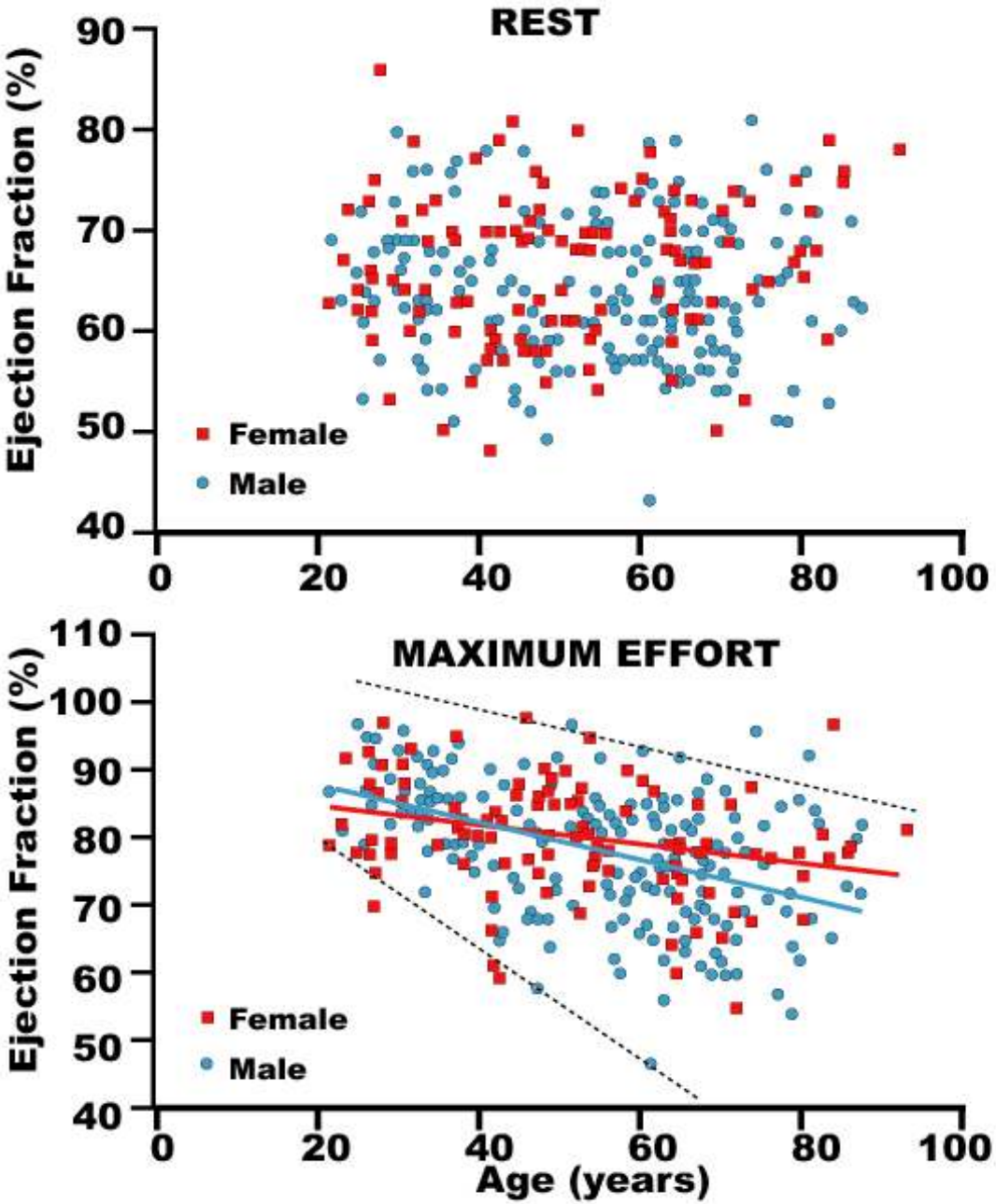

END SYSTOLIC VOLUME INDEX
ESVI (mL/m2)
35
30
25
20
15
10
5
Supine
Sit*
Submax*
Max*
10 20 30 40 50 60 70 80 90 100
AGE (years)

Ejection Fraction During Prolonged Upright Submaximal (70% peak VO_2) Cycle Exercise



There is a Marked Variability of the Basal EF Among All Persons and of EF Reserve Among Older Persons.

Variability of EF Among Individuals

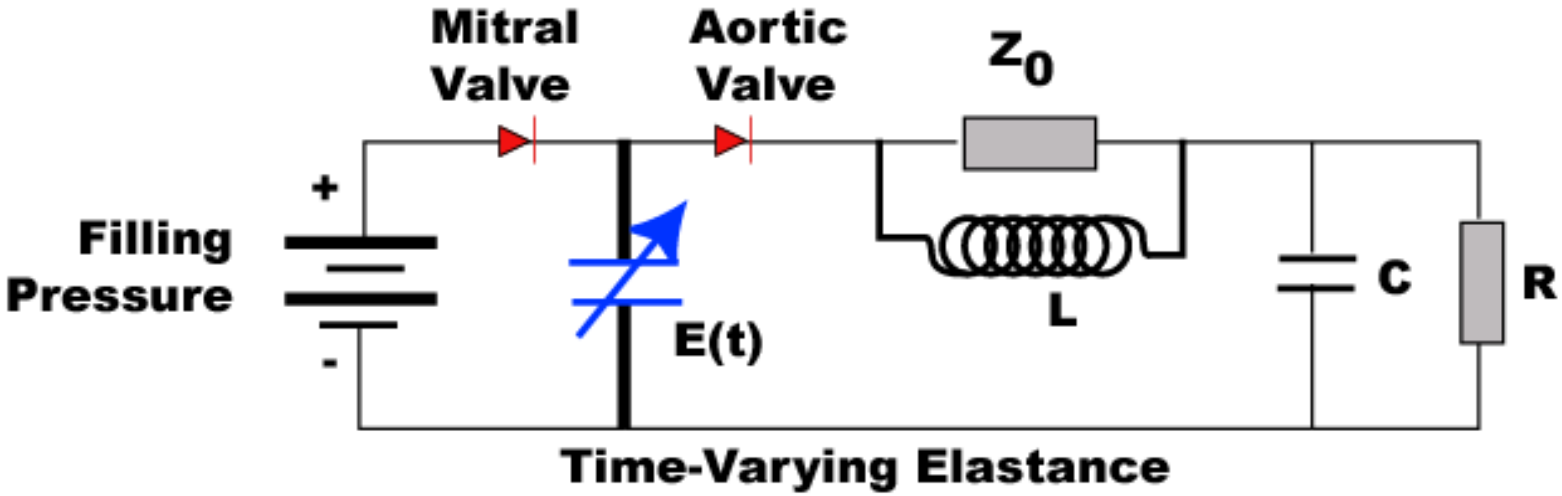


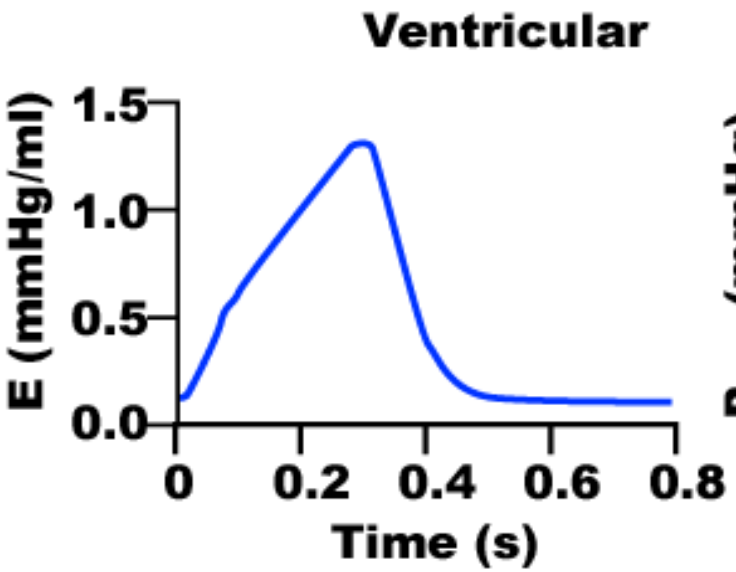
Failure of End Systolic Volume Reduction and Ejection Fraction Reserve

- ⬇ Intrinsic Myocardial Contractility
- ⬆ Afterload
- ⬇ **Arterio-Ventricular Coupling**
- ⬇ Autonomic Modulation of Contractility and Afterload

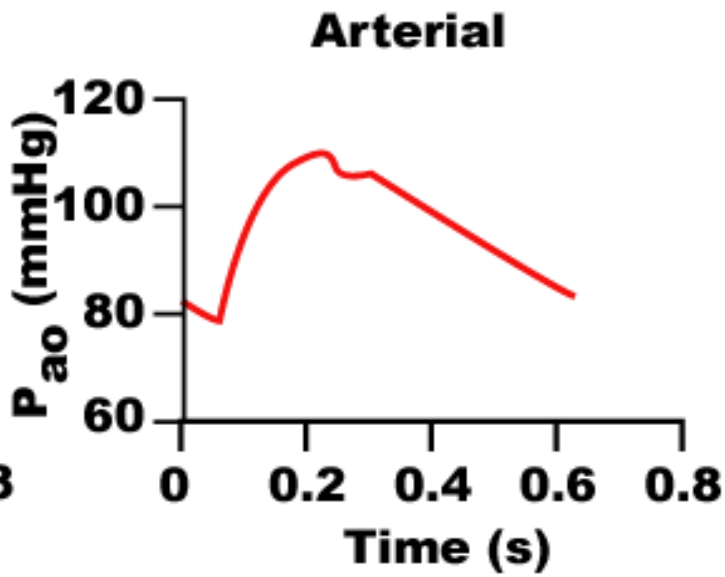
EF is Not a Measure of Heart Function but of Arterial-Ventricular Elastance Coupling (E_a/E_{LV}).

Heart-Arterial Interaction Model



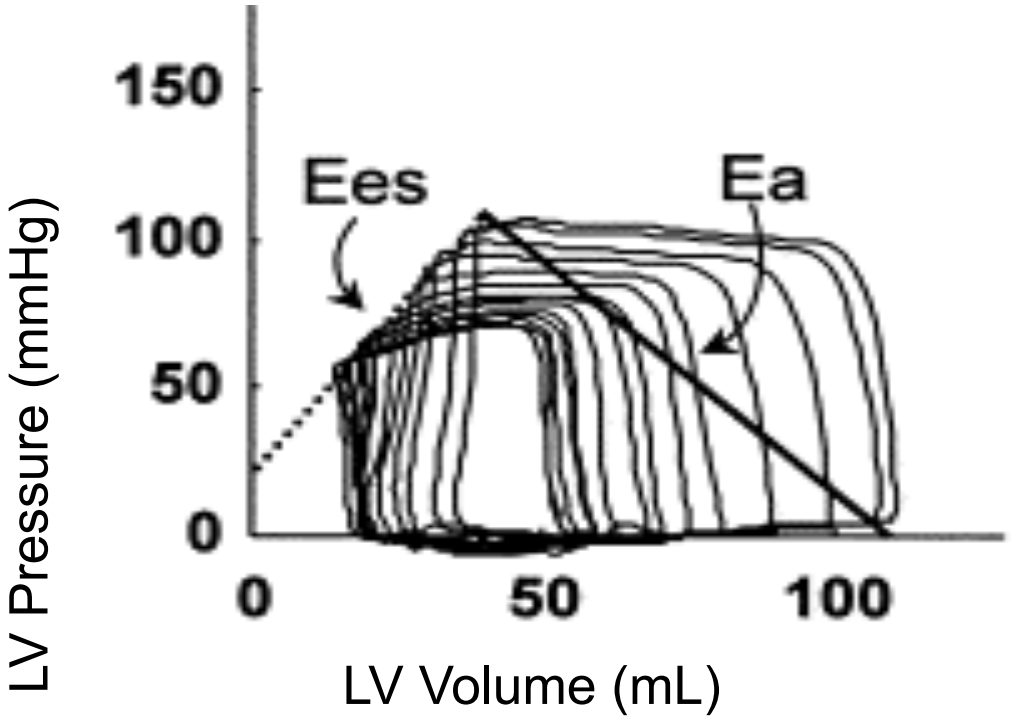


$$E_{ES} \quad \frac{ESP}{ESV}$$



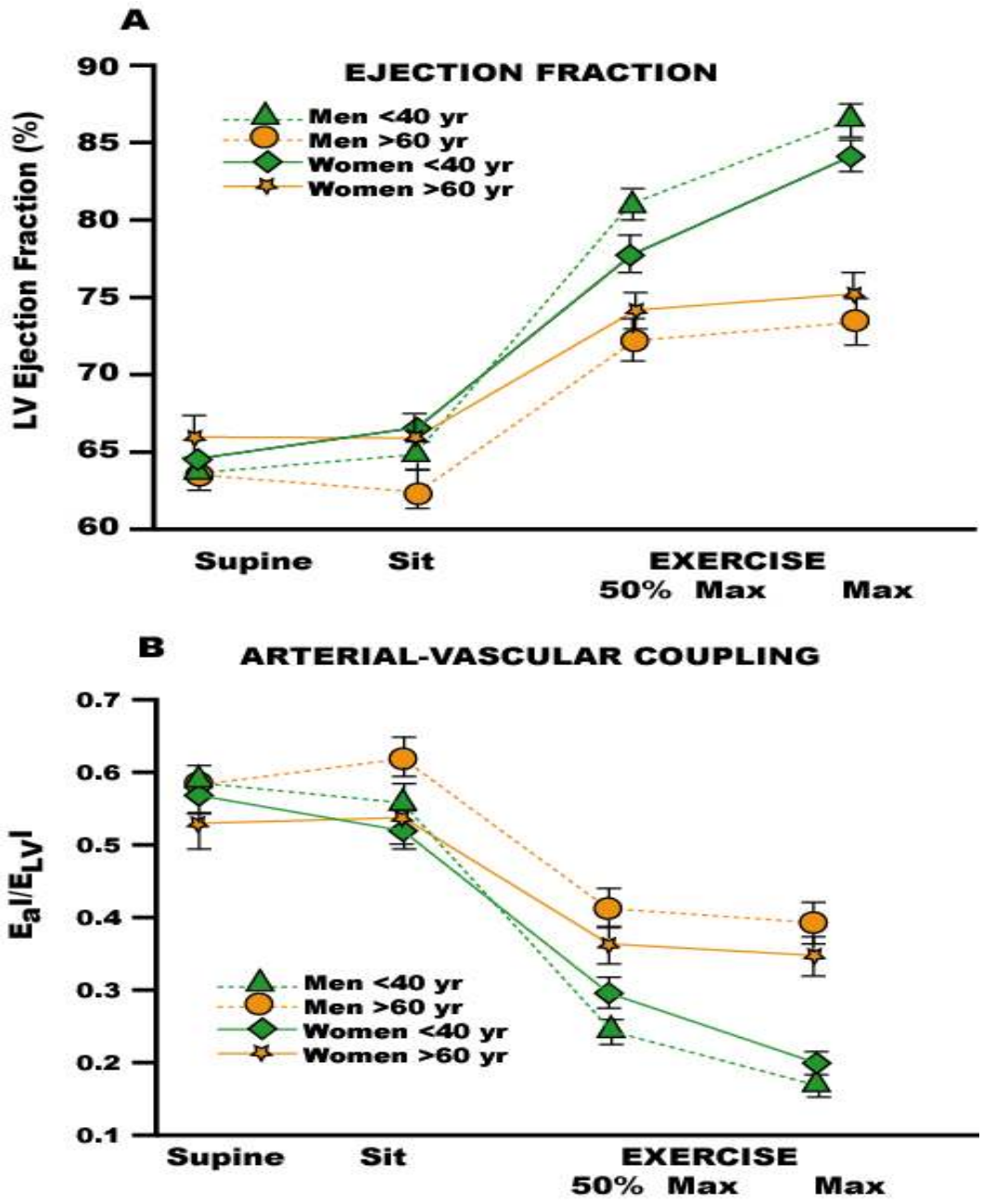
$$E_a \quad \frac{ESP}{SV}$$

Arterial-Ventricular Coupling and Ejection Fraction

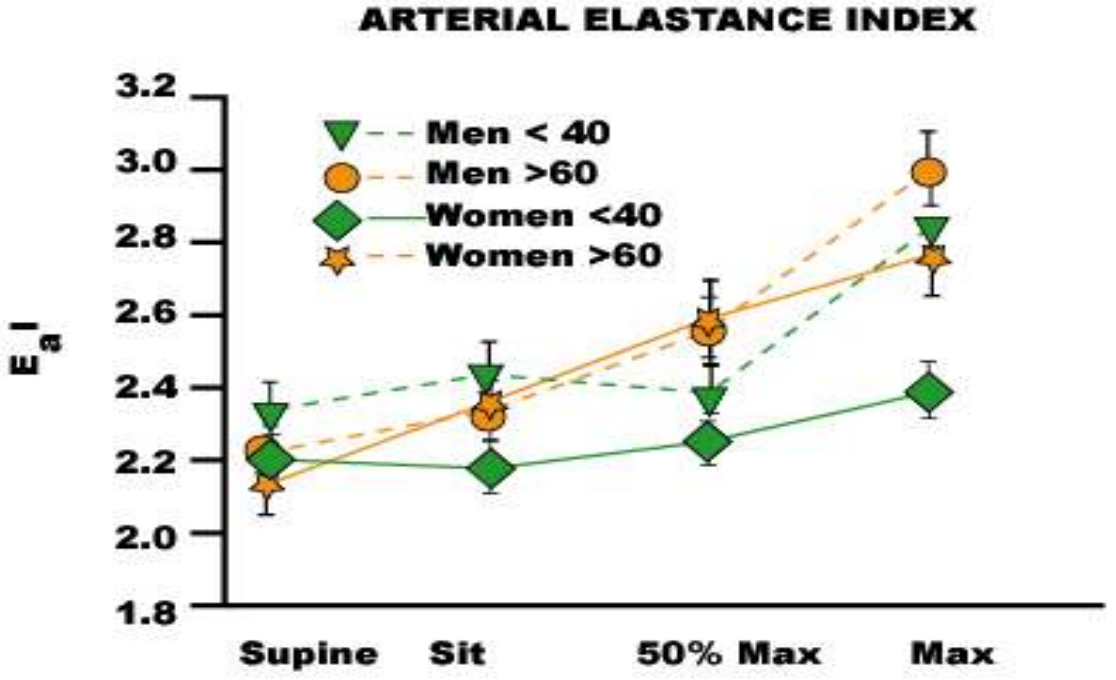


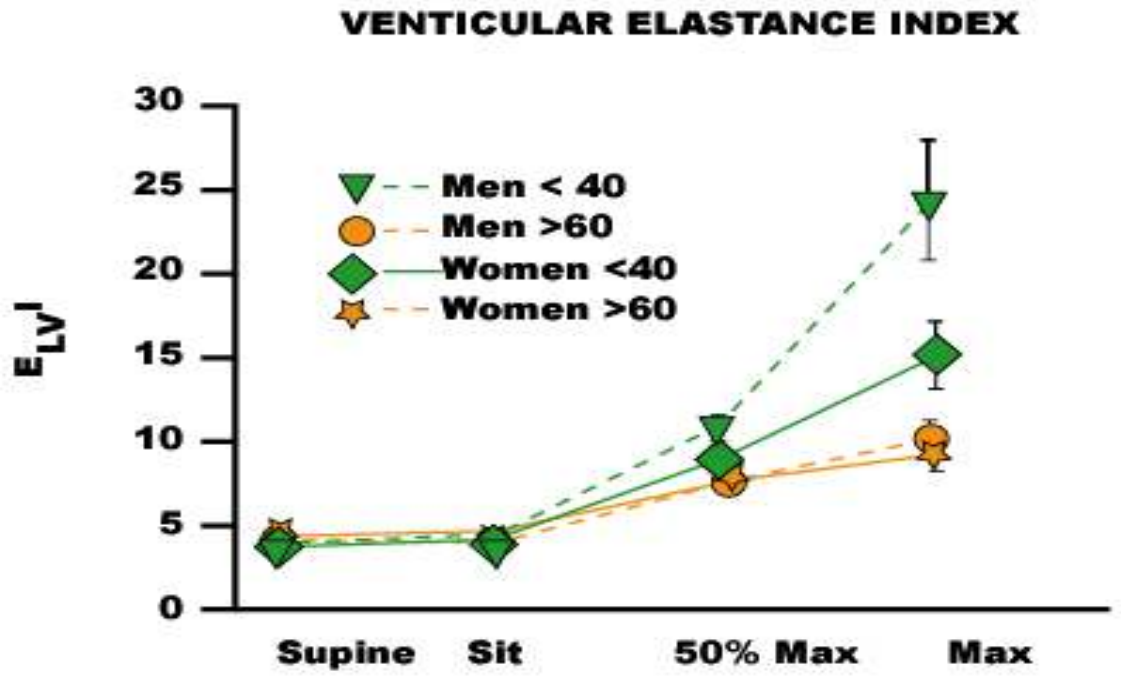
$$\frac{Ea}{E_{es}} = \frac{ESP/SV}{ESP/ESV} = \frac{ESV}{SV} = (1/EF) - 1$$

Arterial-ventricular Elastance Coupling At Rest Indexed By Non-invasive Measures, Is Not Affected By Age. But A-V Uncoupling In Older Persons Occurs During Stress, When Blood Volume Shifts From The Peripheral To The Central Circulation, And Arterial Pressure Increases.



Prescreened for BP < 140/90 in subjects in Panel A

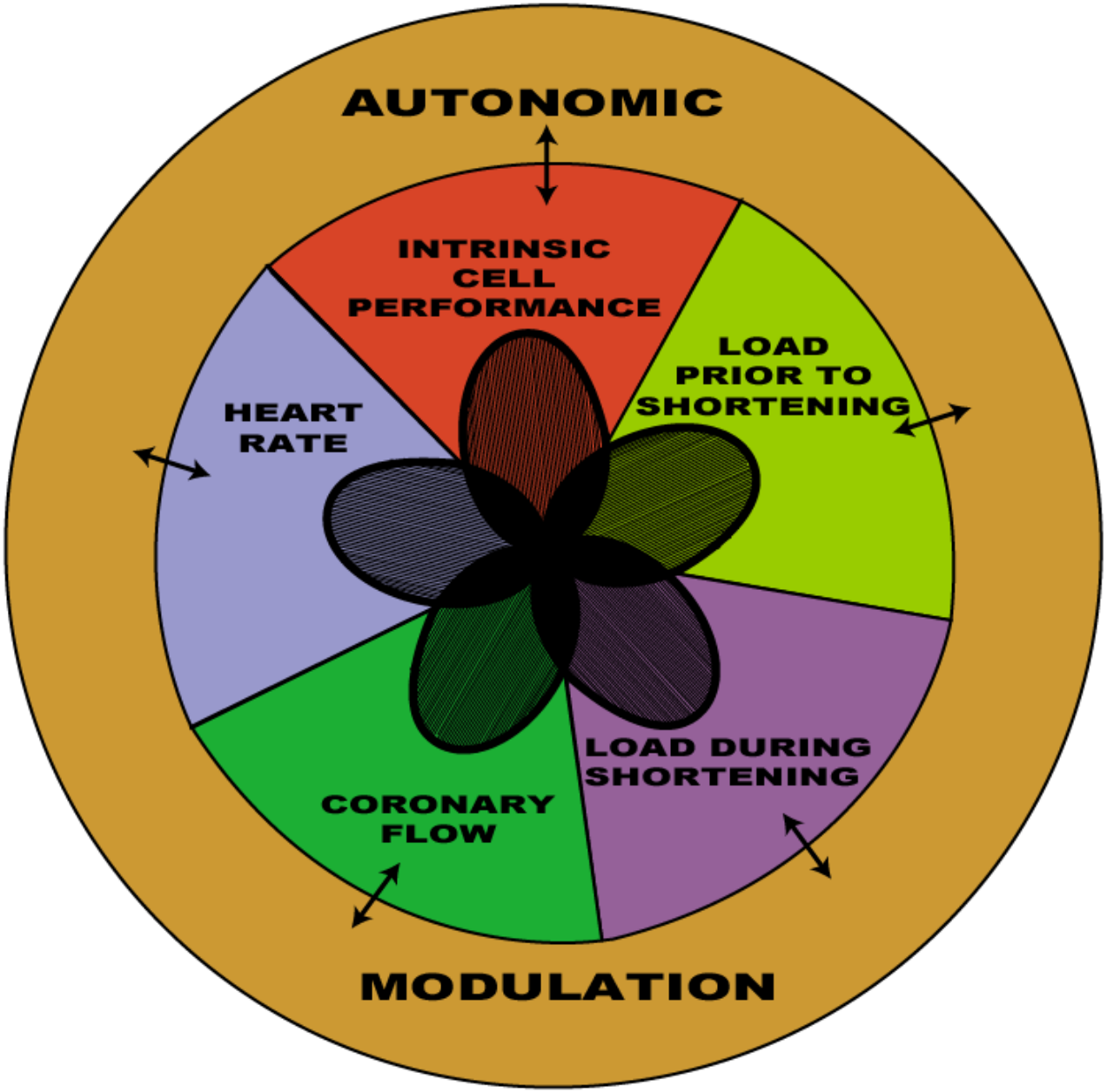

ARTERIAL ELASTANCE INDEX
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
$E_a I$
Men < 40
Men >60
Women <40
Women >60
Supine
Sit
50% Max
Max

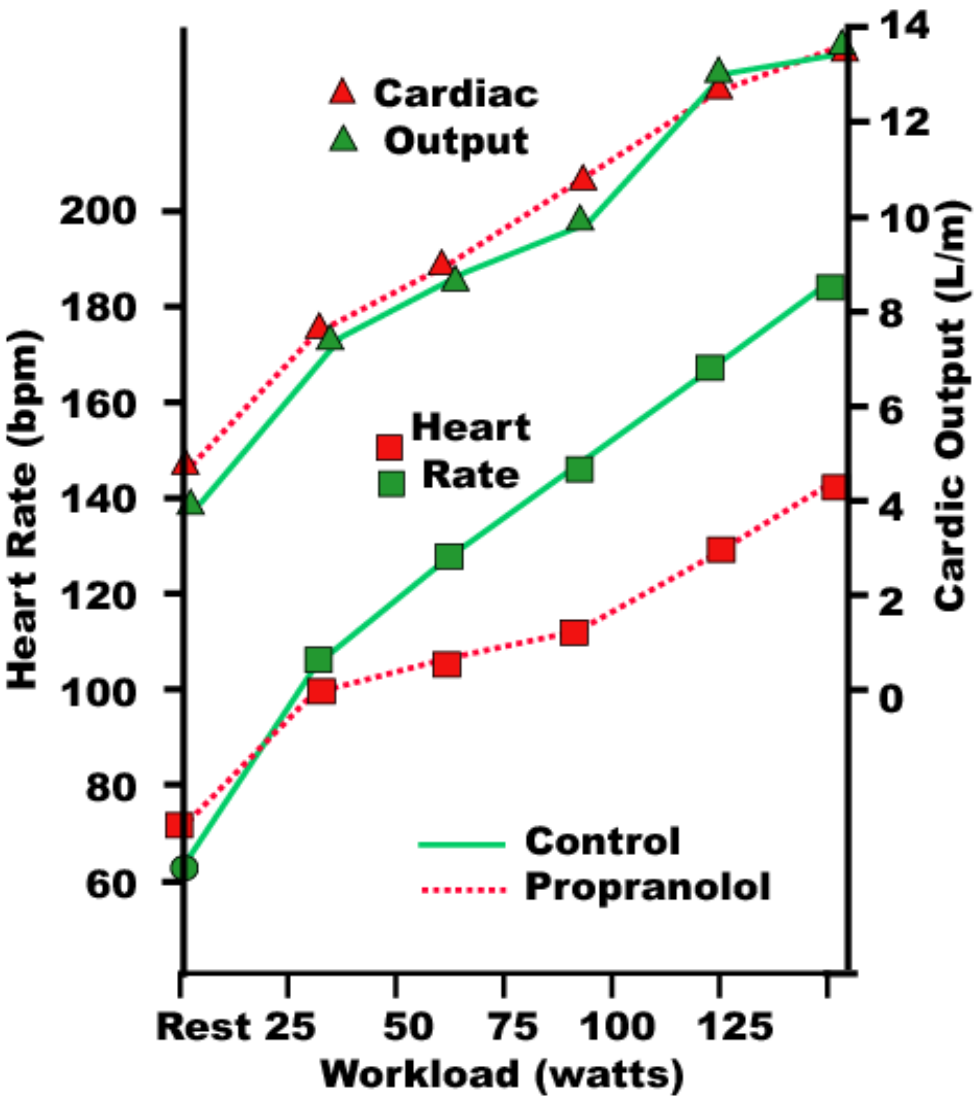

VENTICULAR ELASTANCE INDEX
30
25
20
15
10
5
0
$E_{LV} I$
Men < 40
Men >60
Women <40
Women >60
Supine
Sit
50% Max
Max

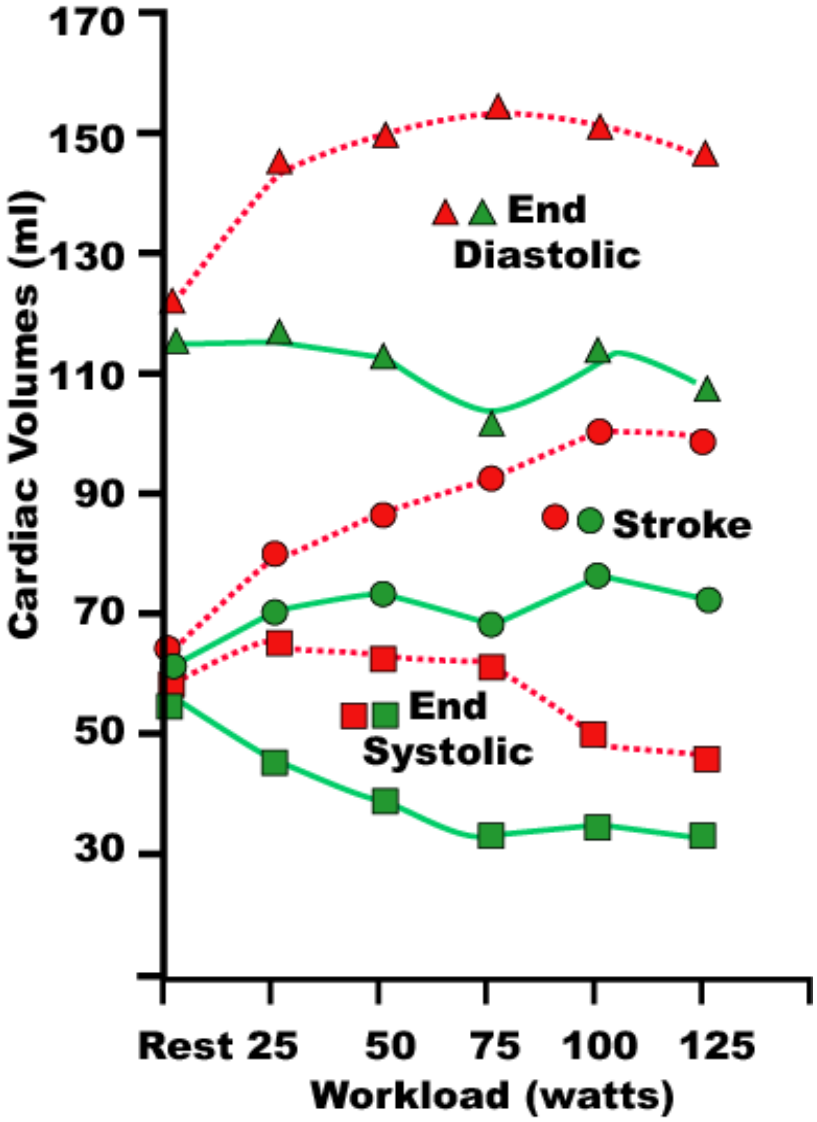
Failure of End Systolic Volume Reduction and Ejection Fraction Reserve

- ⬇ Intrinsic Myocardial Contractility
- ⬆ Afterload
- ⬇ Arterio-Ventricular Coupling
- ⬇ **Autonomic Modulation of Contractility and Afterload**

DETERMINANTS OF CARDIAC OUTPUT



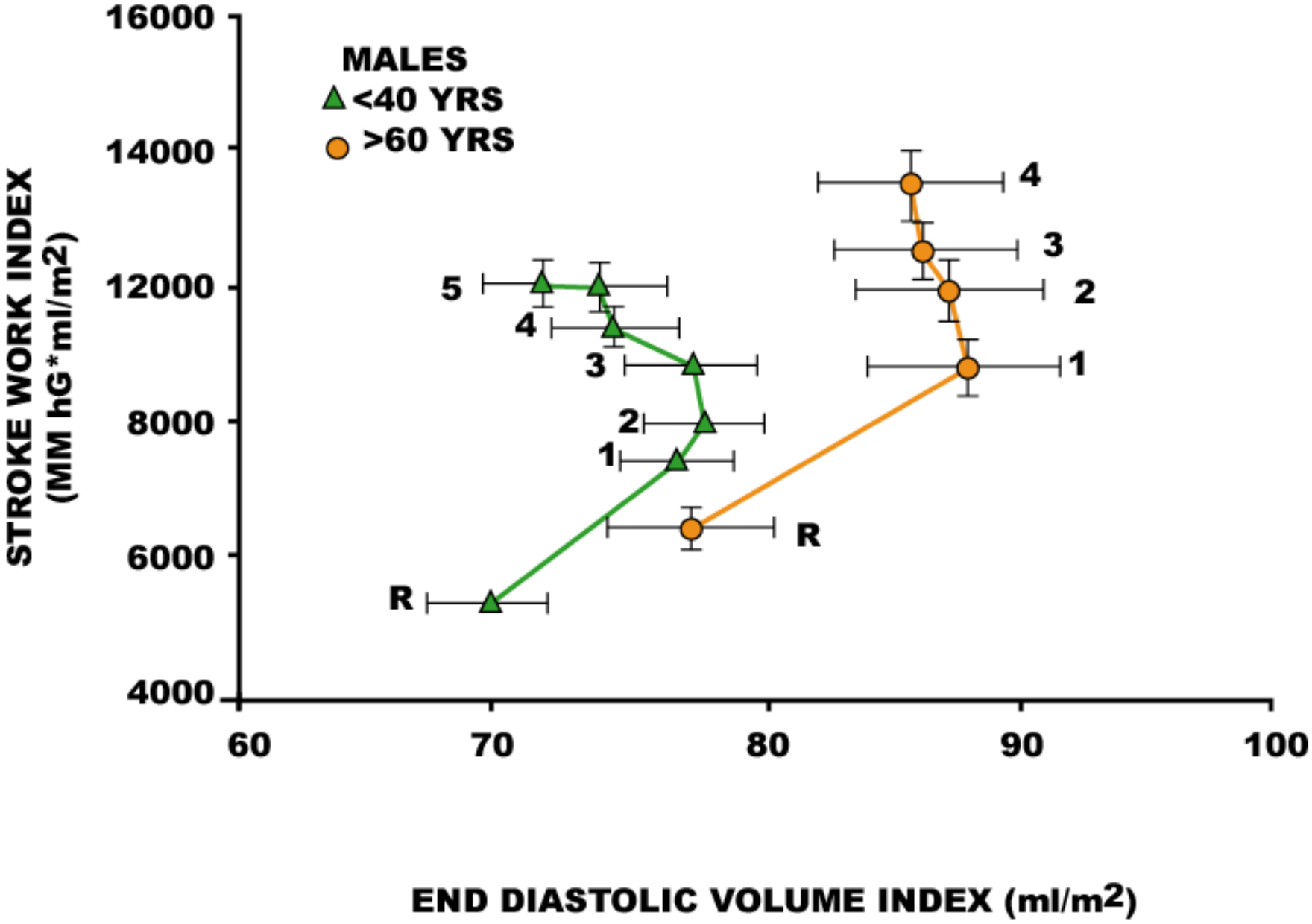

Cardiac
Output
Heart
Rate
Control
Propranolol
Heart Rate (bpm)
Cardic Output (L/m)
200
180
160
140
120
100
80
60
14
12
10
8
6
4
2
0
Rest 25
50
75
100
125
Workload (watts)

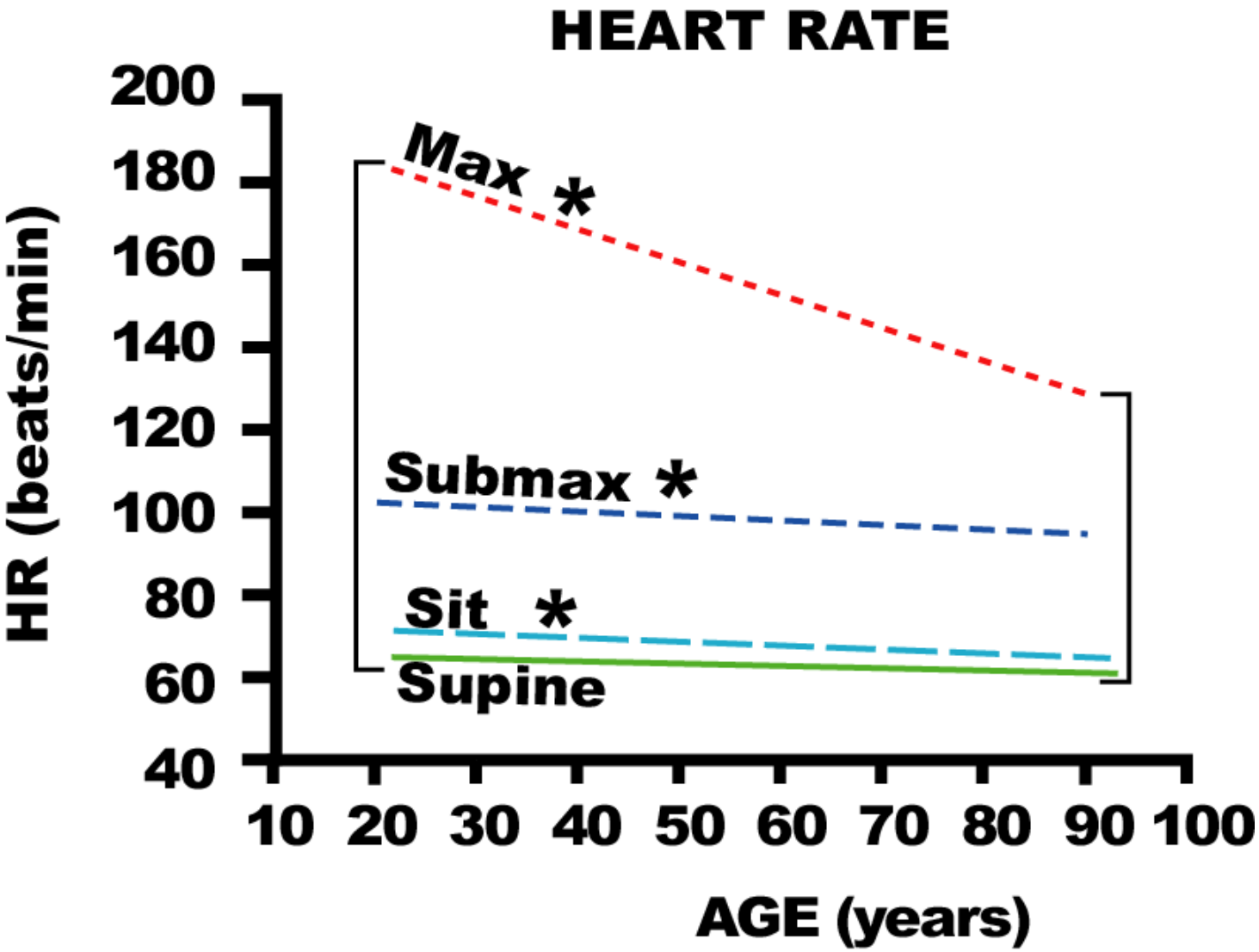

End
Diastolic
Stroke
End
Systolic
Cardiac Volumes (ml)
170
150
130
110
90
70
50
30
Rest 25
50
75
100
125
Workload (watts)

The Role of Withering β-Adrenergic Signaling in the Age Associated Reduction of Cardiovascular Reserve

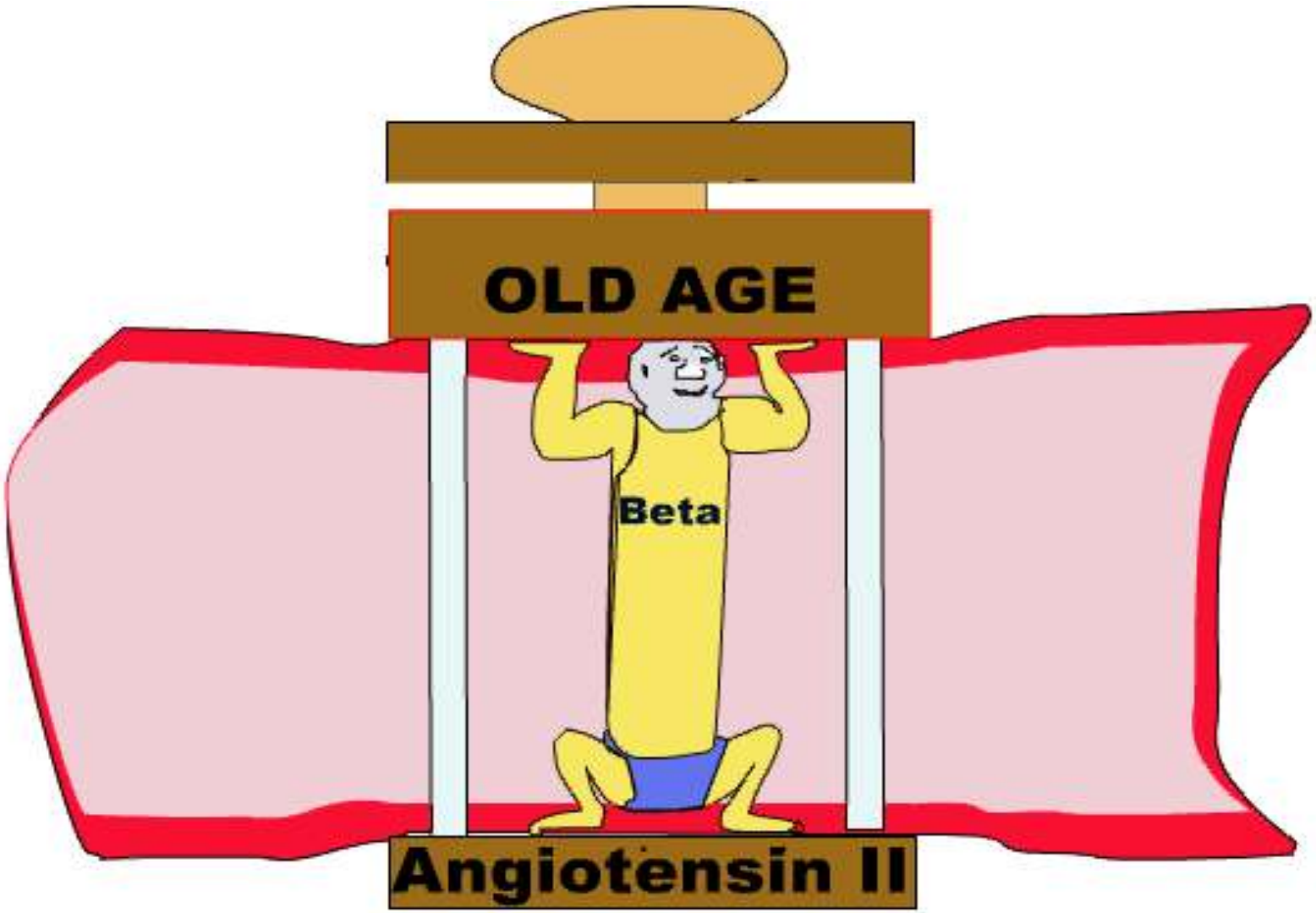
During a Dynamic Exercise Stress, Older Persons Maintain an Acute Increase in Systolic Performance in the Context of LV Dilatation at End Diastole and a Reduced Heart Rate.

STROKE WORK INDEX




HEART RATE
HR (beats/min)
200
180
160
140
120
100
80
60
40
Max *
Submax *
Sit *
Supine
10 20 30 40 50 60 70 80 90 100
AGE (years)

Β ADRENERGIC RECEPTOR SIGNALLING WHITHERS WITH ADVANCING AGE

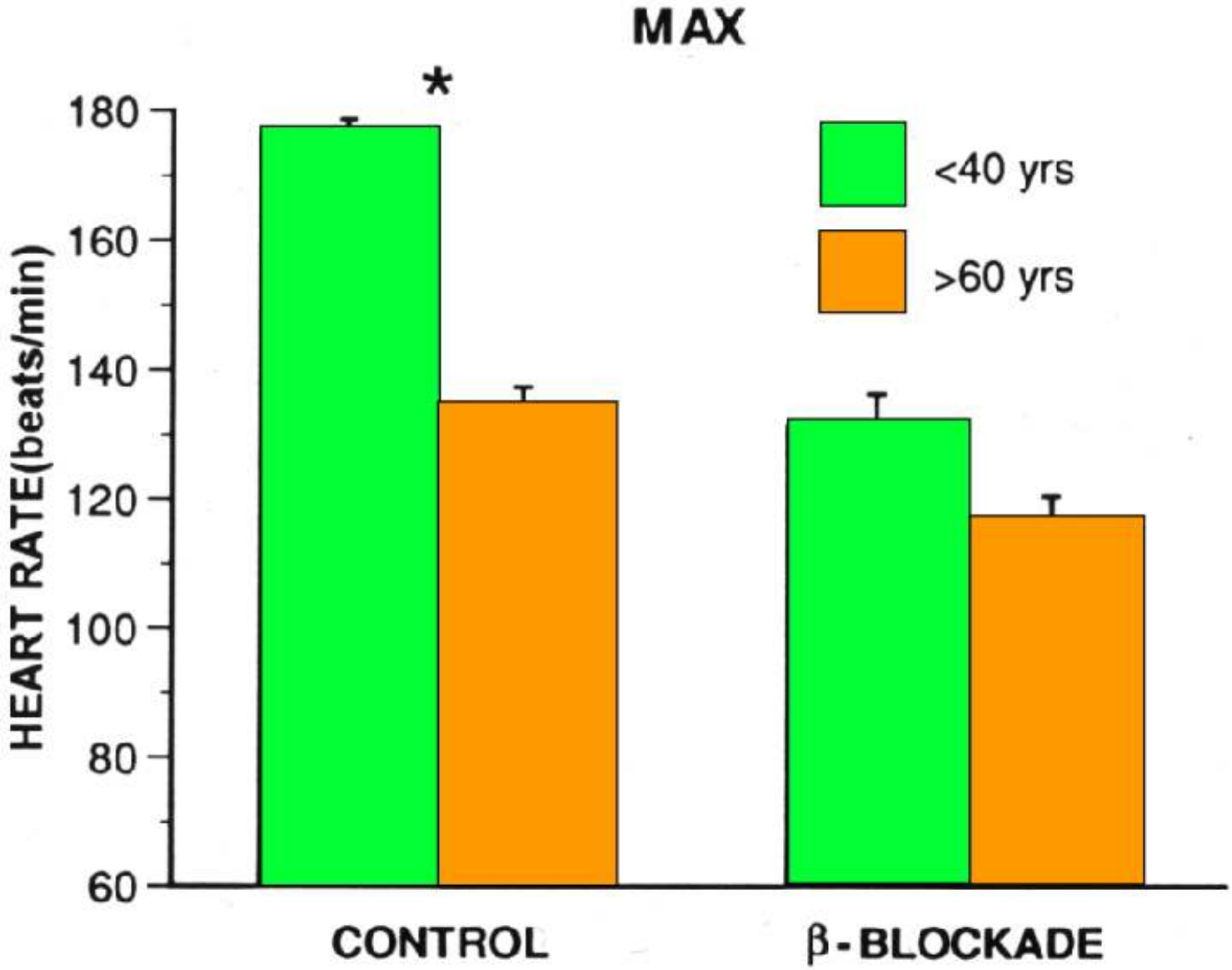


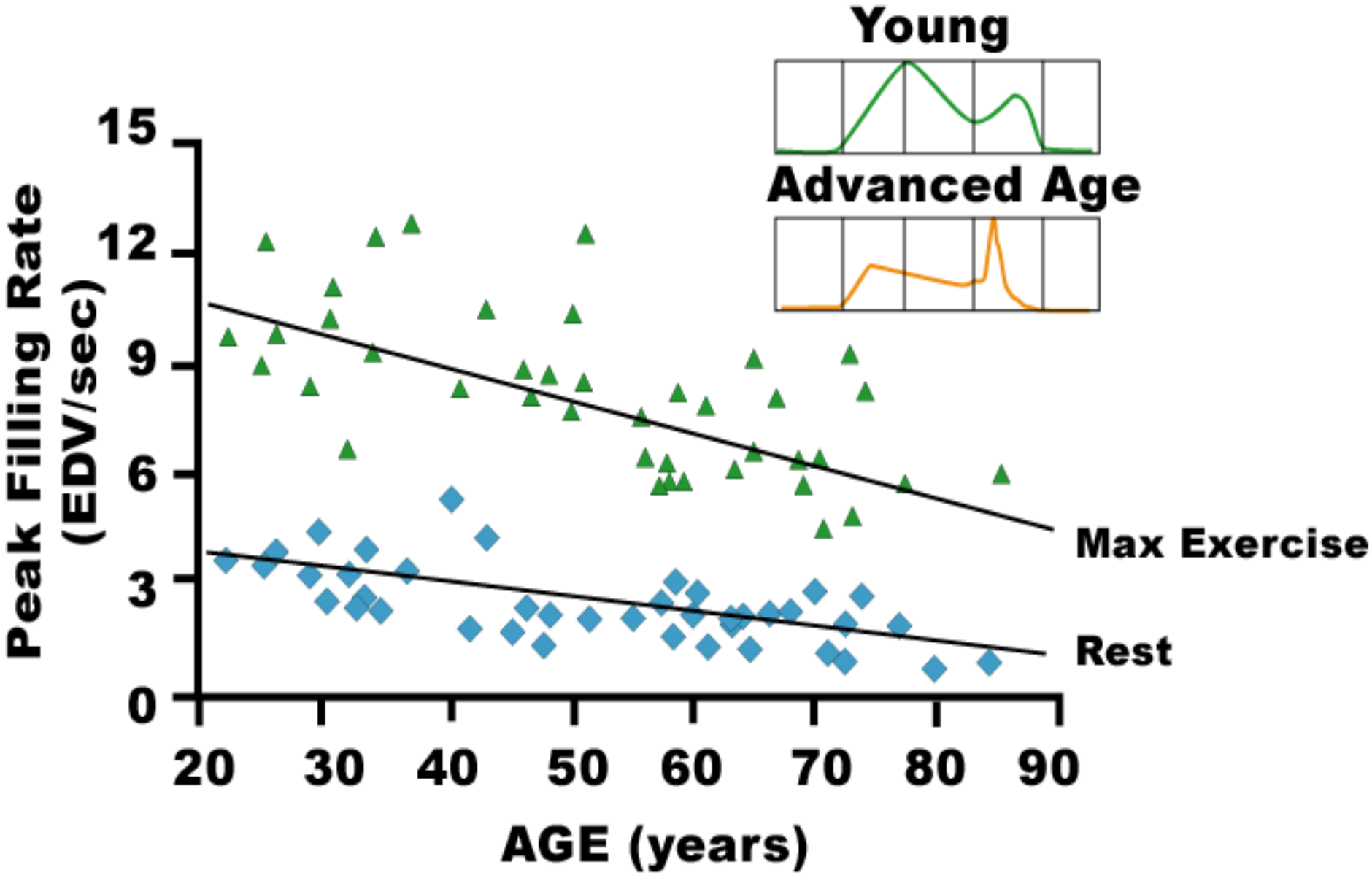
Diminished Cardiovascular Response to β-Adrenergic Receptor Stimulation with Advancing Age

- Heart rate response to β-adrenergic receptor agonists
- Arterial dilation
- Venous dilation
- Myocardial contractile response
- Myocardial relaxation

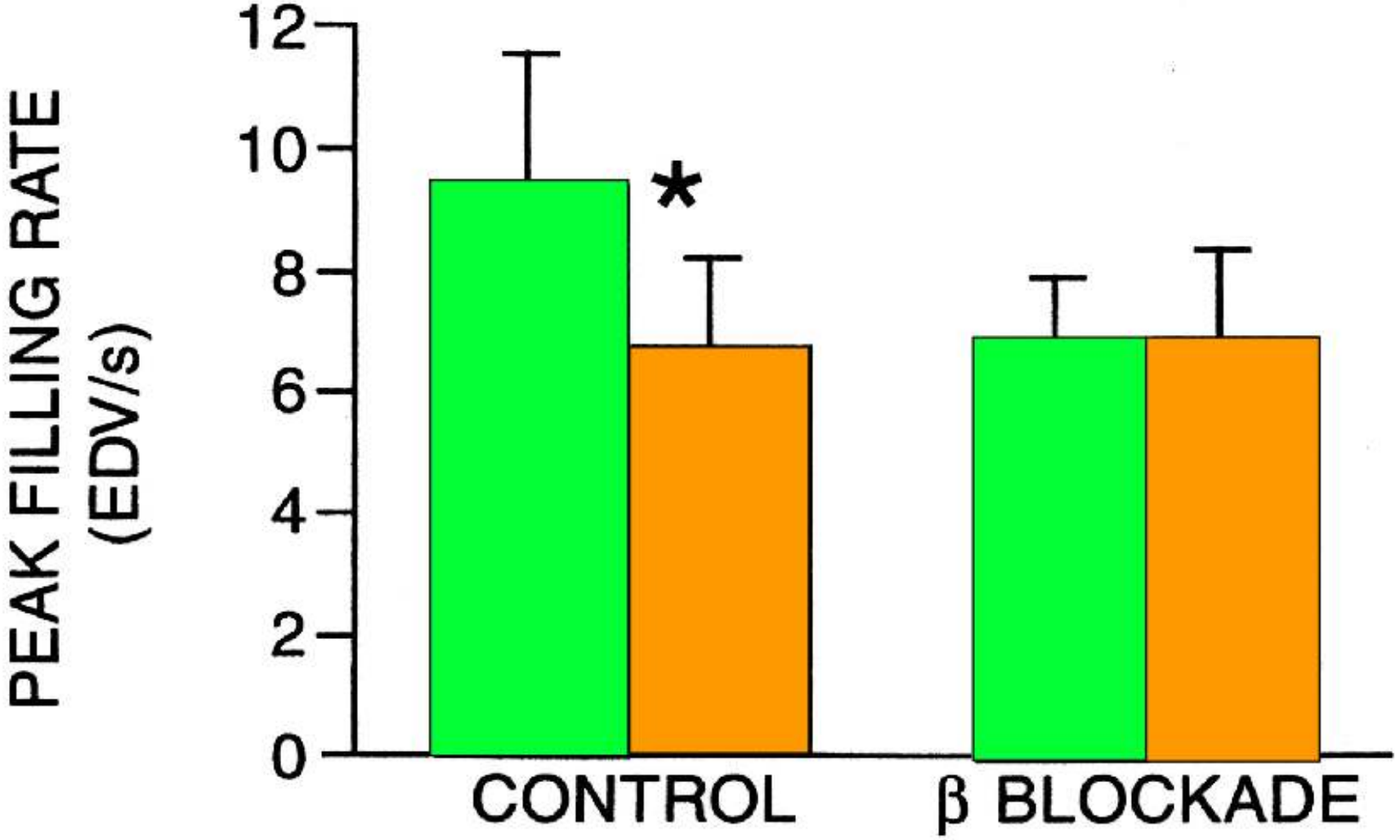
β Adrenergic Receptor Blockade Makes Younger Persons Hearts Look Older During Vigorous Exercise

ADRENERGIC RECEPTOR BLOCKADE MAKES YOUNGER PERSONS HEART LOOK OLD DURING VIGOROUS EXERCISE

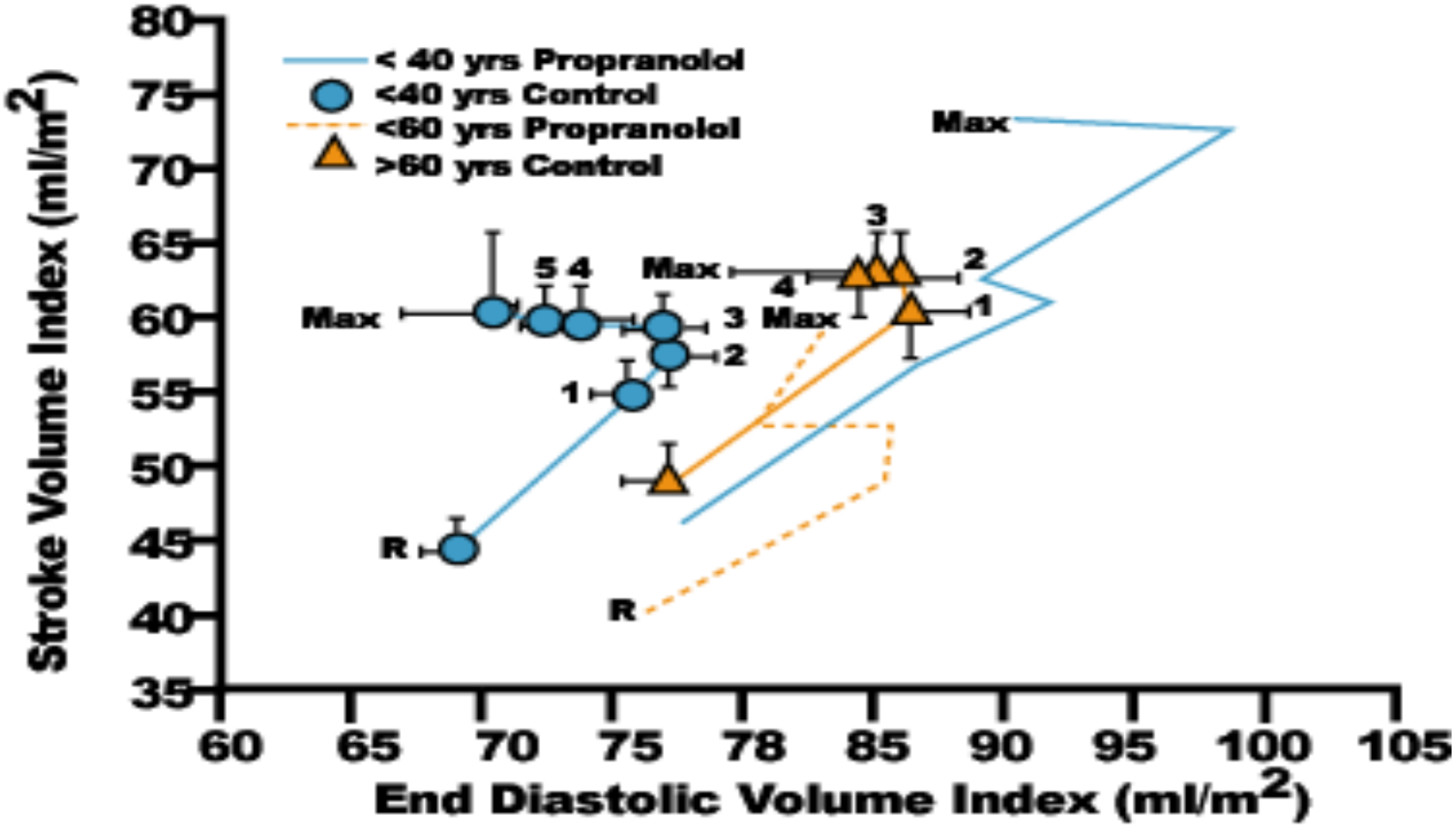



Young
Advanced Age
Peak Filling Rate
(EDV/sec)
15
12
9
6
3
0
20
30
40
50
60
70
80
90
AGE (years)
Max Exercise
Rest

ADRENERGIC RECEPTOR BLOCKADE MAKES YOUNGER PERSONS HEART LOOK OLD DURING VIGOROUS EXERCISE



ADRENERGIC RECEPTOR BLOCKADE MAKES YOUNGER PERSONS HEART LOOK OLD DURING VIGOROUS EXERCISE



SUMMARY

Human Cardiac Aging in the Absence of a Textbook Clinical Disease Diagnosis

- ↑ Left Ventricular (LV) Wall Thickness
- ↓ Early Diastolic Filling
- ↑ Atrial Contribution to Filling
- ↑ Vascular Afterload
- ↓ Cardiac Reserve
  - Increased filling volume but impaired efficacy of Frank Starling Mechanism due to impaired LV ejection
  - Impaired myocardial contractile reserve
  - Impaired heart rate acceleration

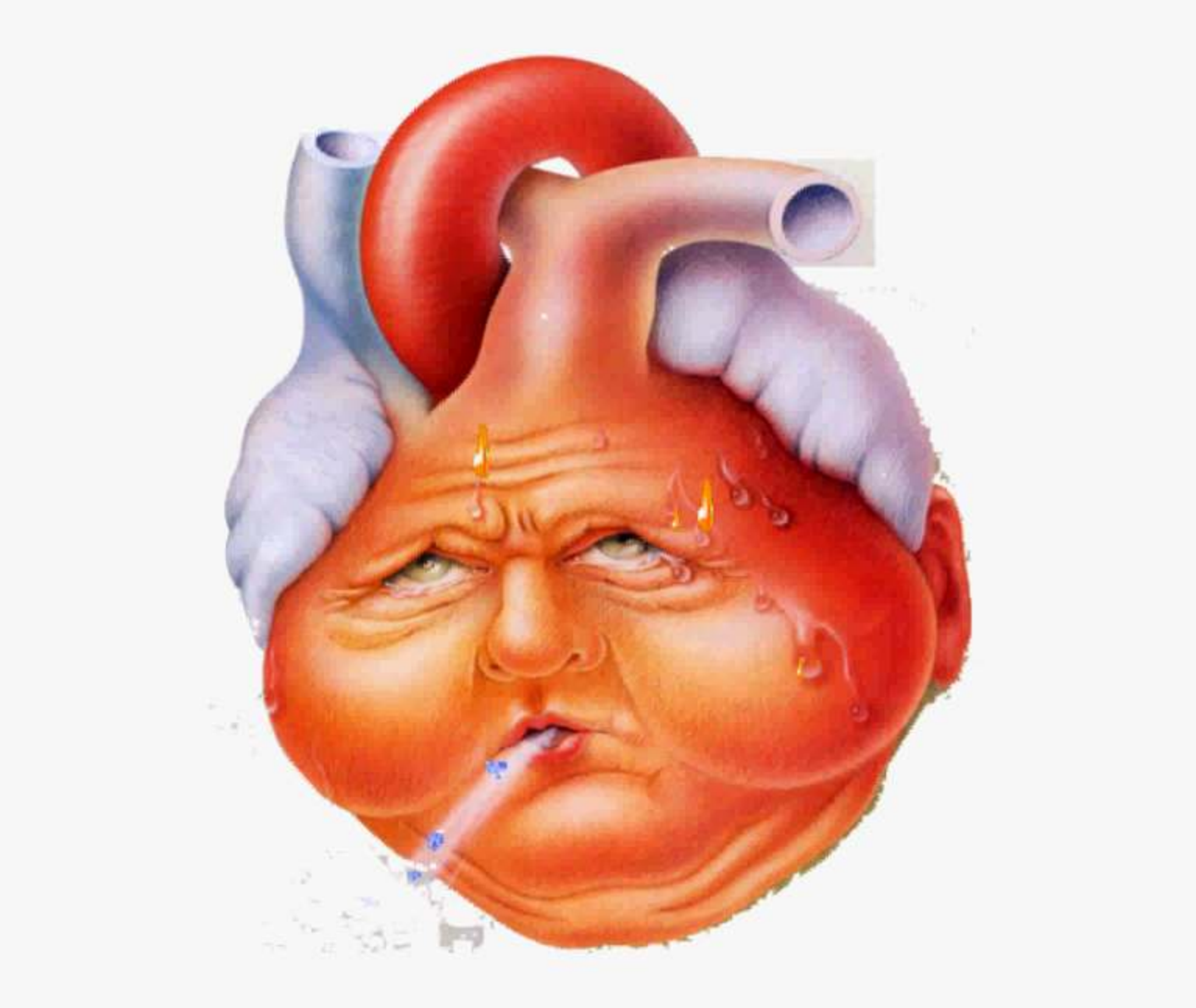
↓Efficacy of Sympathetic Drive

Impaired Arterial-Ventricular Coupling

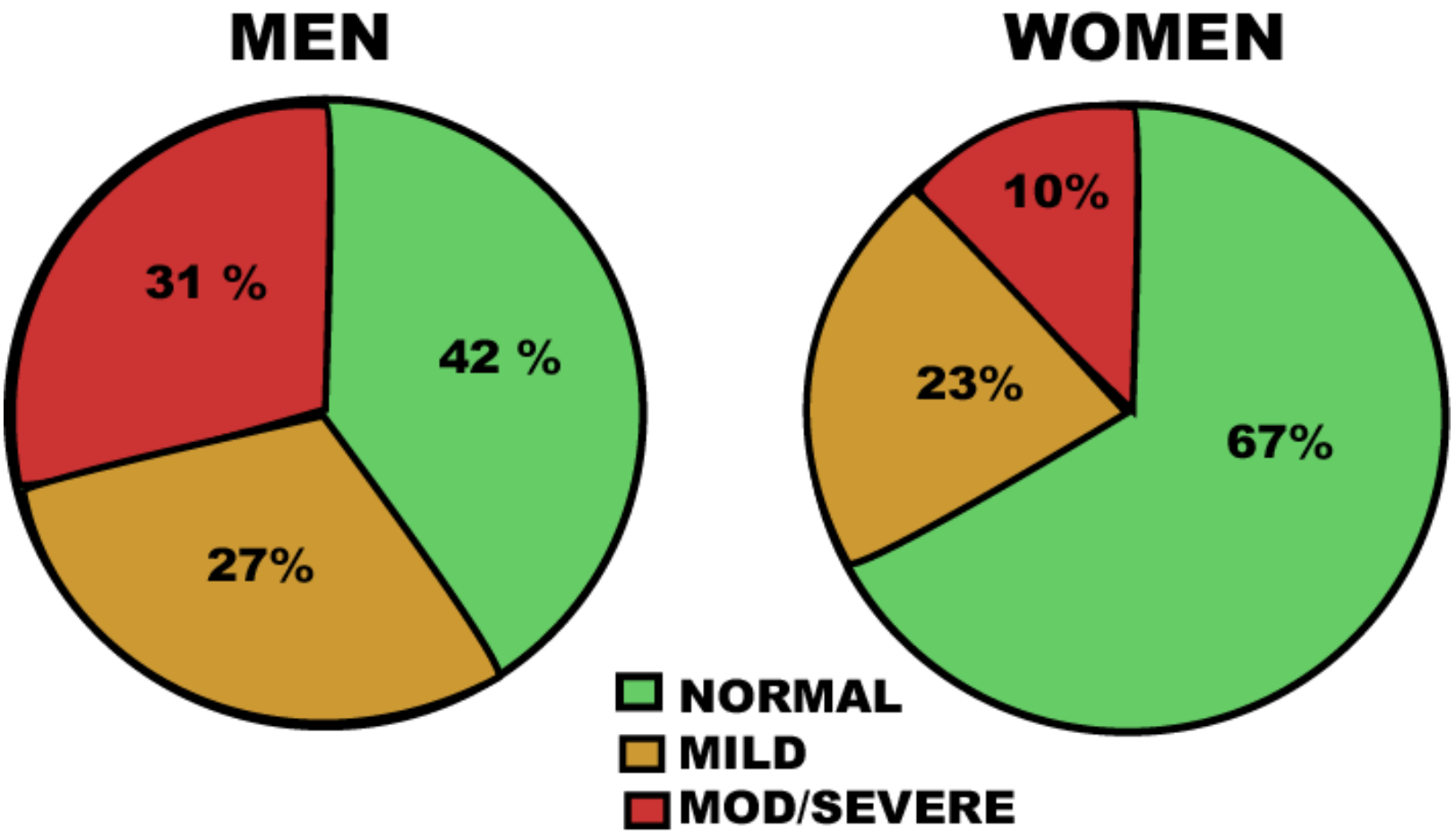
↑ Likelihood of Arrhythmias

But-No Common Clinical Signs of Heart Failure

Chronic Heart Failure



Systolic Function in Older (Age 79±6 yrs) Patients with CHF



Kitzman DW, et al. Am J Cardiol.2001;87:413-419.

Do we know why "diastolic heart failure", or more appropriately designated "heart failure with apparently normal or nearly normal systolic function at rest," occurs essentially in older persons?

EF Spans a Dynamic Range and Varies with Demand. Knowing EF at Rest is Equivalent to Knowing Nothing

Resting Ejection Fraction Fails To Detect Other Abnormalities In "Diastolic Heart Failure"

"Wise men of heart were persuaded
To tell the hearts function when faded
For the dilated case,
Resting ejection fraction had grace,
But for non-dilated hearts it was jaded."

Eduardo di Baltimora, 2004

PROBLEM – We don't know much about CV reserve capacity in patients with "Diastolic Heart Failure"

We do have a clue to why "diastolic heart failure", or more appropriately called, heart failure with apparently normal or nearly normal systolic function occurs essentially in older persons.

During acute stress, i.e., when venous return and LV afterload are simultaneously increased, the cardiovascular system of older, healthy persons "**operates on the edge**" of its reserve function.

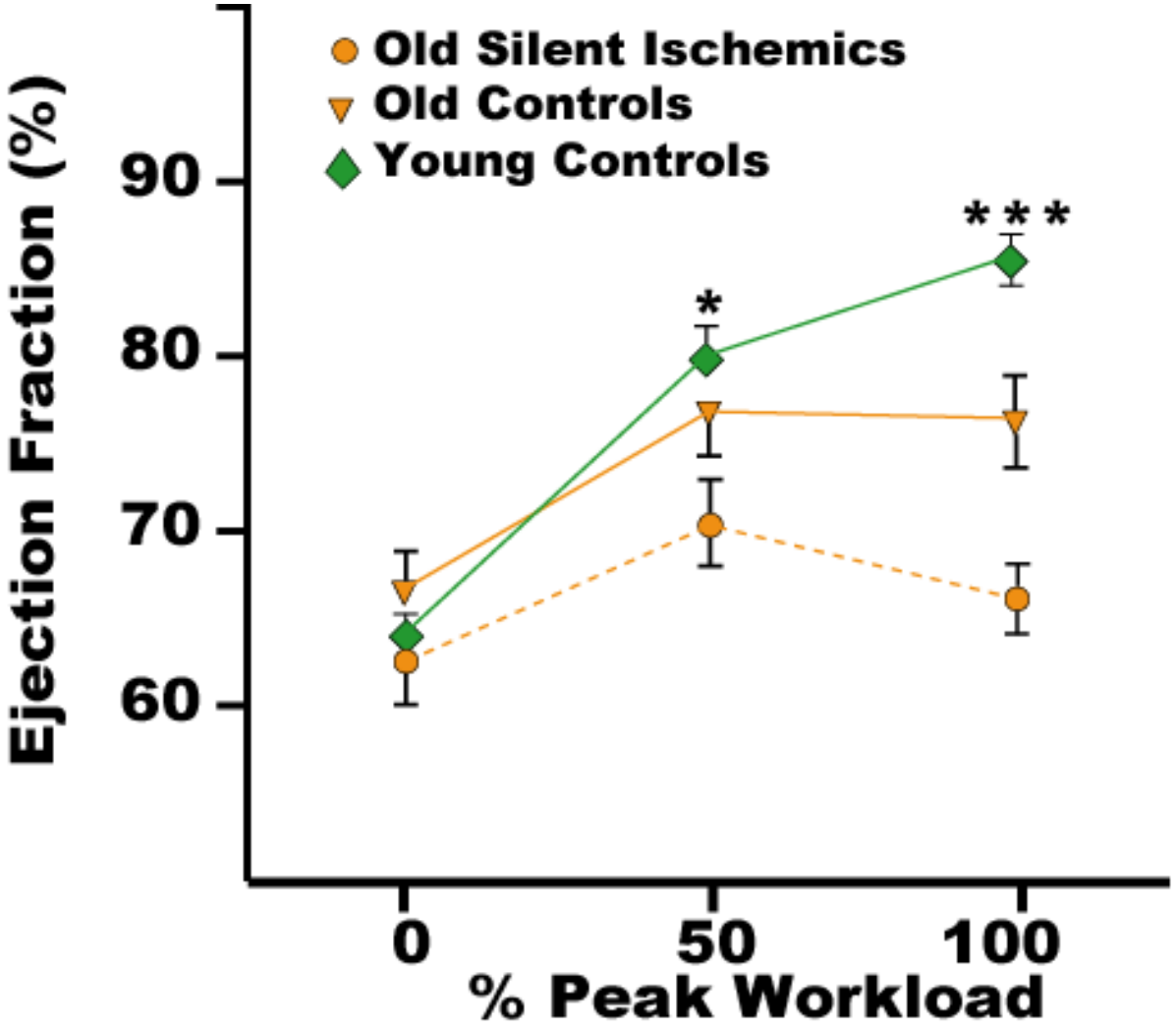
SUMMARY

Age Associated Changes in Determinants of Cardivascular Reserve Function in the Absence of a Textbook Clinical Diagnosis

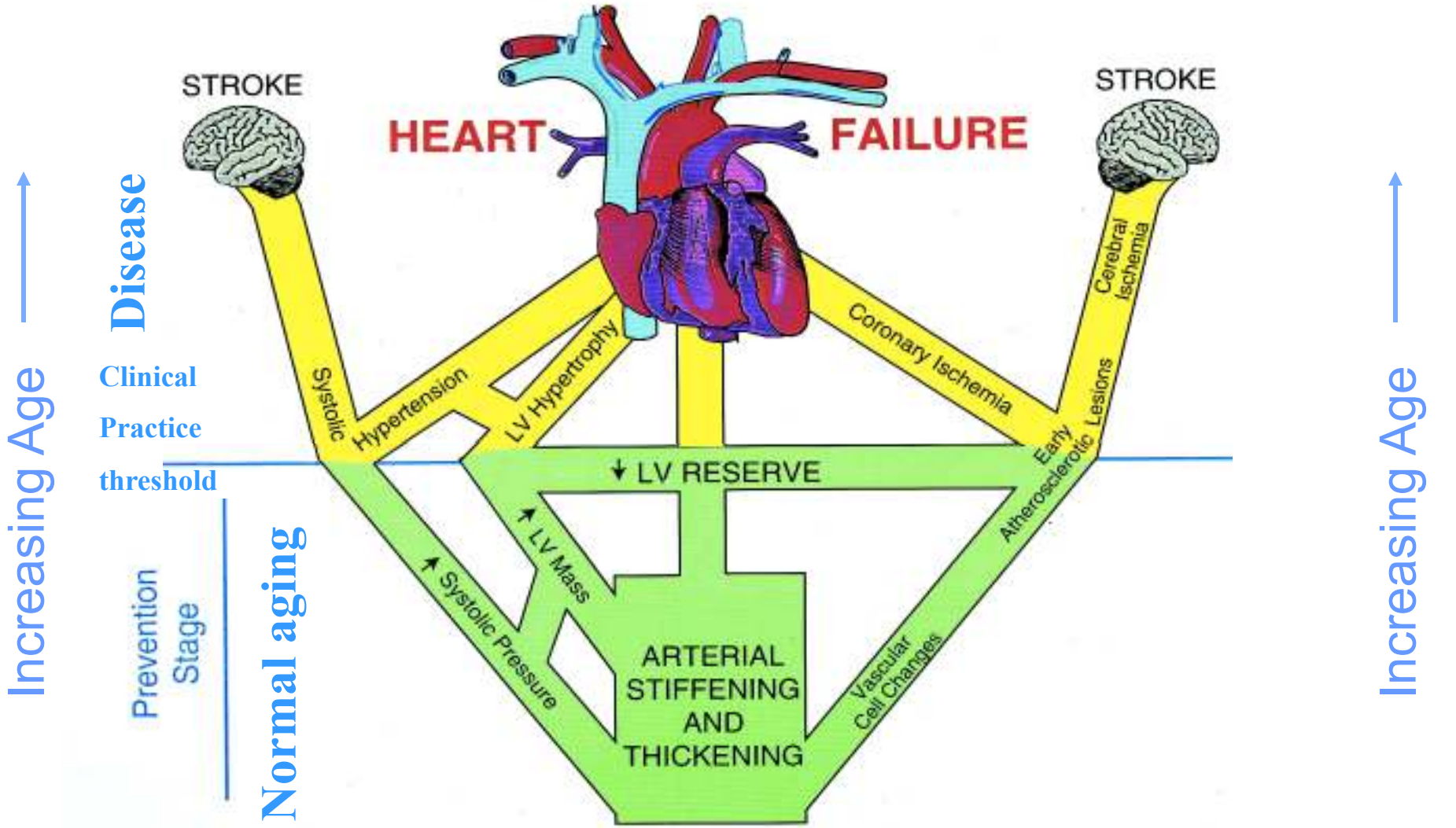
- ↓ Heart Rate
- ↑ Afterload
- ↑ Preload
- ↓ LV Intrinsic Contractility
- ↓ B Modulation of Afterload,Contractility,
- ↓ Heart Rate
- ↓ Arterio-ventricular Coupling

MILD forms of cardiovascular diseases, e.g., hypertension, ischemia, diabetes, that do not result in exaggerated LV remodeling, per se, push the older heart's systolic function **"over the edge"** during stress when shifts of blood into the lungs and dyspnea, occur without gross LV dilation, i.e., a clinical scenario presently misnamed as "Diastolic Heart Failure"

Coronary Artery Disease in Older Persons further Impairs EF, and therefore, A-V Coupling



Aging: The Major Risk Factor for Cardiovascular Morbidity and Mortality



"Future" Practice of Geriatrics

Prevention of cardiovascular diseases that accompany aging

by retarding cardiovascular aging

THE END

Thank You For Your Attention !