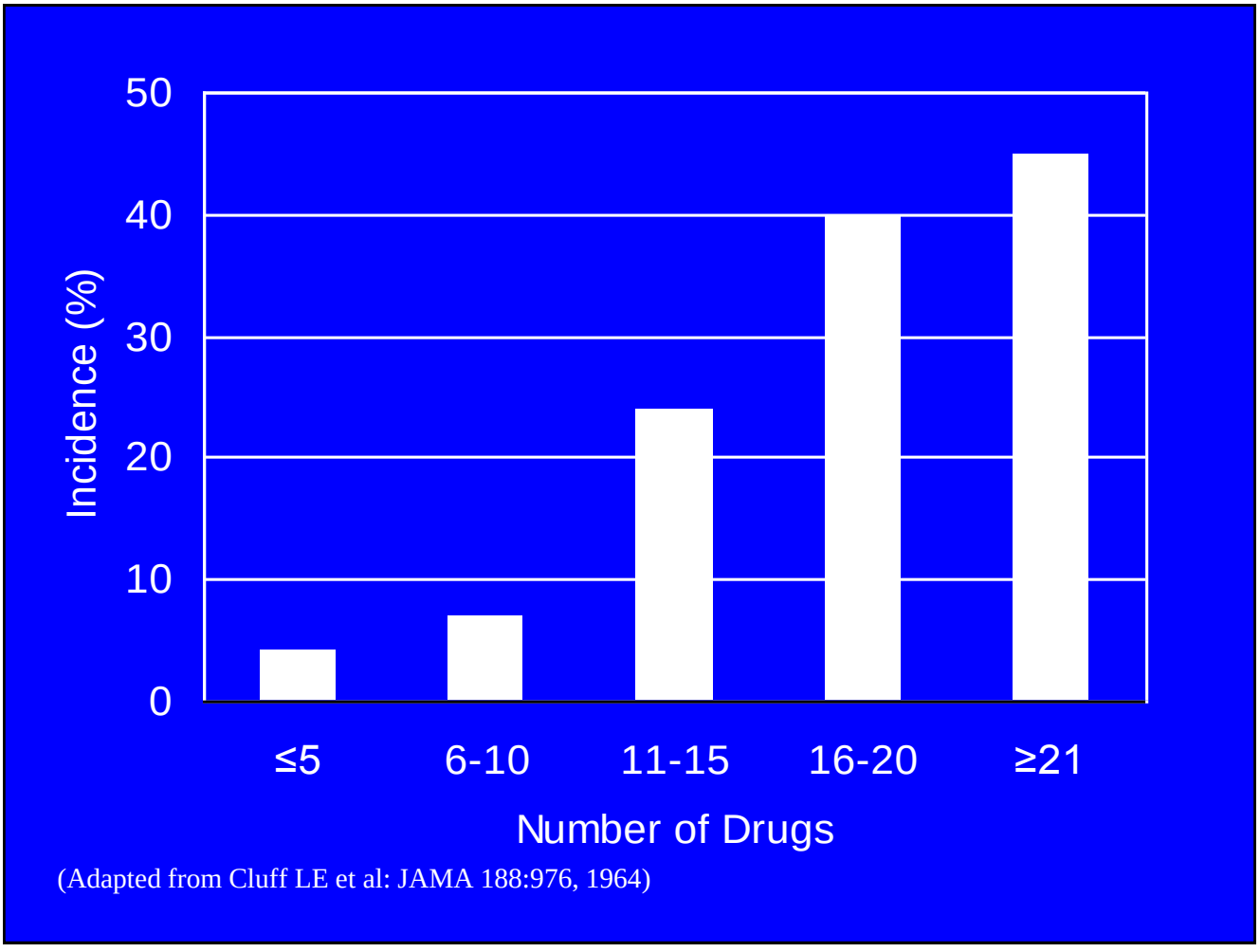
PHARMACODYNAMICS OF AGING: NARROWING OF THE THERAPEUTIC INDEX IN THE FACE OF THERAPEUTIC OPPORTUNITY

Darrell R. Abernethy, M.D., Ph.D.
Associate Director for Drug Safety
Office of Clinical Pharmacology
Food and Drug Administration

February 24, 2011

Pharmacodynamics of Aging

- Systemic Cardiovascular
- Local Cardiovascular
- Other Effector Systems



(Adapted from Cluff LE et al: JAMA 188:976, 1964)

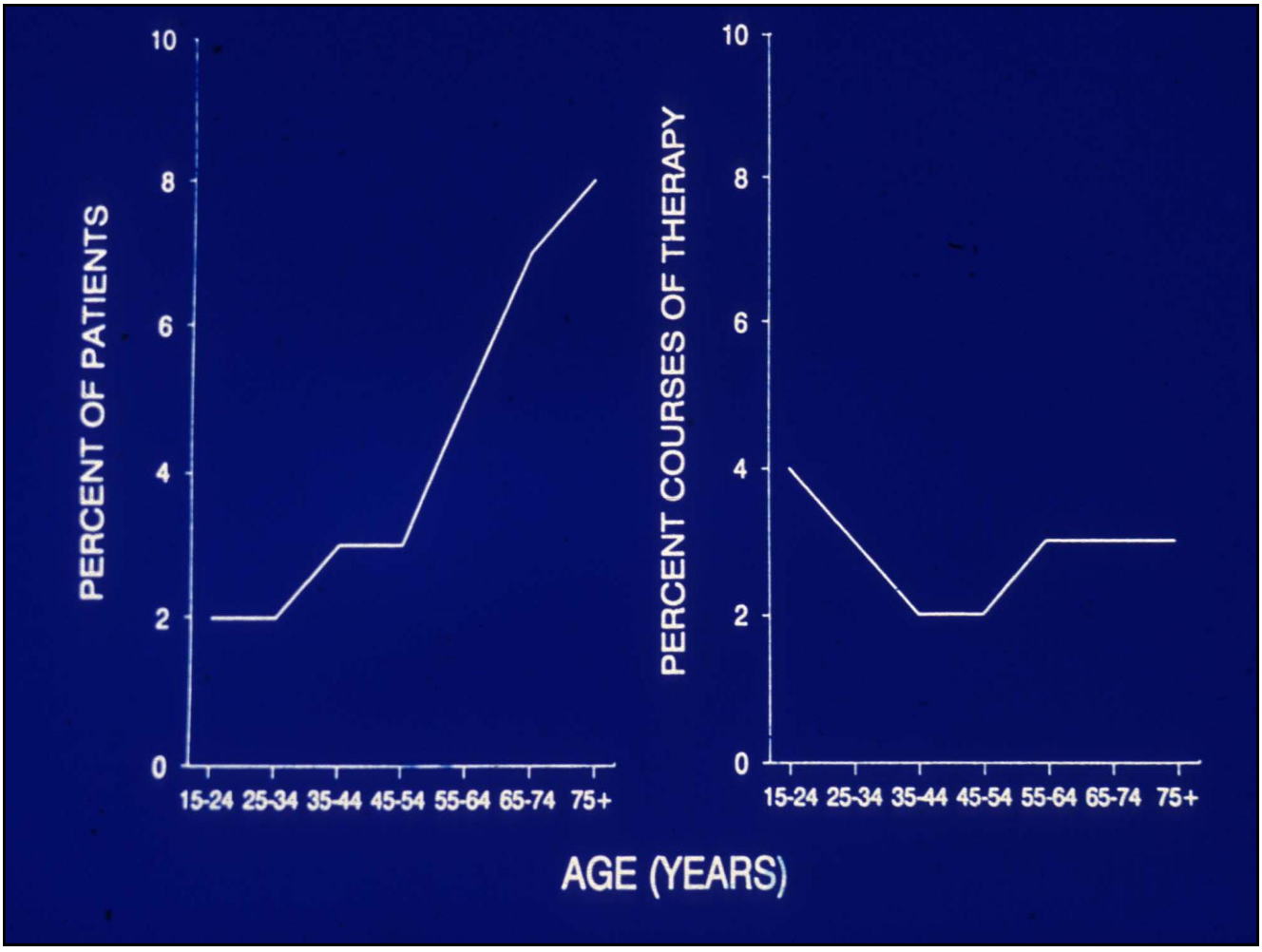

PERCENT OF PATIENTS
10
8
6
4
2
0
15-24 25-34 35-44 45-54 55-64 65-74 75+
PERCENT COURSES OF THERAPY
10
8
6
4
2
0
15-24 25-34 35-44 45-54 55-64 65-74 75+
AGE (YEARS)

Table 1. Types of the 189 Side-Effects of Drug-Drug Interactions

Type of Effect	%
Neuropsychological disorder and/or cognitive impairment	44.1
Global or orthostatic arterial hypotension	21.8
Acute renal failure secondary to dehydration	15.7
Hypo/hyperkalemia	5.6
Impairment of heart automatism, conduction, or rhythm	4.5
Increased anticholinergic effects	3.3
Other side effects	5.0

Distribution of Office Visits by Number of Drugs Administered or Prescribed for Patients ≥85 Years of Age

Number of Drugs	Office Visits: Number*	Per Cent
0	2,168,000	32.1
1	1,431,000	21.2
2	797,000	11.8
3	1,084,000	16.0
4	530, 000	7.8
5	363,000	5.4
6	160,000	2.4
7	117,000	1.7
8	14,000	0.2
9	73,000	1.1
≥10	27,000	0.4

* Total number of visits = 6, 763, 000, within rounding error.

Knapp, et al, J Amer Ger Soc. 1984:32:138-143.

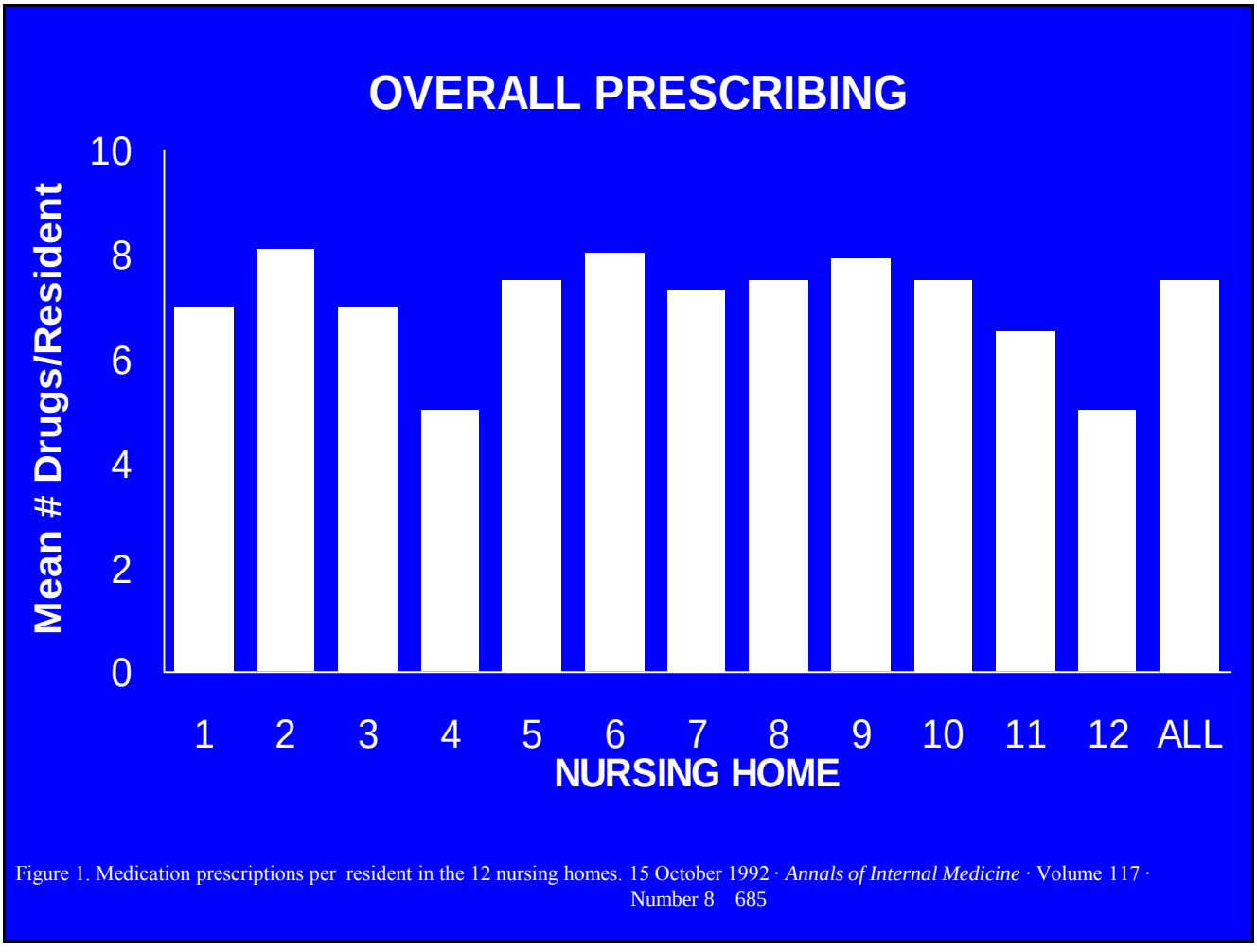
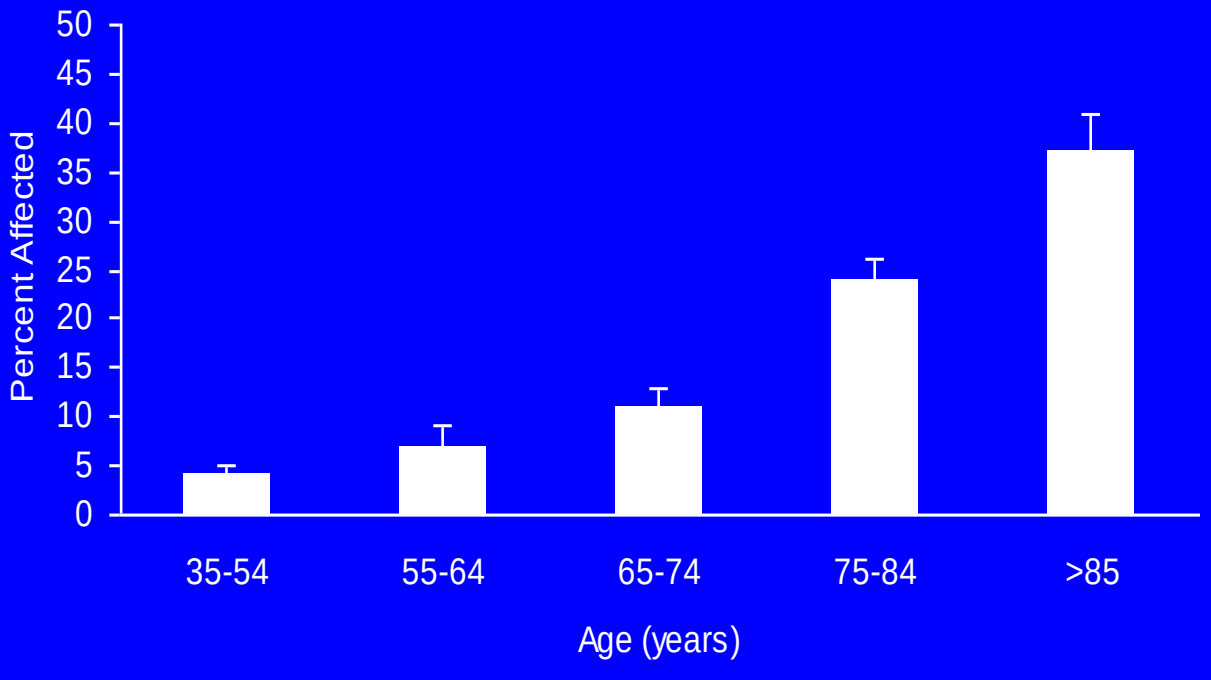


Figure 1. Medication prescriptions per resident in the 12 nursing homes. 15 October 1992 · *Annals of Internal Medicine* · Volume 117 · Number 8 685

Table 1. Age-related chronic medical conditions*

MEDICAL CONDITION	FREQUENCY PER 1000 PERSONS IN USA		
	Age <45 y	Age 46 - 64 y	Age > 65 y
Arthritis	30	241	481
Hypertension	129	244	372
Hearing impairment	37	141	321
Heart disease	31	134	295
Diabetes	9	57	99
Visual impairment	19	48	79
Cerebrovascular disease	1	16	63
Constipation	11	19	60

* From Zisook S, Downs NS. J Clin Psych 1998, 59 (suppl 4):80-91, data from Dorgan CA, editor. Statistical record of health and medicine. New York:International Thompson Publishing Co. 1995.



***Cognitive Impairment Defined by 6 or more Errors in the Mini-Mental Status Exam**

Data from: Robins LN, Regier DA, eds.: Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: The Free Press, 1991

Alterations in the Cardiovascular System of the Elderly

Cardiovasular hemodynamics

- Tendency to contracted intravascular volume
- Increased peripheral vascular resistance
- Tendency to lowered cardiac output
- Decreased baroreceptor sensitivity
- Increased blood pressure variability
- Suppressed plasma renin activity
- Decreased vascular endothelium production of nitric oxide

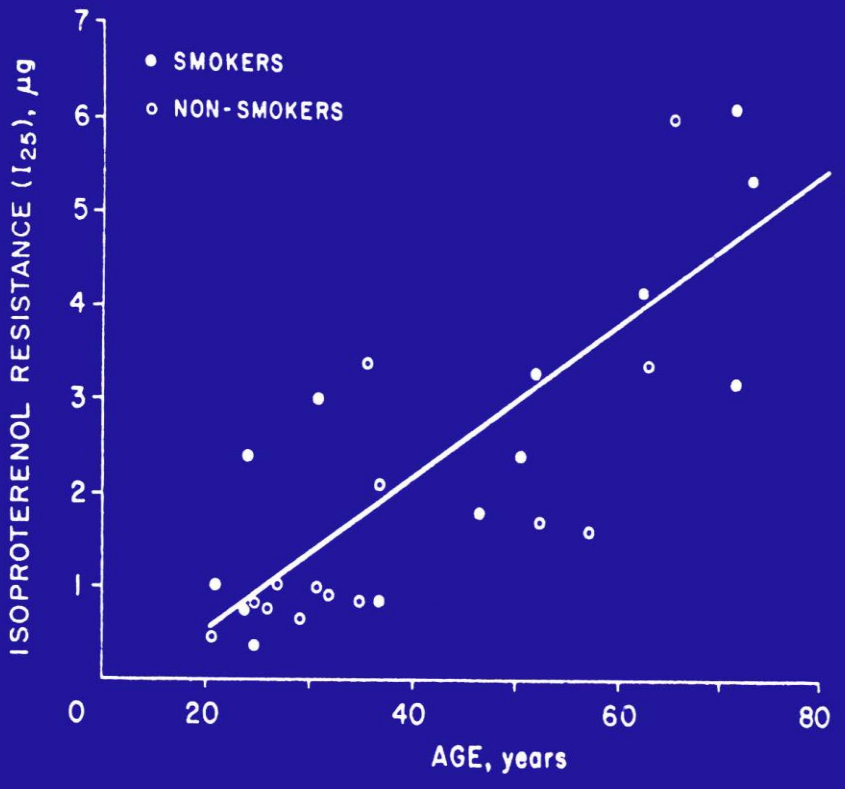


Fig. 1. Relationship between isoproterenolol resistance and age in smokers (●) and nonsmokers (○).

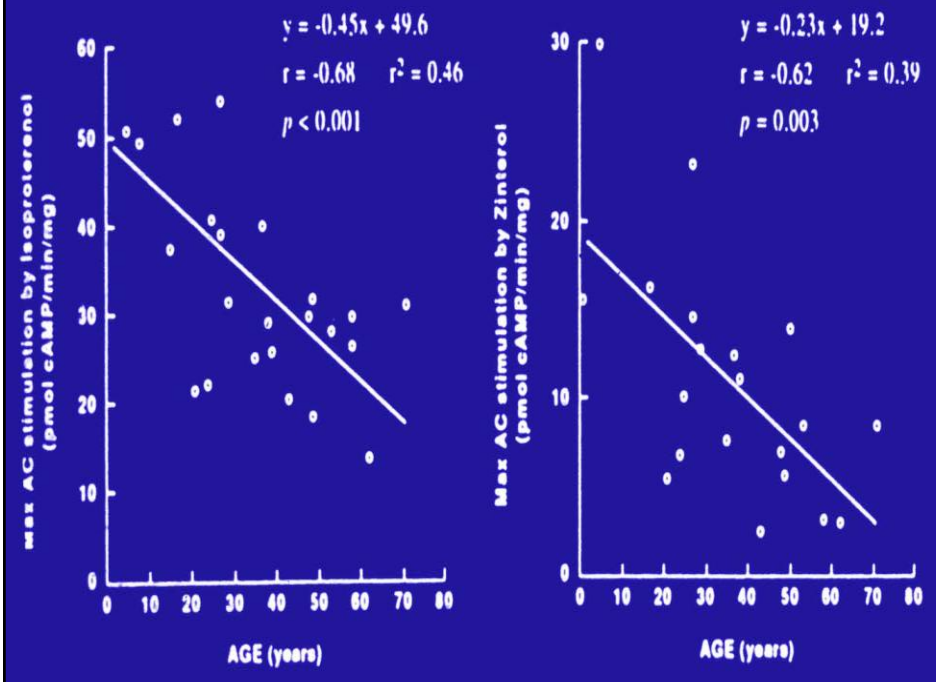


FIG 6. Scatterplots: Net maximum adenylyl cyclase (AC) stimulation by isoproterenol (left) and zinterol (right) for left ventricular myocardial preparations in relation to donor age.

White, et al, Circulation, 1994; 90: 1225-1238

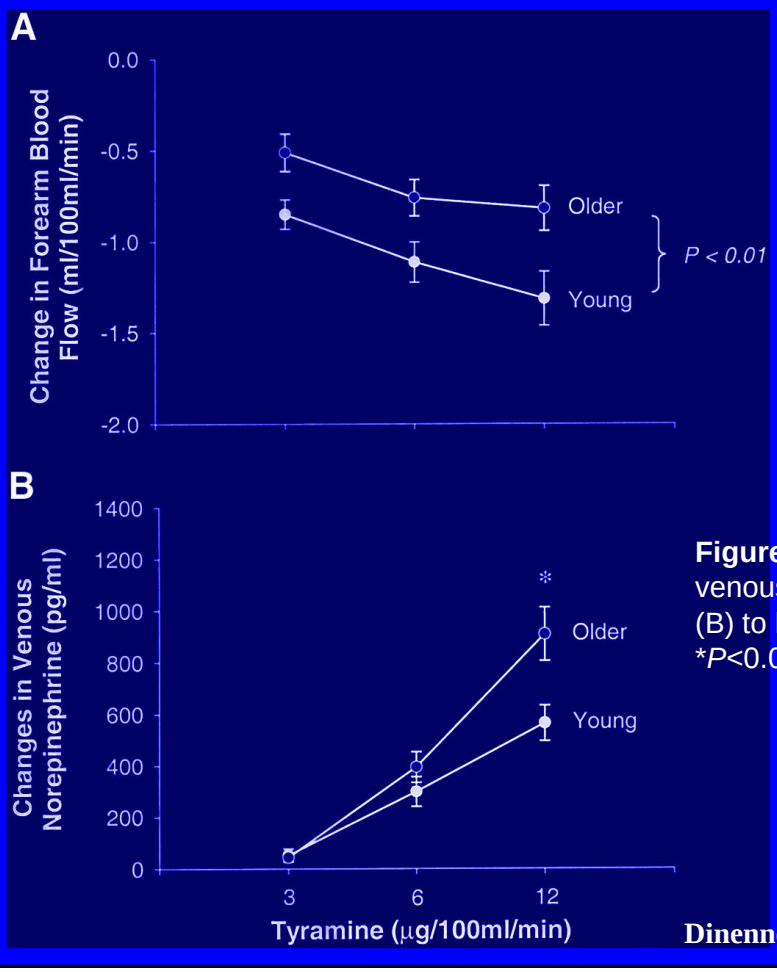


Figure 2. Changes in FBF (A) and deep venous norepinephrine concentrations (B) to local tyramine administration. *P<0.001 vs young men.

Dinenno et al., *Circulation*. 2002;106:1349-54

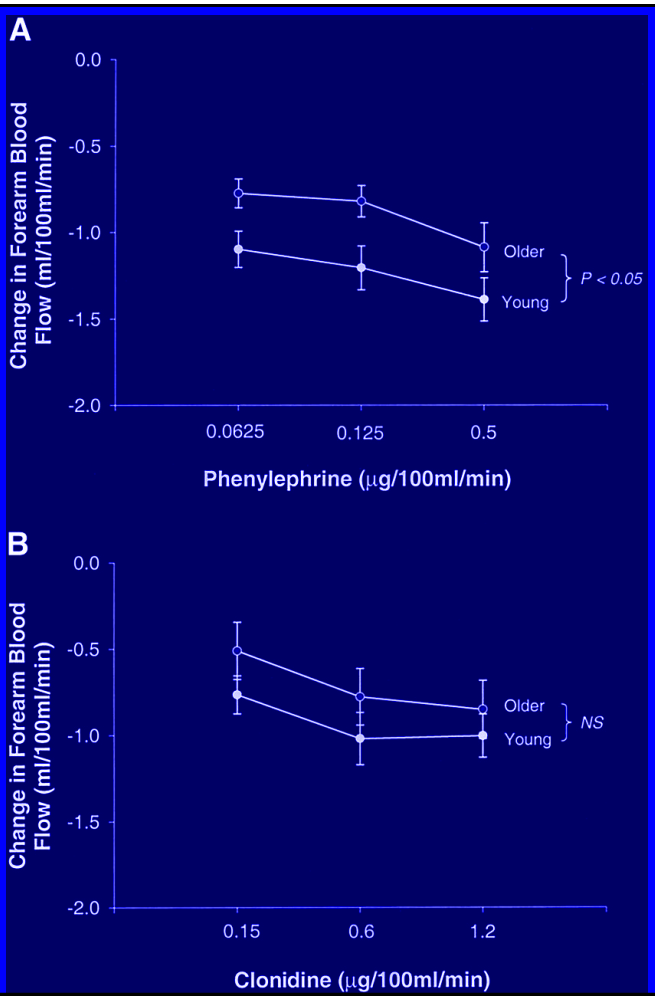


Figure 4. Forearm vasoconstrictor responses to phenylephrine are blunted in older men (A), whereas responses to clonidine are not significantly different (B).

Dinenno et al., *Circulation*. 2002;106:1349-54

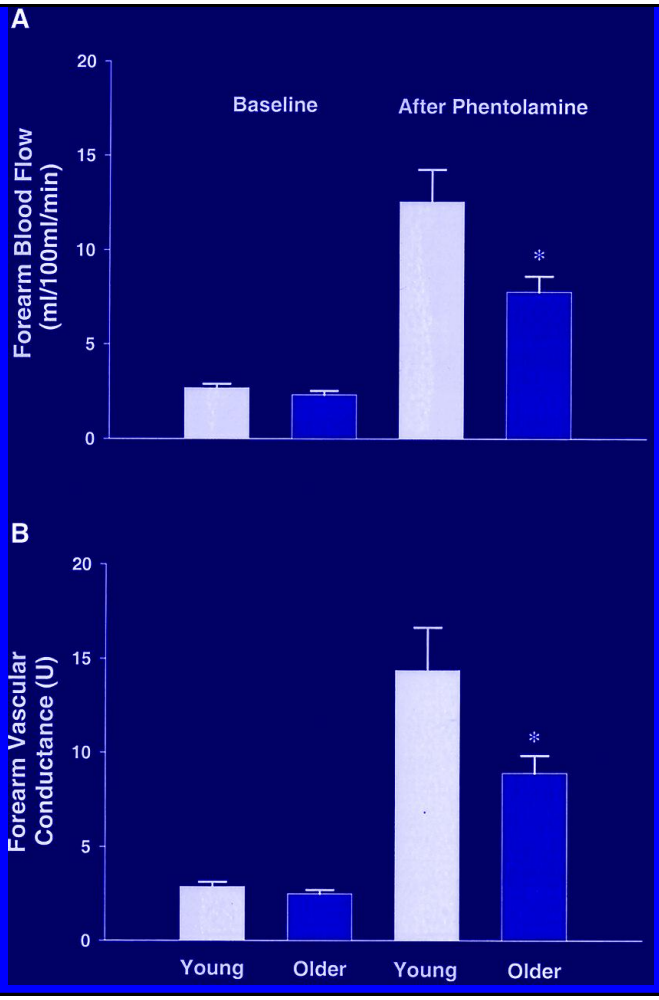
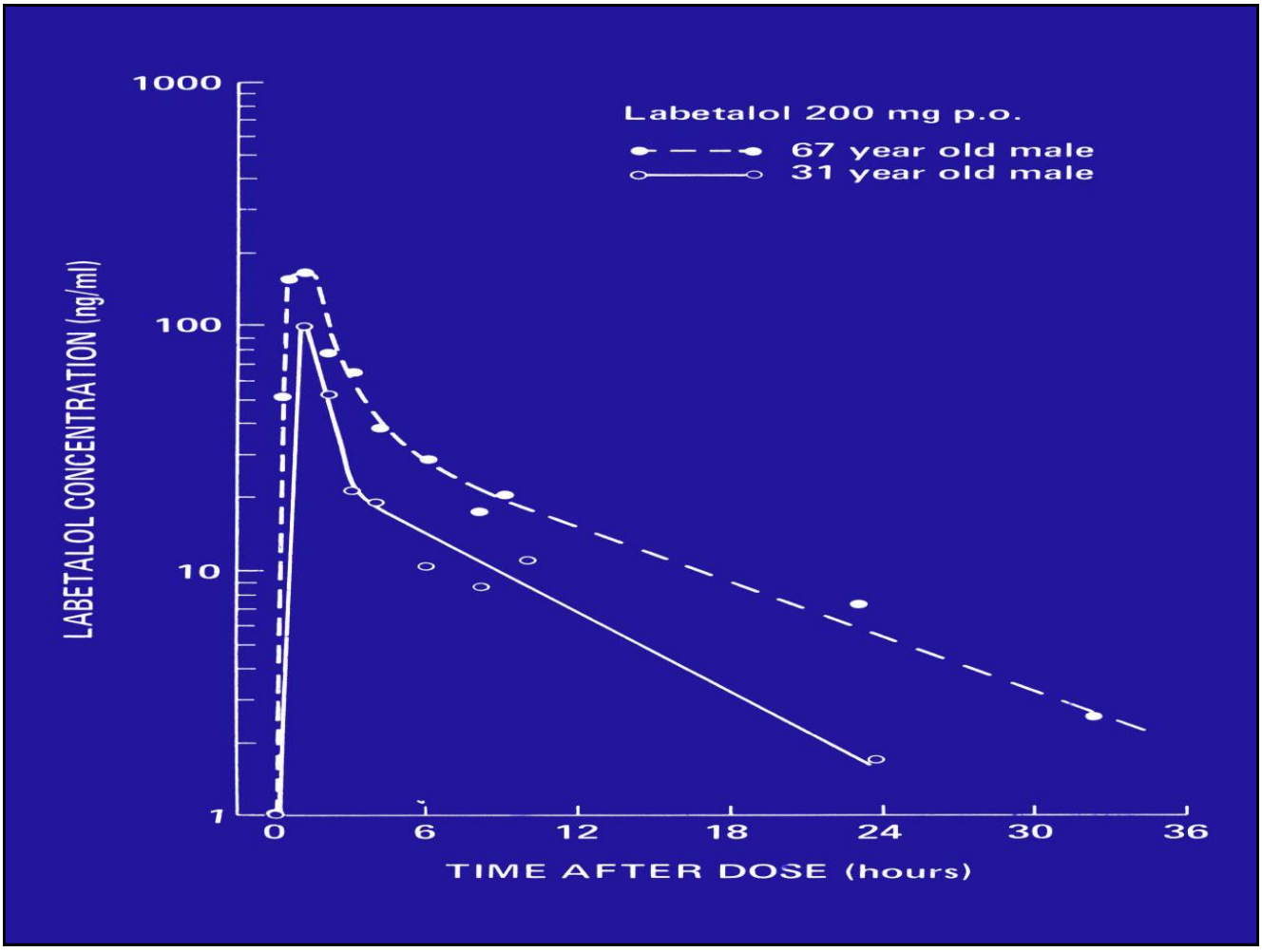
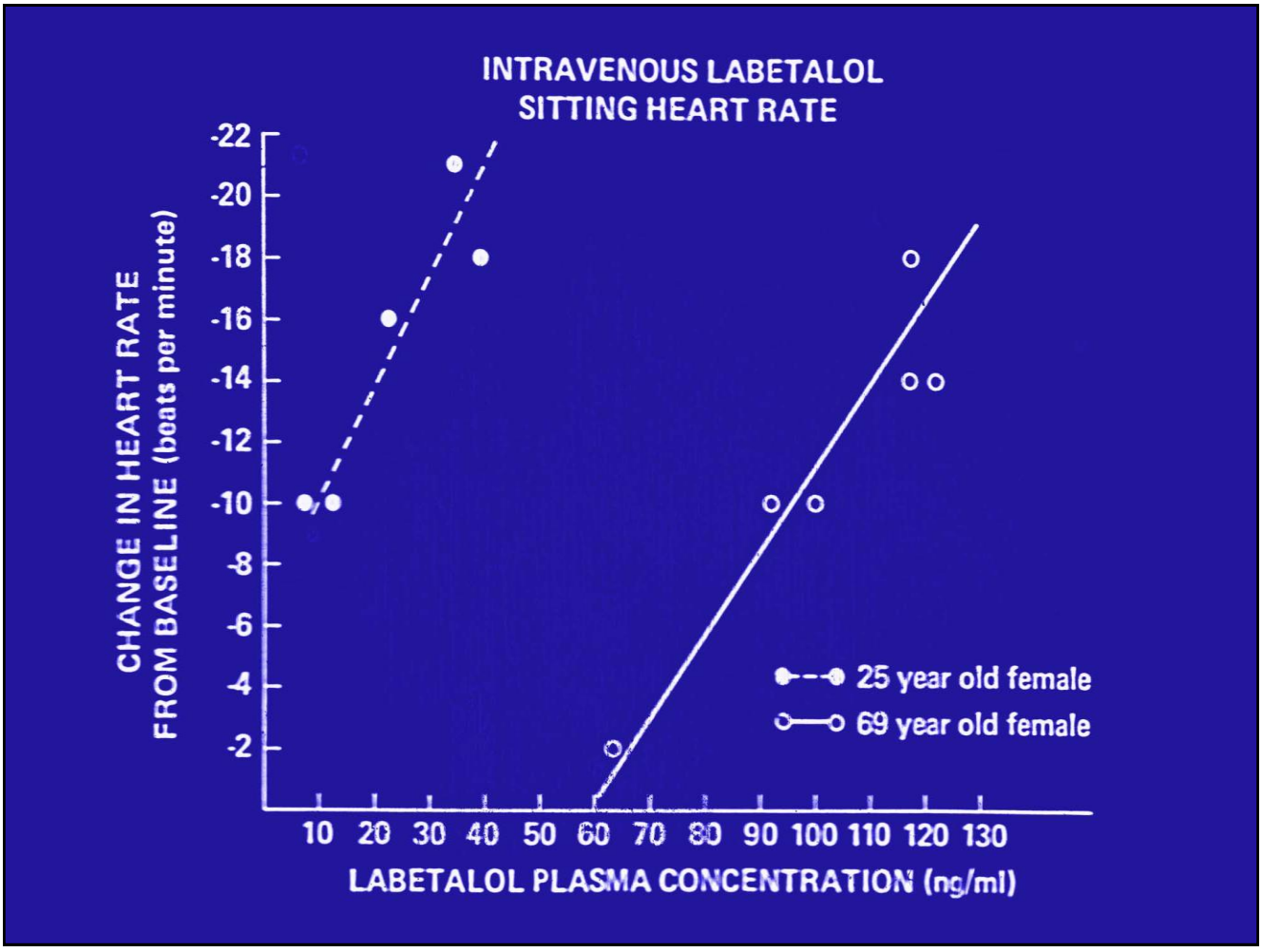
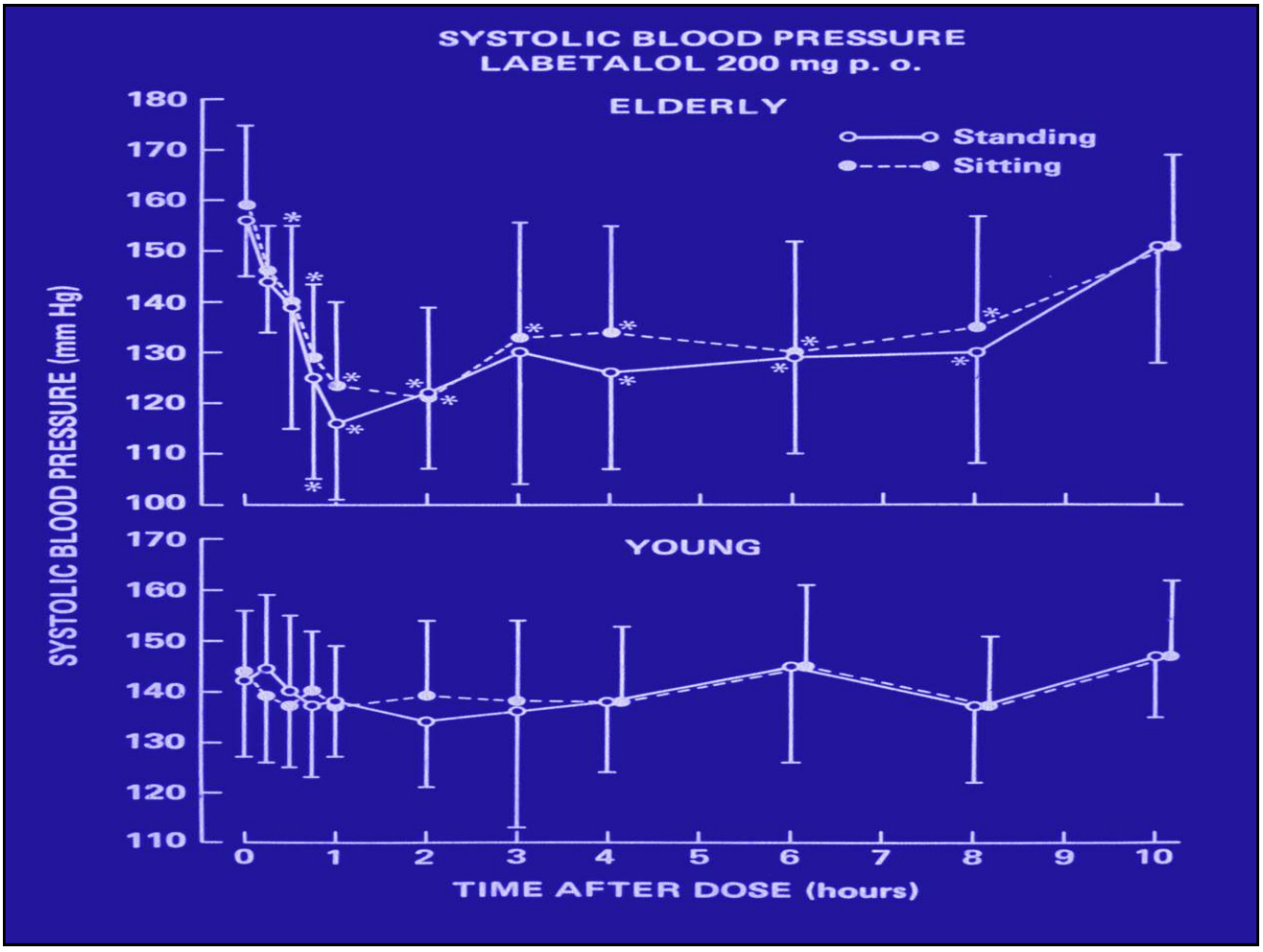


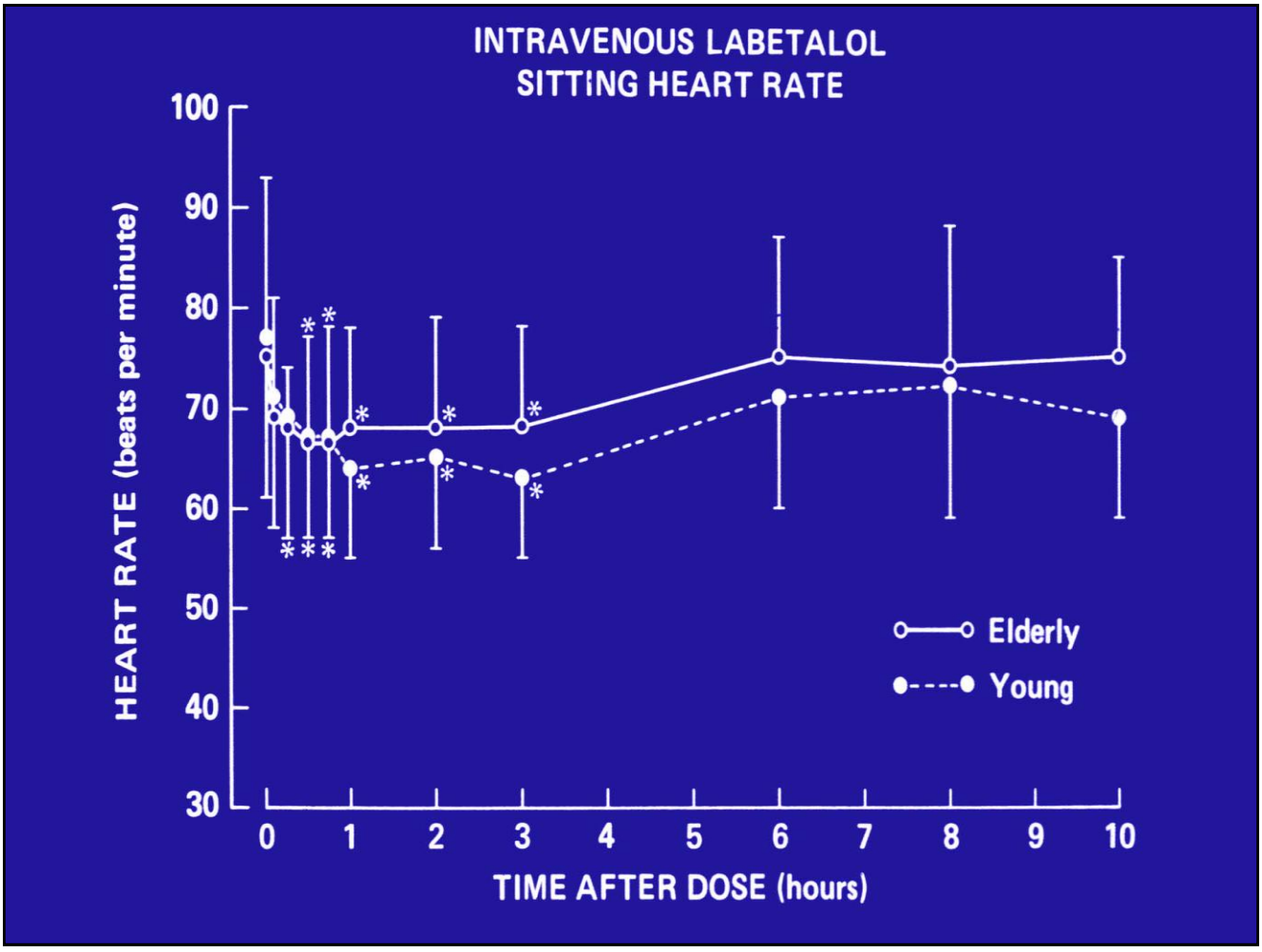
Figure 5. Forearm hemodynamics at rest and after local α-adrenergic blockade with phentolamine. *P<0.001 vs young men.

Dinenno et al., *Circulation*. 2002;106:1349-54


Labetalol 200 mg p.o.
67 year old male
31 year old male
LABETALOL CONCENTRATION (ng/ml)
1000
100
10
1
0
6
12
18
24
30
36
TIME AFTER DOSE (hours)


INTRAVENOUS LABETALOL
SITTING HEART RATE
CHANGE IN HEART RATE
FROM BASELINE (beats per minute)
-22
-20
-18
-16
-14
-12
-10
-8
-6
-4
-2
10 20 30 40 50 60 70 80 90 100 110 120 130
LABETALOL PLASMA CONCENTRATION (ng/ml)
25 year old female
69 year old female


SYSTOLIC BLOOD PRESSURE
LABETALOL 200 mg p. o.
ELDERLY
Standing
Sitting
YOUNG
SYSTOLIC BLOOD PRESSURE (mm Hg)
180
170
160
150
140
130
120
110
100
0
1
2
3
4
5
6
7
8
9
10
TIME AFTER DOSE (hours)


INTRAVENOUS LABETALOL
SITTING HEART RATE
HEART RATE (beats per minute)
100
90
80
70
60
50
40
30
0
1
2
3
4
5
6
7
8
9
10
TIME AFTER DOSE (hours)
Elderly
Young

Arterial Changes Related to Aging

Increased Calcium and Collagen

Reduces Elasticity and Compliance

Increased Pulse Pressure

Decreased Baroreceptor Sensitivity

Hyaline Thickening in Arterioles, Small Arteries

Increased Peripheral Resistance

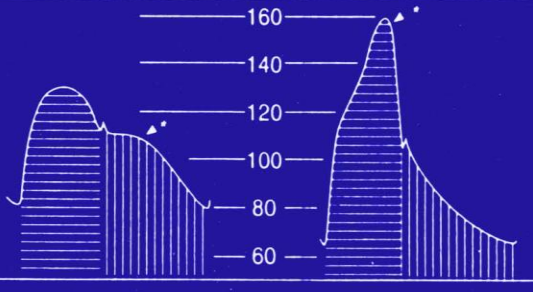
	Normal Aorta (Young Adults)		Stiff Aorta (Older Adults)
1. Aortic BP *(mm Hg)*	130 80	Systolic Diastolic	140 70
2. PWV *(m/s)*	5.0		10.0
3. Reflected Wave	Early Diastole		Late Systole
4. Pulse Wave Shape			
5. Aortic BP *(mm Hg)*	130 80	Systolic Diastolic	160 70

Figure. Development of aortic pressure abnormalities due to age-related aortic stiffening. 1. Increased systolic blood pressure (*BP*) and decreased diastolic blood pressure due to decreased aortic distensibility. **2.** Increased pulse wave velocity (*PWV*) as a result of decreased aortic distensibility. **3.** Return of the reflected primary pulse to the central aorta in systole rather than diastole because of faster wave travel. **4.** Change in the shape of the pulse wave because of early wave reflection. Note the reduction in diastolic pressure-time despite the increase in systolic pressure. Horizontal lines indicate systole; vertical lines indicate diastole. **5.** The aortic blood pressure resulting from decreased aortic distensibility and early reflected waves. * Primary reflected wave. Adapted from reference 18; pulse calibrations added by the authors.

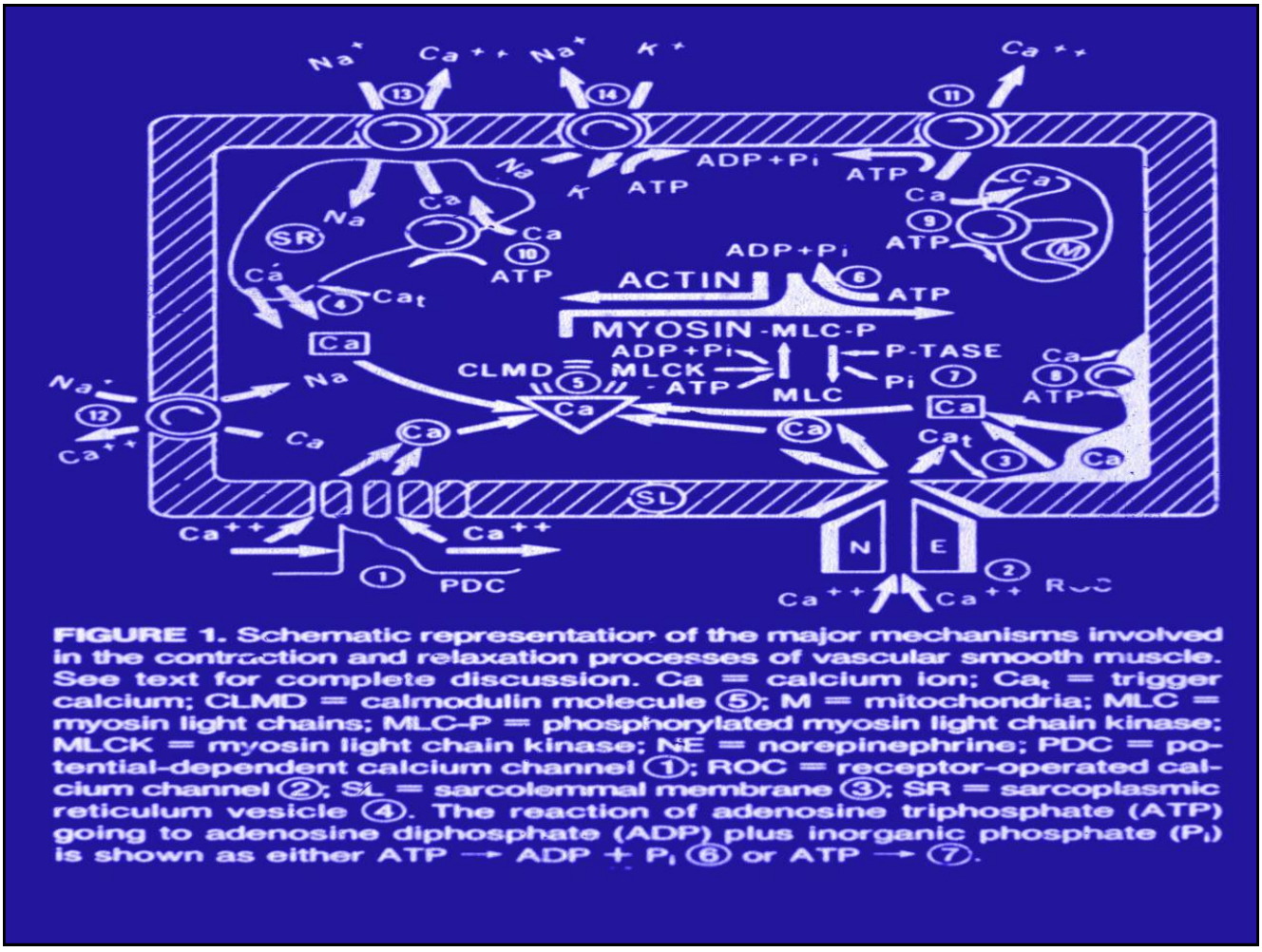
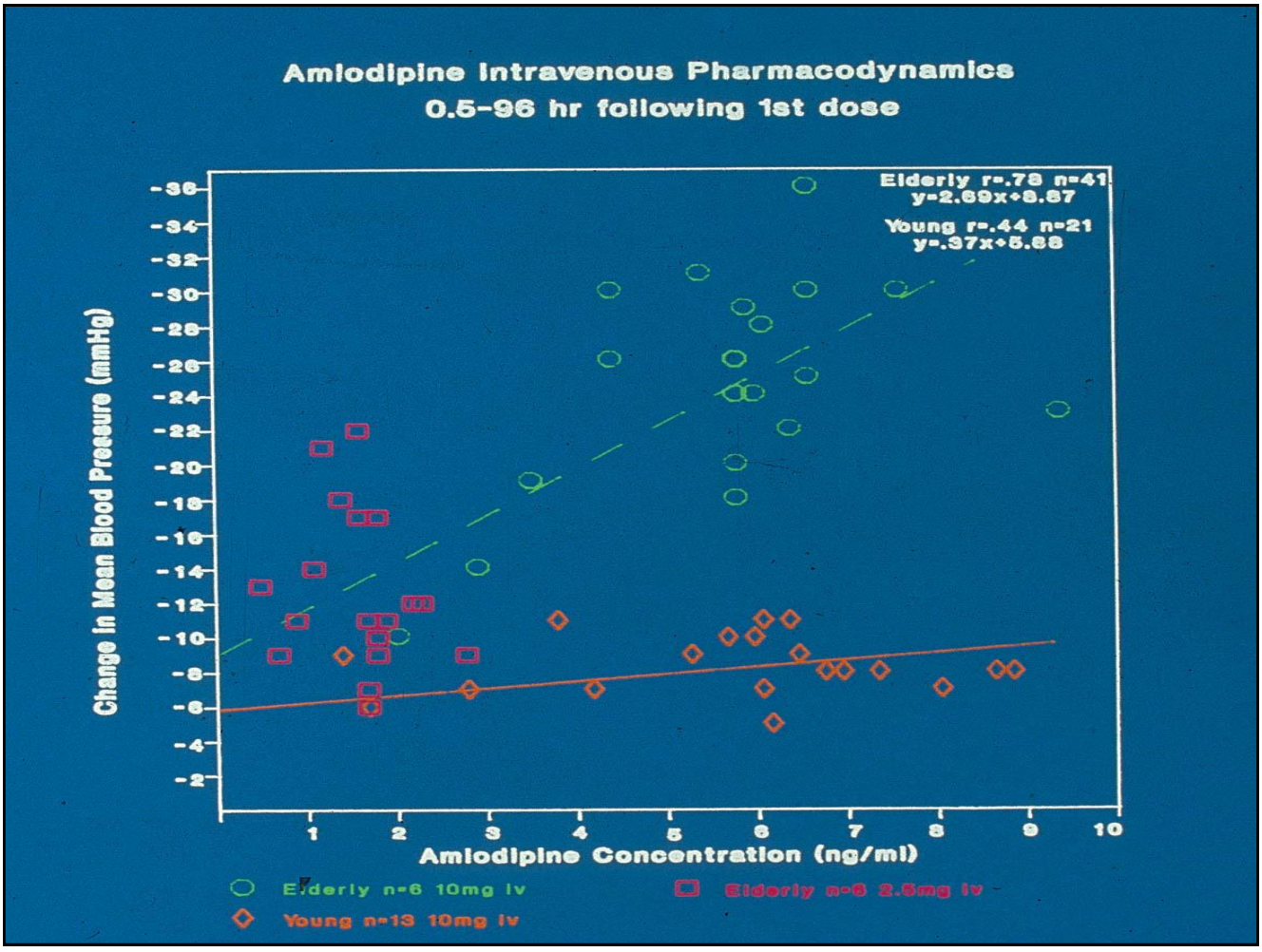
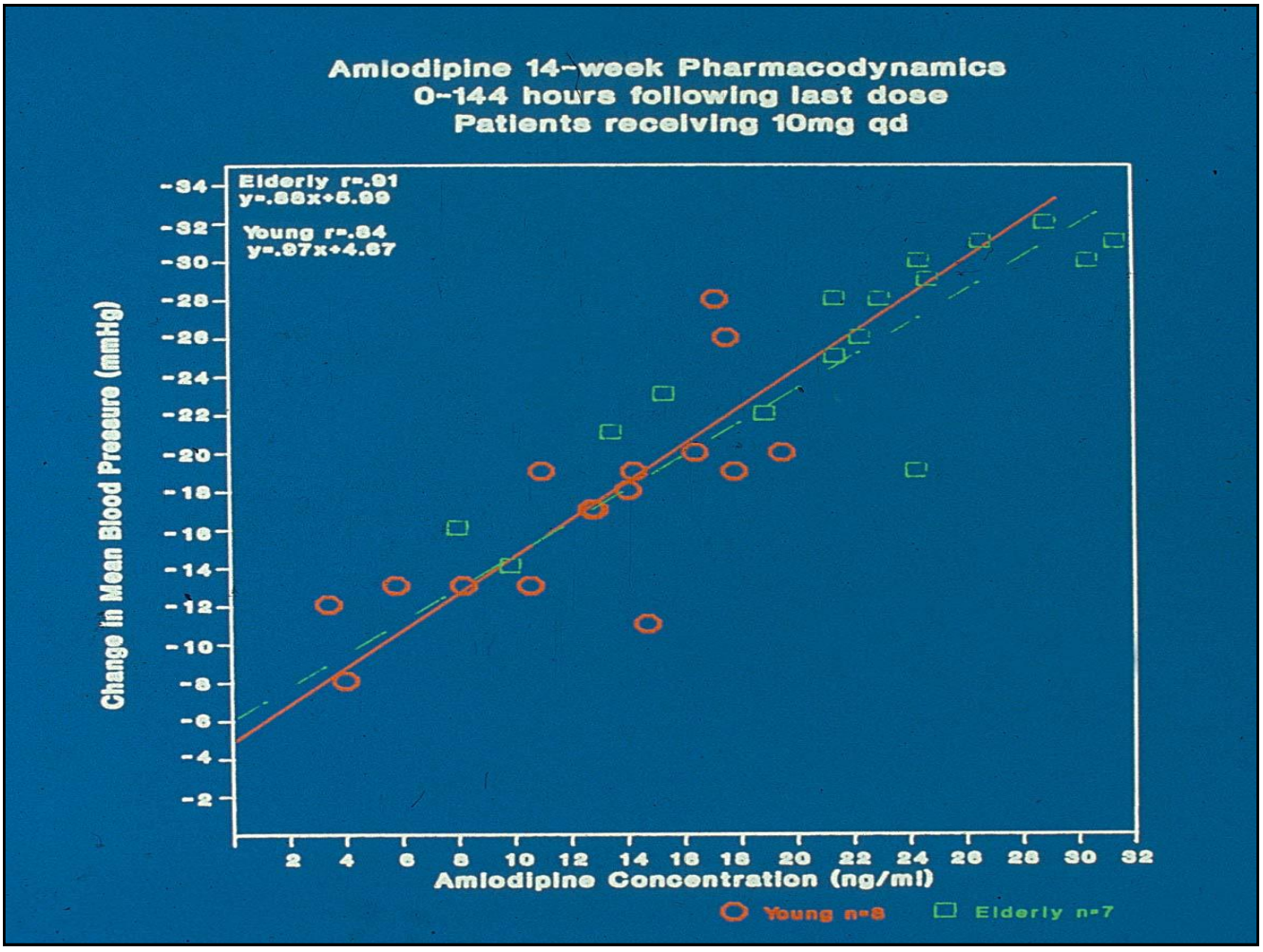
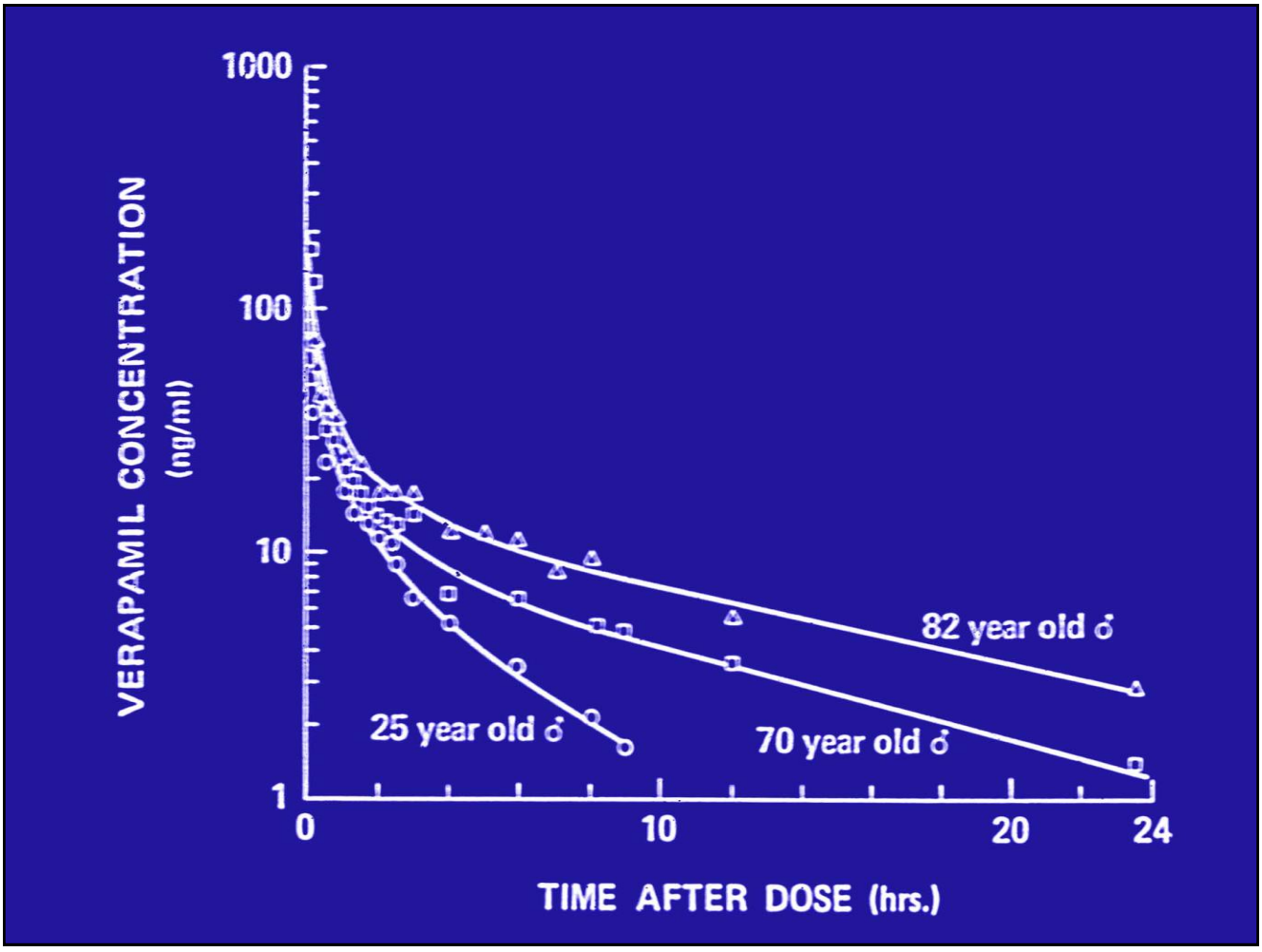
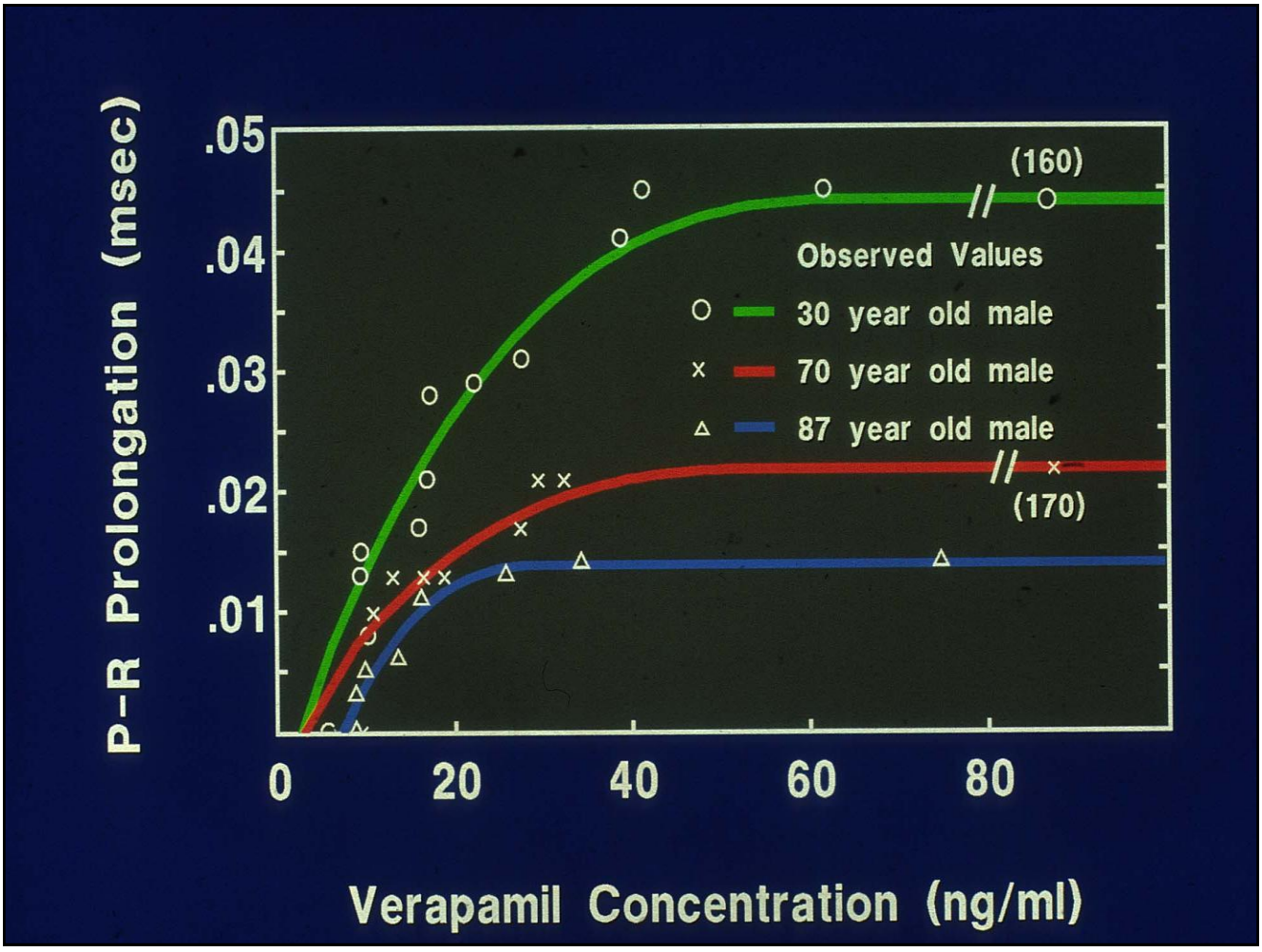


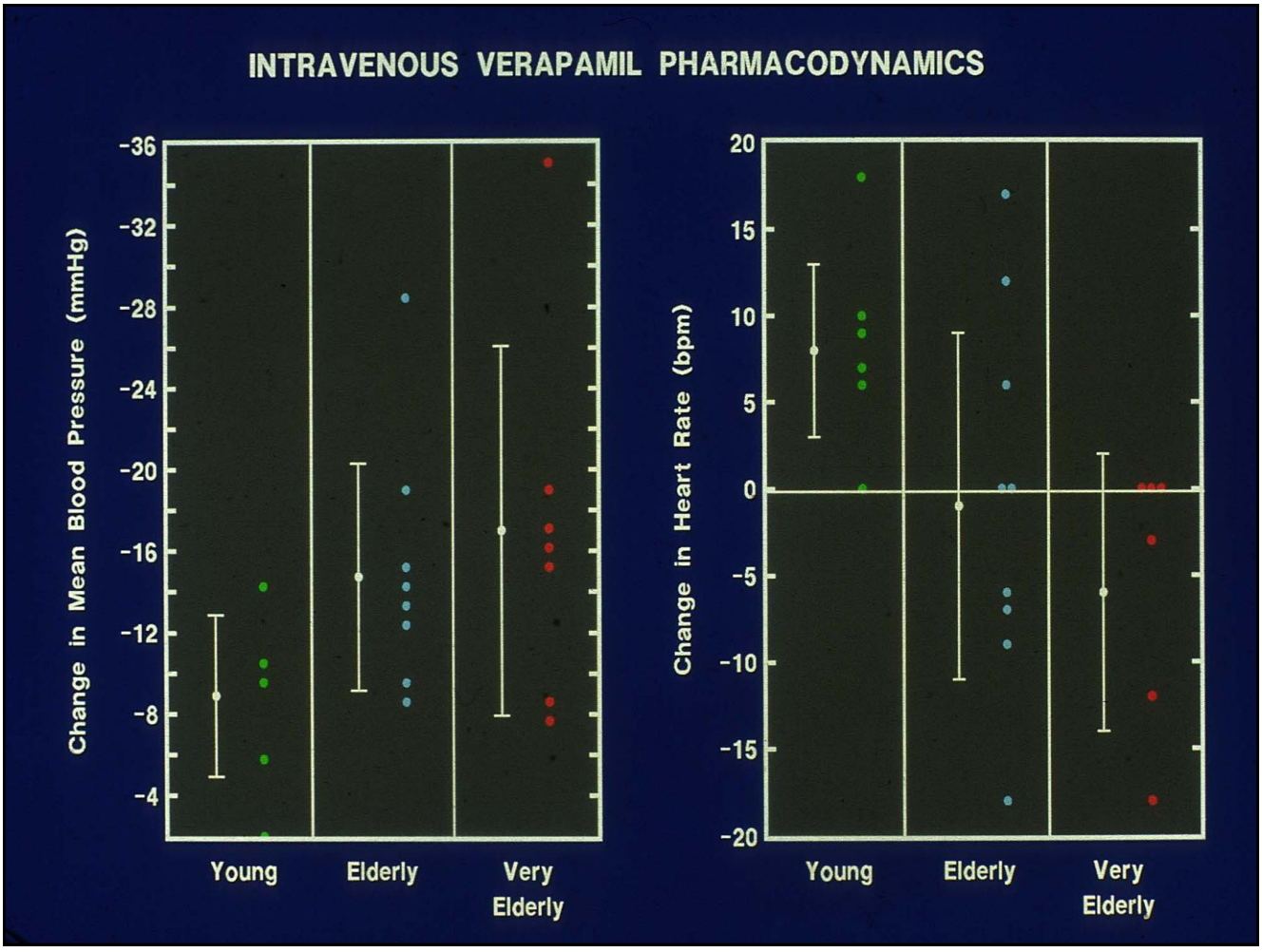
FIGURE 1. Schematic representation of the major mechanisms involved in the contraction and relaxation processes of vascular smooth muscle. See text for complete discussion. Ca = calcium ion; Ca_t = trigger calcium; CLMD = calmodulin molecule ⑤; M = mitochondria; MLC = myosin light chains; MLC-P = phosphorylated myosin light chain kinase; MLCK = myosin light chain kinase; NE = norepinephrine; PDC = potential-dependent calcium channel ①; ROC = receptor-operated calcium channel ②; SL = sarcolemmal membrane ③; SR = sarcoplasmic reticulum vesicle ④. The reaction of adenosine triphosphate (ATP) going to adenosine diphosphate (ADP) plus inorganic phosphate (P_i) is shown as either ATP → ADP + P_i ⑥ or ATP → ⑦.

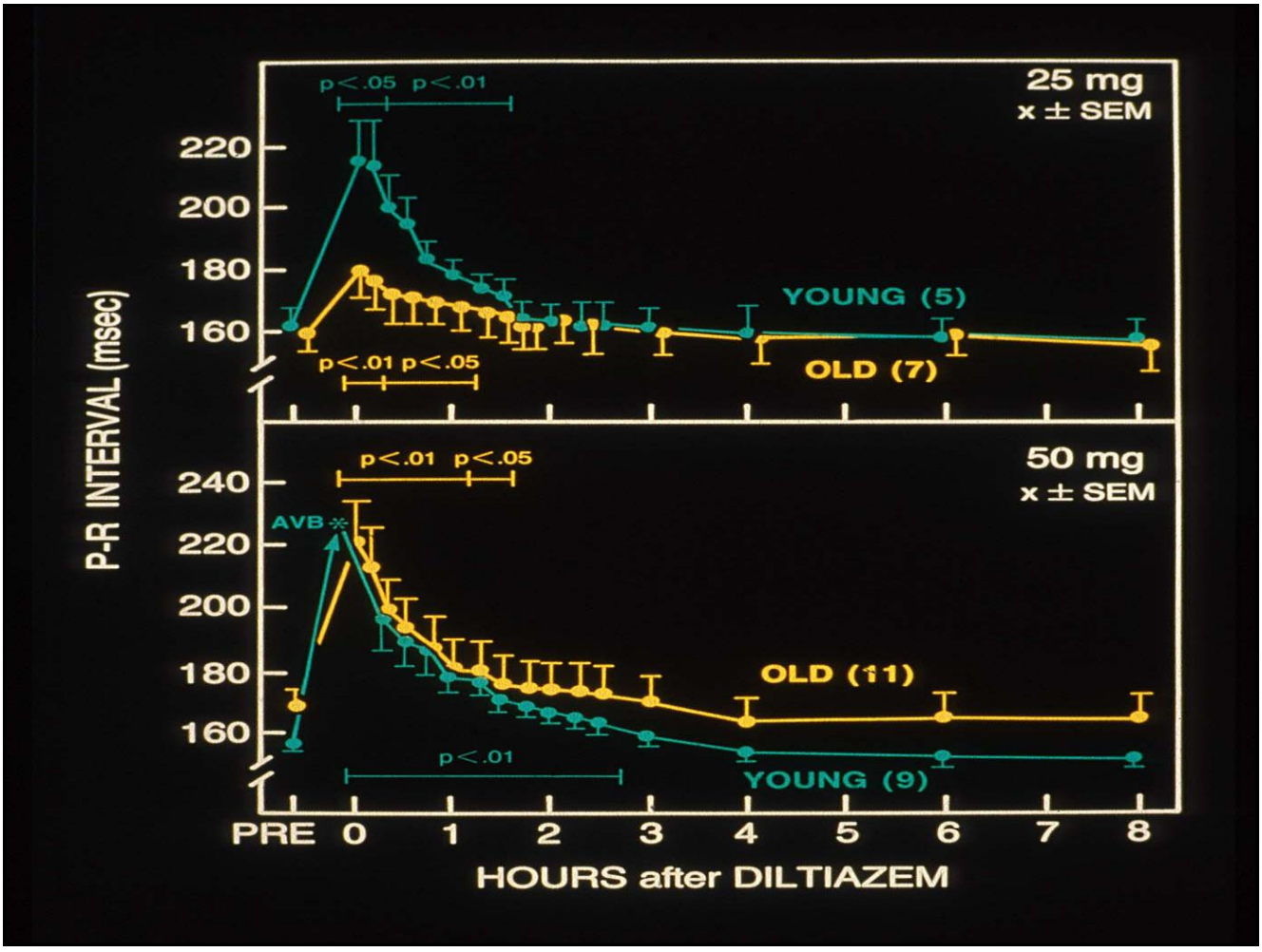

Amlodipine Intravenous Pharmacodynamics
0.5–96 hr following 1st dose
Elderly r=.78 n=41
y=2.69x+8.87
Young r=.44 n=21
y=.97x+5.88
Change in Mean Blood Pressure (mmHg)
-36
-34
-32
-30
-28
-26
-24
-22
-20
-18
-16
-14
-12
-10
-8
-6
-4
-2
1
2
3
4
5
6
7
8
9
10
Amlodipine Concentration (ng/ml)
Elderly n=6 10mg iv
Elderly n=6 2.5mg iv
Young n=13 10mg iv

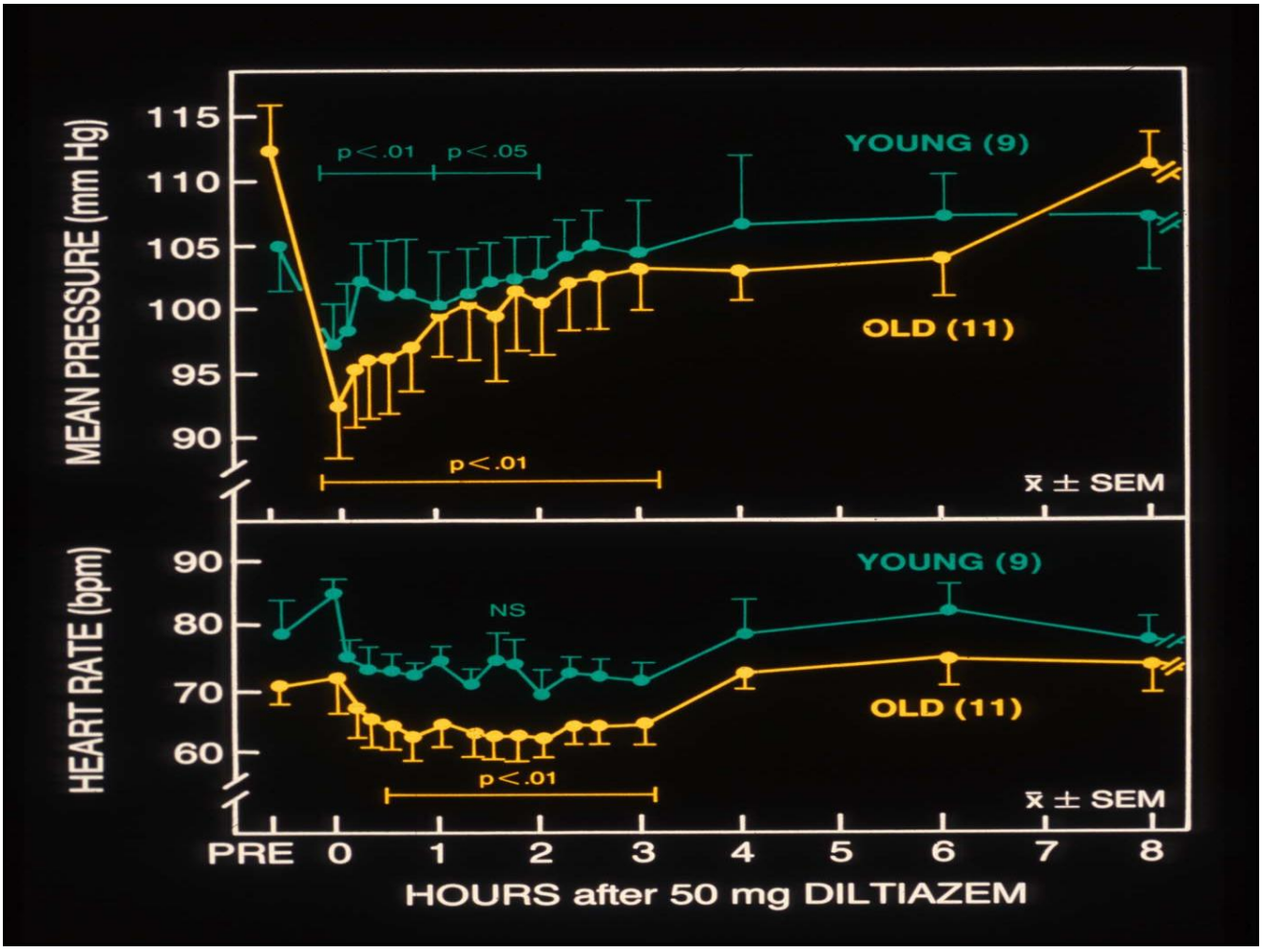

Amlodipine 14-week Pharmacodynamics
0-144 hours following last dose
Patients receiving 10mg qd
Elderly r=.91
y=.88x+6.09
Young r=.84
y=.97x+4.67
Change in Mean Blood Pressure (mmHg)
-34
-32
-30
-28
-26
-24
-22
-20
-18
-16
-14
-12
-10
-8
-6
-4
-2
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
Amlodipine Concentration (ng/ml)
Young n=8
Elderly n=7


VERAPAMIL CONCENTRATION
(ng/ml)
1000
100
10
1
0
10
20
24
TIME AFTER DOSE (hrs.)
82 year old ♂
70 year old ♂
25 year old ♂


P-R Prolongation (msec)
.05
.04
.03
.02
.01
0
20
40
60
80
(160)
(170)
Observed Values
30 year old male
70 year old male
87 year old male
Verapamil Concentration (ng/ml)


INTRAVENOUS VERAPAMIL PHARMACODYNAMICS
Change in Mean Blood Pressure (mmHg)
-36
-32
-28
-24
-20
-16
-12
-8
-4
Young
Elderly
Very Elderly
Change in Heart Rate (bpm)
20
15
10
5
0
-5
-10
-15
-20
Young
Elderly
Very Elderly


p<.05 p<.01
25 mg
x ± SEM
220
200
180
160
YOUNG (5)
OLD (7)
p<.01 p<.05
p<.01 p<.05
50 mg
x ± SEM
240
220
200
180
160
AVB
OLD (11)
p<.01
YOUNG (9)
P-R INTERVAL (msec)
PRE 0 1 2 3 4 5 6 7 8
HOURS after DILTIAZEM


MEAN PRESSURE (mm Hg)
115
110
105
100
95
90
p<.01
p<.05
YOUNG (9)
OLD (11)
p<.01
x̄ ± SEM
HEART RATE (bpm)
90
80
70
60
NS
YOUNG (9)
OLD (11)
p<.01
x̄ ± SEM
PRE
0
1
2
3
4
5
6
7
8
HOURS after 50 mg DILTIAZEM

HEART RATE RESPONSES

- DECREASED RATE RESPONSES
  - Parasympathetic
  - Sympathetic
- DIFFERING SENSITITVITY TO CALCIUM CHANNEL BLOCKADE OF THE SINUS NODE

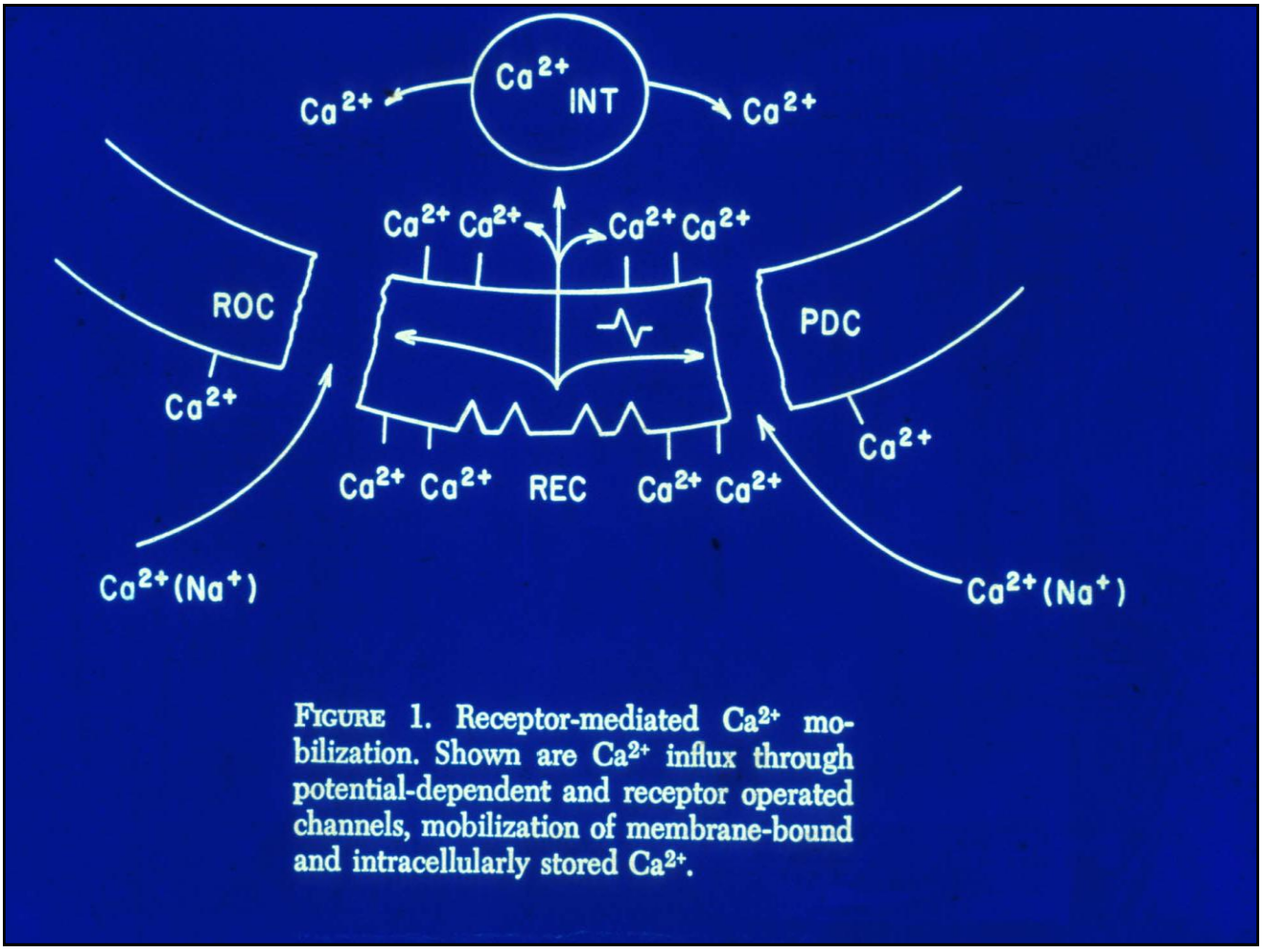


FIGURE 1. Receptor-mediated Ca^{2+} mobilization. Shown are Ca^{2+} influx through potential-dependent and receptor operated channels, mobilization of membrane-bound and intracellularly stored Ca^{2+}.

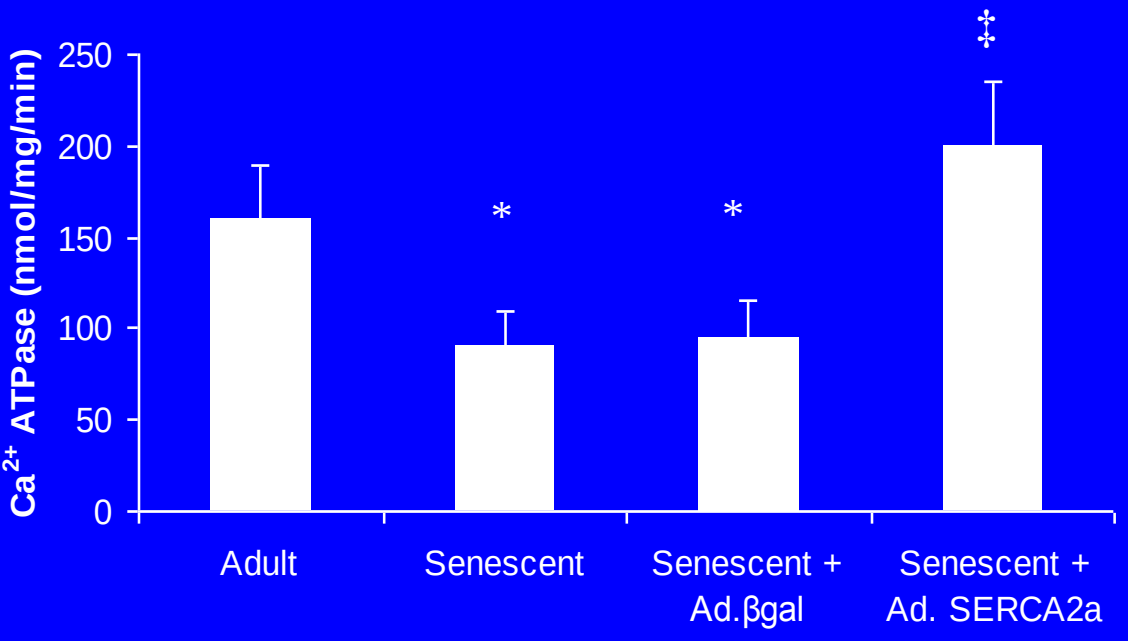


Figure 3. ATPase activity measured at 10 μmol/L Ca^{2+} in membrane preparations from adult uninfected rat hearts (n=4), preparations from senescent uninfected rat hearts (n=4), preparations of senescent hearts infected with Ad.β-Gal at day 2 (n=4), and preparations of senescent hearts infected with Ad.SERCA2a at day 2 (n=4). *P<0.05 compared with adult. ‡P<0.05 compared with senescent group plus Ad.β-Gal.

Schmidt et al., *Circulation*. 2002; 101:790-6

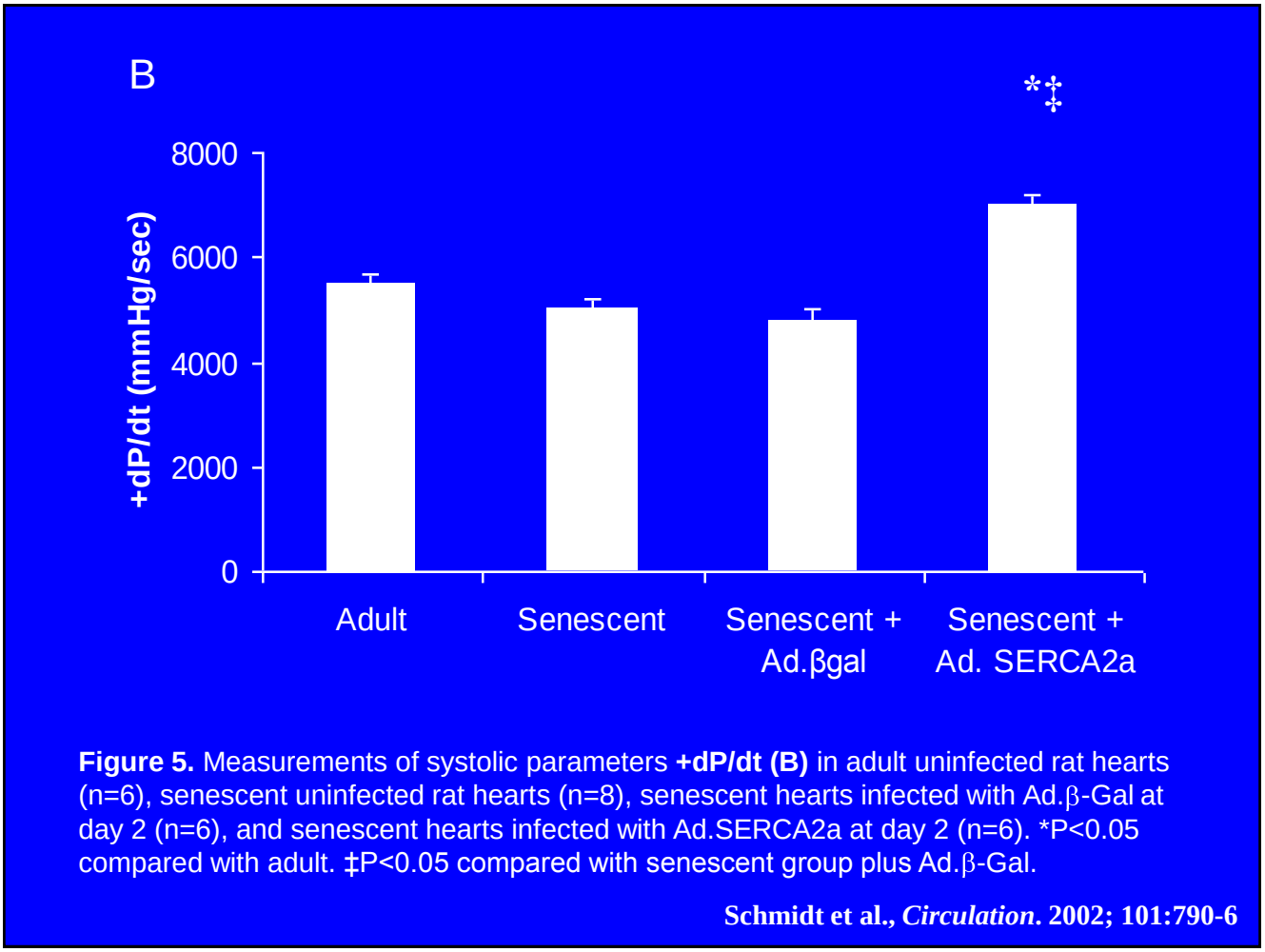
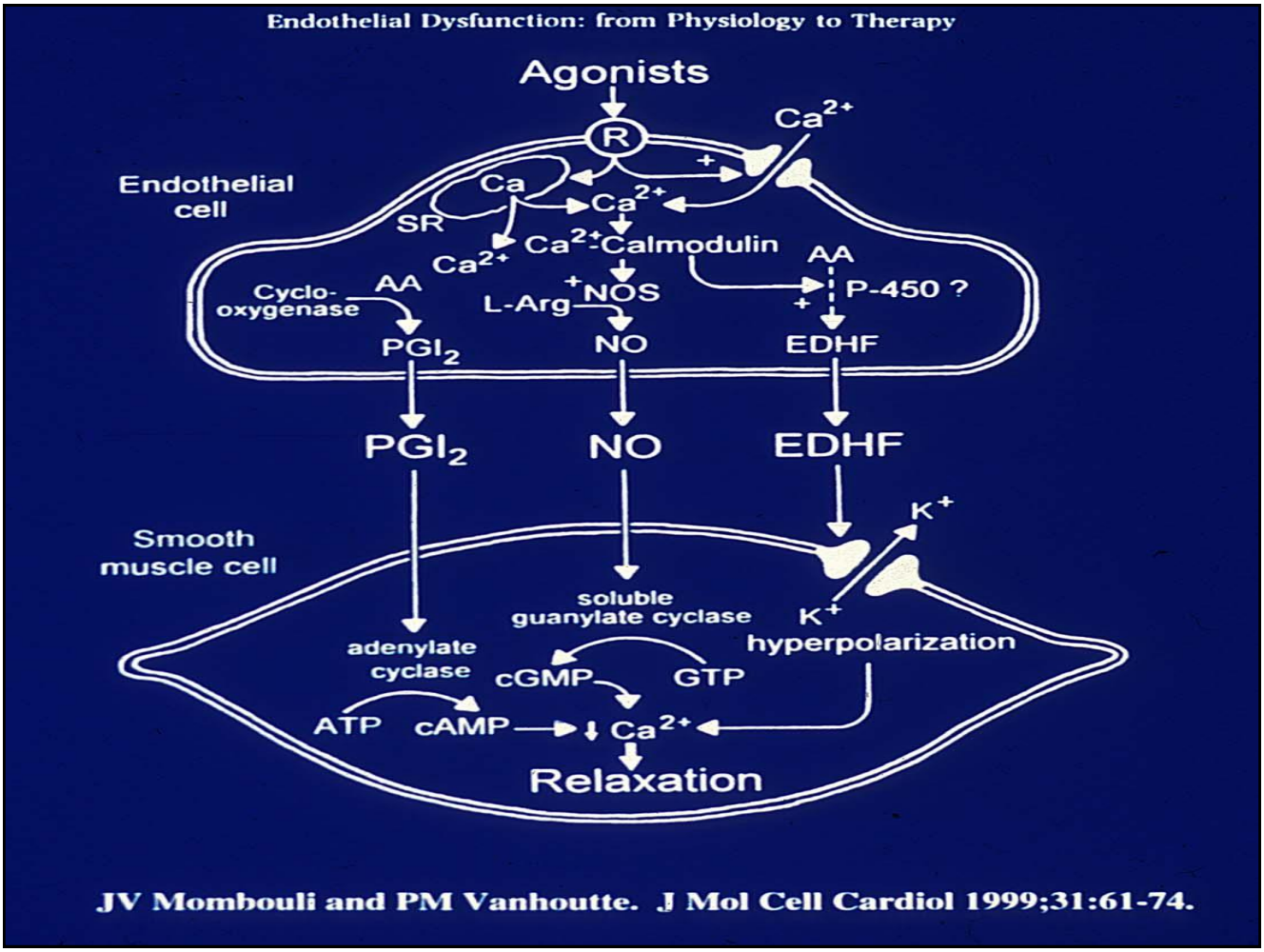
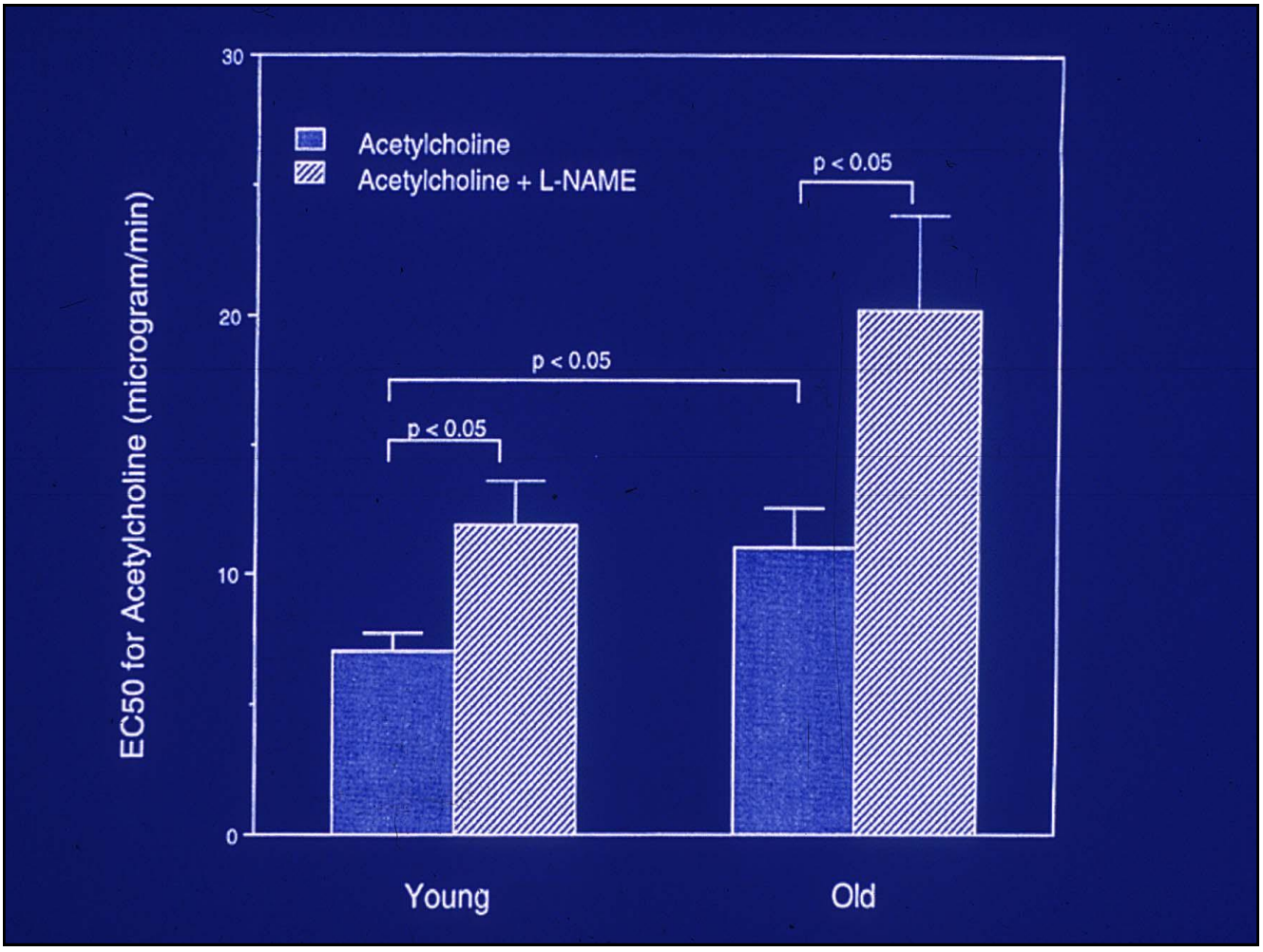


Figure 5. Measurements of systolic parameters **+dP/dt (B)** in adult uninfected rat hearts (n=6), senescent uninfected rat hearts (n=8), senescent hearts infected with Ad.β-Gal at day 2 (n=6), and senescent hearts infected with Ad.SERCA2a at day 2 (n=6). *P<0.05 compared with adult. ‡P<0.05 compared with senescent group plus Ad.β-Gal.

Schmidt et al., *Circulation*. 2002; 101:790-6


Endothelial Dysfunction: from Physiology to Therapy
Agonists
R
Ca2+
Endothelial cell
Ca
Ca2+
SR
Ca2+
Ca2+-Calmodulin
AA
Cyclo-oxygenase
AA
L-Arg
+NOS
+
P-450 ?
PGI2
NO
EDHF
PGI2
NO
EDHF
K+
Smooth muscle cell
soluble guanylate cyclase
K+
hyperpolarization
adenylate cyclase
cGMP
GTP
ATP
cAMP
Ca2+
Relaxation
JV Mombouli and PM Vanhoutte. J Mol Cell Cardiol 1999;31:61-74.


30
20
10
0
EC50 for Acetylcholine (microgram/min)
Acetylcholine
Acetylcholine + L-NAME
p < 0.05
p < 0.05
p < 0.05
Young
Old

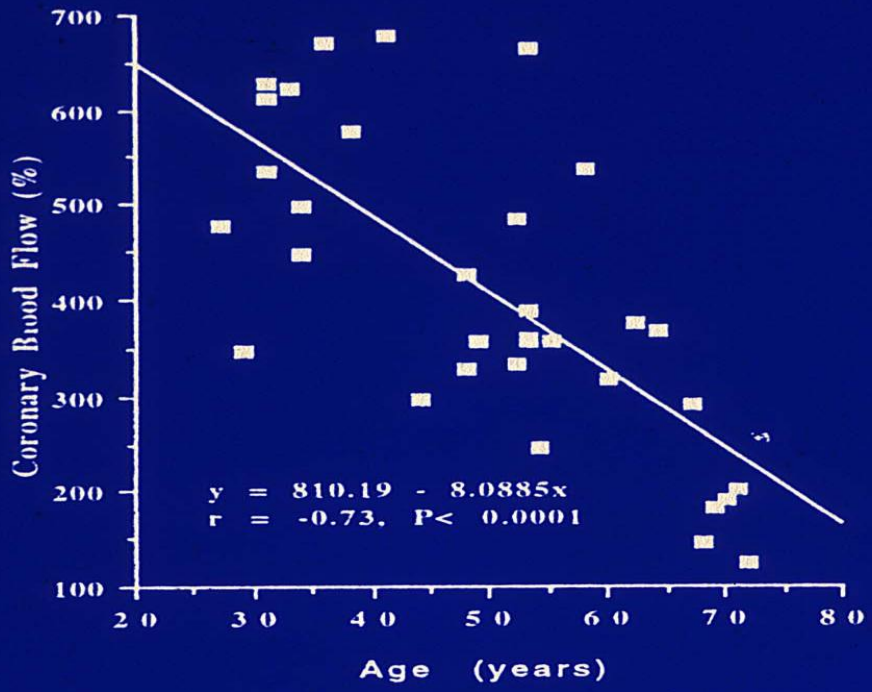
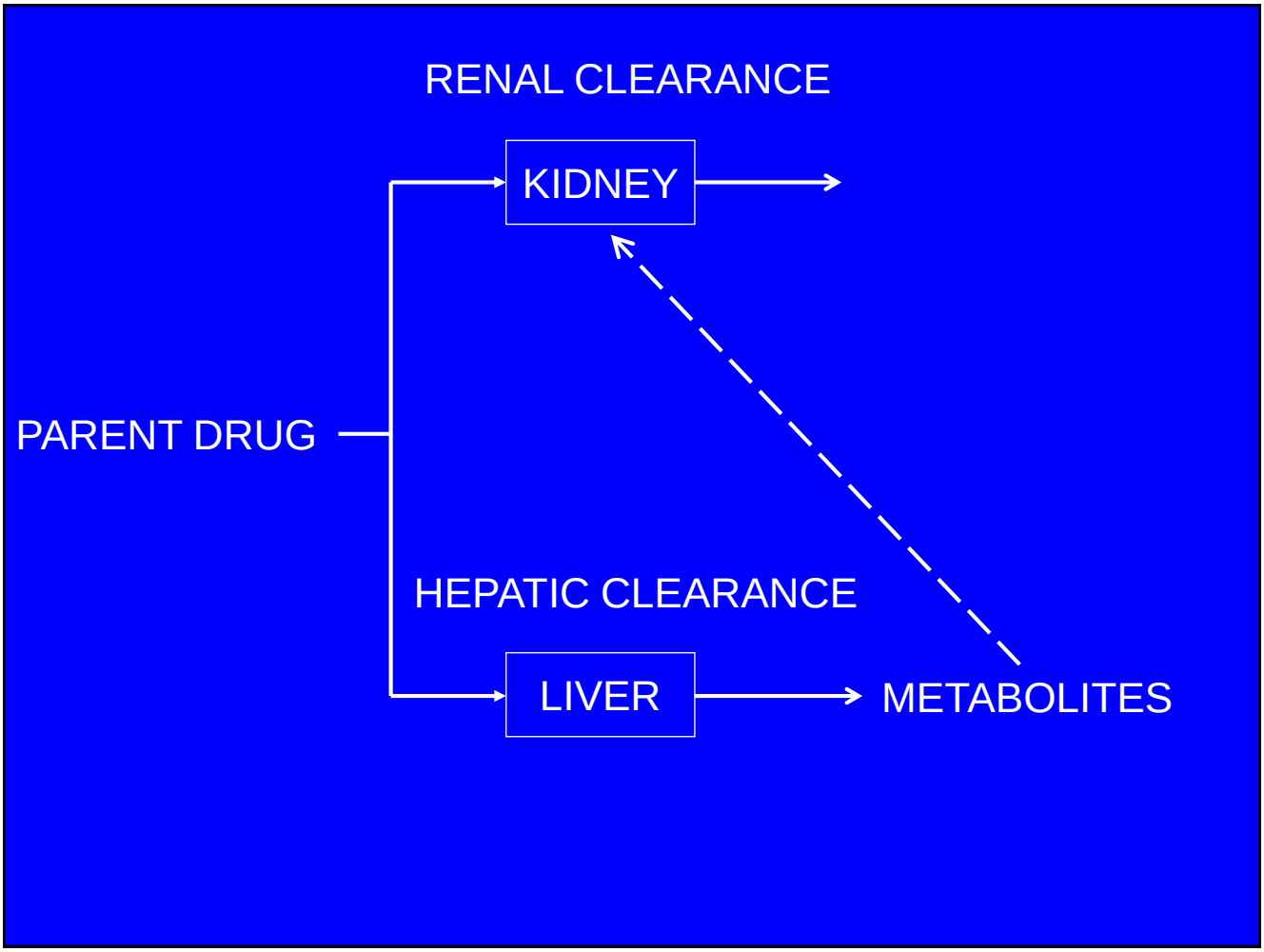
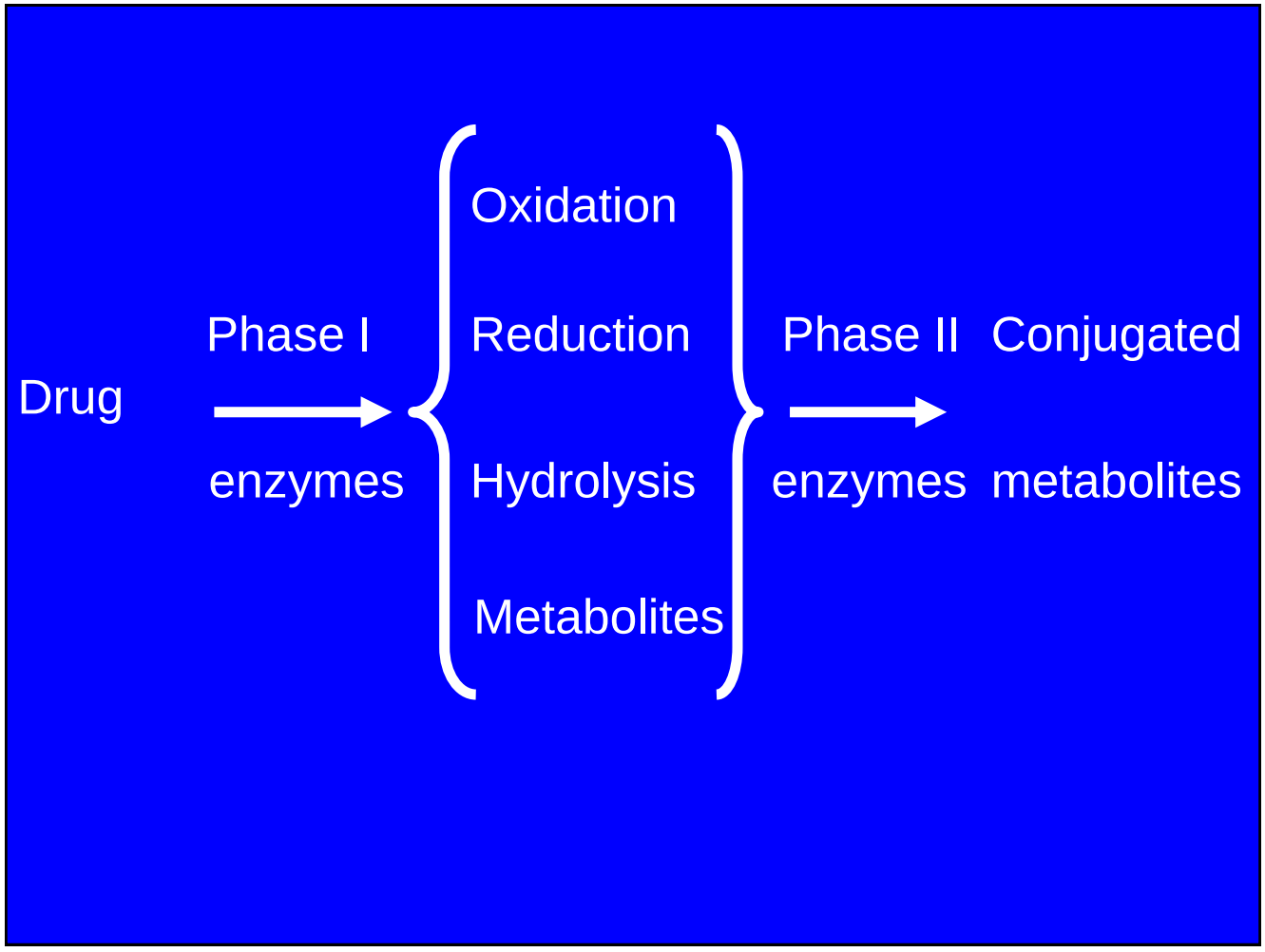


Figure 2. Scatterplot of correlation of age and peak (percent of control values) coronary blood flow response to acetylcholine.

Chauhan, et al, JACC, 1996; 28: 1796-1804

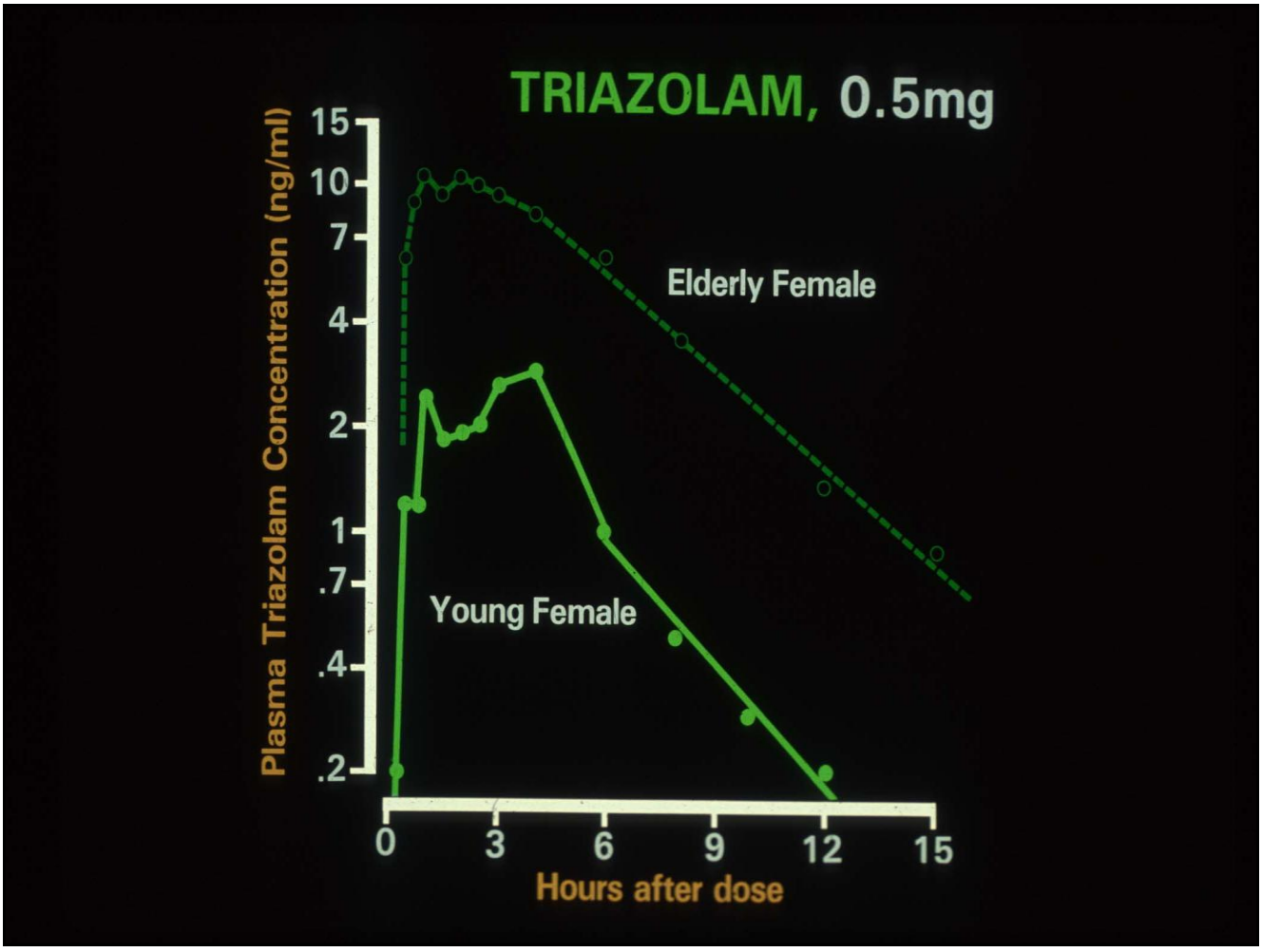

RENAL CLEARANCE
KIDNEY
PARENT DRUG
HEPATIC CLEARANCE
LIVER
METABOLITES


Drug
Phase I
enzymes
Oxidation
Reduction
Hydrolysis
Metabolites
Phase II
enzymes
Conjugated
metabolites

DRUGS METABOLIZED BY KNOWN P450s

- 3A (4)
  - -- Loratadine (in part)
  - -- Terfenadine
  - -- Astemizole
  - -- Verapamil
  - -- Nifedipine
  - -- Diltiazem
  - -- Felodipine
  - -- Nimodipine
  - -- Diazepam
  - -- Midazolam
  - -- Triazolam
  - -- Cyclosporine
  - -- Tacrolimus
  - -- Lovastatin
  - -- Progesterone
  - -- Testosterone
  - -- Cisapride
  - -- Lansoprazole

Modified from Flockart. *J Psychopharm*.


TRIAZOLAM, 0.5mg
Plasma Triazolam Concentration (ng/ml)
15
10
7
4
2
1
.7
.4
.2
Elderly Female
Young Female
0
3
6
9
12
15
Hours after dose

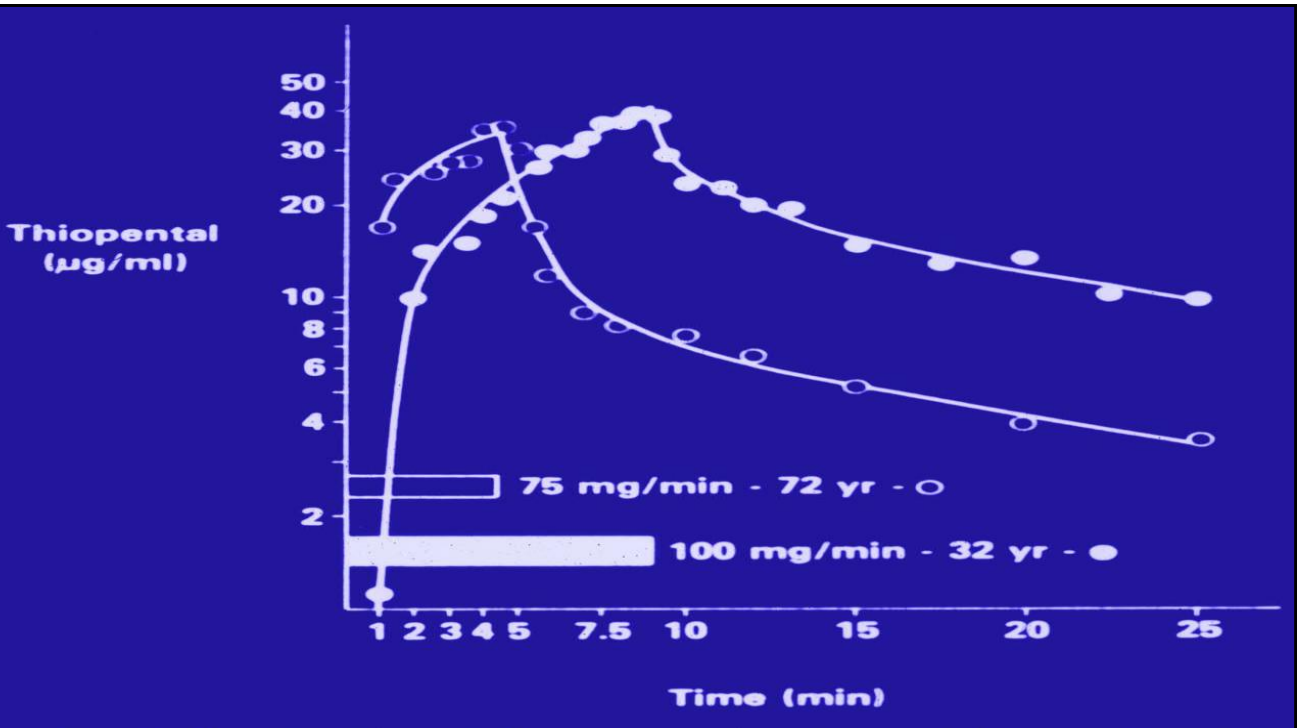


FIG. 5. Serum thiopental concentration (log scale) *versus* time for the young (filled circles and bars) and the elderly (unfilled circles and bars) patients shown in figure 3. All of the measured thiopental concentrations for the patients are indicated in this figure, whereas all data could not be displayed in figure 3. The horizontal bars represent length of the thiopental infusions; solid lines represent fitted data from the pharmacokinetic model.

Homer and Stanski, Anesthesiology, 1985;62:714-724.

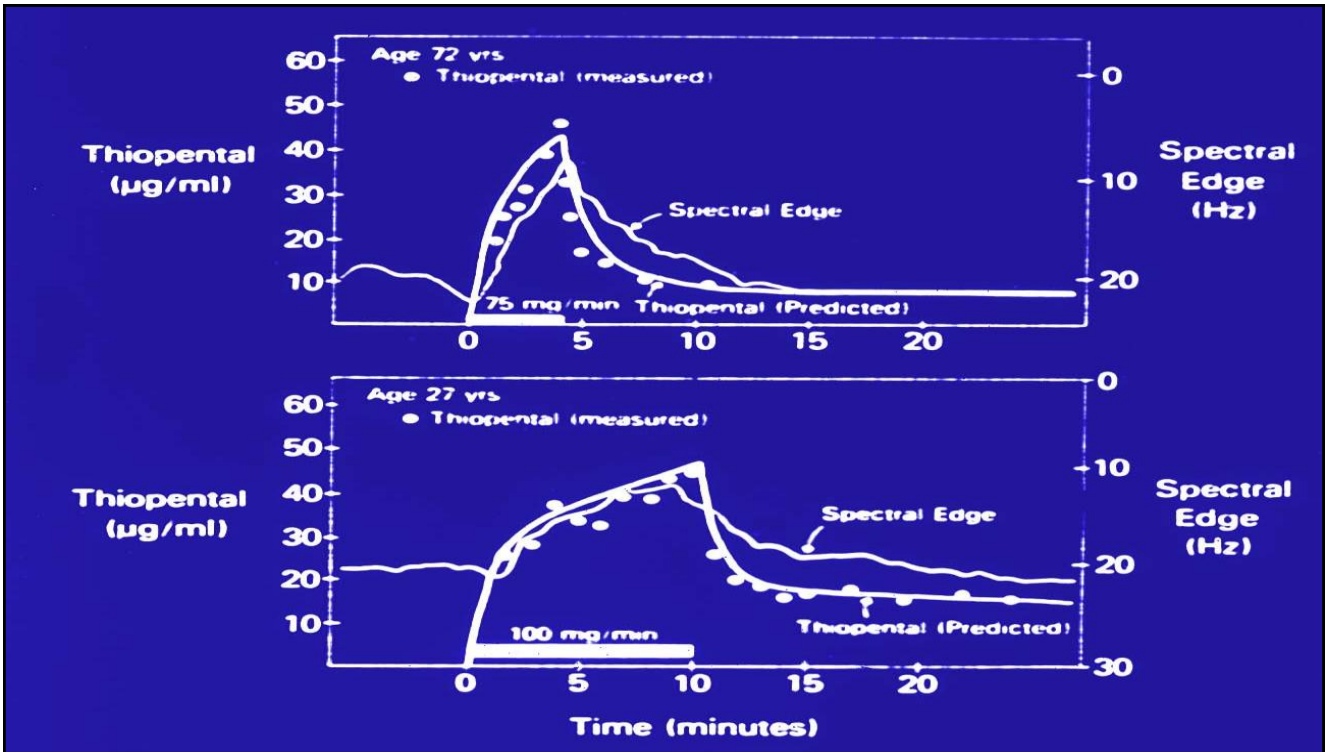


FIG. 3. The concentration of thiopental *versus* 1) time and 2) spectral edge in an elderly patient (top figure) and in a younger patient (bottom figure). Solid horizontal bars represent the length of thiopental infusion. Dots represent the measured thiopental concentration (linear scale), and the solid line next to them, the fitted data

Homer and Stanski, Anesthesiology, 1985;62:714-724.

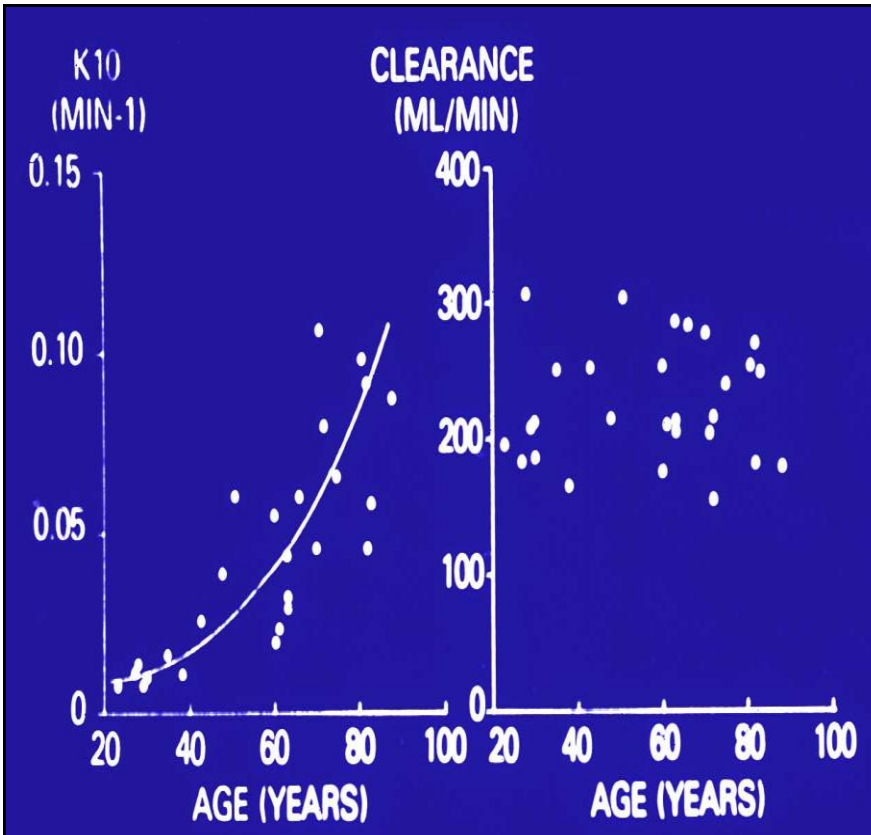


Fig. 8. K_{10} and clearance versus age. Dots represent the rate constants or clearance derived from the pharmacokinetic analysis derived for each patient. K_{10}, the first-order rate constant of drug elimination (metabolism) from the body, has an exponential relationship with age. This relationship (solid curve) was determined using nonlinear regression (see table 2). Because clearance is the product of K_{10} and V_1, clearance and age are not related.

Bowe and Stanski, Anesthesiology, 1985;62:711-724.

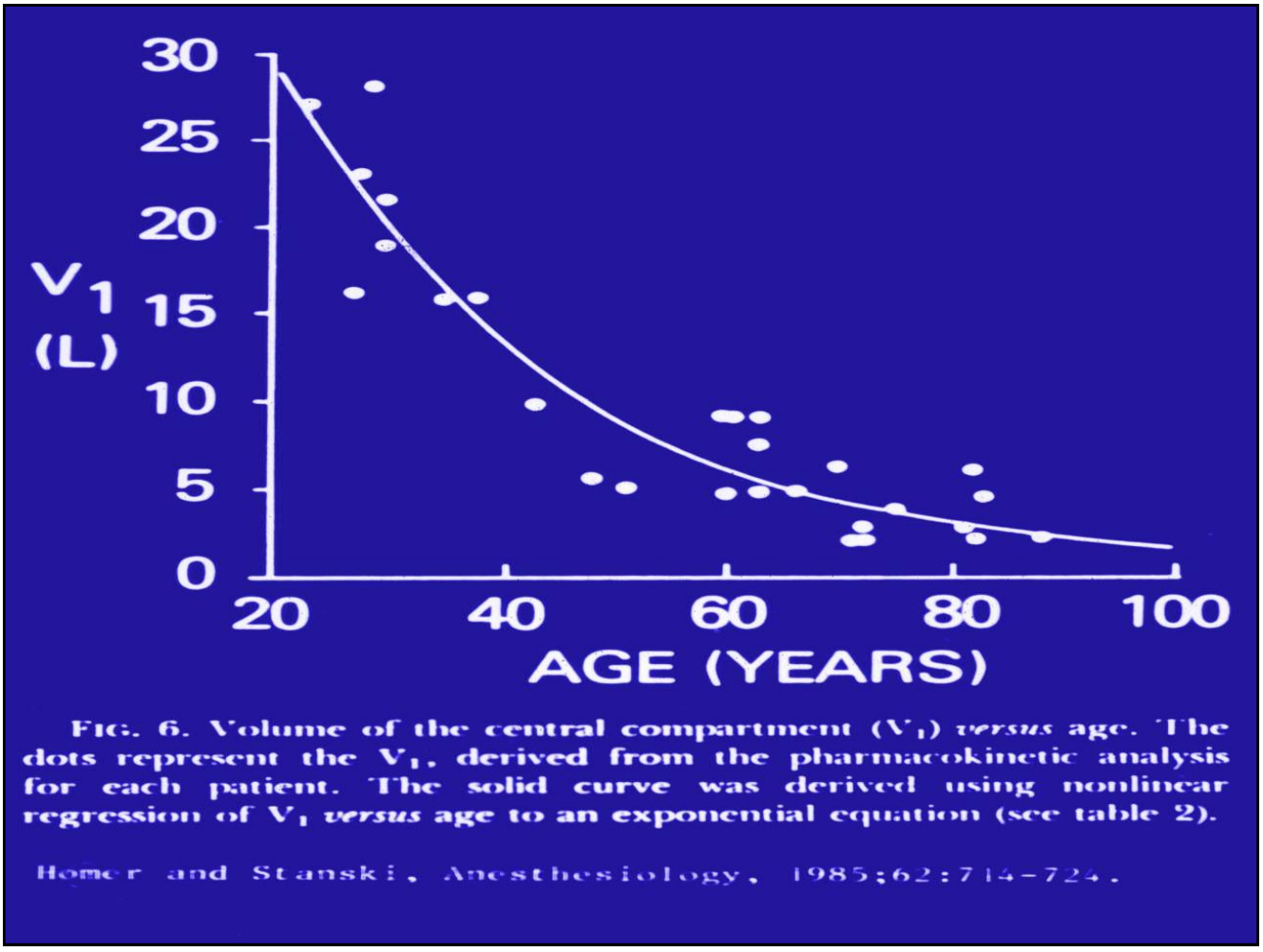
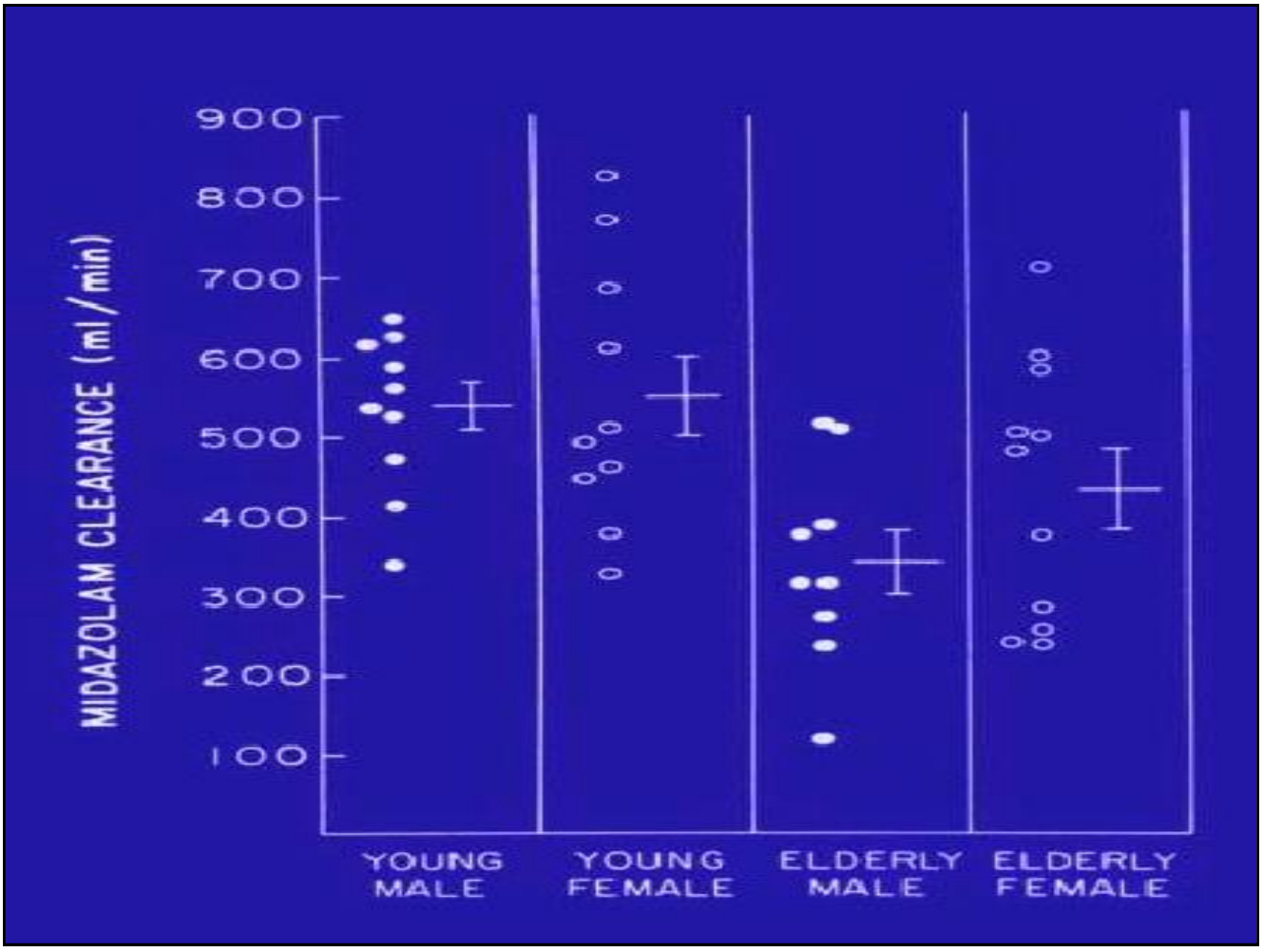
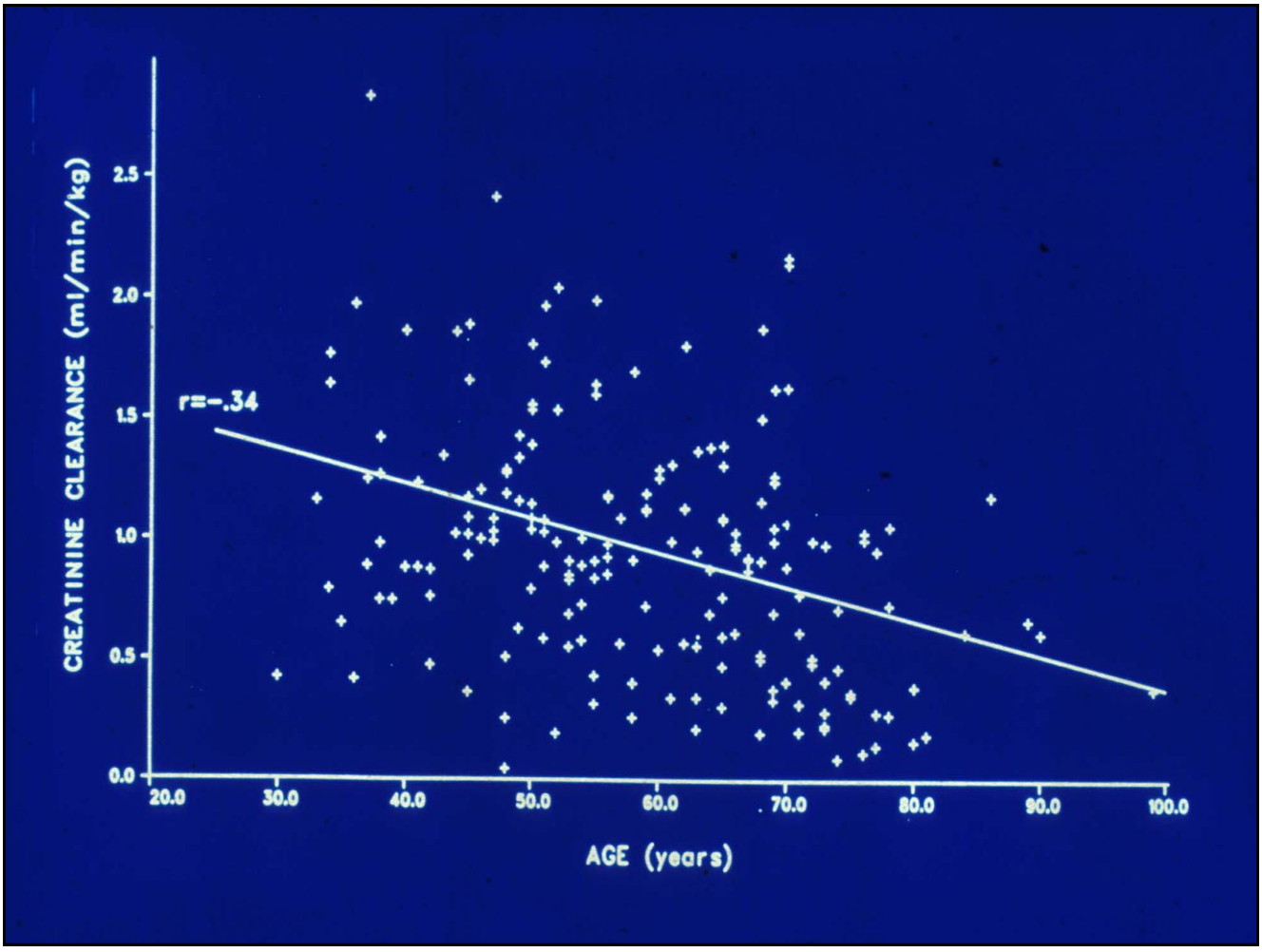


FIG. 6. Volume of the central compartment (V_1) *versus* age. The dots represent the V_1, derived from the pharmacokinetic analysis for each patient. The solid curve was derived using nonlinear regression of V_1 *versus* age to an exponential equation (see table 2).

Homer and Stanski, Anesthesiology, 1985;62:714-724.


MIDAZOLAM CLEARANCE (ml / min)
900
800
700
600
500
400
300
200
100
YOUNG MALE
YOUNG FEMALE
ELDERLY MALE
ELDERLY FEMALE


CREATININE CLEARANCE (ml/min/kg)
2.5
2.0
1.5
1.0
0.5
0.0
r=-.34
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
AGE (years)

PARTIAL LIST OF DRUGS THAT UNDERGO SIGNIFICANT RENAL EXCRETION IN HUMANS

Amantadine
Aminoglycoside antibiotics
Cimetidine
Digoxin
Furosemide
Lithium
Nitrofurantoin
Ouabain
Penicillin antibiotics
Phenobarbital
Quinidine
Sulfonamides
Tetracycline

COCKCROFT & GAULT EQUATION

$$CL_{Cr} = \frac{(140 - \text{age})\ (\text{weight in kg})}{72\ (\text{serum Cr in mg/dL})}$$

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.

Table 2. Some drugs with decreased clearance in the elderly

ROUTE OF CLEARANCE	REPRESENTATIVE DRUGS
Renal	All aminoglycosides Vancomycin Digoxin Procainamide Lithium Sotalol Atenolol Dofetilide Cimetidme
Single Phase I metabolic pathway CYP3A CYP2C CYP1A2	Alprazolam Midazolam Triazolam Diltiazem Dihydropyridine calcium channel blockers Lidocaine Diazepam Phenytoin Celecoxib Theophylline

Table 2. Some drugs with decreased clearance in the elderly cont.

ROUTE OF CLEARANCE	REPRESENTATIVE DRUGS
Multiple Phase I metabolic pathways	Imipramine Desipramine Trazodone Hexobarbital Flurazepam

PHARMACOKINETIC CHANGES IN THE ELDERLY

PROCESS	CHANGE WITH AGE
Gastrointestinal Absorption	none
Drug Distribution	
Central Compartment Volume	none or
Peripheral Compartment Volume	
Lipophilic Drugs	
Hydrophilic Drugs	
Plasma Protein Binding	
Binding to Albumin	
Binding to α_1-acid Glycoprotein	none or

PHARMACOKINETIC CHANGES IN THE ELDERLY

Process	Change with Age
Drug Elimination	
Renal Elimination	
Hepatic Elimination	
Phase I Reactions	
CYP3A	
CYP1A2,2D6,2C9,2C19,2E1	**↔ or**
Phase II Reactions	
Glucuronidation	**↔**
Sulfation	**↔**
Acetylation	**↔**

The Goals for Treating the Older Patient

- ↓ Morbidity & Mortality
- Avoid or Minimize Drug-Related Problems
- Improve the Quality of Life

By the time a man gets well into the seventies, his continued existence is a mere miracle

R.L. Stevenson:AES Triplex

“Come grow old along with me,
the best of things are yet to be.”

“Rabbi Ben Ezra,”
Robert Browning (1812 – 1889)