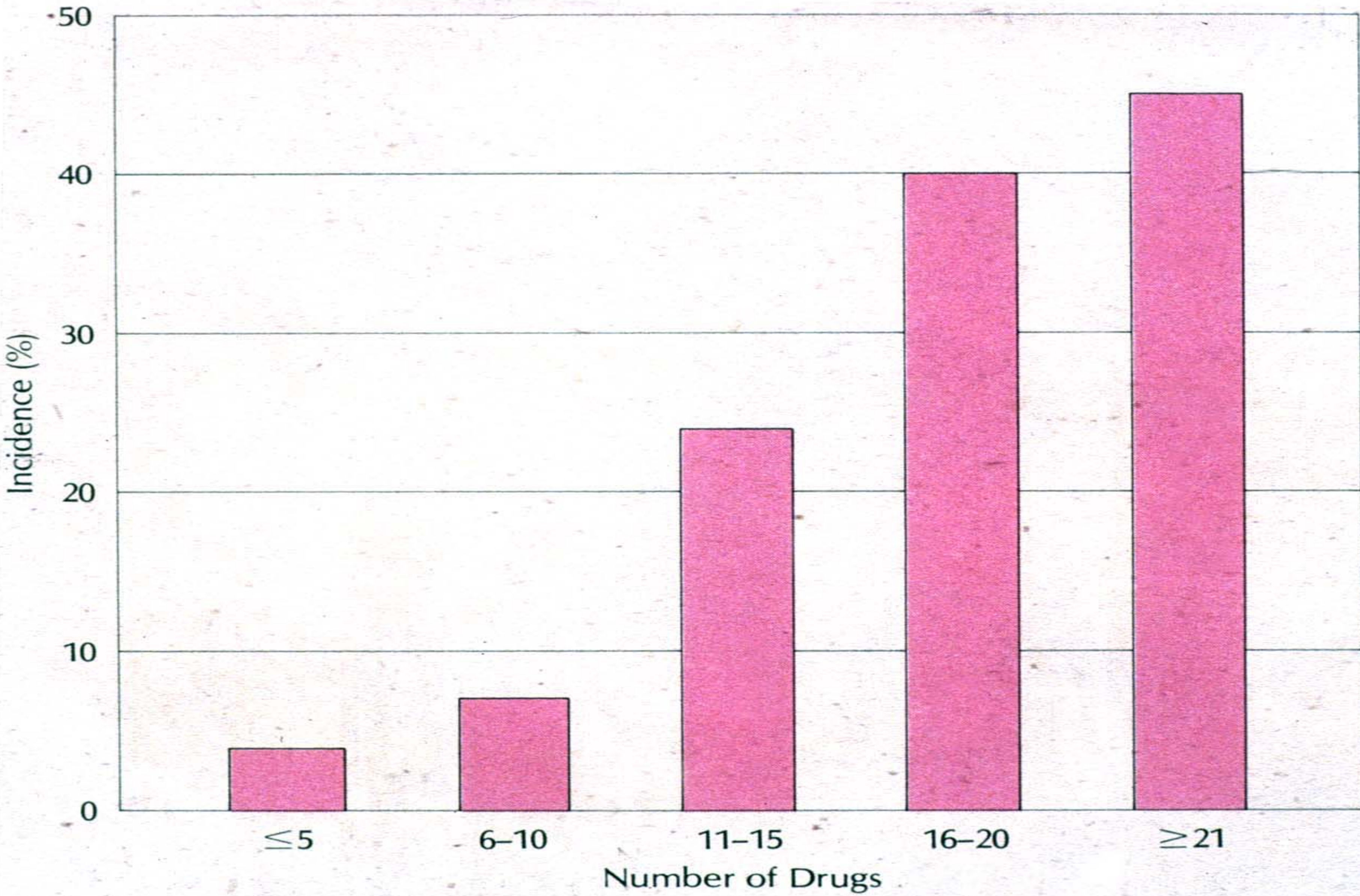
PHARMACODYNAMICS OF AGING: NARROWING OF THE THERAPEUTIC INDEX IN THE FACE OF THERAPEUTIC OPPORTUNITY

Darrell R. Abernethy, M.D., Ph.D.
Chief, Laboratory of Clinical Investigation
National Institute on Aging

Pharmacodynamics of Aging

- Systemic Cardiovascular
- Local Cardiovascular
- Other Effector Systems



Taking multiple drugs contributes to the risk of adverse reactions. When up to five drugs are taken, the approximate incidence of adverse reactions is 4%. When 11 to 15 drugs are taken, the incidence jumps to 24%, and when 21 or more drugs are taken, it almost doubles to 45%. (Adapted from Cluff LE et al: JAMA 188:976, 1964)

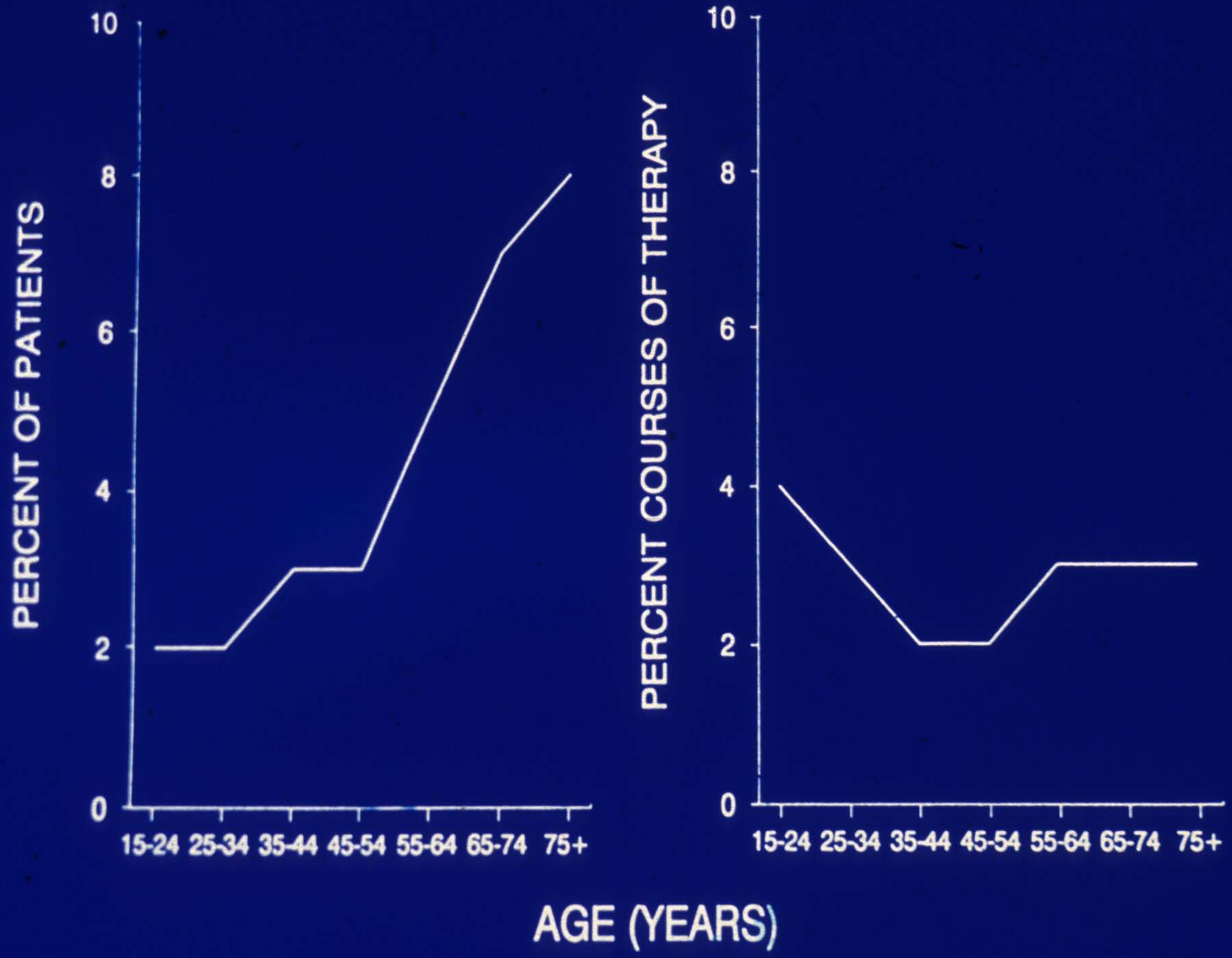

10
8
6
4
2
0
PERCENT OF PATIENTS
15-24
25-34
35-44
45-54
55-64
65-74
75+
10
8
6
4
2
0
PERCENT COURSES OF THERAPY
15-24
25-34
35-44
45-54
55-64
65-74
75+
AGE (YEARS)

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/hyperkaliemia	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.

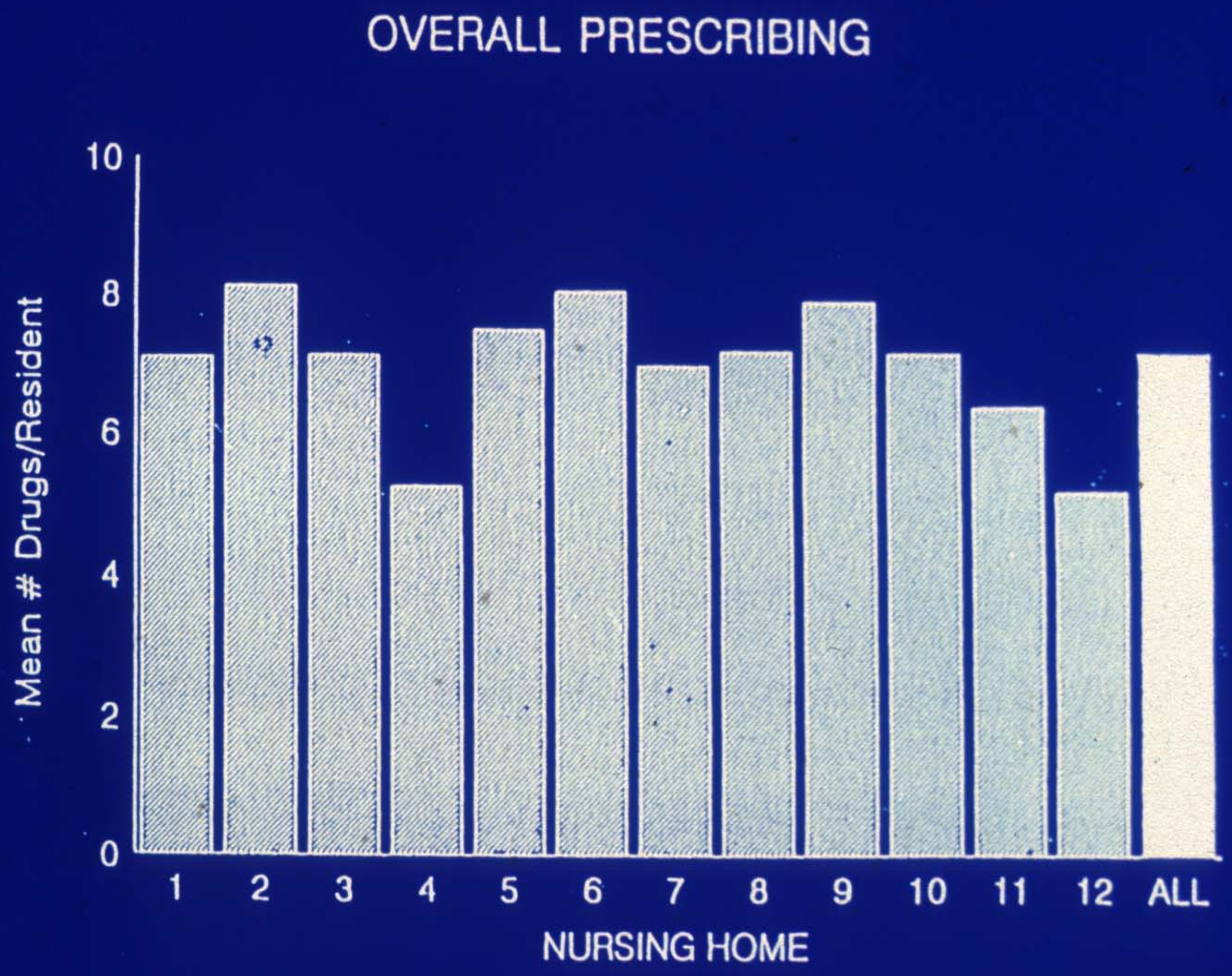


Figure 1. Medication prescriptions per resident in the 12 nursing homes.

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.

FIGURE 1. AGE-RELATED COGNITIVE IMPAIRMENT

*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

TABLE II

Alterations in the Cardiovascular System of the Elderly

Cardiovascular 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

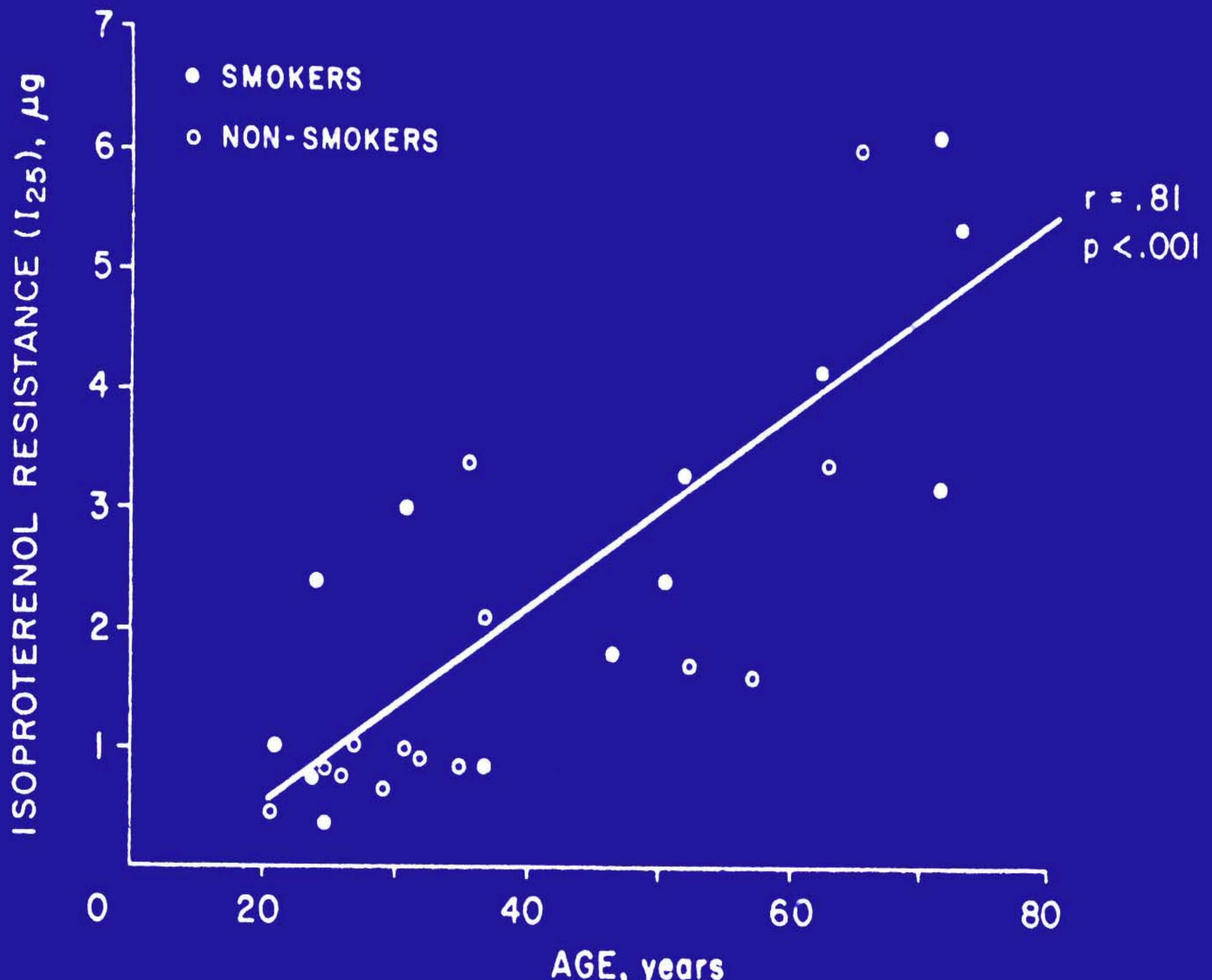


Fig. 1. Relationship between isoproterenolol resistance and age in smokers (●) and nonsmokers (○).

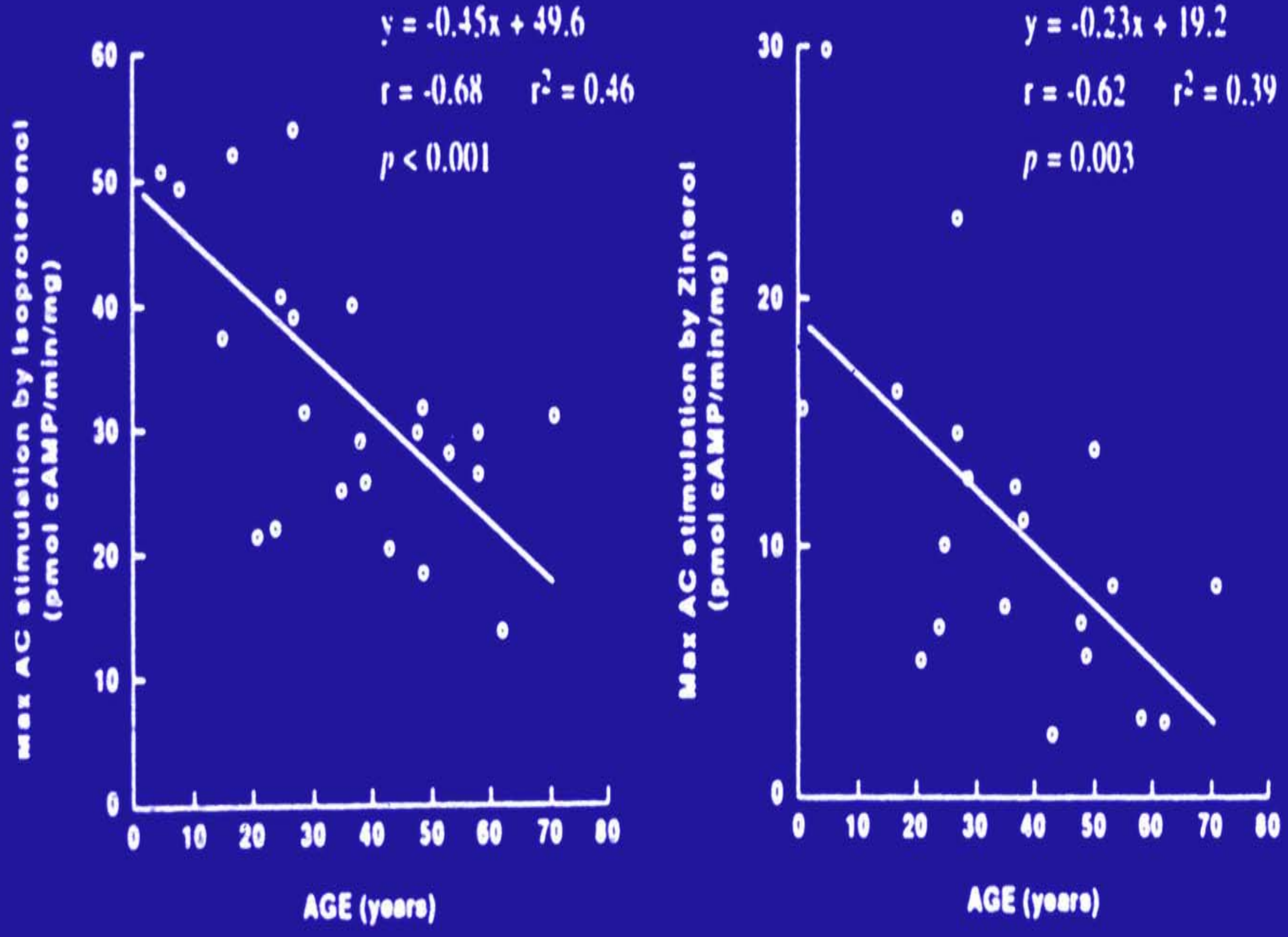


FIG 6. Scatterplots: Net maximum adenylyl cyclase (AC) stimulation by isoproterenol (left) and zinterol (right) for left ventricular myocardial preparations in relation to donor age.

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

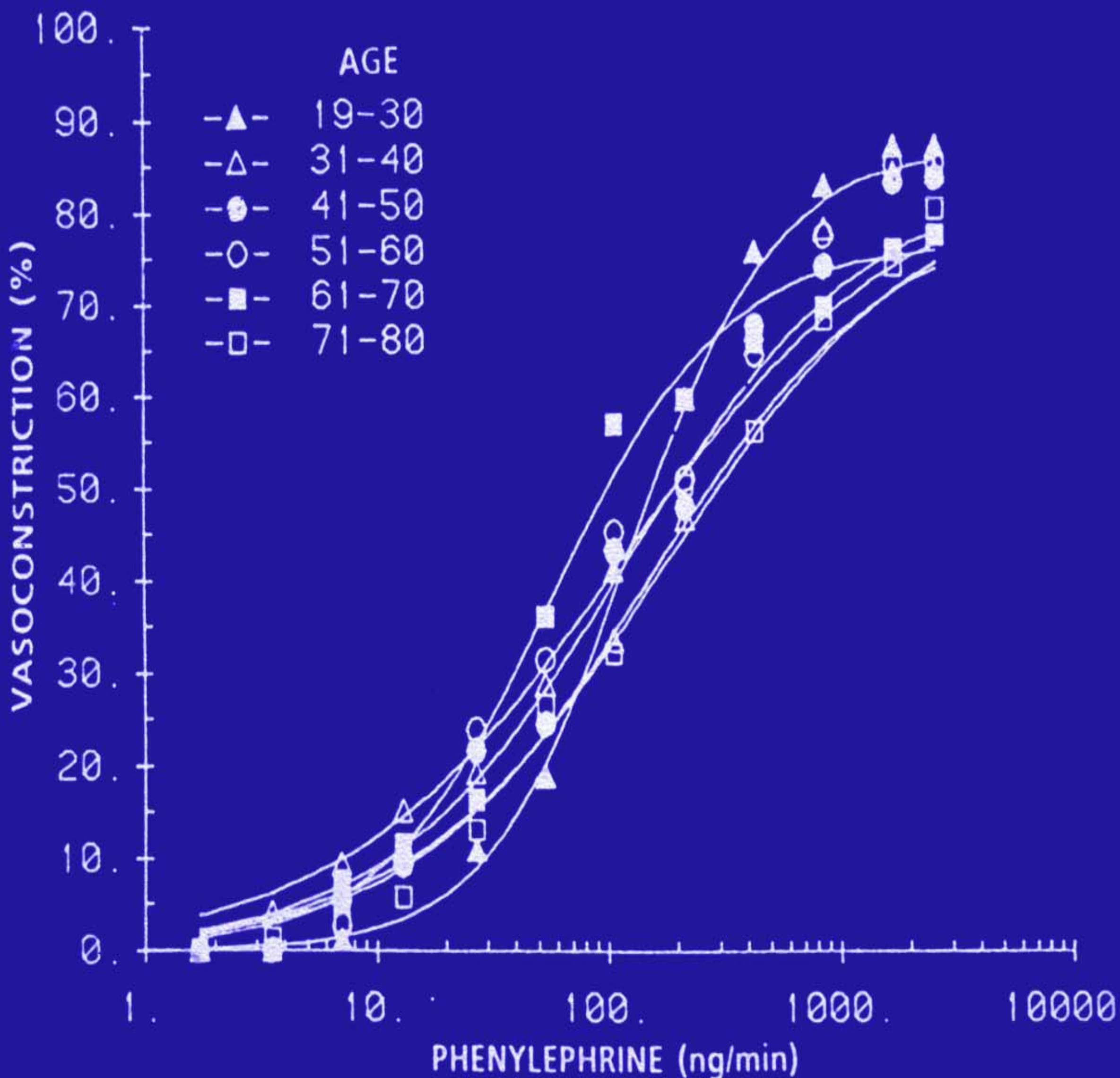
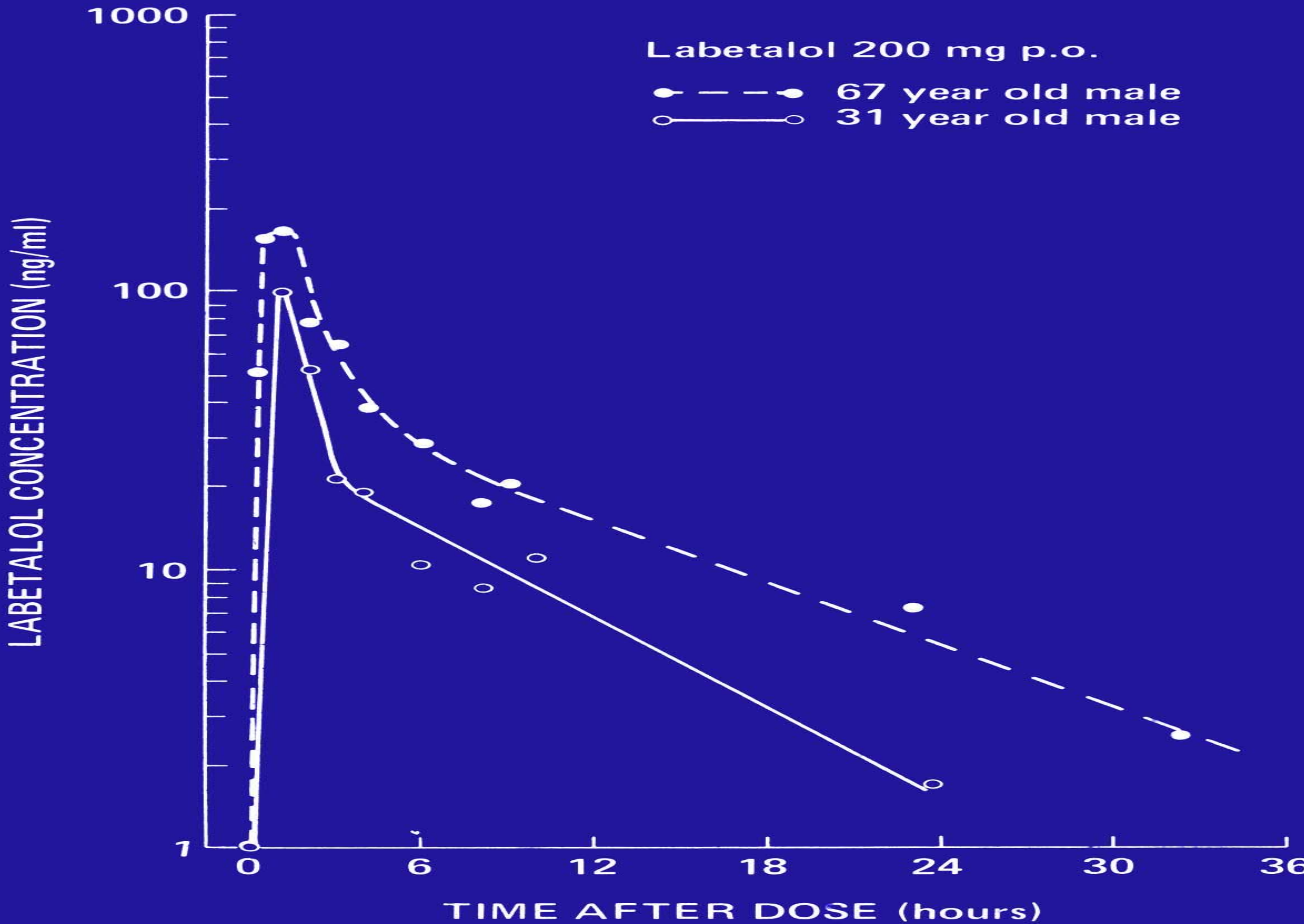
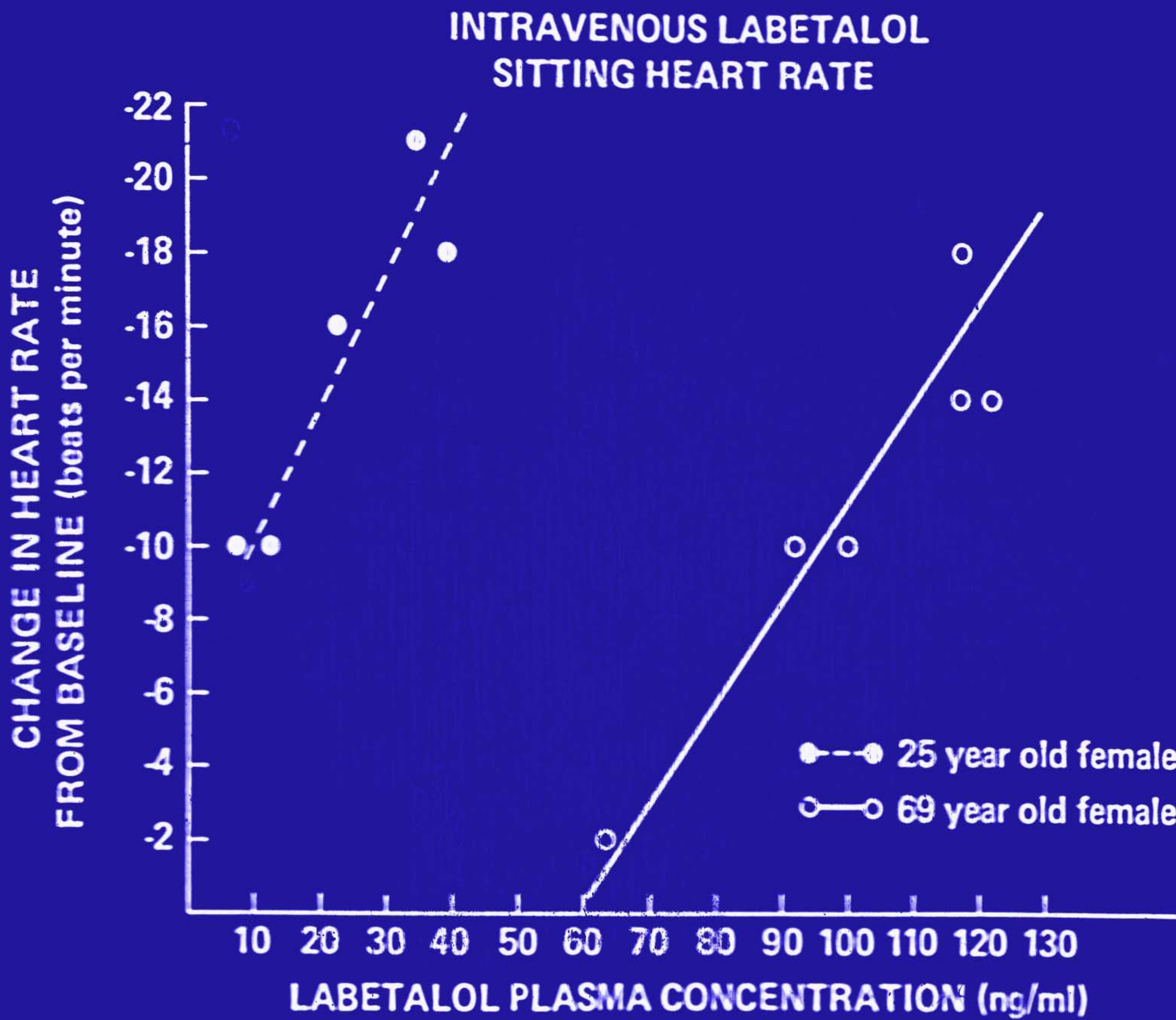


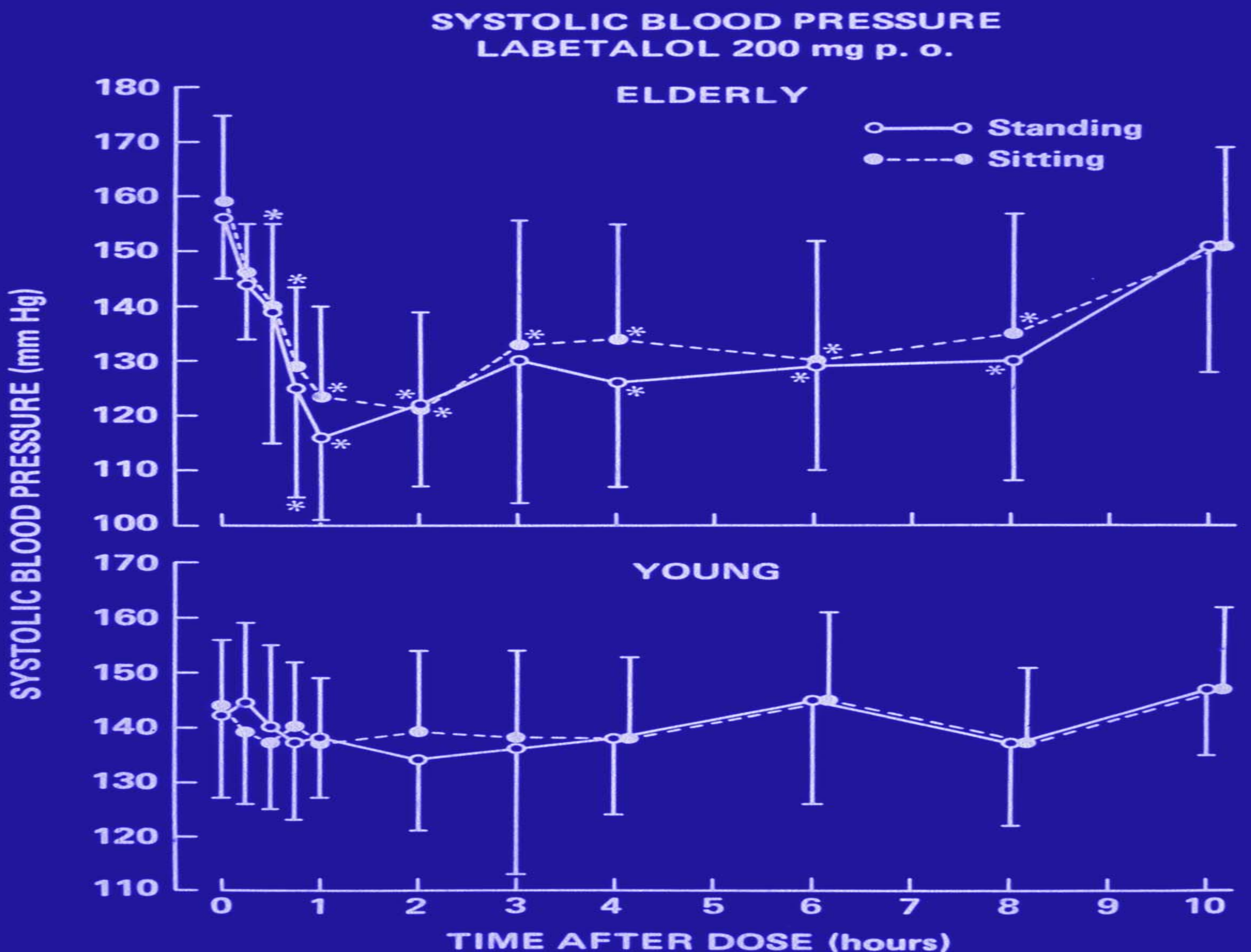
Fig. 1. Effects of phenylephrine infusion in dorsal hand veins in the six populations studied. Each point on the dose-response curve represents the mean value from individual subjects within the same age bracket.

Panza, et al, Journal of Pharmacology and Experimental Therapeutics, 1986; 239: 802-807

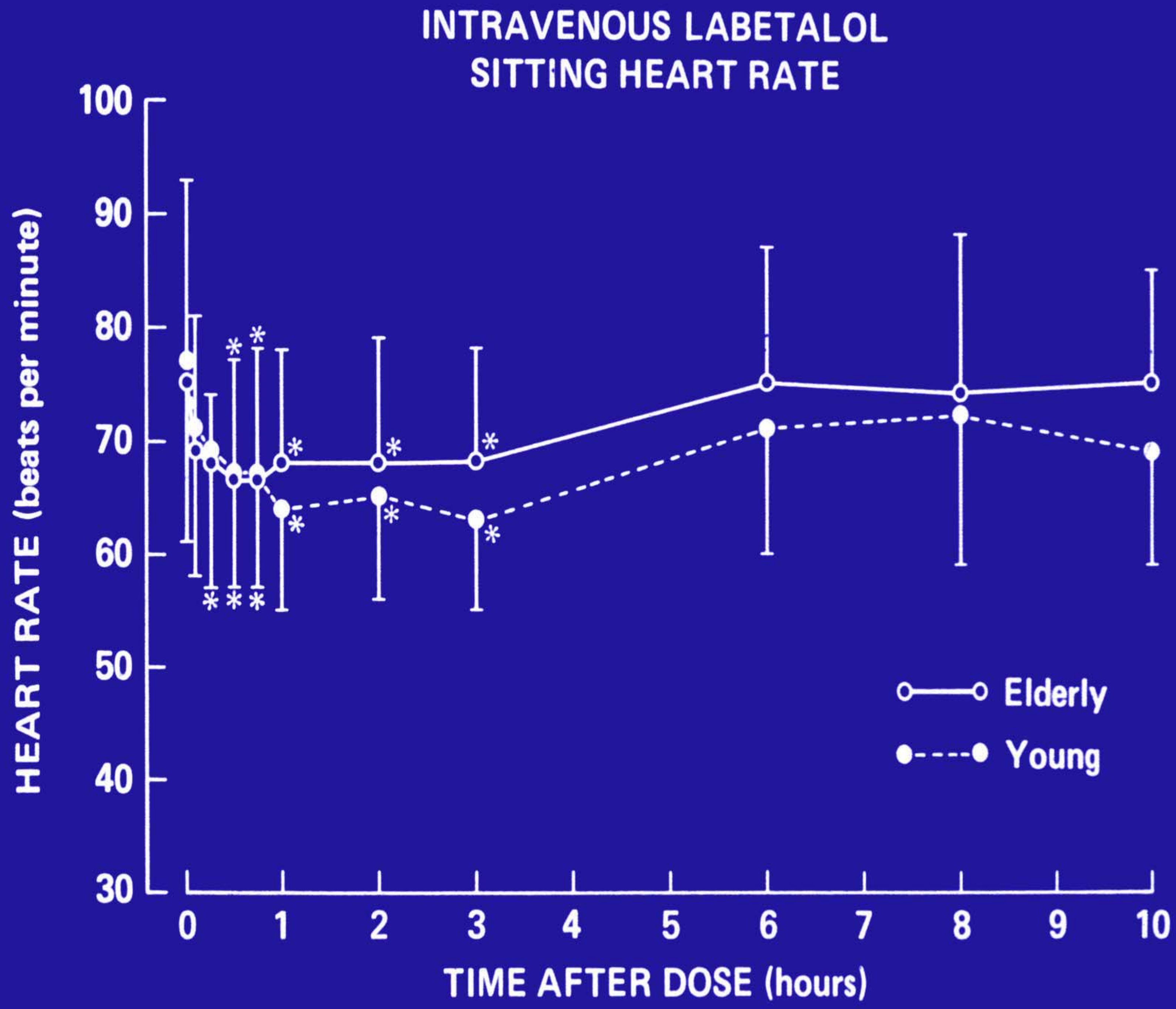


Labetalol 200 mg p.o.
67 year old male
31 year old male
LABETALOL CONCENTRATION (ng/ml)
1000
100
10
1
0
6
12
18
24
30
36
TIME AFTER DOSE (hours)


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)
TIME AFTER DOSE (hours)
180
170
160
150
140
130
120
110
100
0
1
2
3
4
5
6
7
8
9
10



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

Reduced Elasticity and Compliance

Increased Pulse Pressure

Decreased Baroreceptor Sensitivity

Hyaline Thickening in Arterioles, Small Arteries

Increased Peripheral Resistance

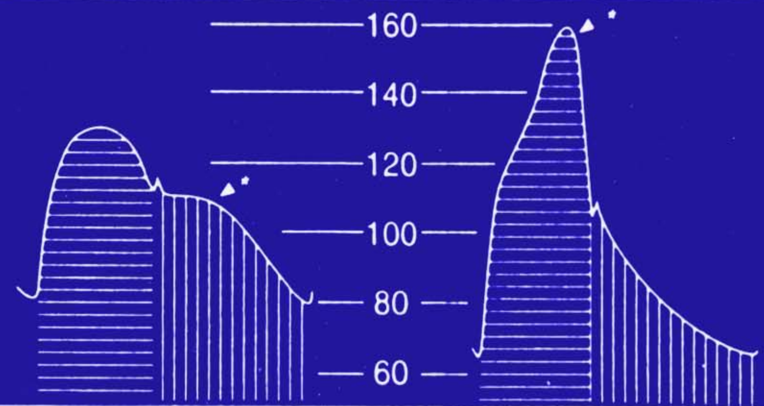
	Normal Aorta (Young Adults)		Stiff Aorta (Older Adults)
1. Aortic BP *(mm Hg)*	130 80	Systolic Diastolic	140 70
2. PWV *(m/s)*	5.0		10.0
3. Reflected Wave	Early Diastole		Late Systole
4. Pulse Wave Shape			
5. Aortic BP *(mm Hg)*	130 80	Systolic Diastolic	160 70

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.

Amlodipine Intravenous Pharmacodynamics
0.5-96 hr following 1st dose

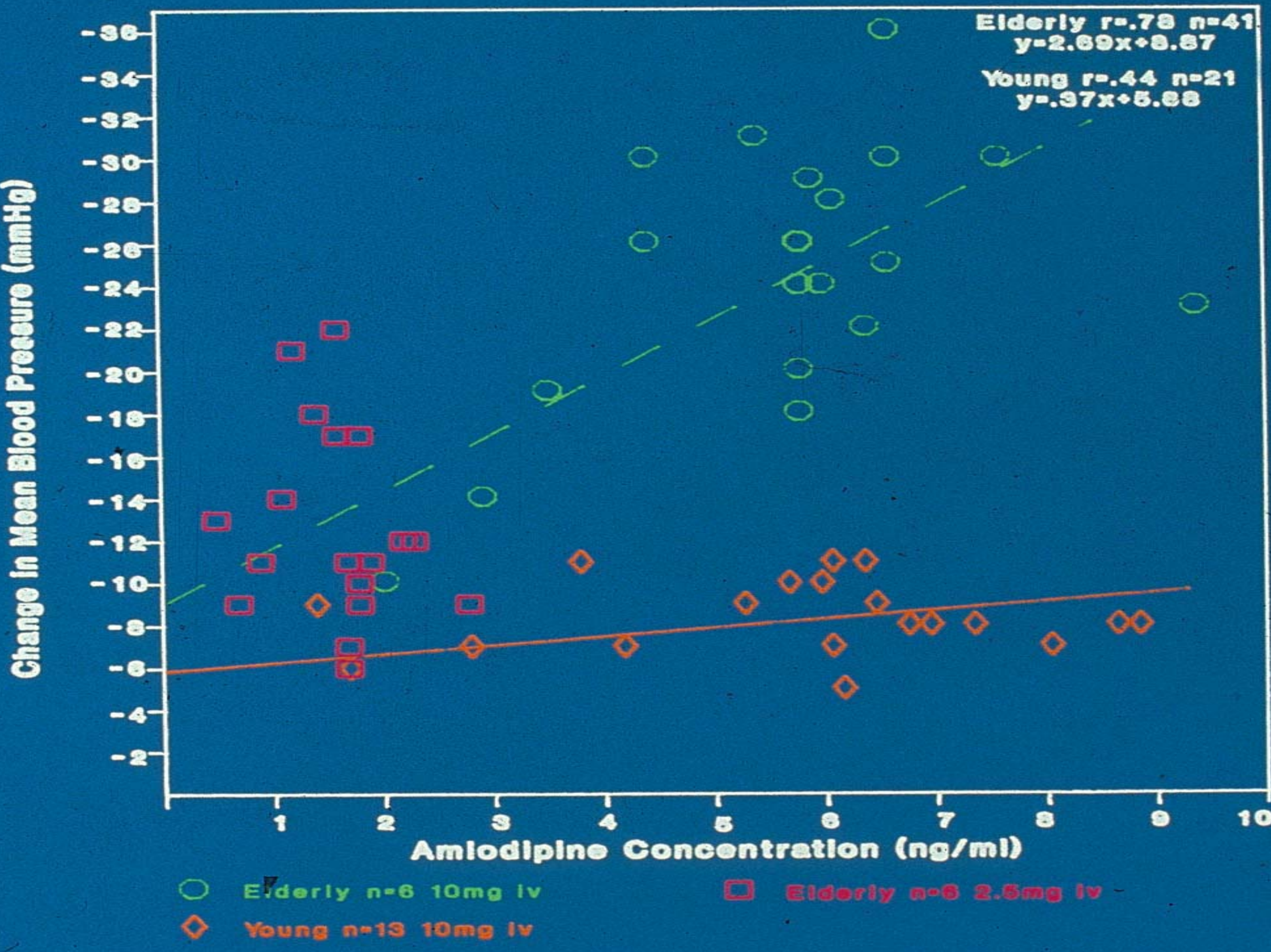
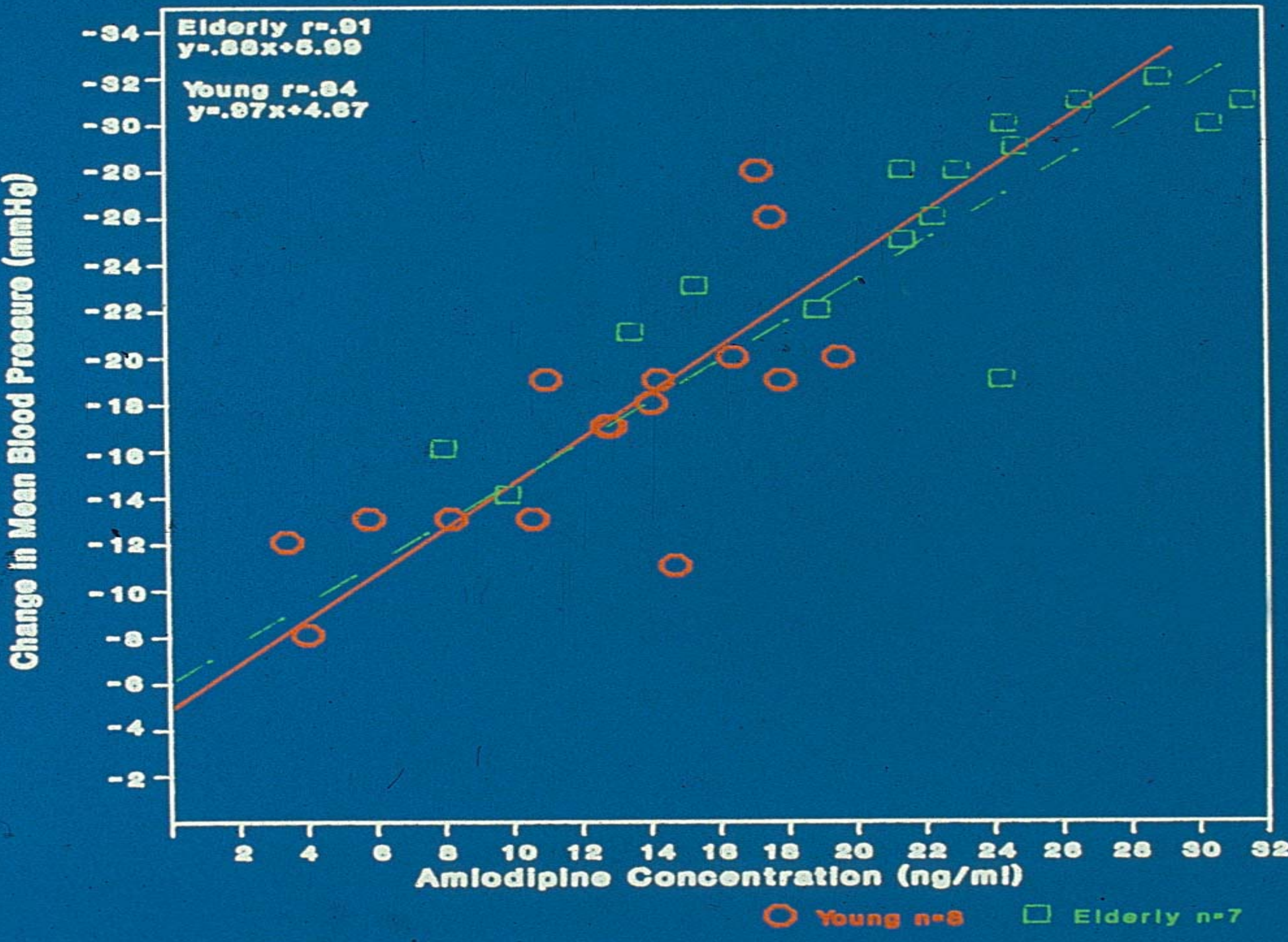
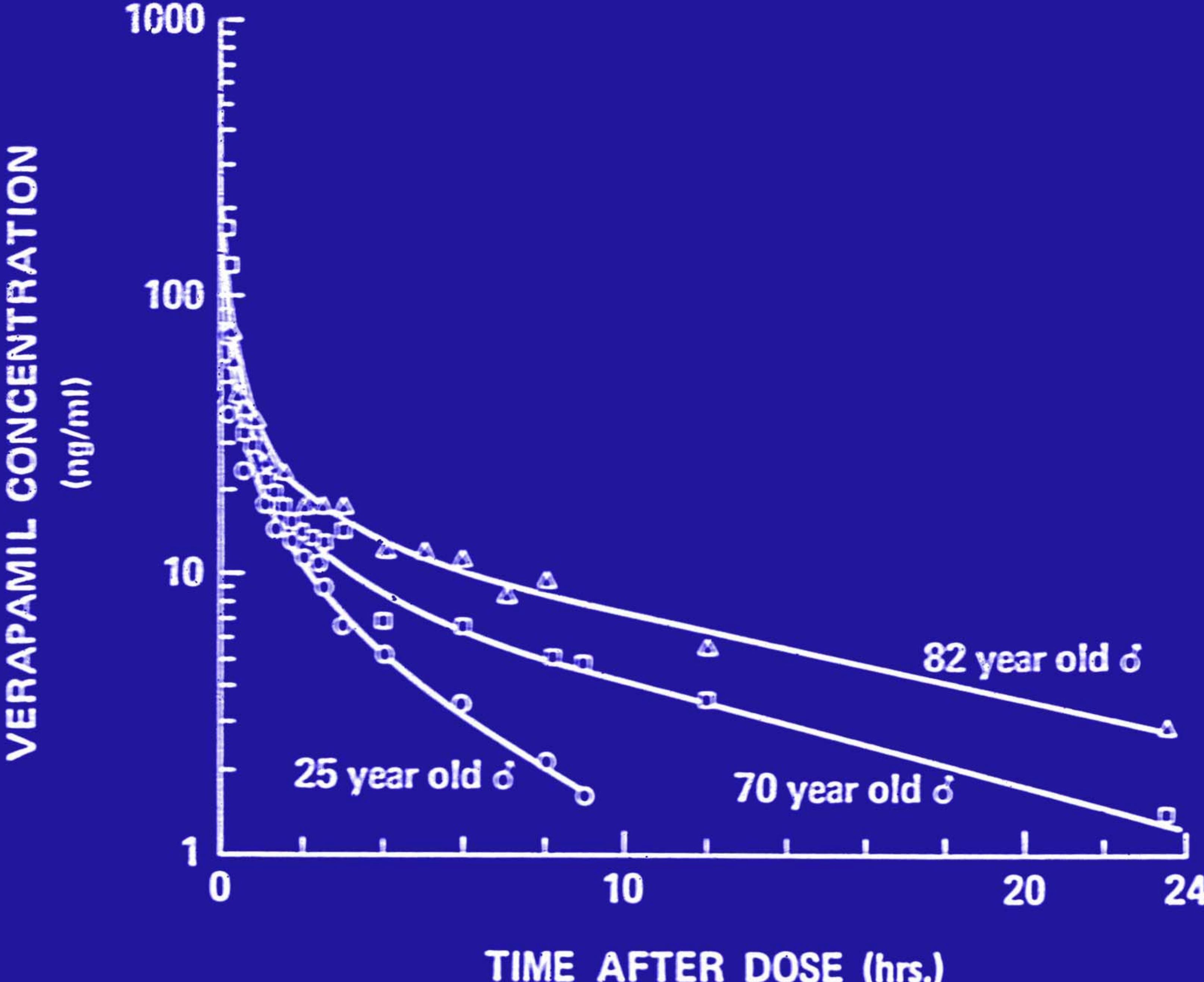


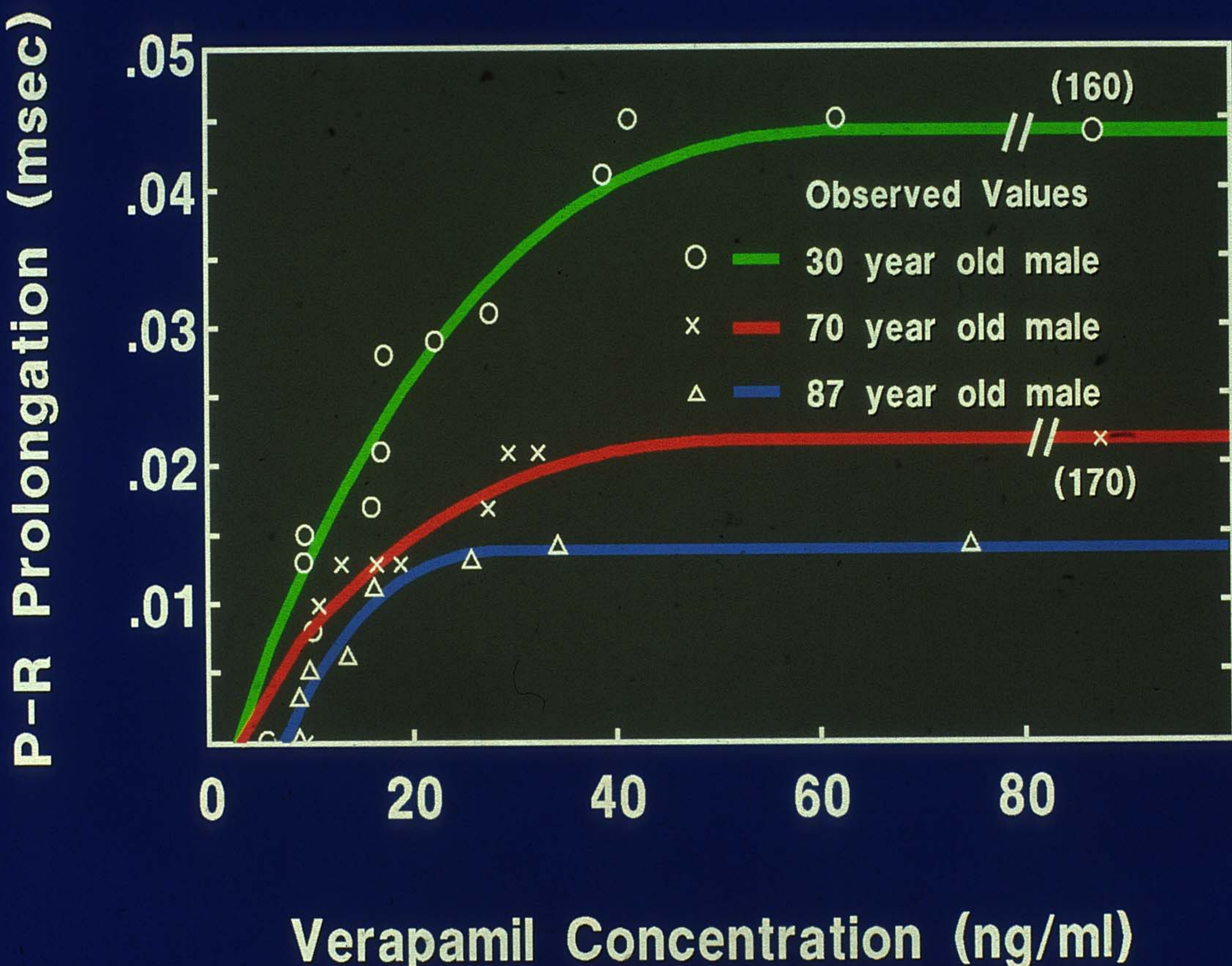
FIGURE 1. Schematic representation of the major mechanisms involved in the contraction and relaxation processes of vascular smooth muscle. See text for complete discussion. Ca = calcium ion; Ca_t = trigger calcium; CLMD = calmodulin molecule ⑤; M = mitochondria; MLC = myosin light chains; MLC-P = phosphorylated 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 14-week Pharmacodynamics
0-144 hours following last dose
Patients receiving 10mg qd



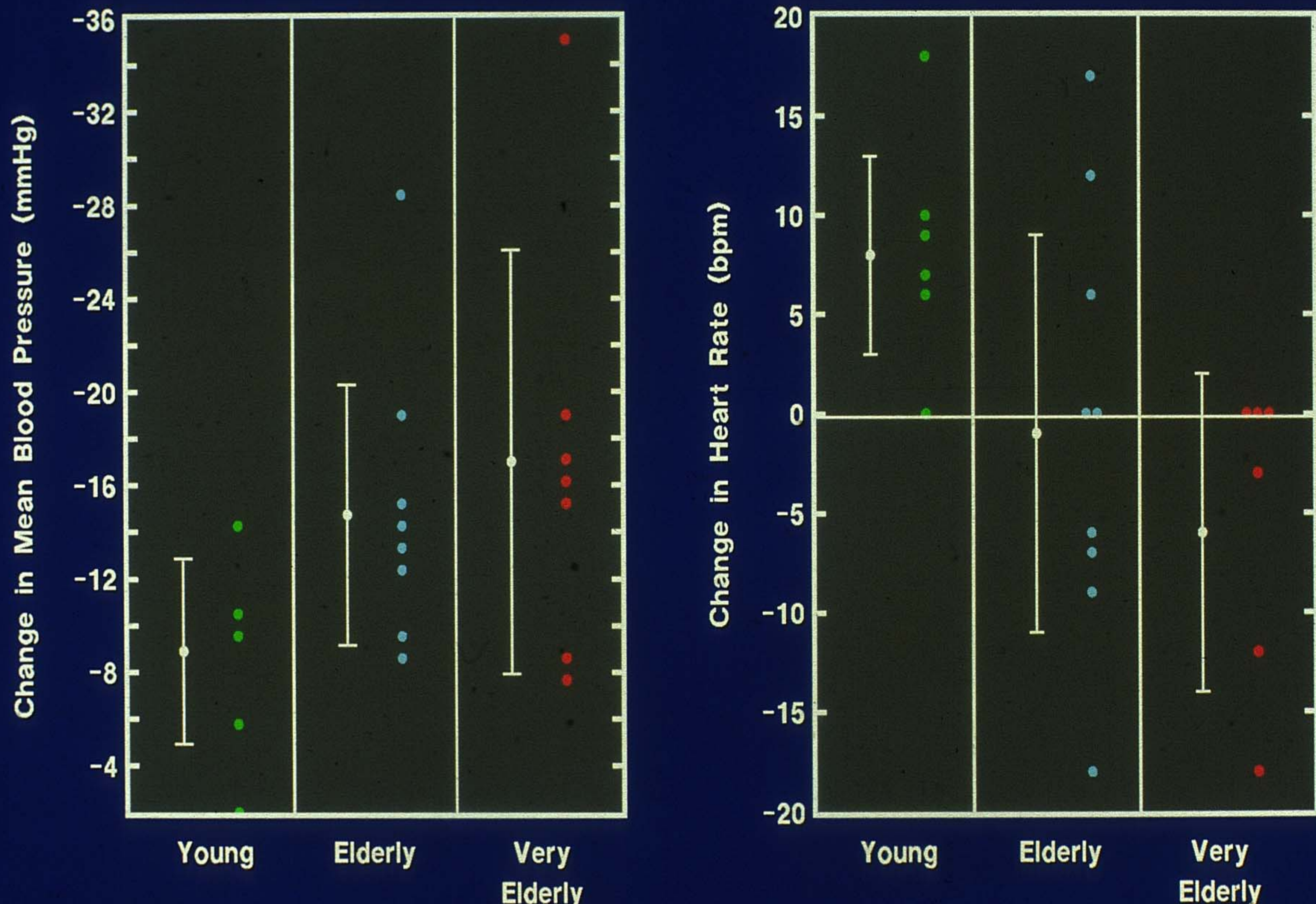


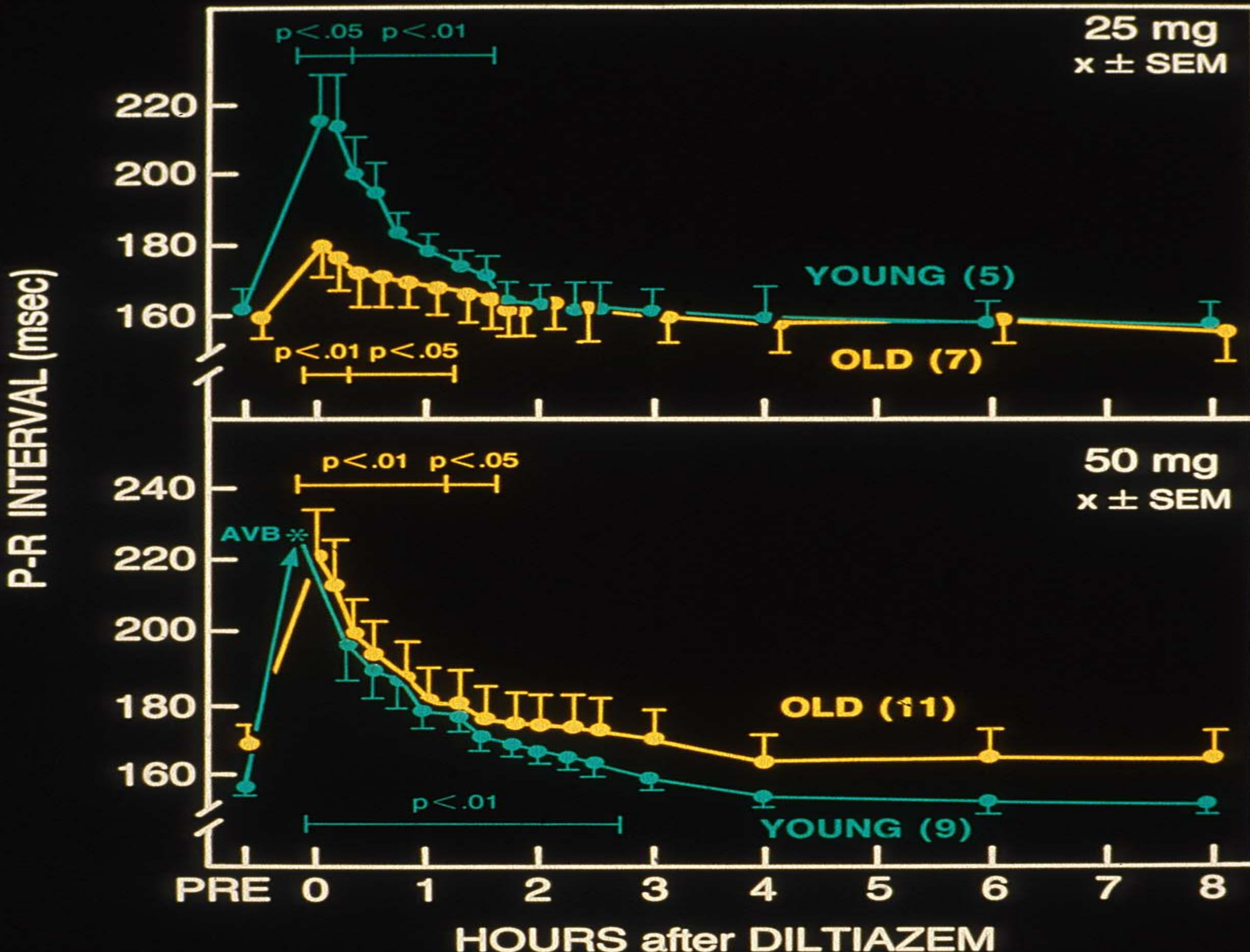
VERAPAMIL CONCENTRATION (ng/ml)
1000
100
10
1
0
10
20
24
TIME AFTER DOSE (hrs.)
82 year old ♂
70 year old ♂
25 year old ♂



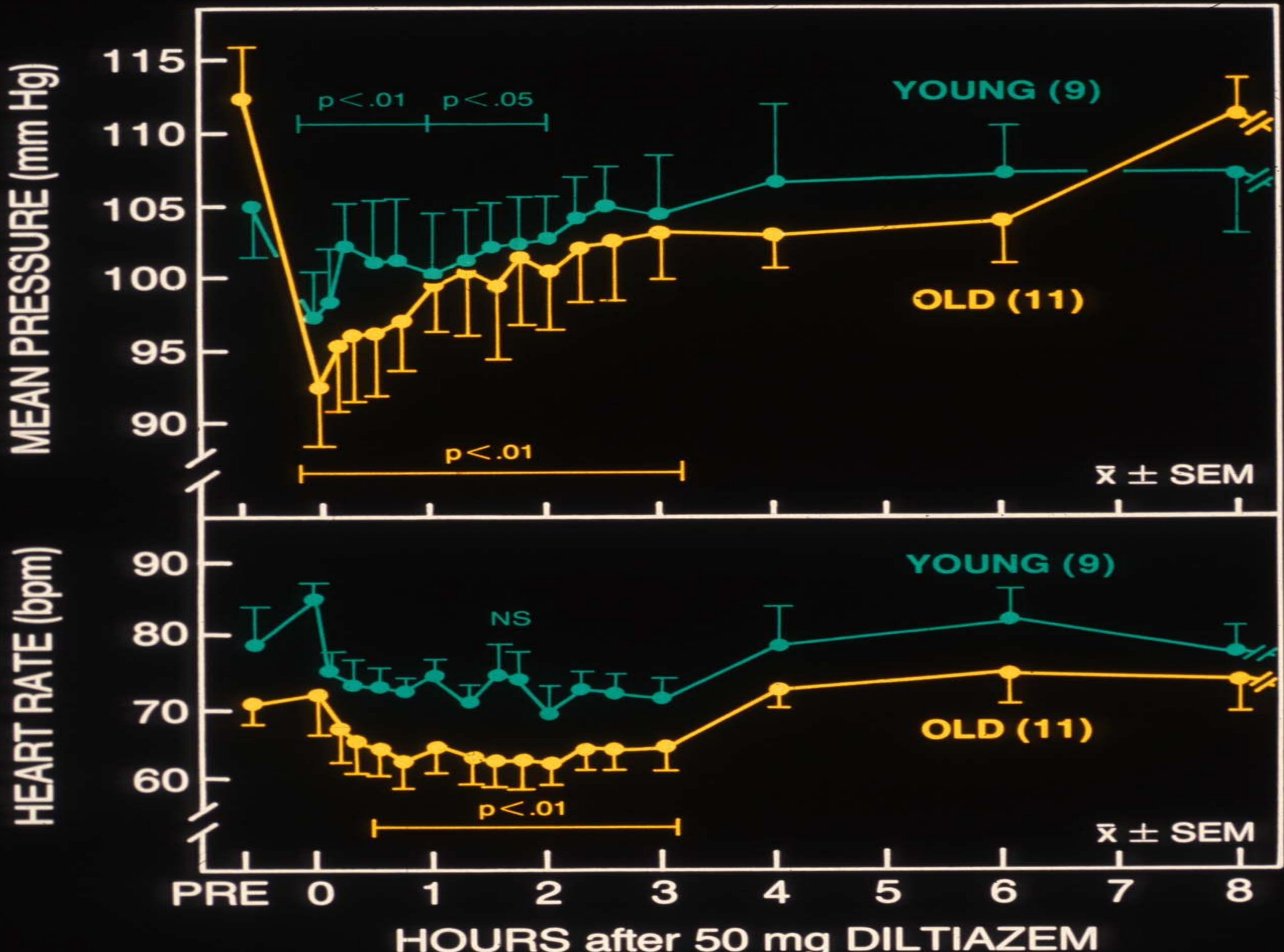
P-R Prolongation (msec)
.05
.04
.03
.02
.01
0
20
40
60
80
Verapamil Concentration (ng/ml)
(160)
(170)
Observed Values
30 year old male
70 year old male
87 year old male

INTRAVENOUS VERAPAMIL PHARMACODYNAMICS





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



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

HEART RATE RESPONSES

- DECREASED REFLEX RESPONSES
  - Parasympathetic
  - Sympathetic
- DIFFERING SENSITIVITY TO CALCIUM CHANNEL BLOCKADE OF THE SINUS NODE

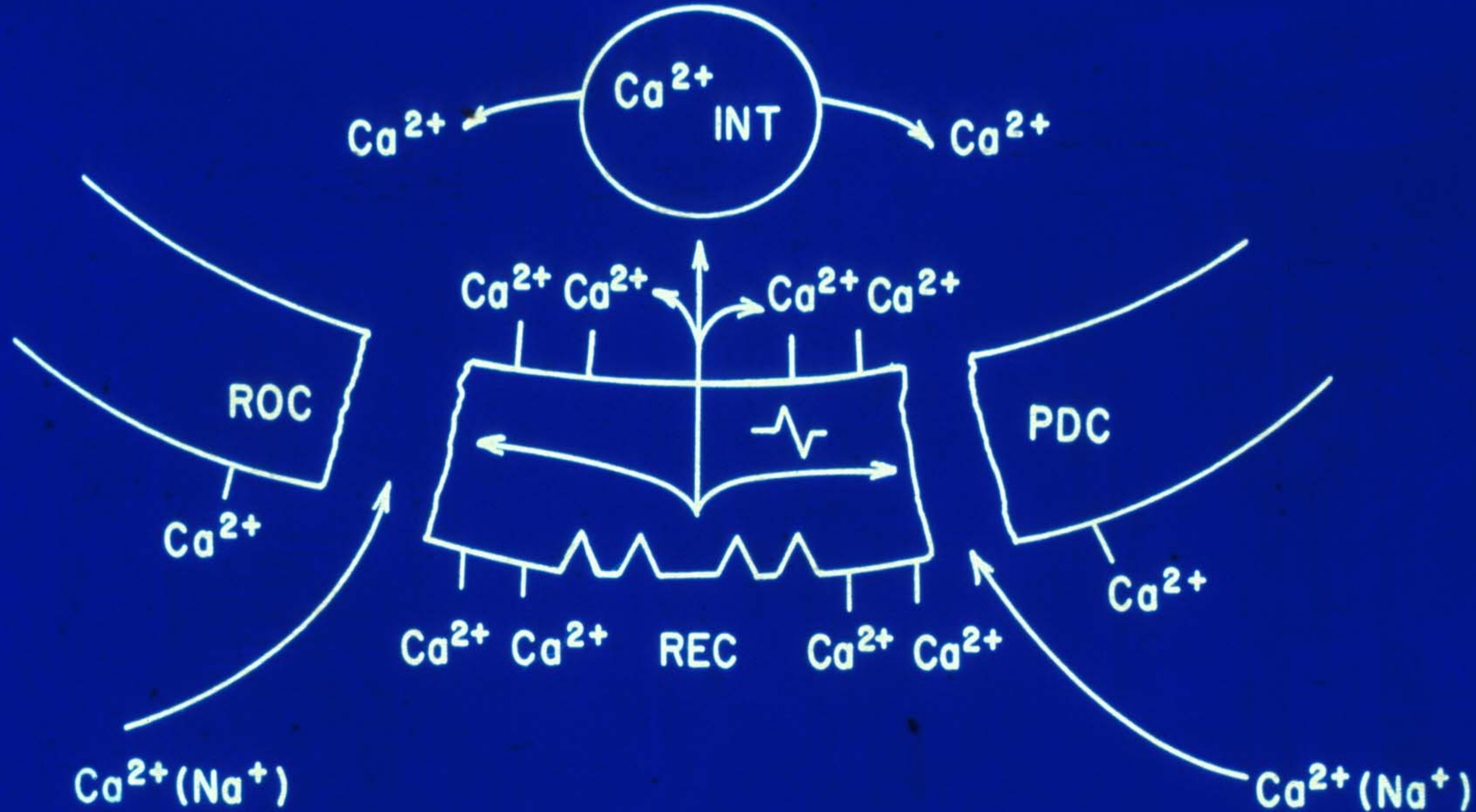
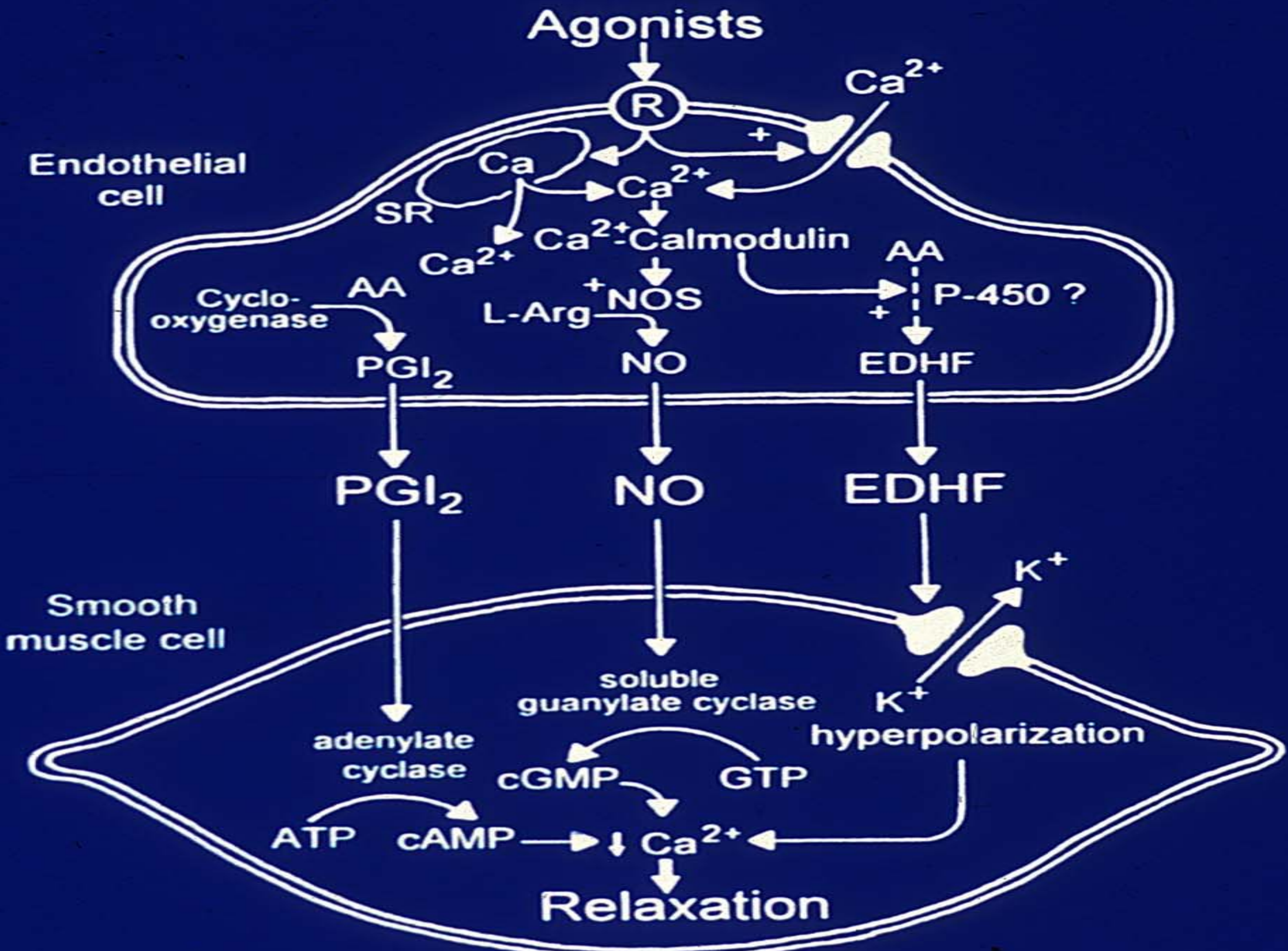
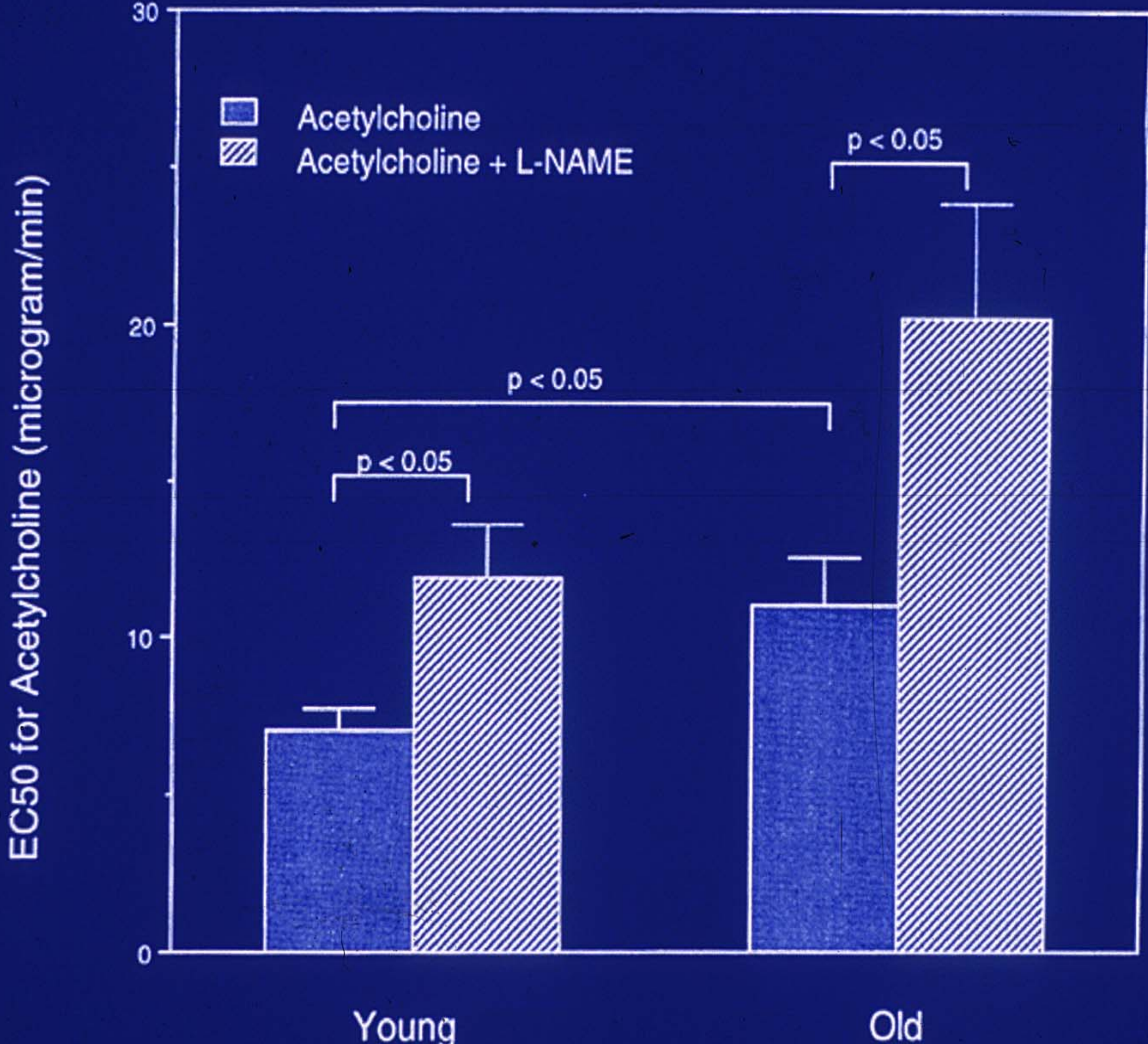


FIGURE 1. Receptor-mediated Ca^{2+} mobilization. Shown are Ca^{2+} influx through potential-dependent and receptor operated channels, mobilization of membrane-bound and intracellularly stored Ca^{2+}.



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

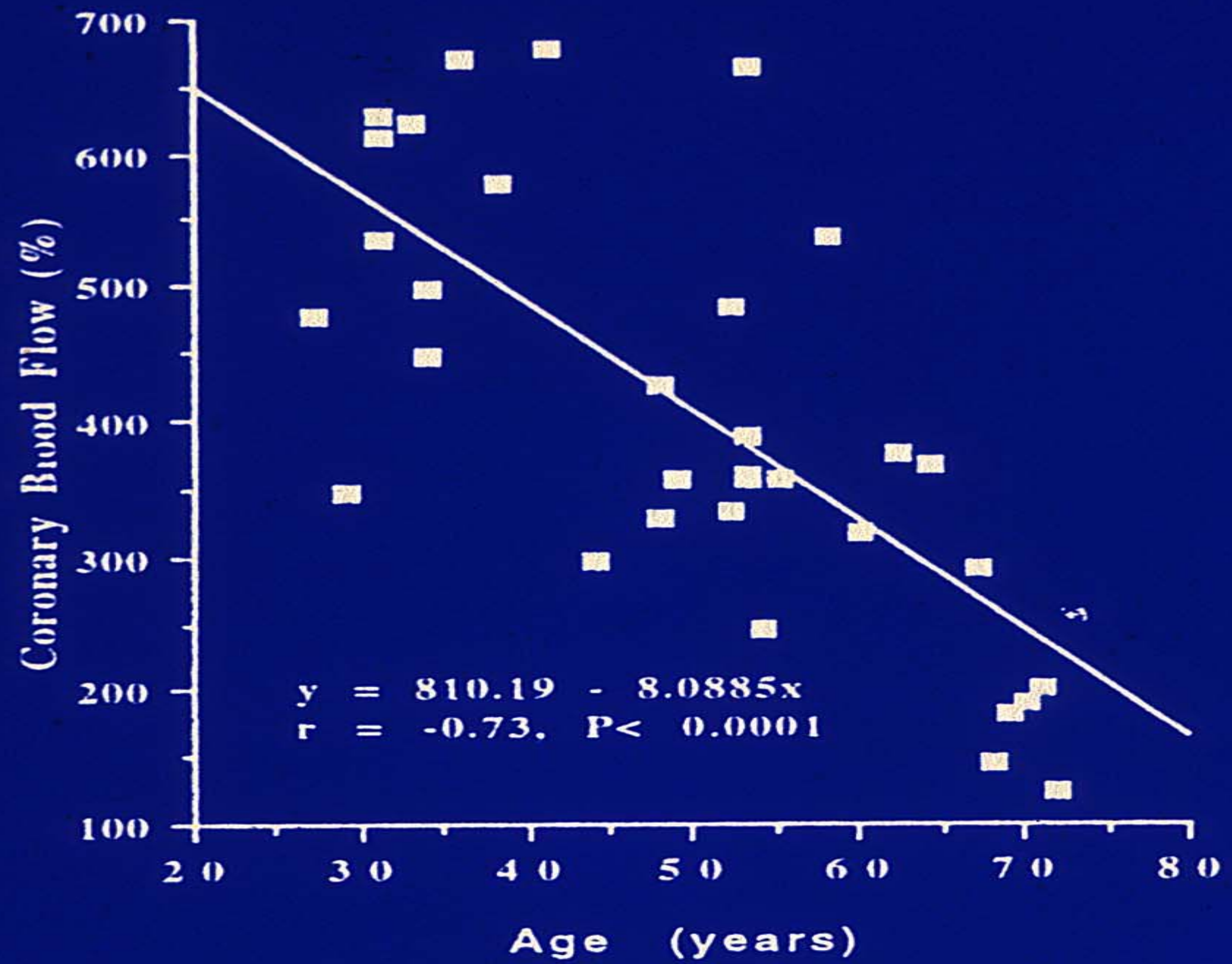
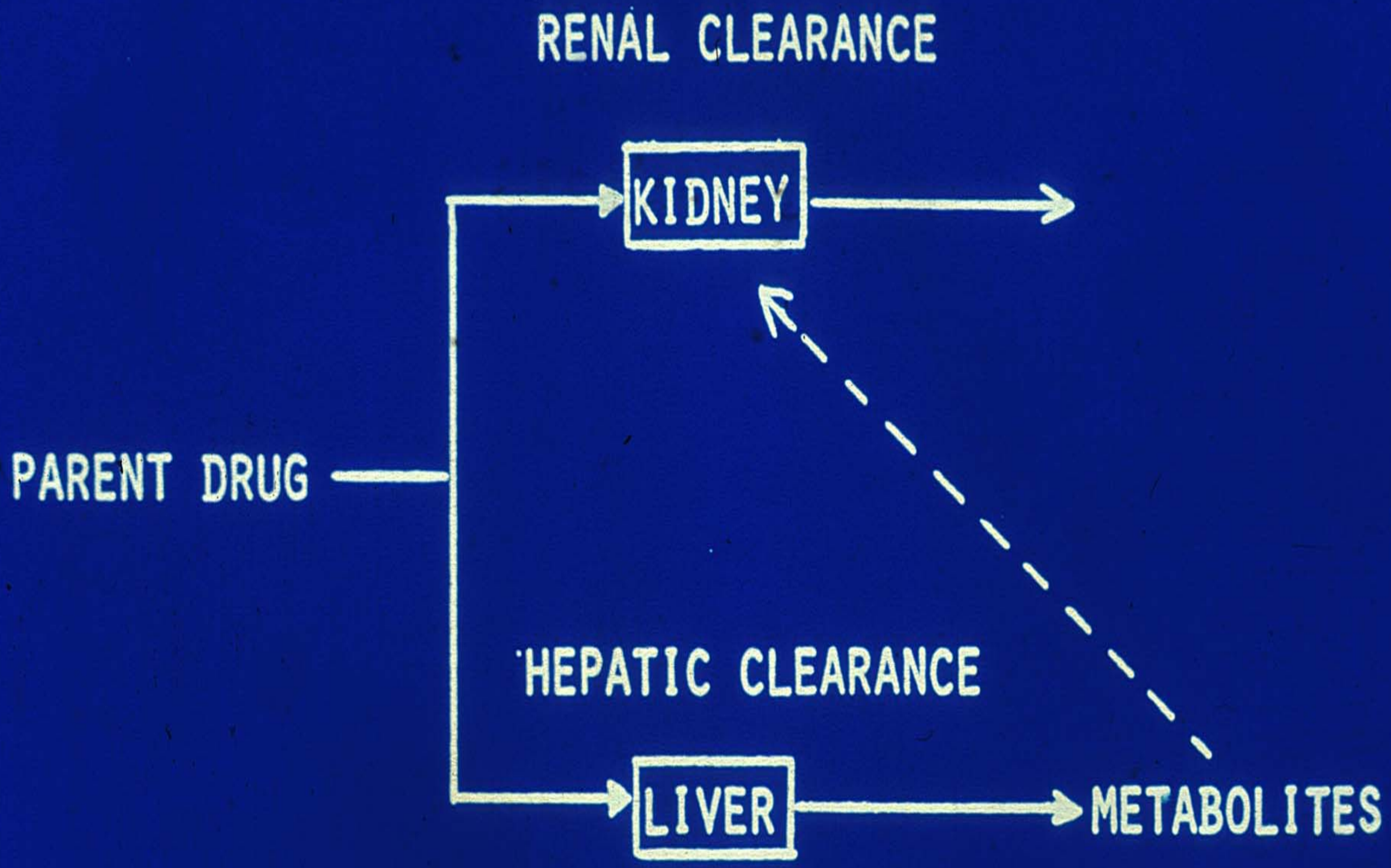


Figure 2. Scatterplot of correlation of age and peak (percent of control values) coronary blood flow response to acetylcholine.

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

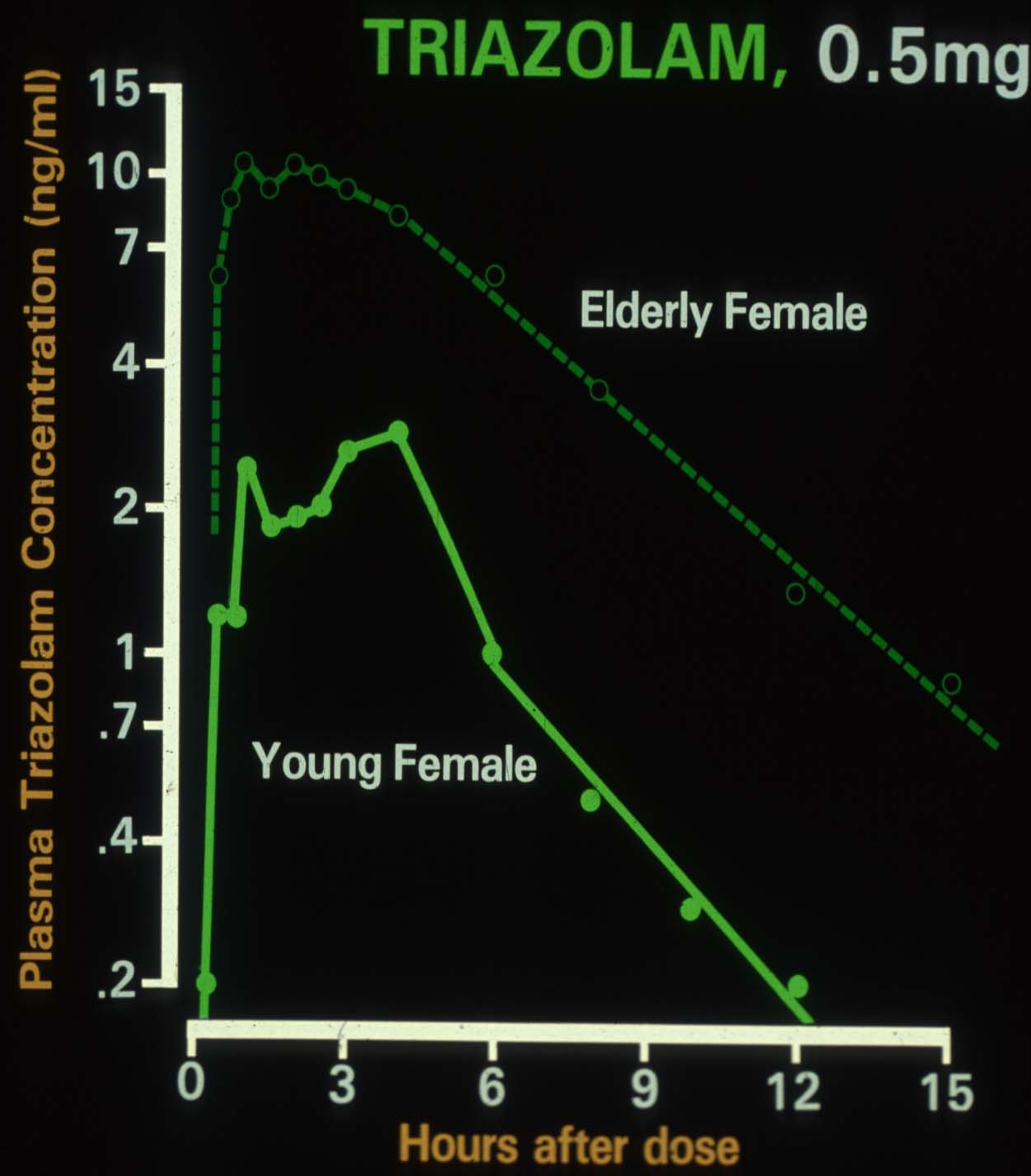

RENAL CLEARANCE
KIDNEY
PARENT DRUG
HEPATIC CLEARANCE
LIVER
METABOLITES

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

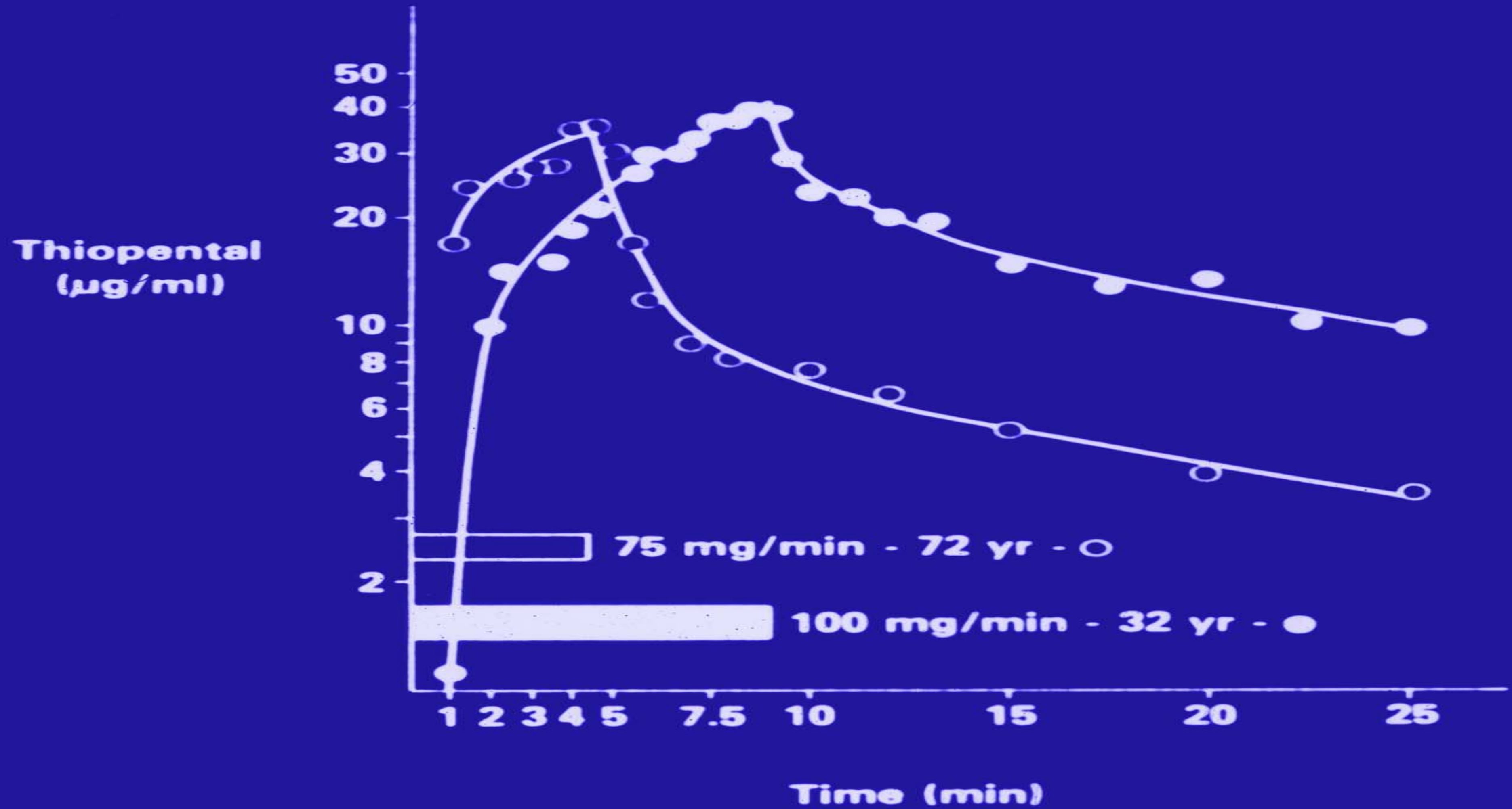


FIG. 5. Serum thiopental concentration (log scale) *versus* time for the young (filled circles and bars) and the elderly (unfilled circles and bars) patients shown in figure 3. All of the measured thiopental concentrations for the patients are indicated in this figure, whereas all data could not be displayed 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.

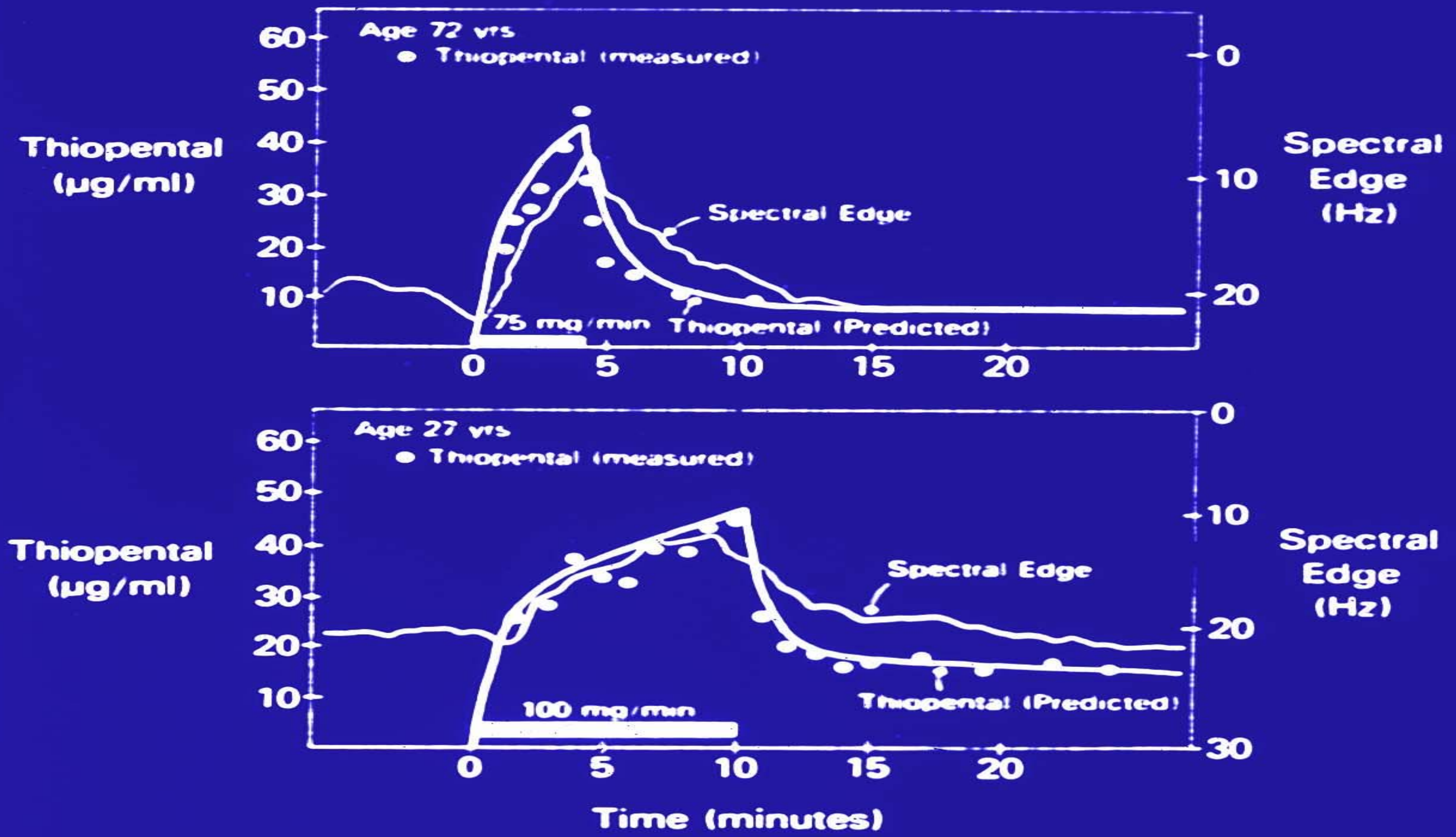


FIG. 3. The concentration of thiopental *versus* 1) time and 2) spectral edge in an elderly patient (top figure) and in a younger patient (bottom figure). Solid horizontal bars represent the length of thiopental infusion. Dots represent the measured thiopental concentration (linear scale), and the solid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

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

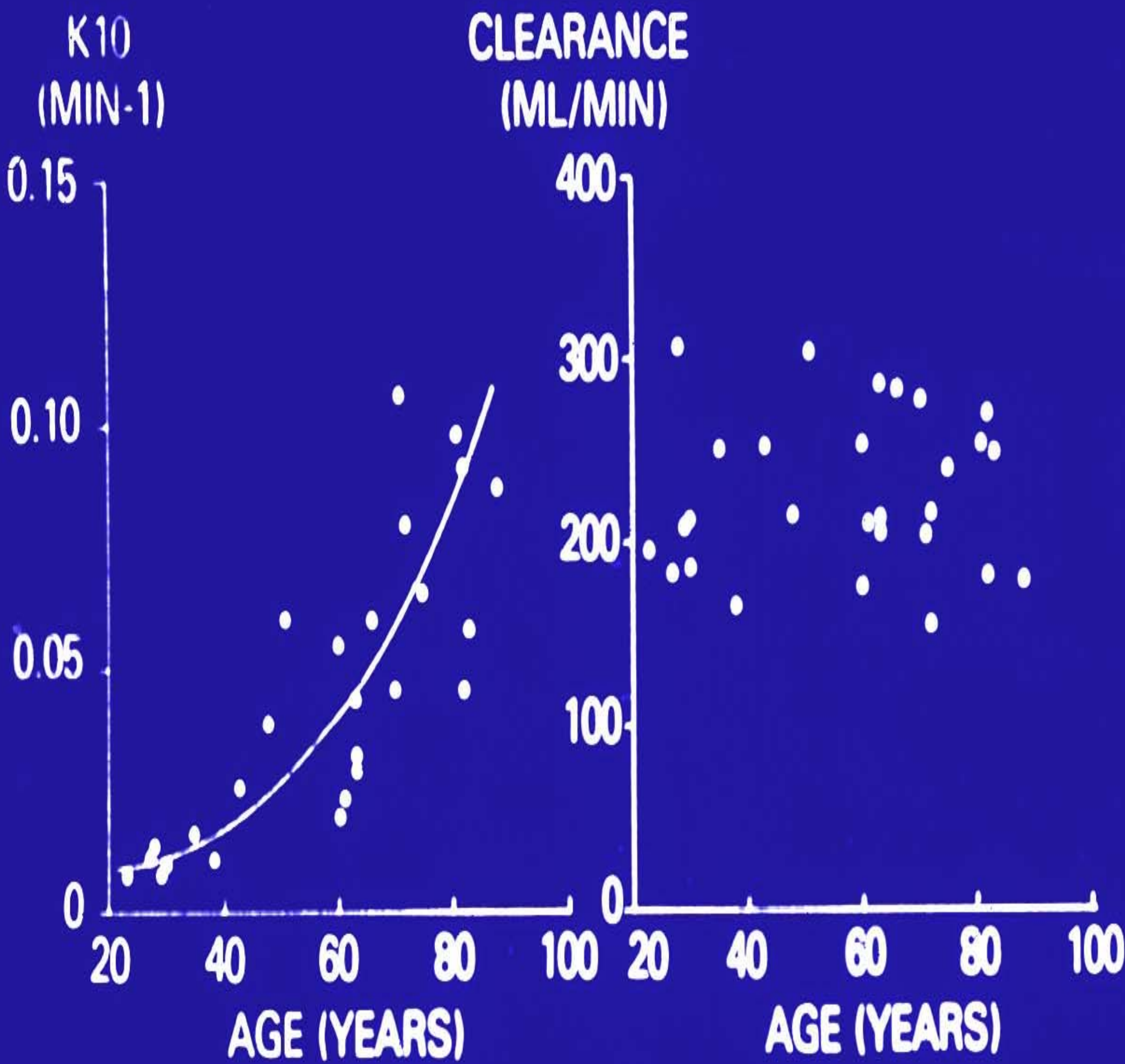


FIG. 8. K_{10} and clearance *versus* age. Dots represent the rate constants or clearance derived from the pharmacokinetic analysis derived for each patient. K_{10}, the first-order rate constant of drug elimination (metabolism) from the body, has an exponential relationship with age. This relationship (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.

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

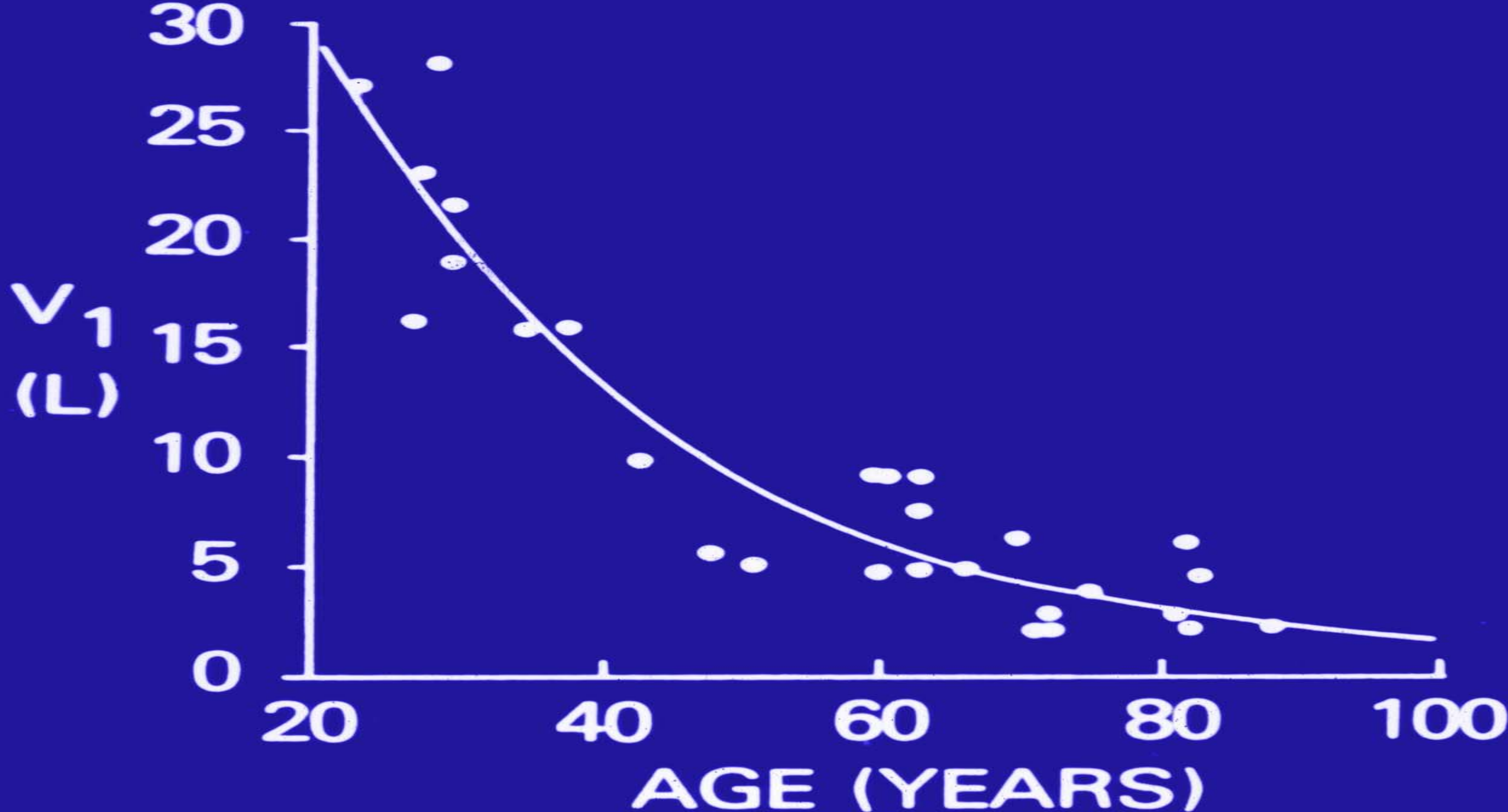
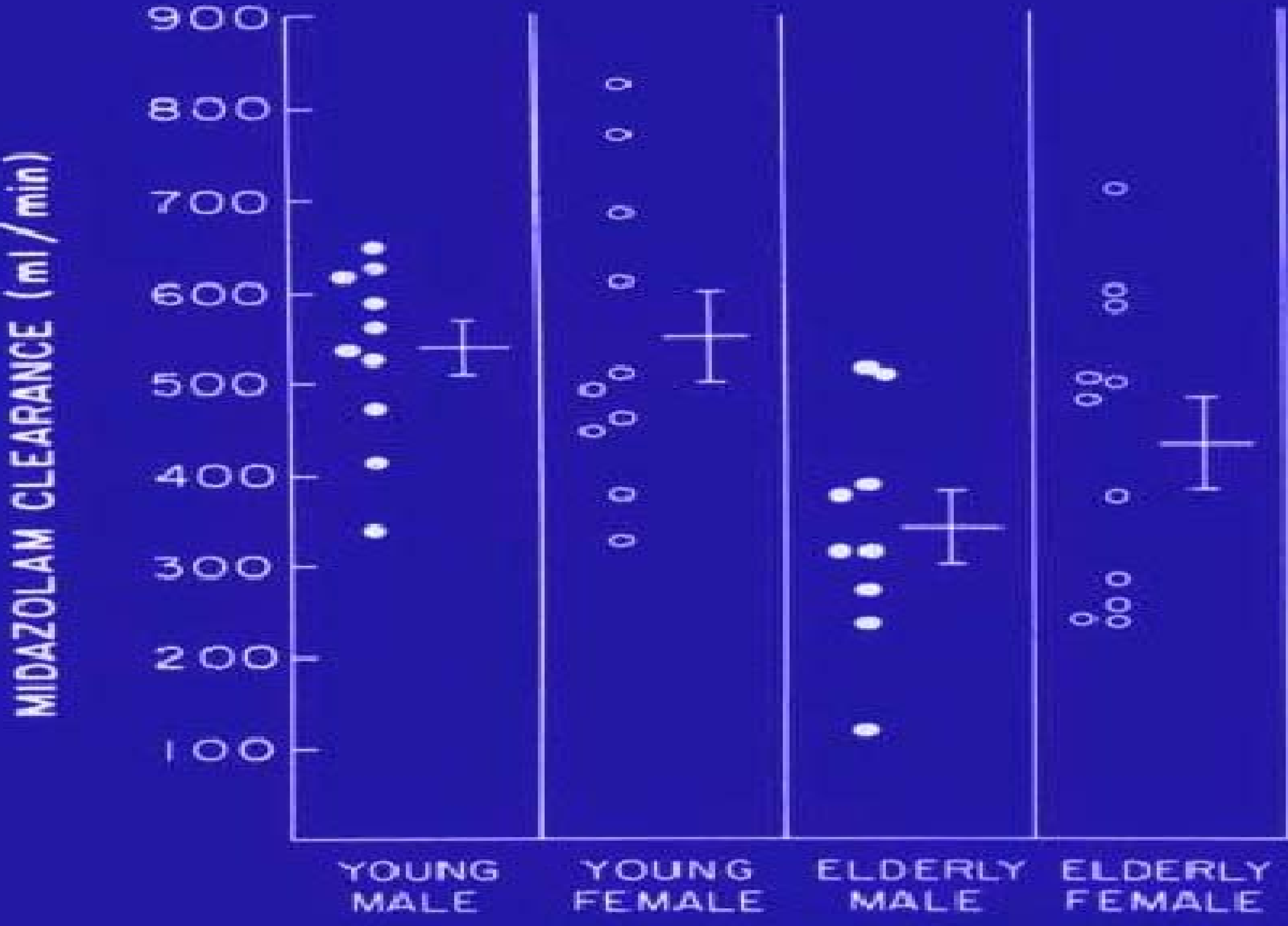
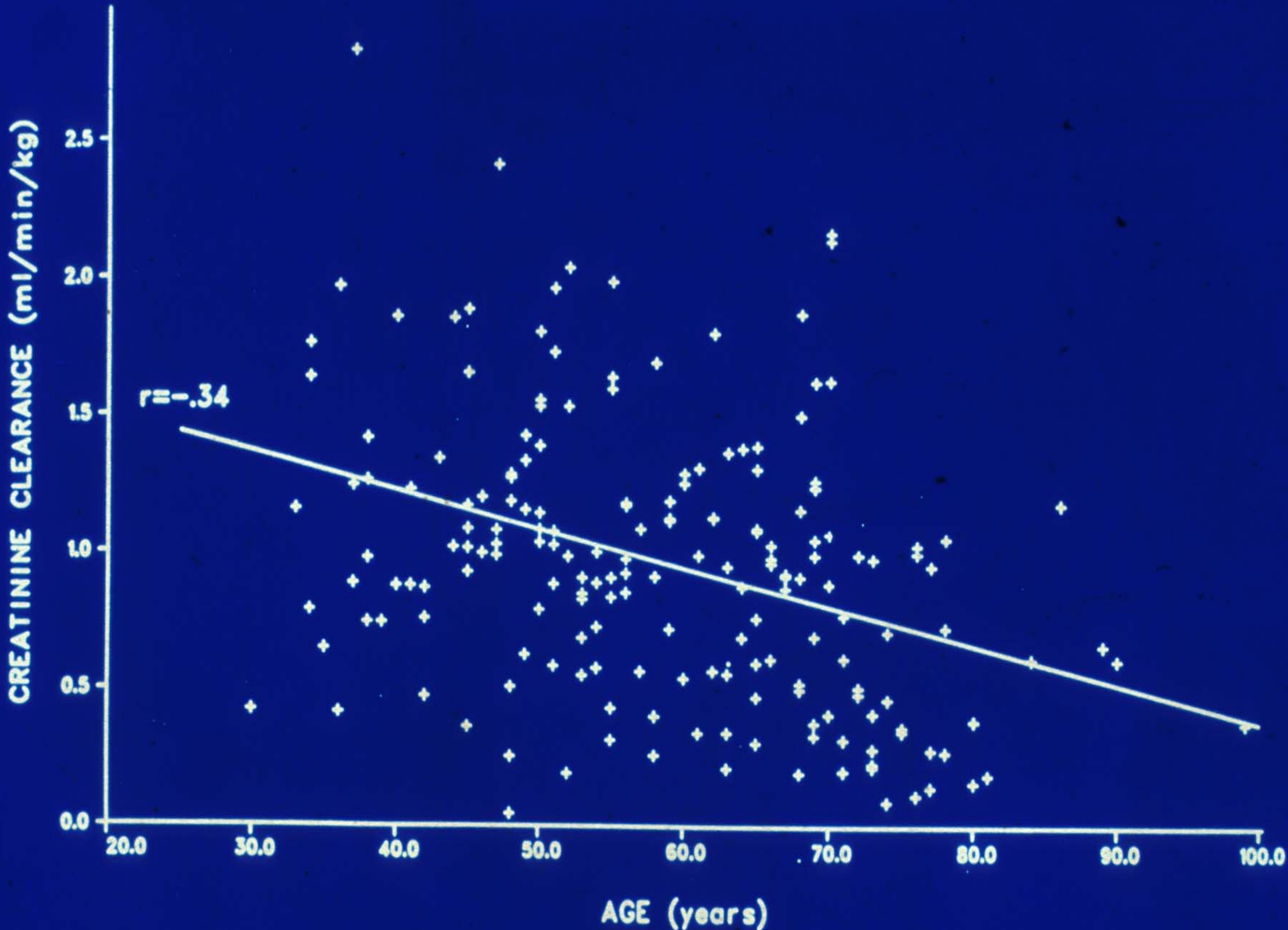


FIG. 6. Volume of the central compartment (V_1) *versus* age. The dots represent the V_1, derived from the pharmacokinetic analysis for each patient. The solid curve was derived using nonlinear regression of V_1 *versus* age to an exponential equation (see table 2).

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)

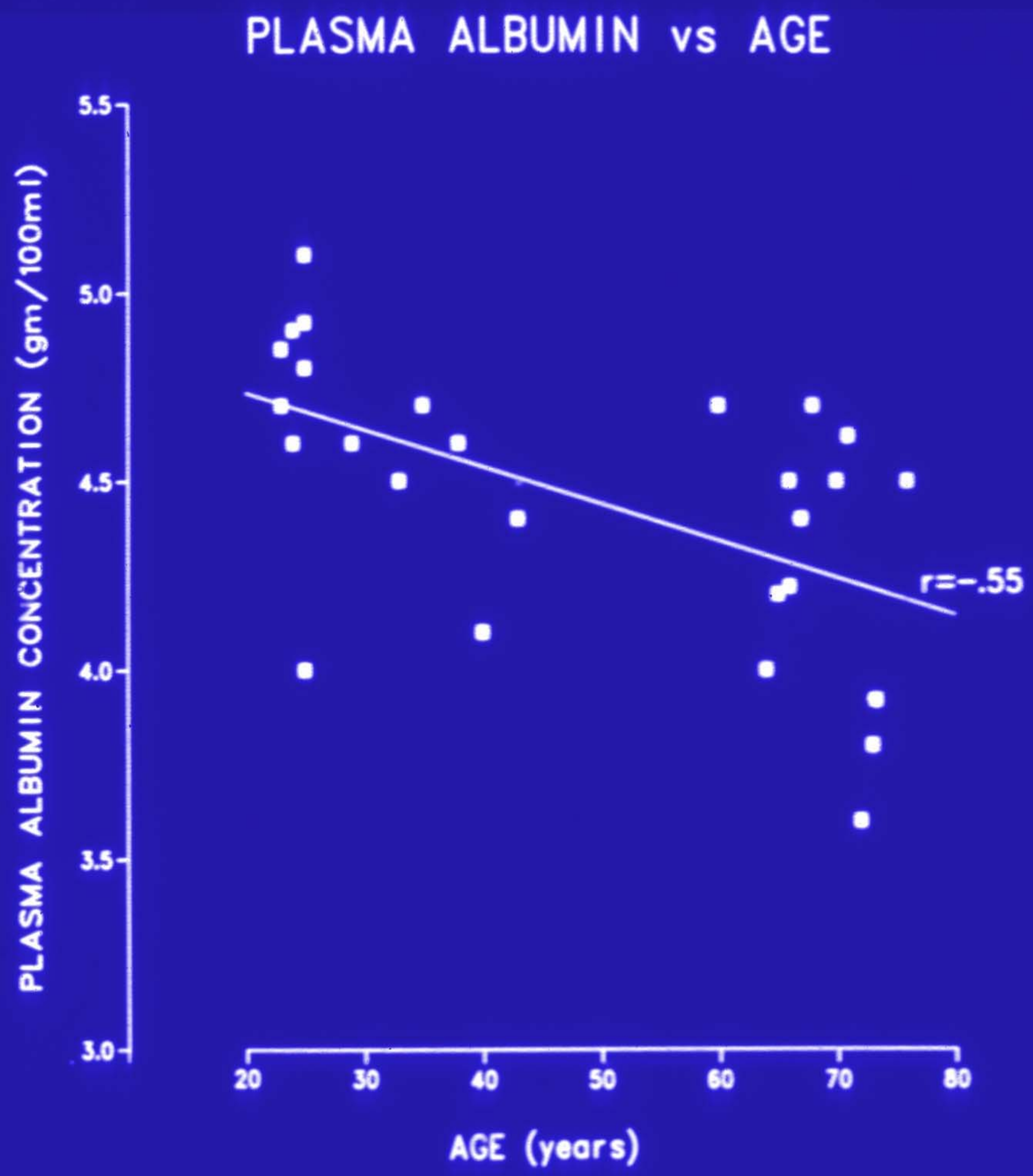
PARTIAL LIST OF DRUGS THAT UNDERGO SIGNIFICANT RENAL EXCRETION IN HUMANS

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

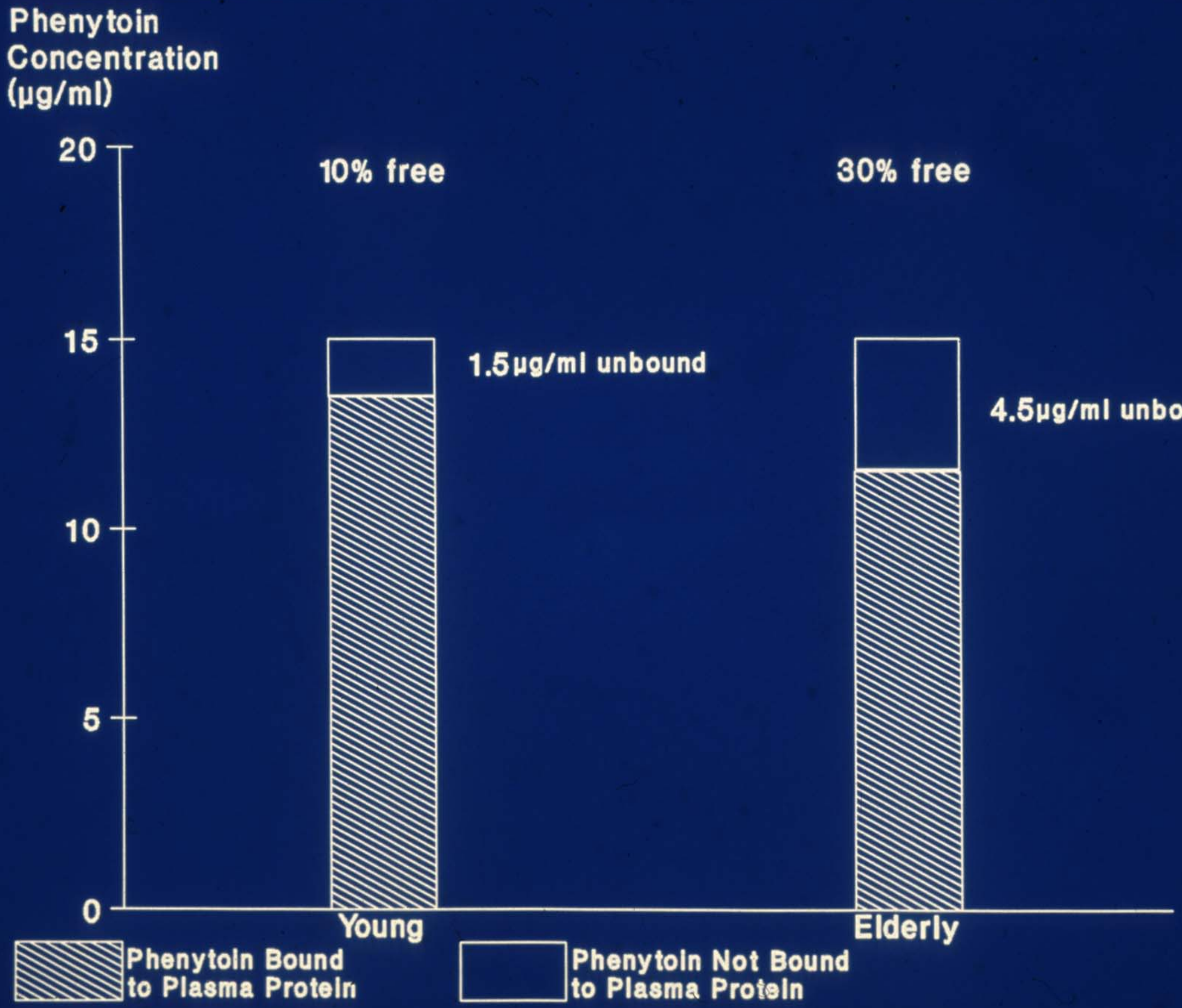
$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}}$$

Table 3. Some drugs with decreased clearance in the elderly

ROUTE OF CLEARANCE	REPRESENTATIVE DRUGS	
Renal	All aminoglycosides Vancomycin Digoxin Procainamide Lithium	Sotalol Atenolol Dofetilide Cimetidine
Single Phase I metabolic pathway		
CYP3A	Alprazolam Midazolam Triazolam Verapamil Diltiazem Dihydropyridine calcium channel blockers Lidocaine	
CYP2C	Diazepam Phenytoin Celecoxib	
CYP1A2	Theophylline	
Multiple Phase I metabolic pathways	Imipramine Desipramine Trazodone Hexobarbital Flurazepam	



PLASMA ALBUMIN vs AGE
PLASMA ALBUMIN CONCENTRATION (gm/100ml)
5.5
5.0
4.5
4.0
3.5
3.0
r=-.55
20
30
40
50
60
70
80
AGE (years)


Phenytoin
Concentration
(μg/ml)
20
15
10
5
0
10% free
30% free
1.5μg/ml unbound
4.5μg/ml unbound
Young
Elderly
Phenytoin Bound
to Plasma Protein
Phenytoin Not Bound
to Plasma Protein

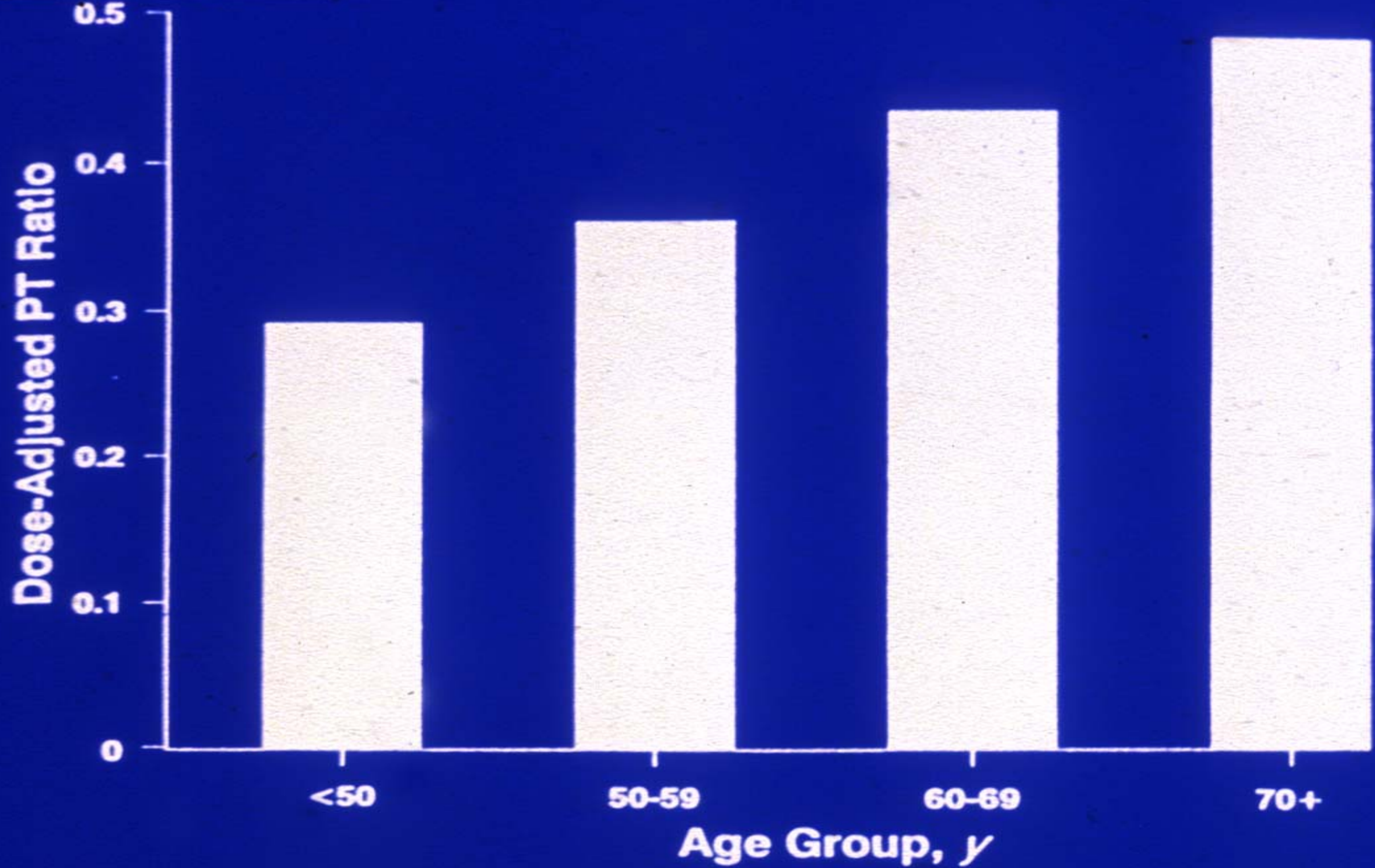


Figure 1. The relationship between the dose-adjusted prothrombin time ratio and age group ($P < 0.001$). PT = prothrombin time.

Gurwitz, et al, Annals of Internal Medicine, 1992; 116: 901-904

Table 2. Pharmacokinetic changes in the elderly

PROCESS	CHANGE WITH AGE
Gastrointestinal absorption	—
Drug distribution	
Central compartment volume	— or ↓
Peripheral compartment volume	
Lipophilic drugs	↑↑
Hydrophilic drugs	↓↓
Plasma protein binding	
Binding to albumin	↓
Binding to α_1-acid glycoprotein	— or ↑
Drug Elimination	
Renal elimination	↓↓
Hepatic metabolism	
Phase I reactions	
CYP3A	↓
CYP1A2	— or ↓
CYP2D6	— or ↓
CYP2C9	— or ↓
CYP2C19	— or ↓
CYP2E1	— or ↓
Phase II reactions	
Glucuronidation	—
Sulfation	—
Acetylation	—

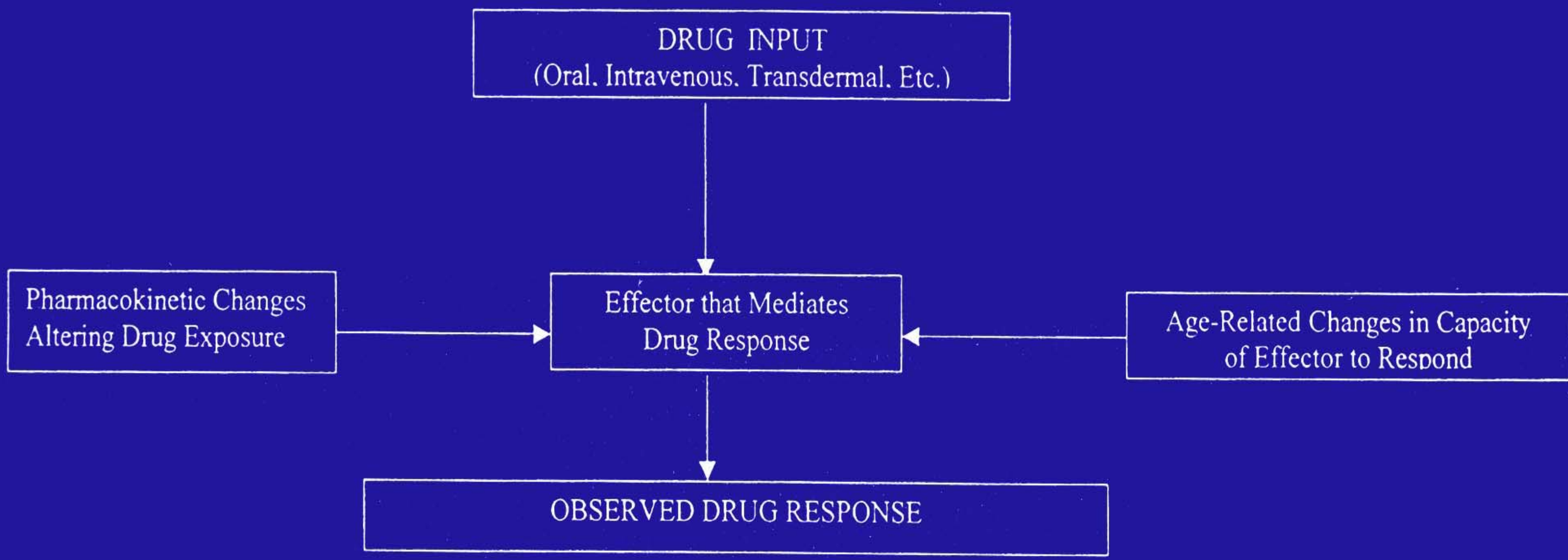

DRUG INPUT
(Oral, Intravenous, Transdermal, Etc.)
Pharmacokinetic Changes Altering Drug Exposure
Effector that Mediates Drug Response
Age-Related Changes in Capacity of Effector to Respond
OBSERVED DRUG RESPONSE

FIGURE 3

The Goals Of Treating The Elderly Hypertensive

- ↓ 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)