

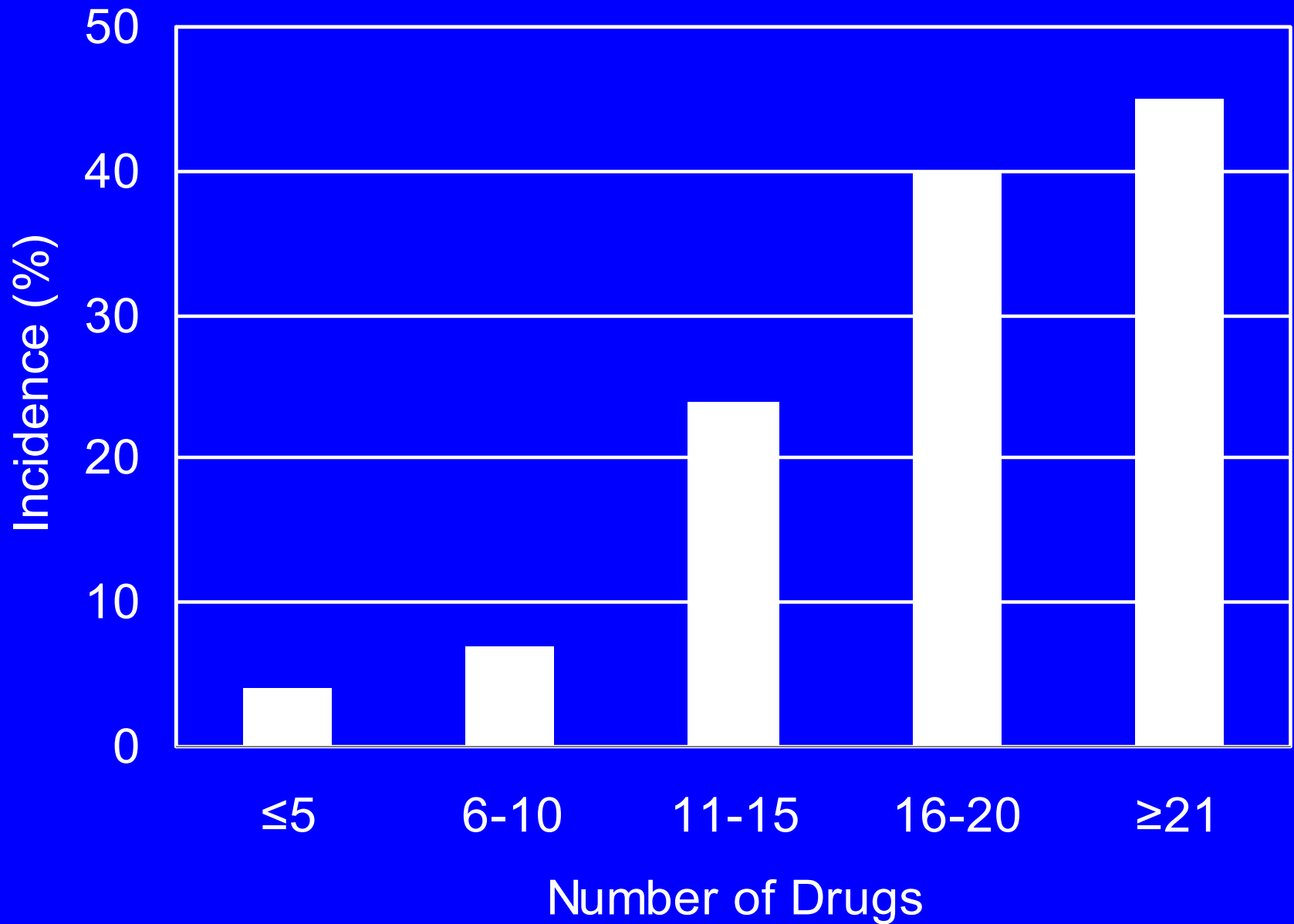
***PHARMACODYNAMICS OF AGING:
NARROWING OF THE THERAPEUTIC
INDEX IN THE FACE OF
THERAPEUTIC OPPORTUNITY***

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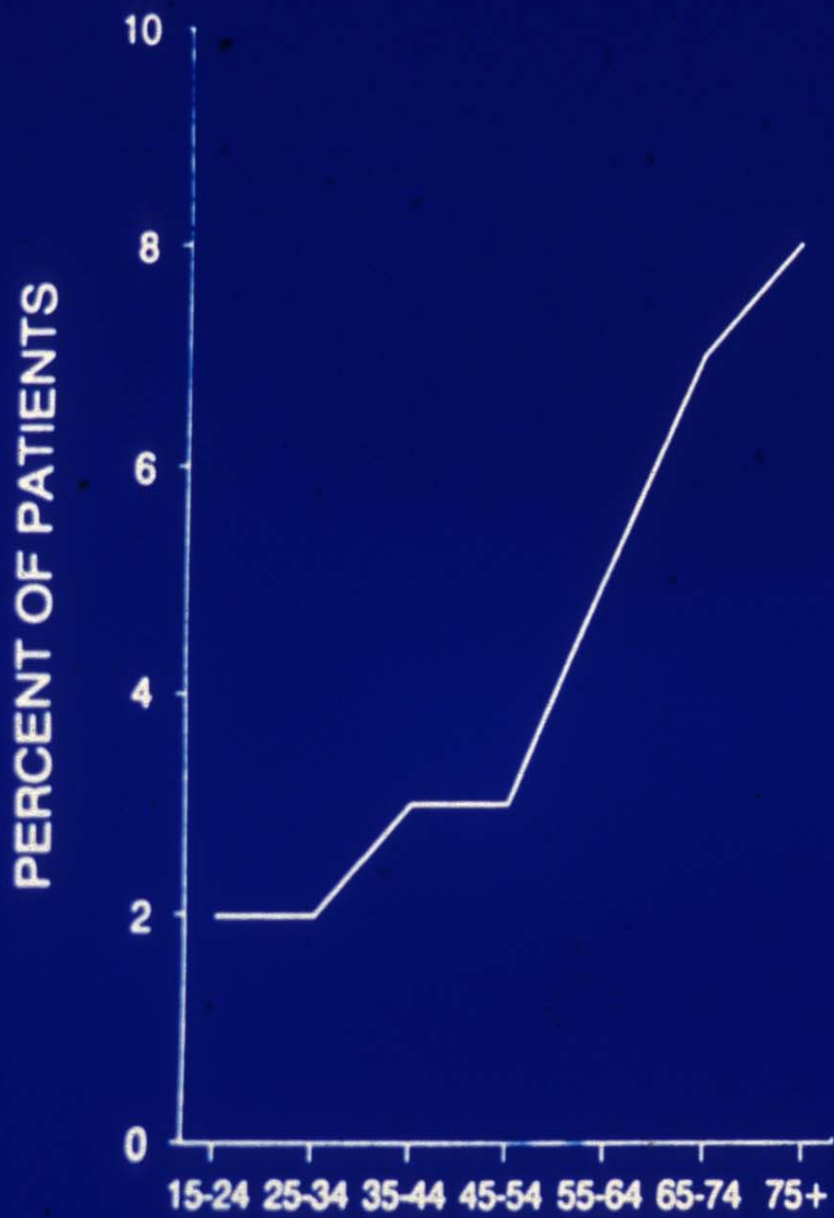
February 28, 2008

Pharmacodynamics of Aging

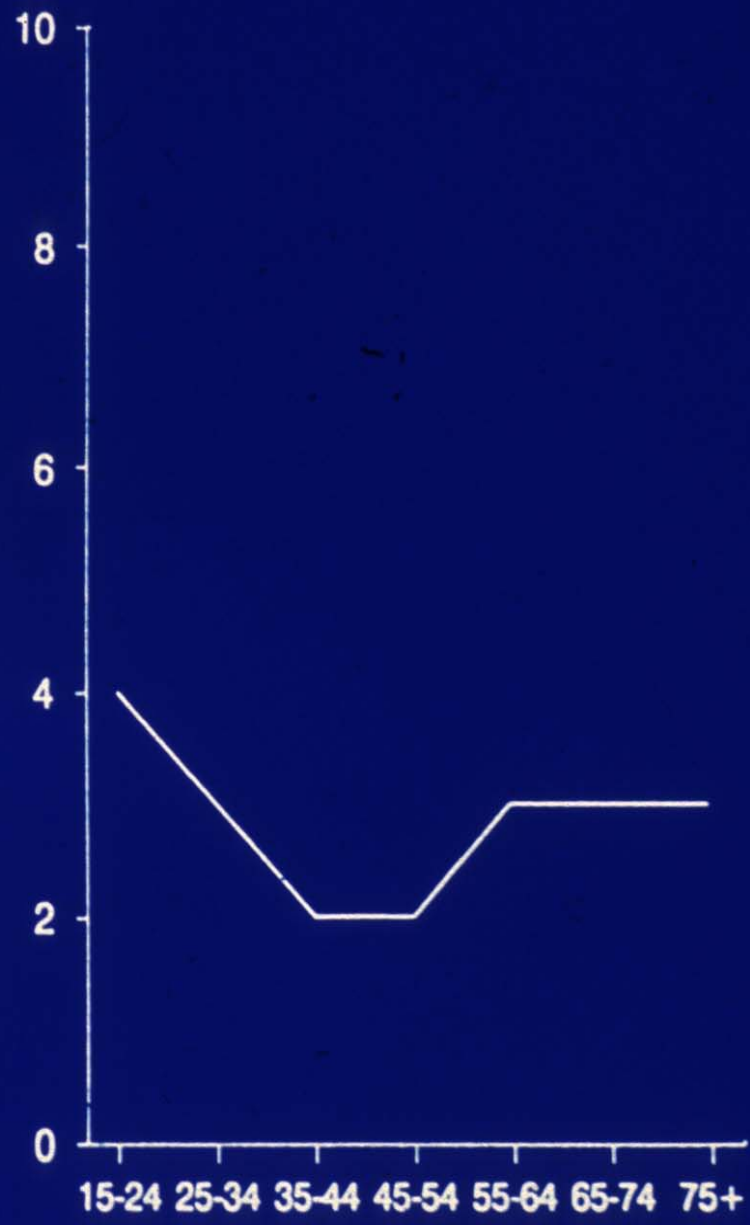
- Systemic Cardiovascular
- Local Cardiovascular
- Other Effector Systems



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



PERCENT COURSES OF THERAPY



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
Office Visits

Number of Drugs	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.

OVERALL PRESCRIBING

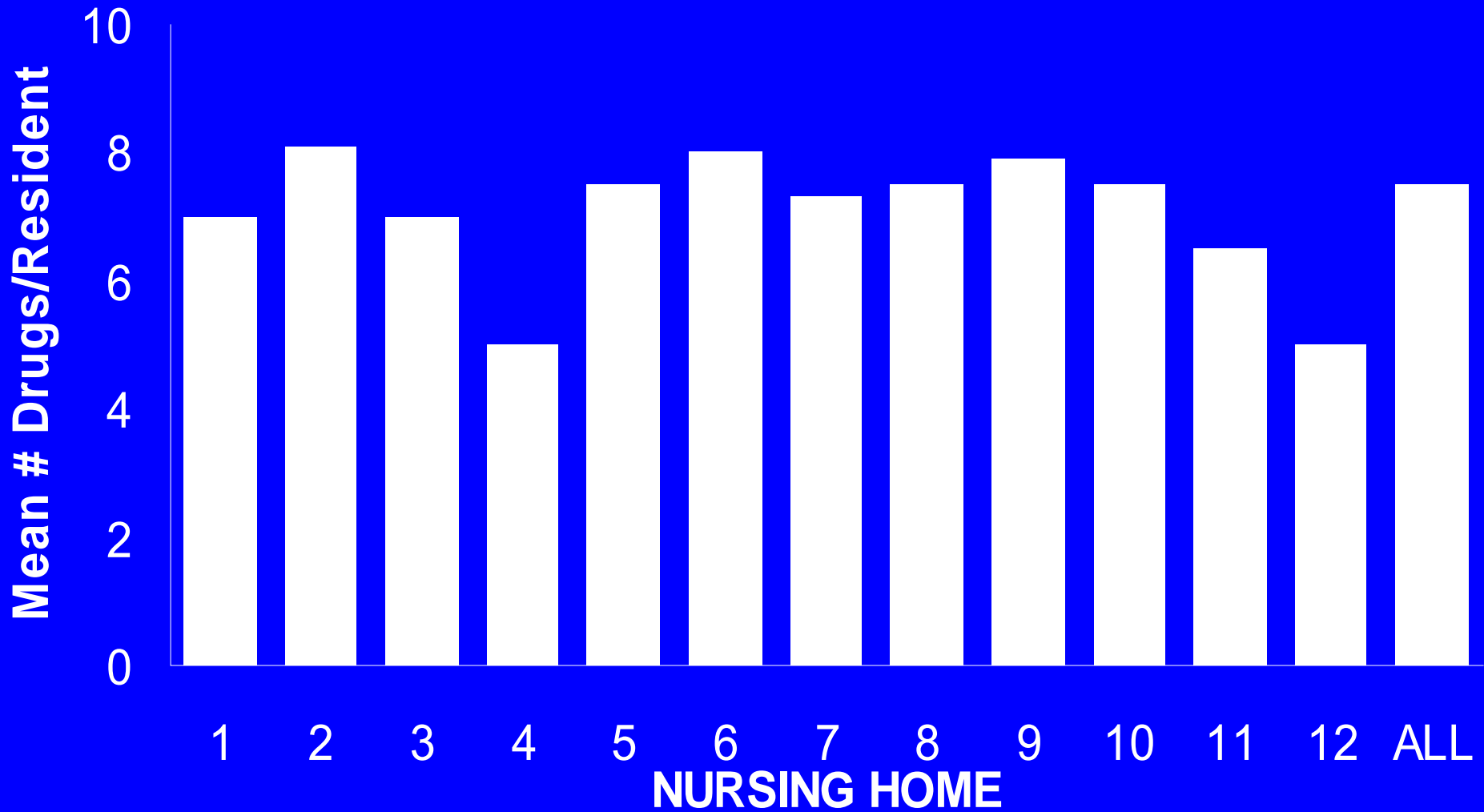
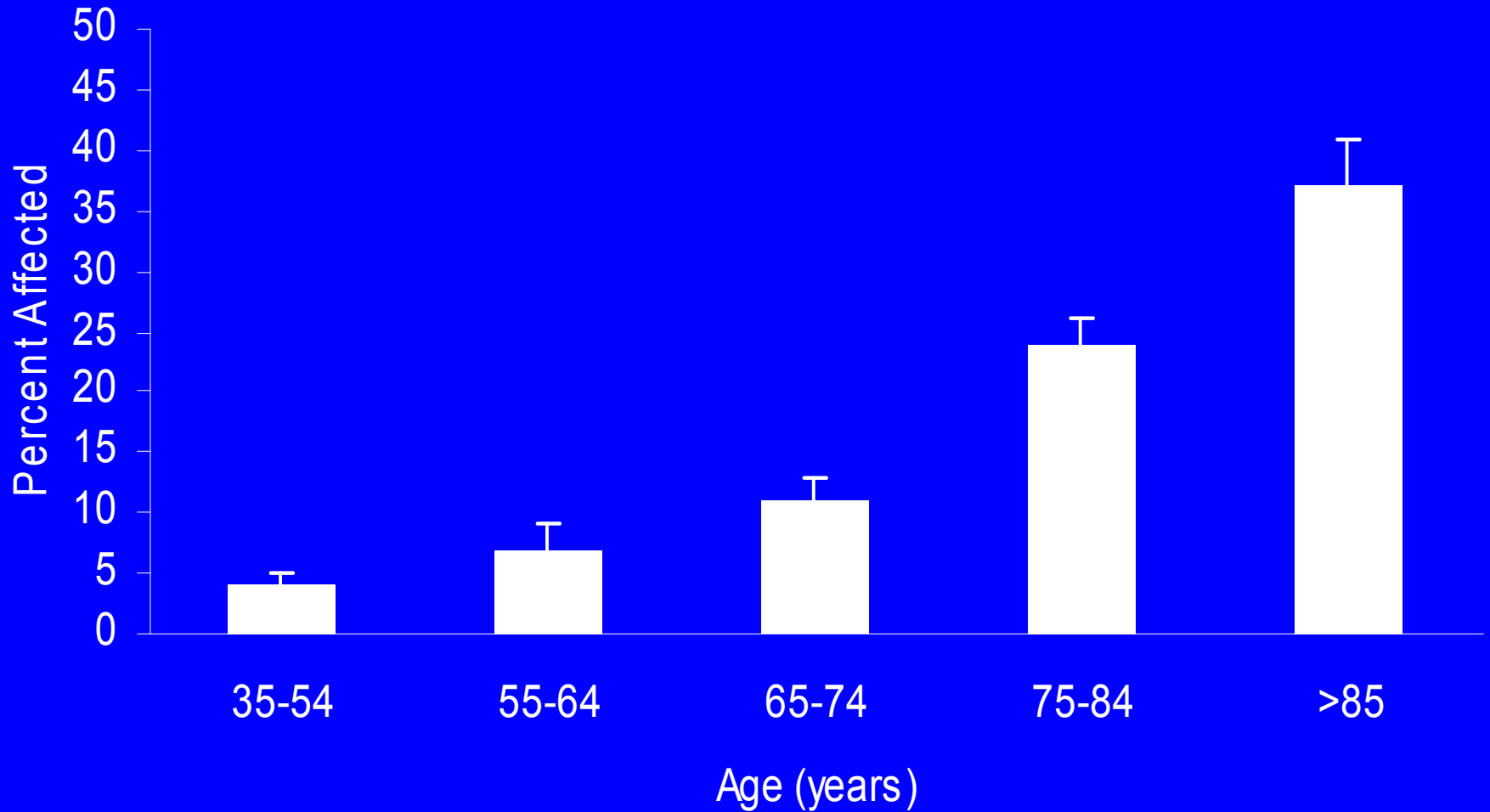


Figure 1. Medication prescriptions per resident in the 12 nursing homes. 15 October 1992 · *Annals of Internal Medicine* · Volume 117 · Number 8 · 685

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

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

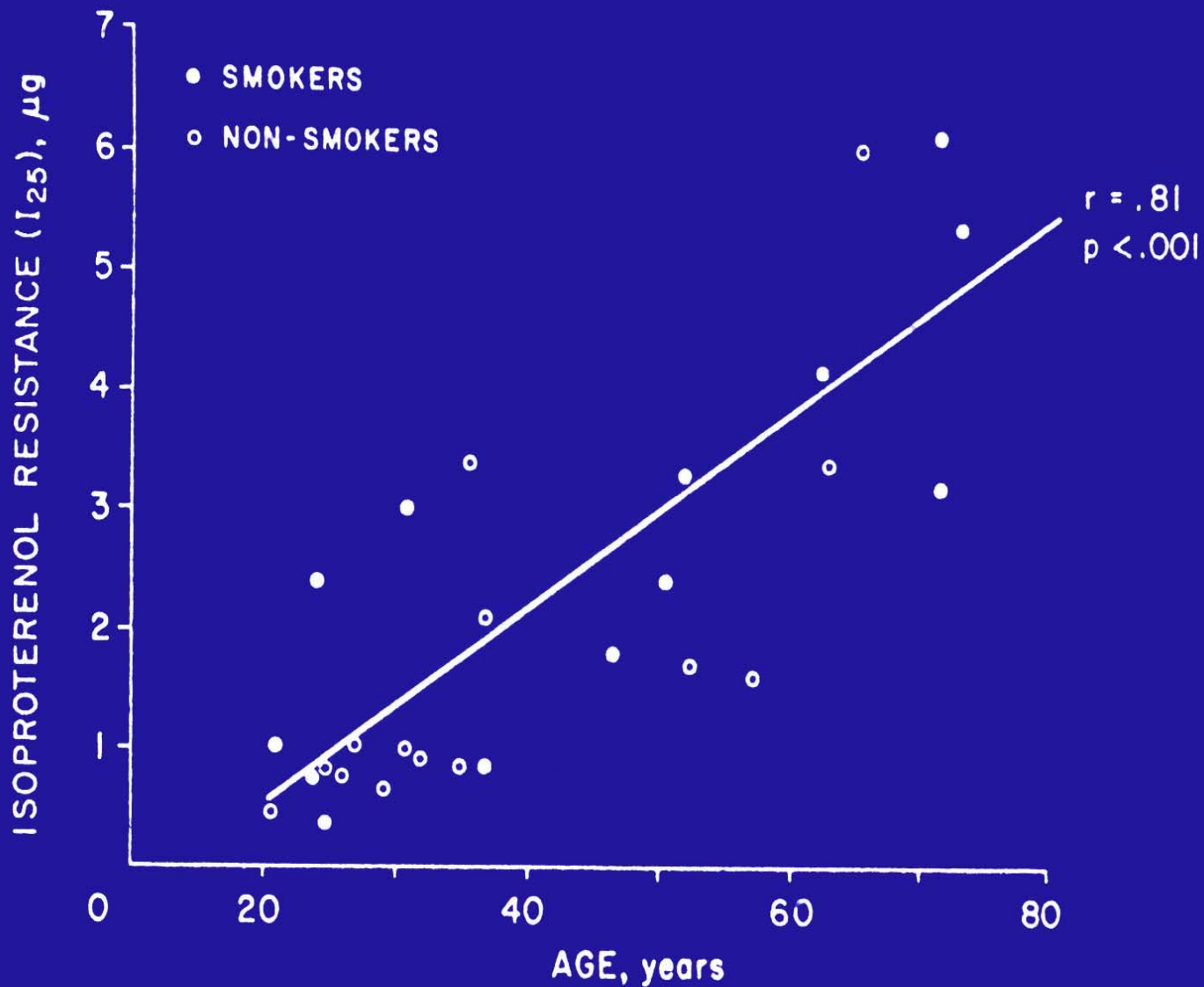


Fig. 1. Relationship between isoproterenolol resistance and age in smokers (●) and nonsmokers (○).

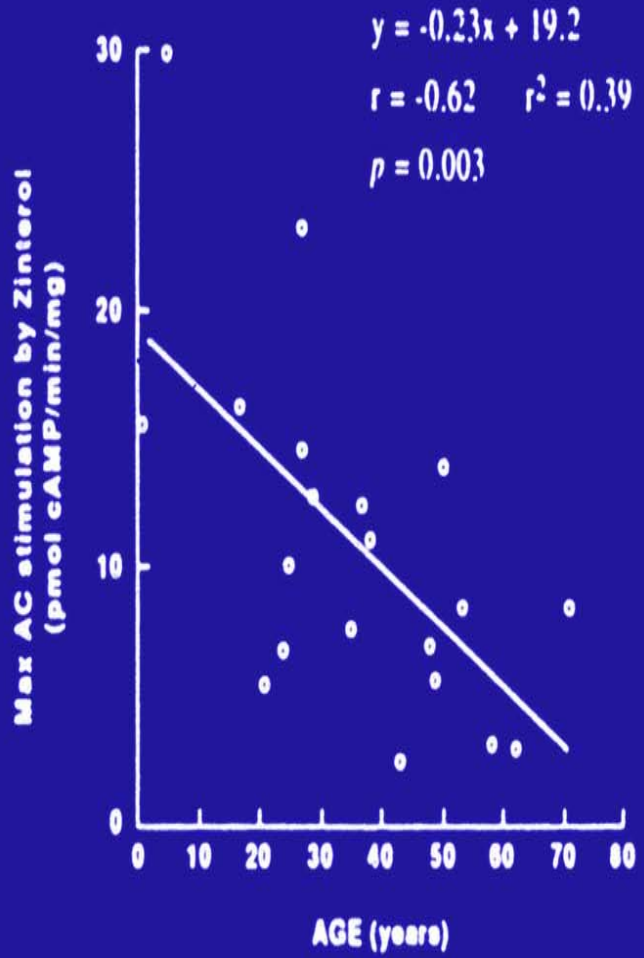
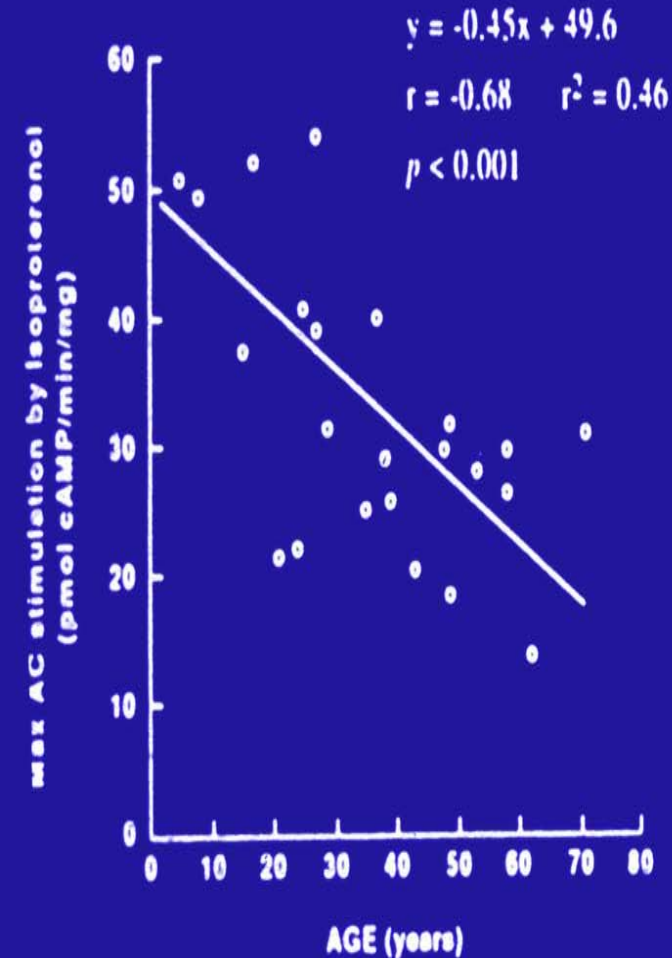


FIG 6. Scatterplots: Net maximum adenylyl cyclase (AC) stimulation by isoproterenol (left) and zinterol (right) for left ventricular myocardial preparations in relation to donor age.

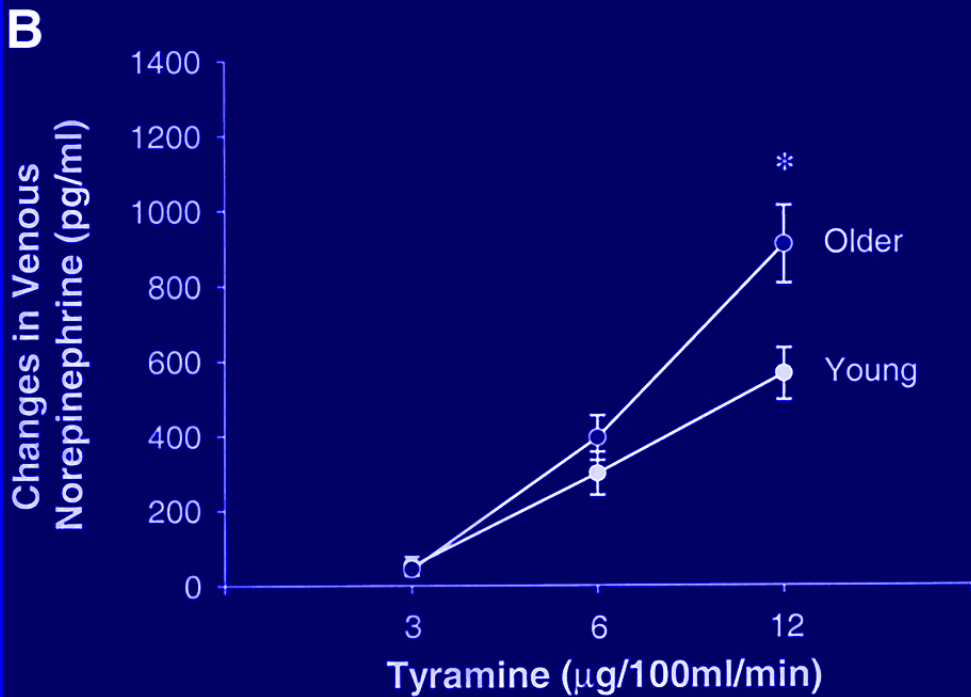
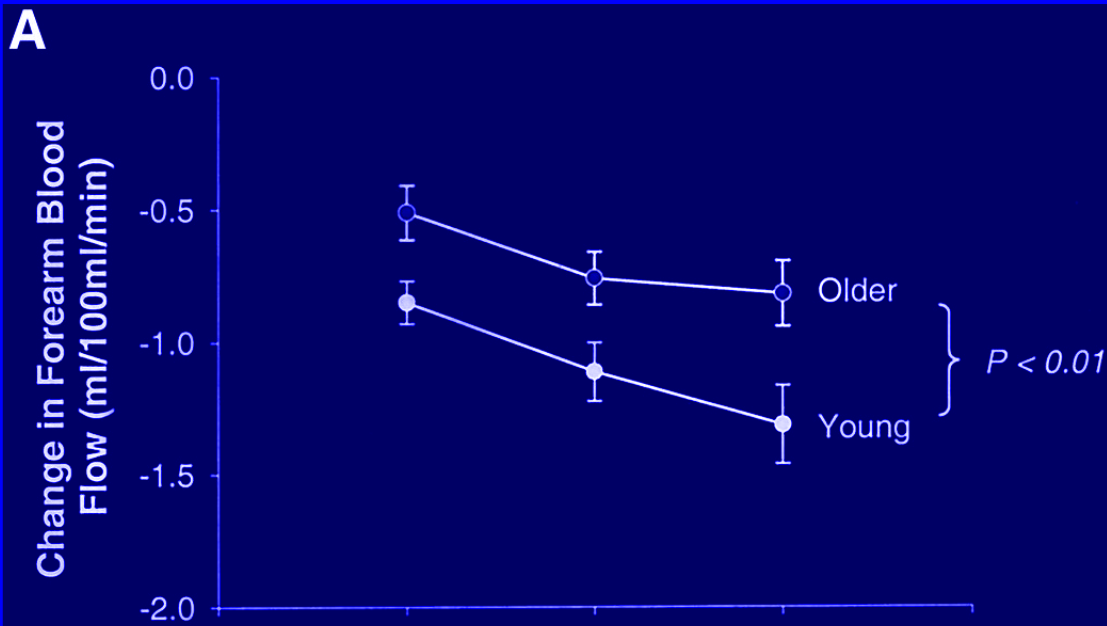


Figure 2. Changes in FBF (A) and deep venous norepinephrine concentrations (B) to local tyramine administration. * $P < 0.001$ vs young men.

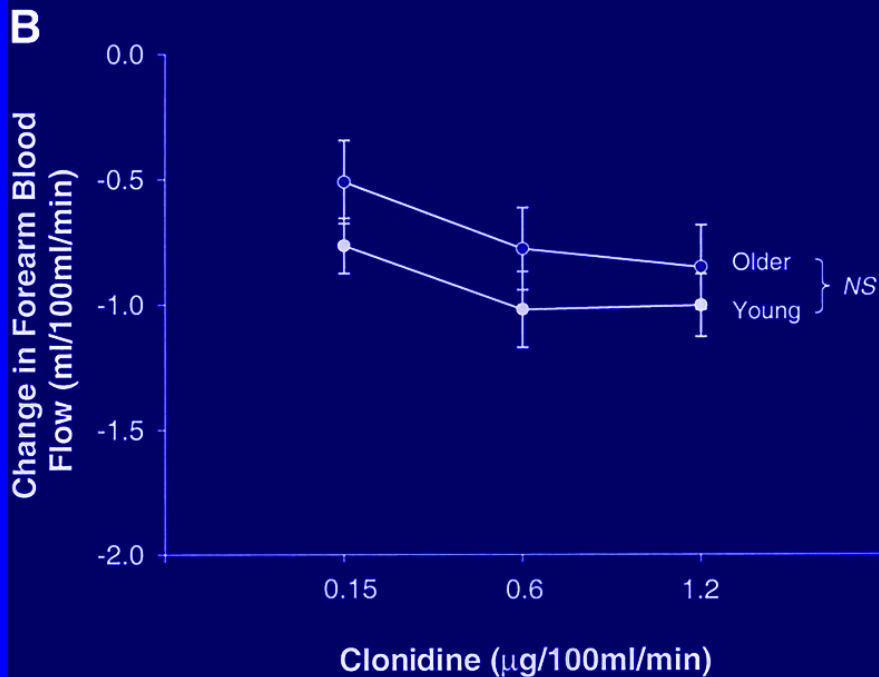
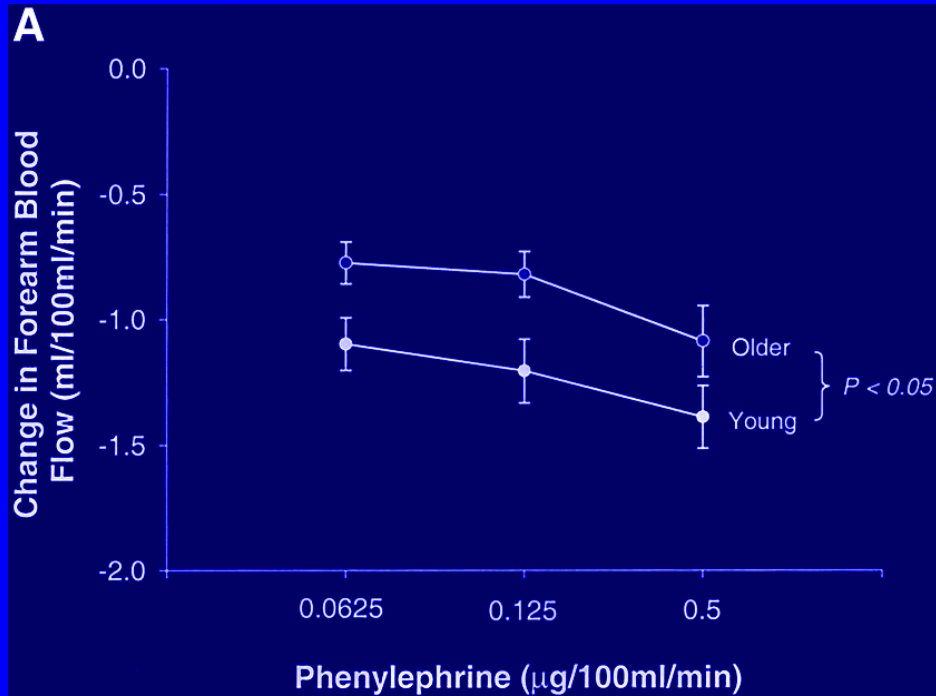


Figure 4. Forearm vasoconstrictor responses to phenylephrine are blunted in older men (A), whereas responses to clonidine are not significantly different (B).

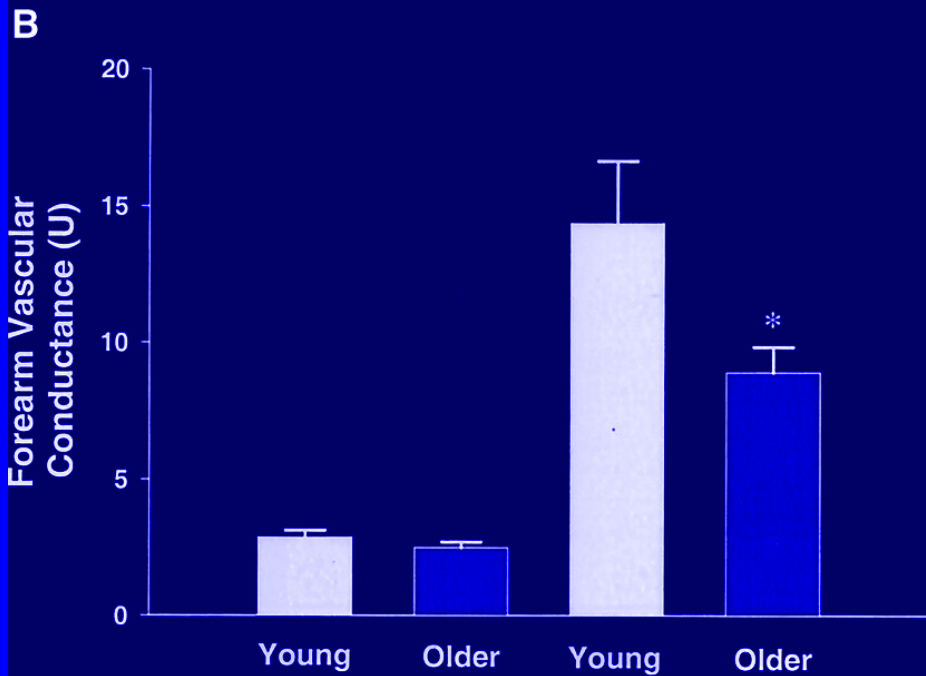
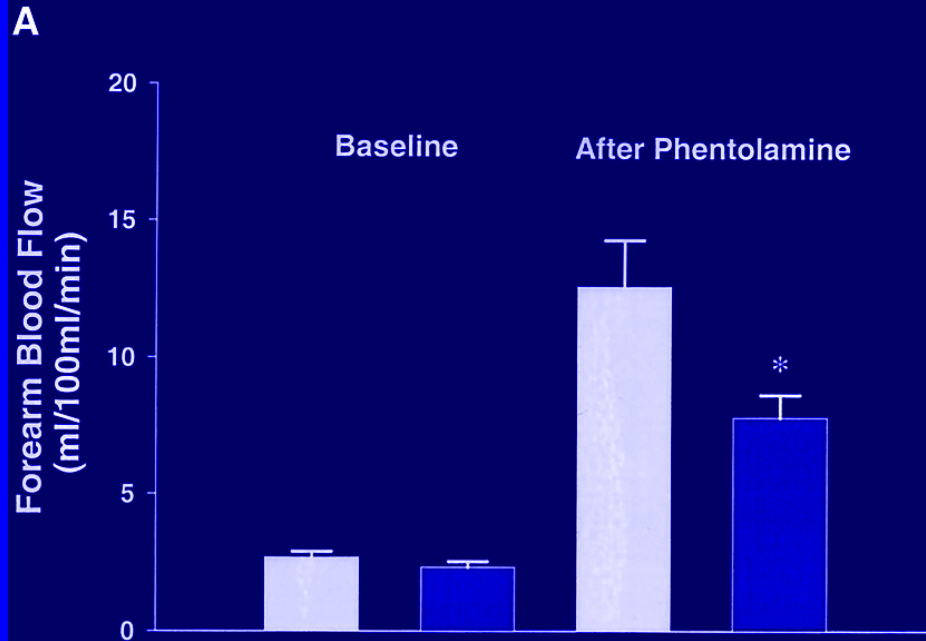
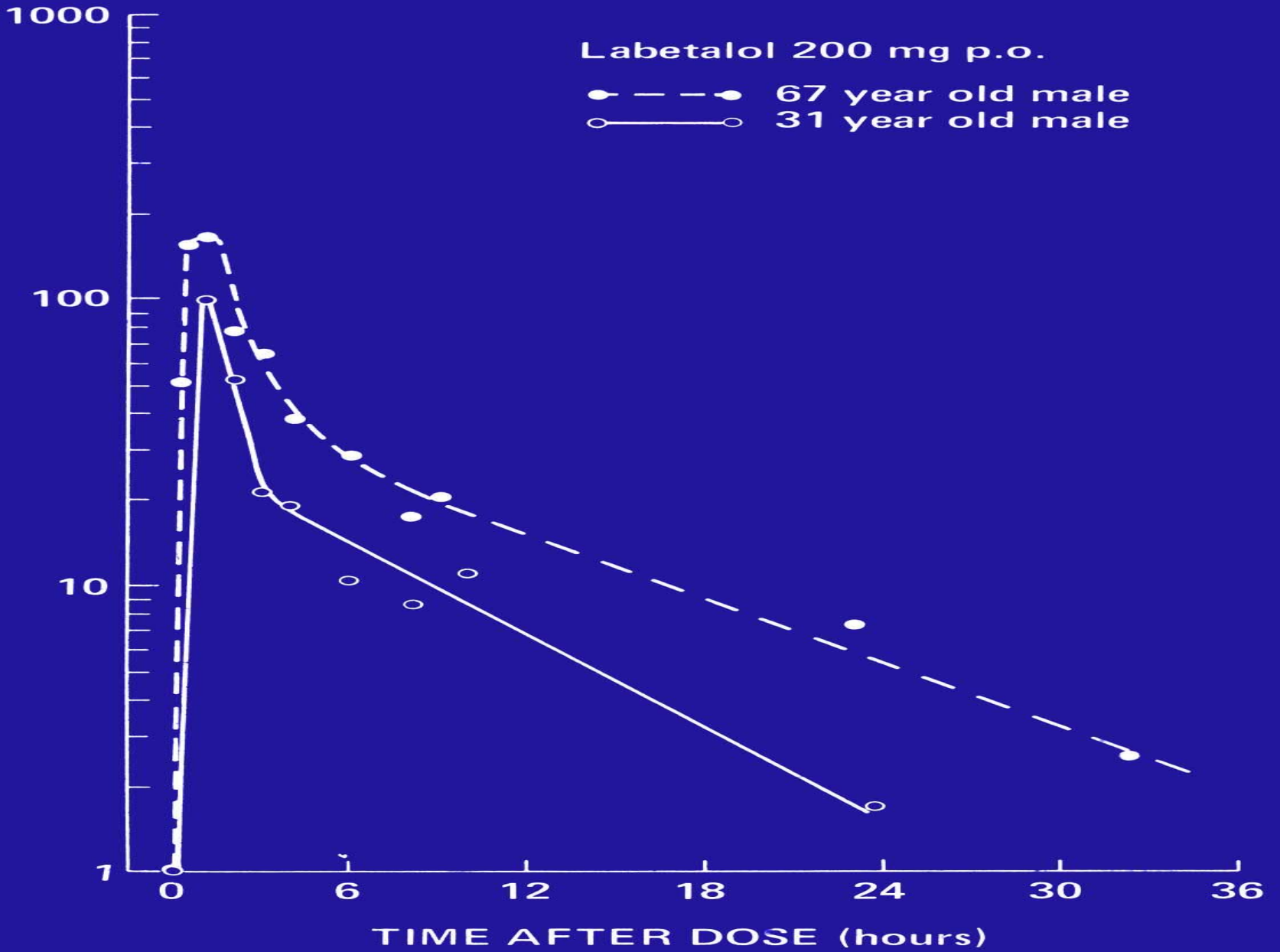


Figure 5. Forearm hemodynamics at rest and after local α -adrenergic blockade with phentolamine. * $P < 0.001$ vs young men.

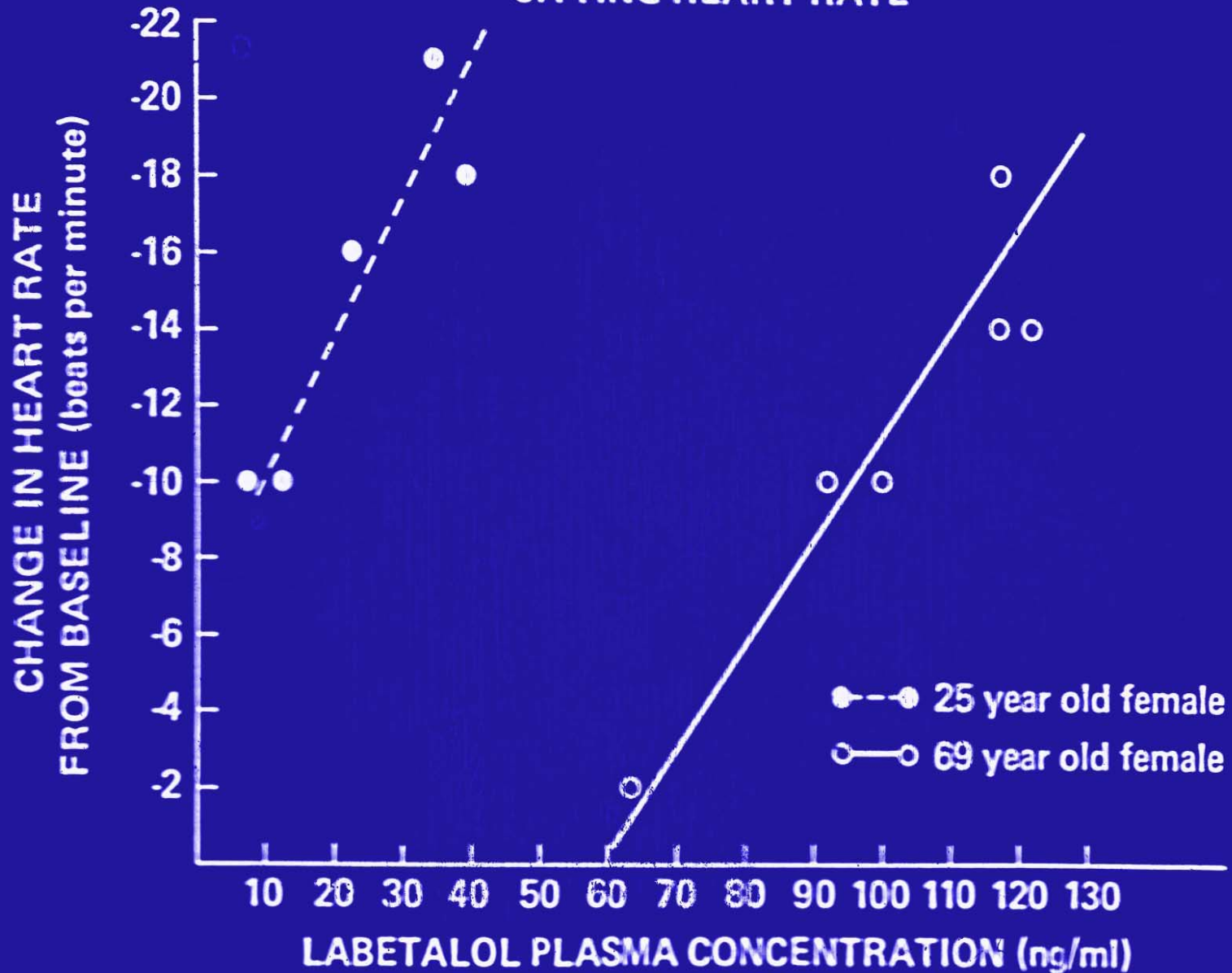
Labetalol 200 mg p.o.

- - - ● 67 year old male
- - - ○ 31 year old male

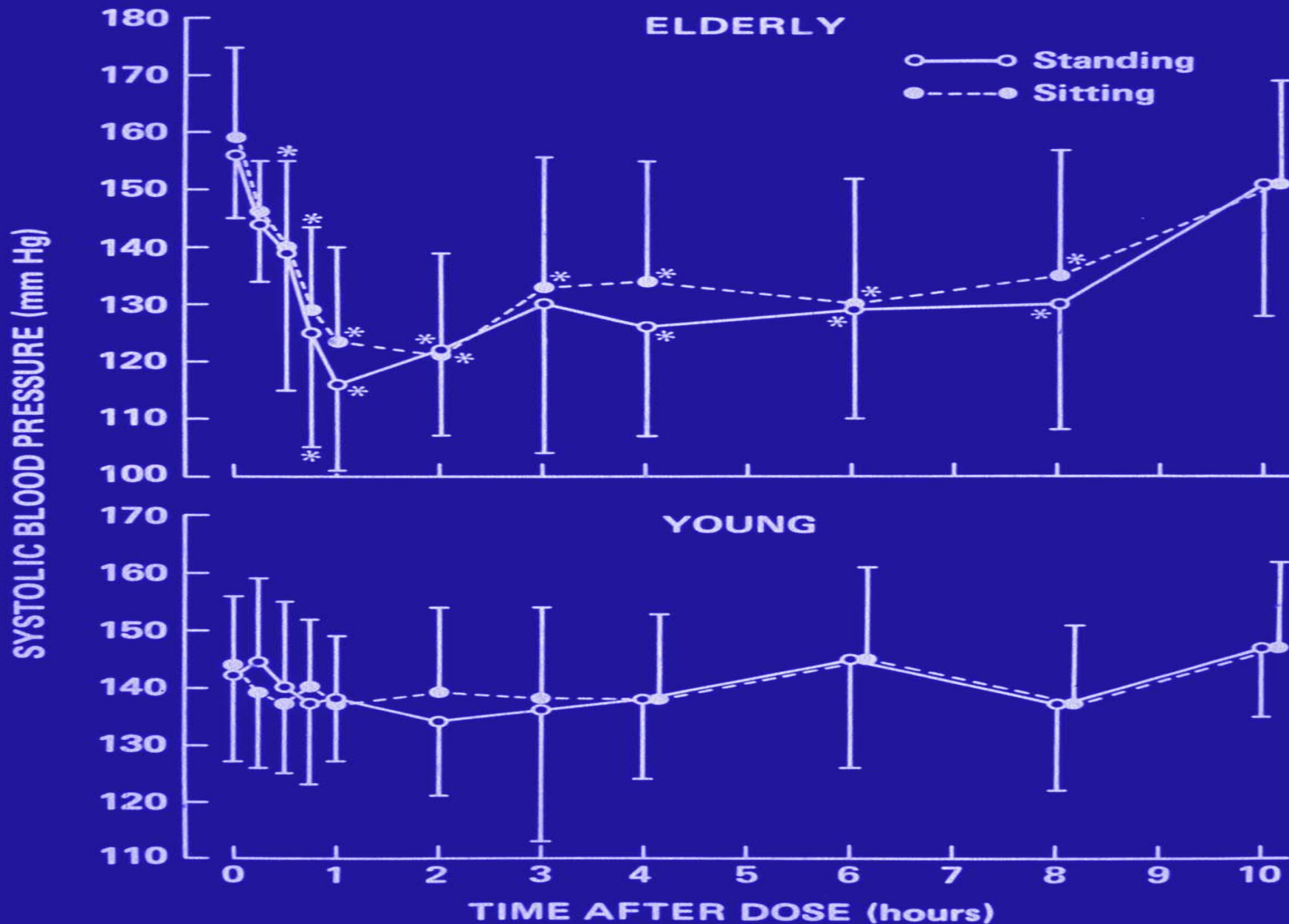
LABELTALOL CONCENTRATION (ng/ml)



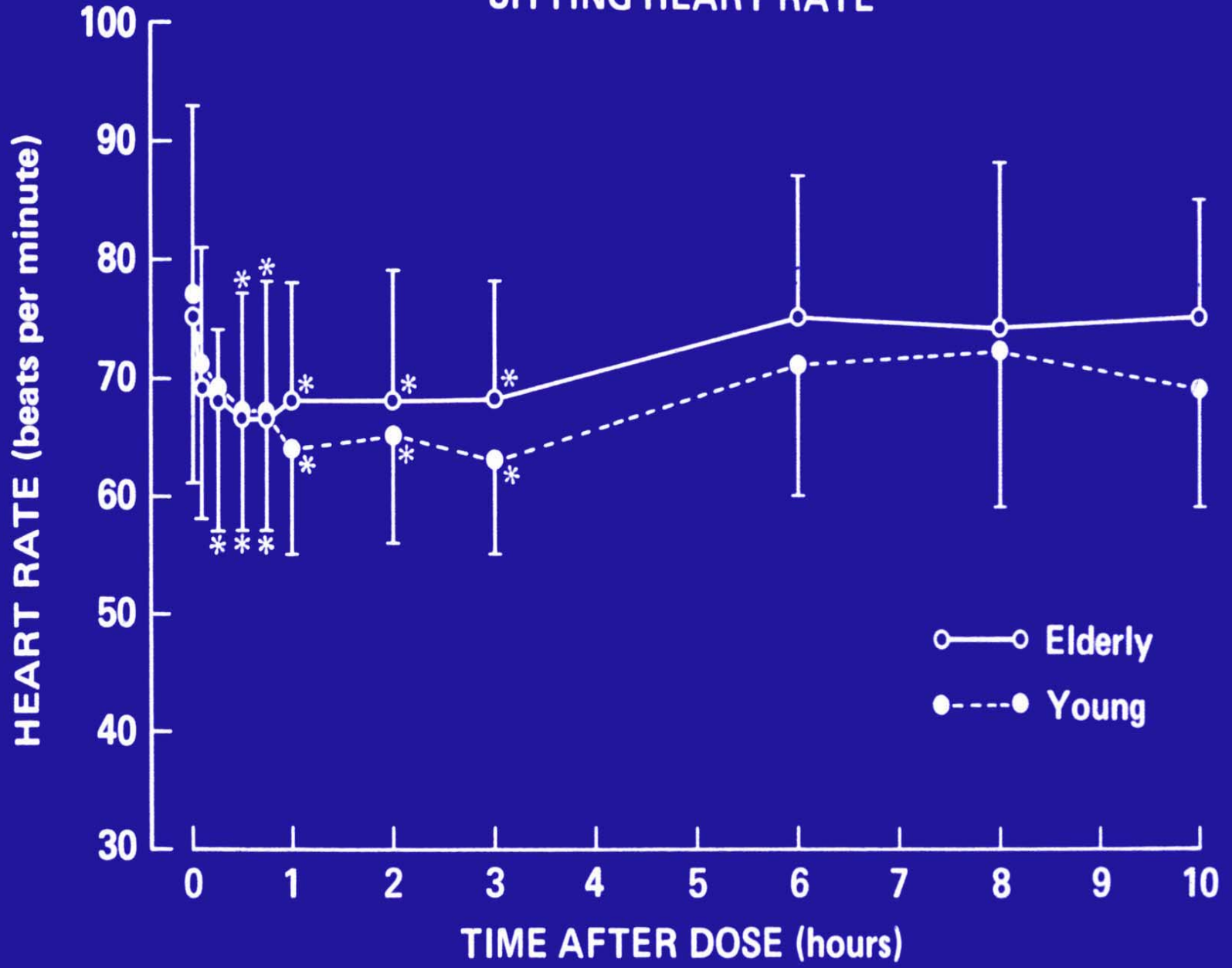
INTRAVENOUS LABETALOL SITTING HEART RATE



SYSTOLIC BLOOD PRESSURE LABETALOL 200 mg p. o.



INTRAVENOUS LABETALOL SITTING HEART RATE



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

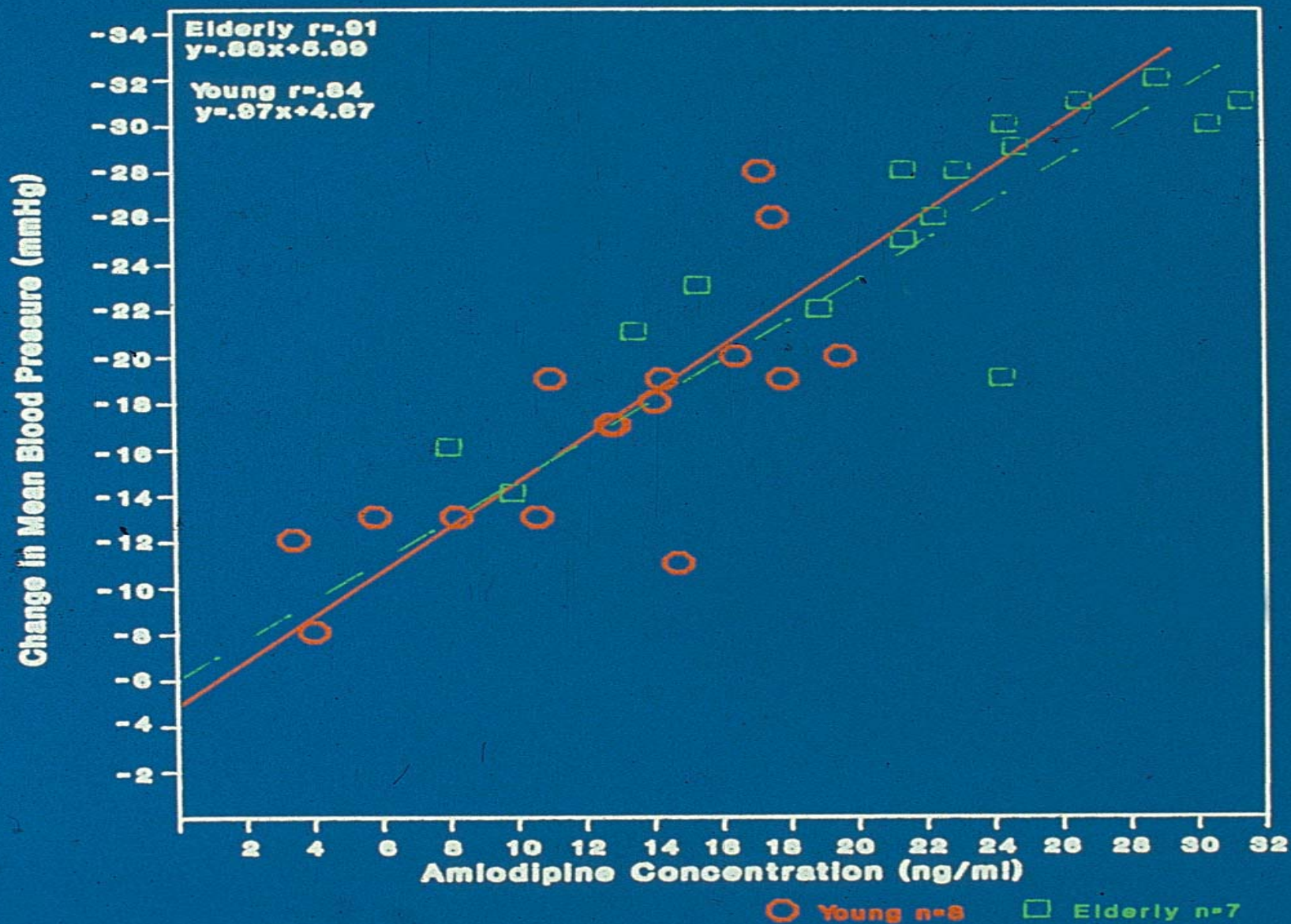
	Normal Aorta (Young Adults)		Stiff Aorta (Older Adults)	
1. Aortic BP (mm Hg)	130	Systolic	140	
	80	Diastolic	70	
2. PWV (m/s)	5.0		10.0	
3. Reflected Wave	Early Diastole		Late Systole	
4. Pulse Wave Shape				
5. Aortic BP (mm Hg)	130	Systolic	160	
	80	Diastolic	70	

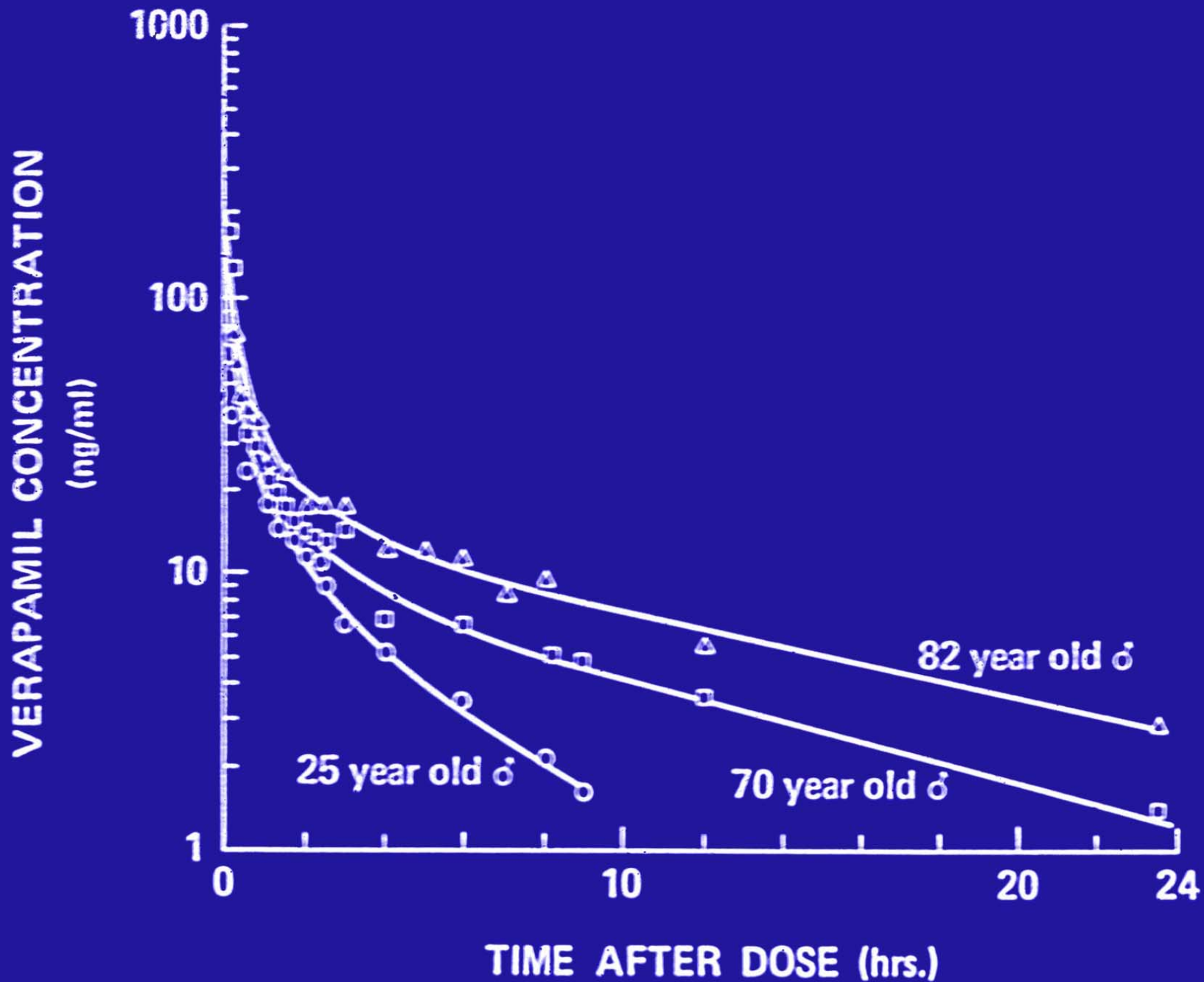
Figure. Development of aortic pressure abnormalities due to age-related aortic stiffening. 1. Increased systolic blood pressure (BP) and decreased diastolic blood pressure due to decreased aortic distensibility. 2. Increased pulse wave velocity (PWV) as a result of decreased aortic distensibility. 3. 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 $ATP \rightarrow ADP + P_i$ (6) or $ATP \rightarrow$ (7).

Amlodipine 14-week Pharmacodynamics
0-144 hours following last dose
Patients receiving 10mg qd



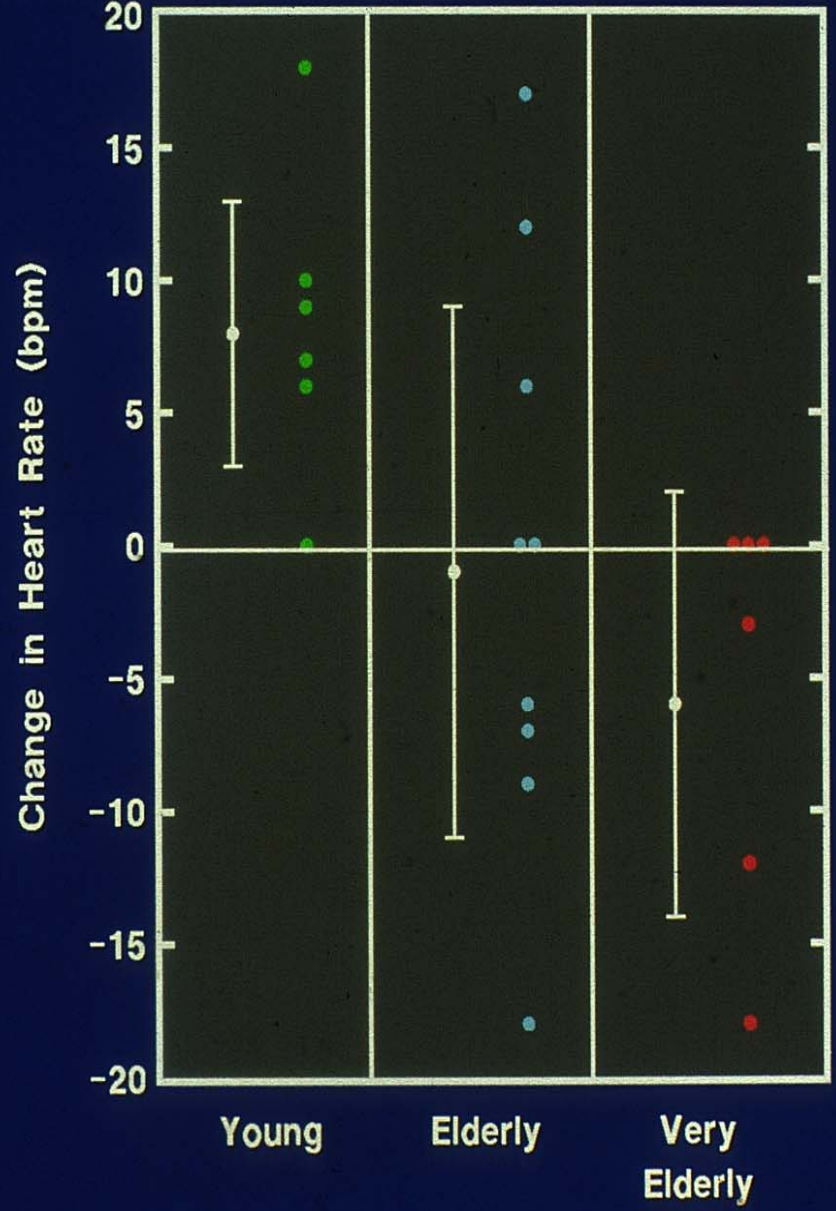
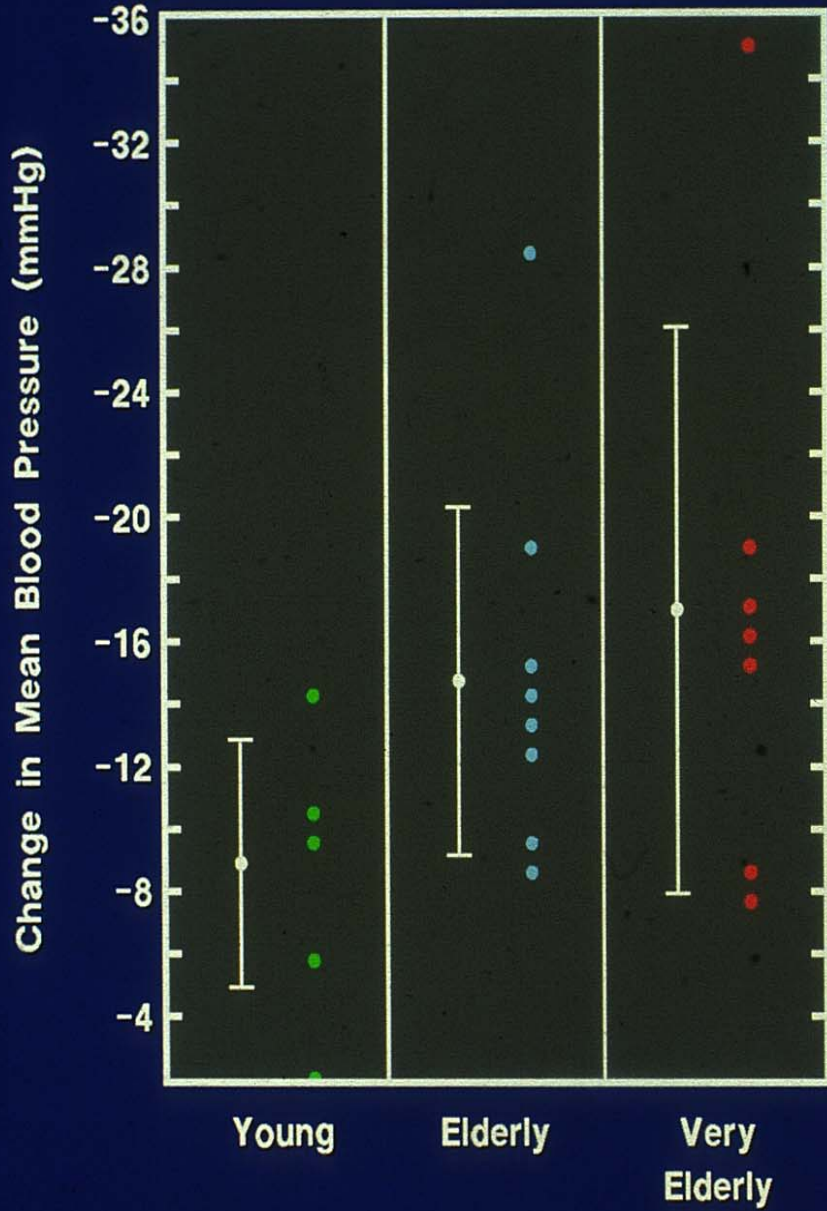


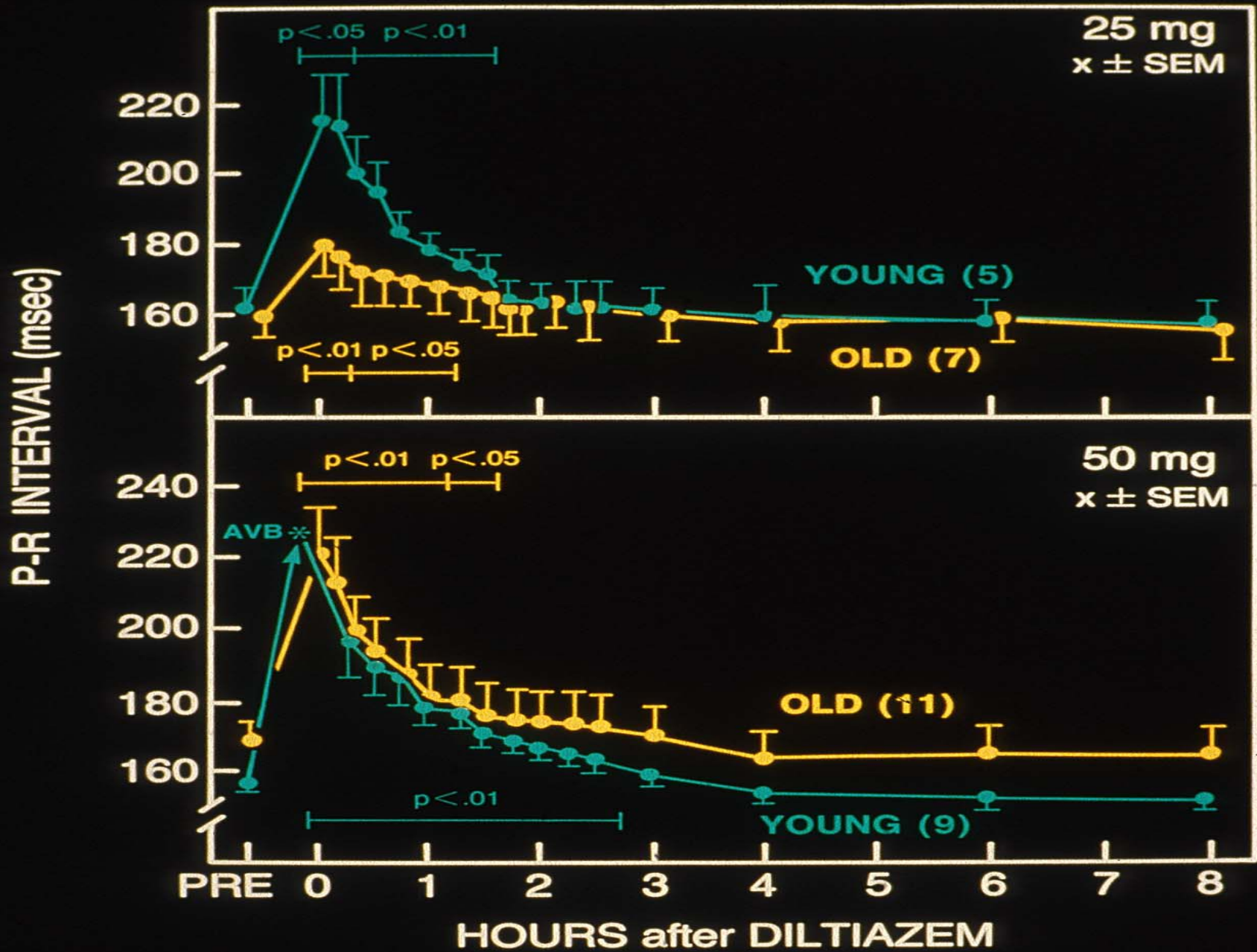
P-R Prolongation (msec)

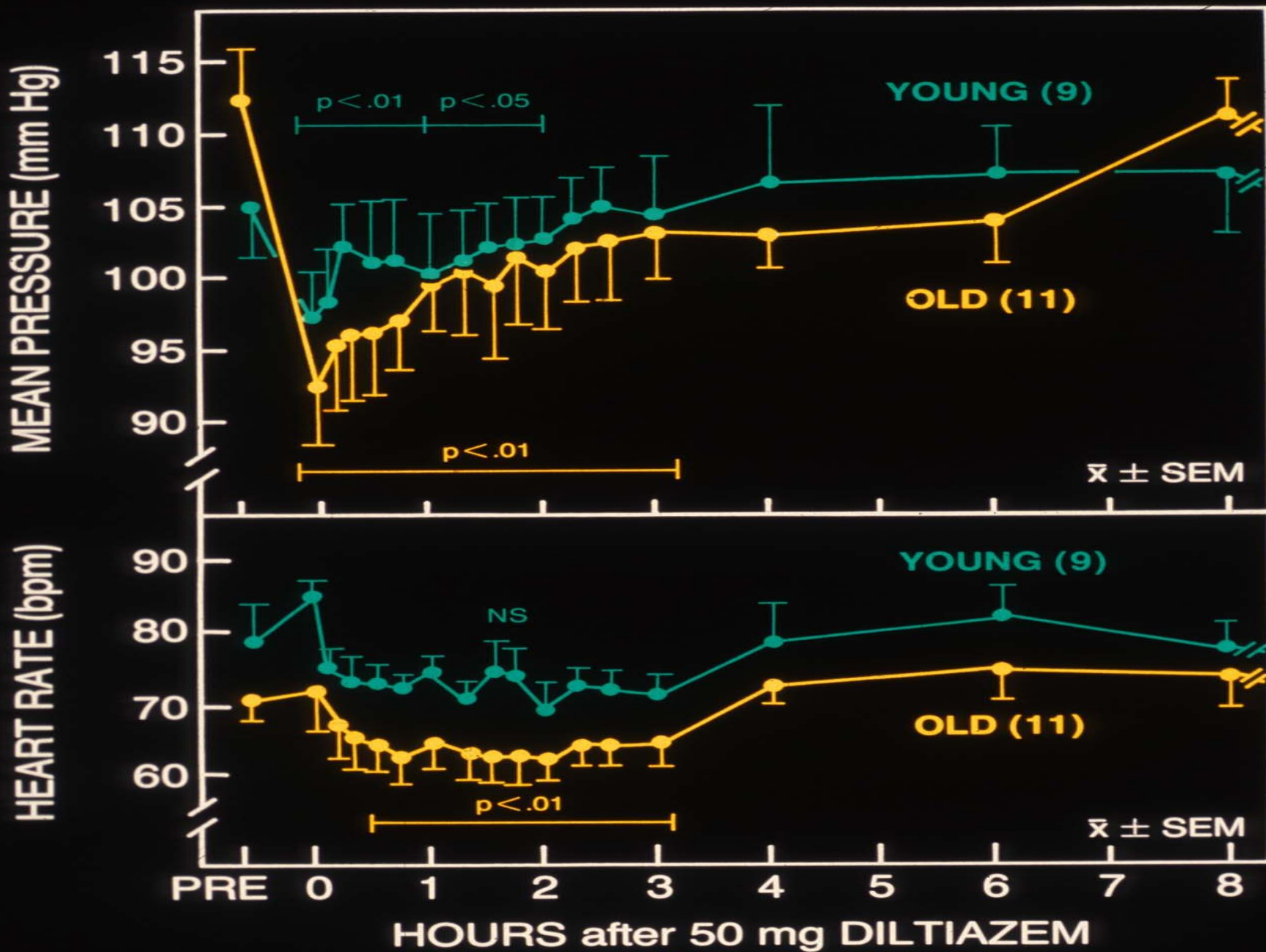


Verapamil Concentration (ng/ml)

INTRAVENOUS VERAPAMIL PHARMACODYNAMICS







HEART RATE RESPONSES

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

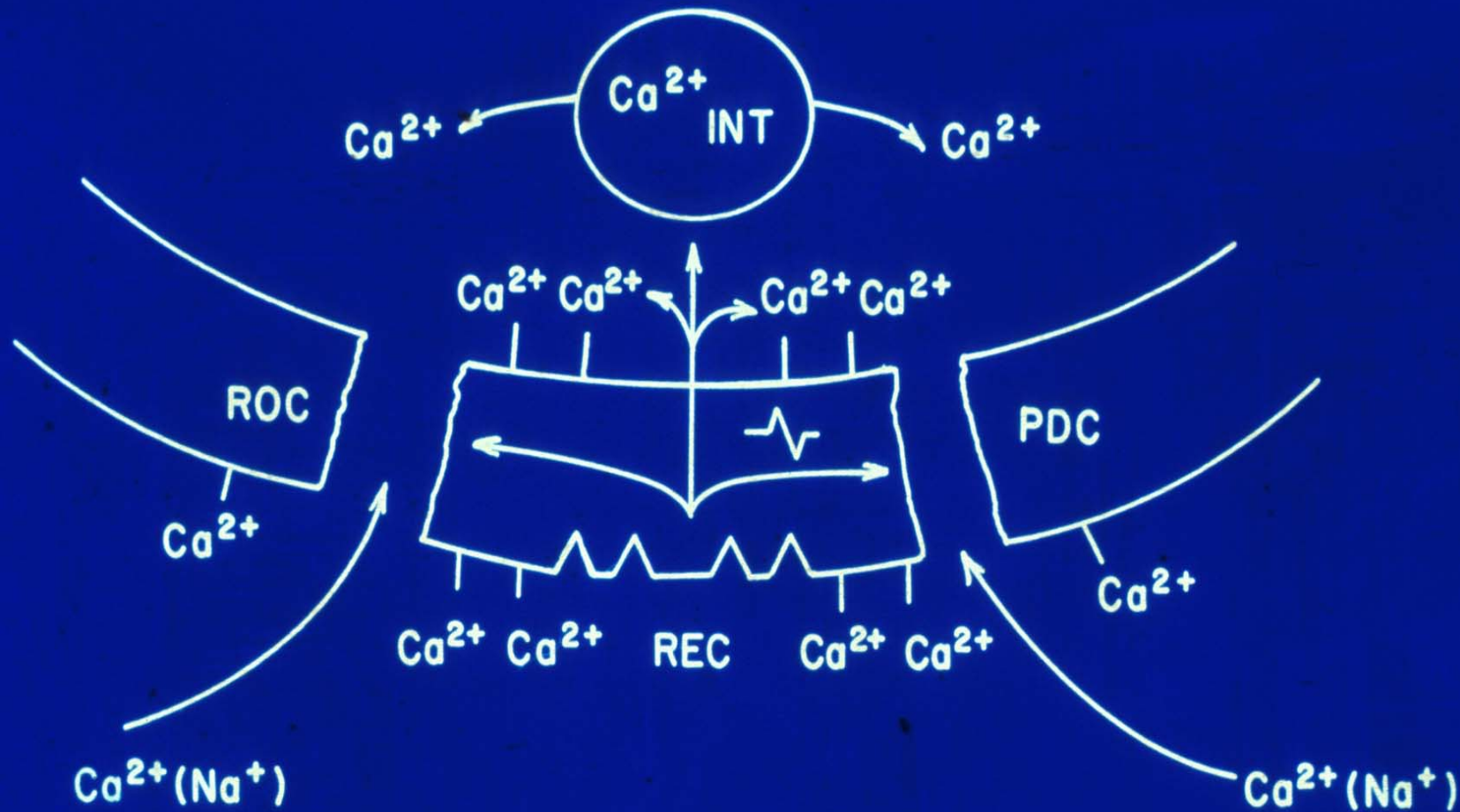


FIGURE 1. Receptor-mediated Ca²⁺ mobilization. Shown are Ca²⁺ influx through potential-dependent and receptor operated channels, mobilization of membrane-bound and intracellularly stored Ca²⁺.

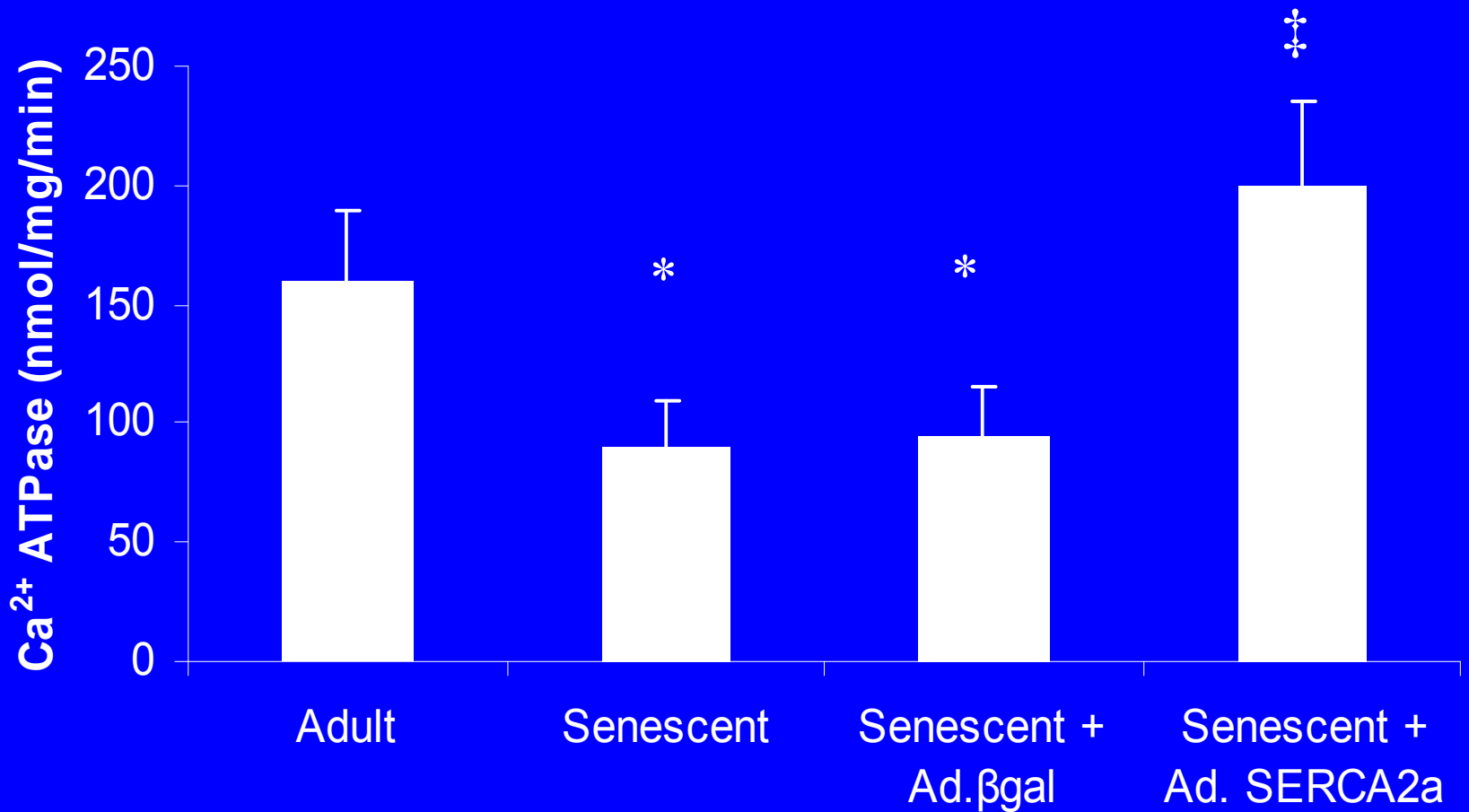


Figure 3. ATPase activity measured at 10 $\mu\text{mol/L}$ Ca^{2+} in membrane preparations from adult uninfected rat hearts (n=4), preparations from senescent uninfected rat hearts (n=4), preparations of senescent hearts infected with Ad. β -Gal at day 2 (n=4), and preparations of senescent hearts infected 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.

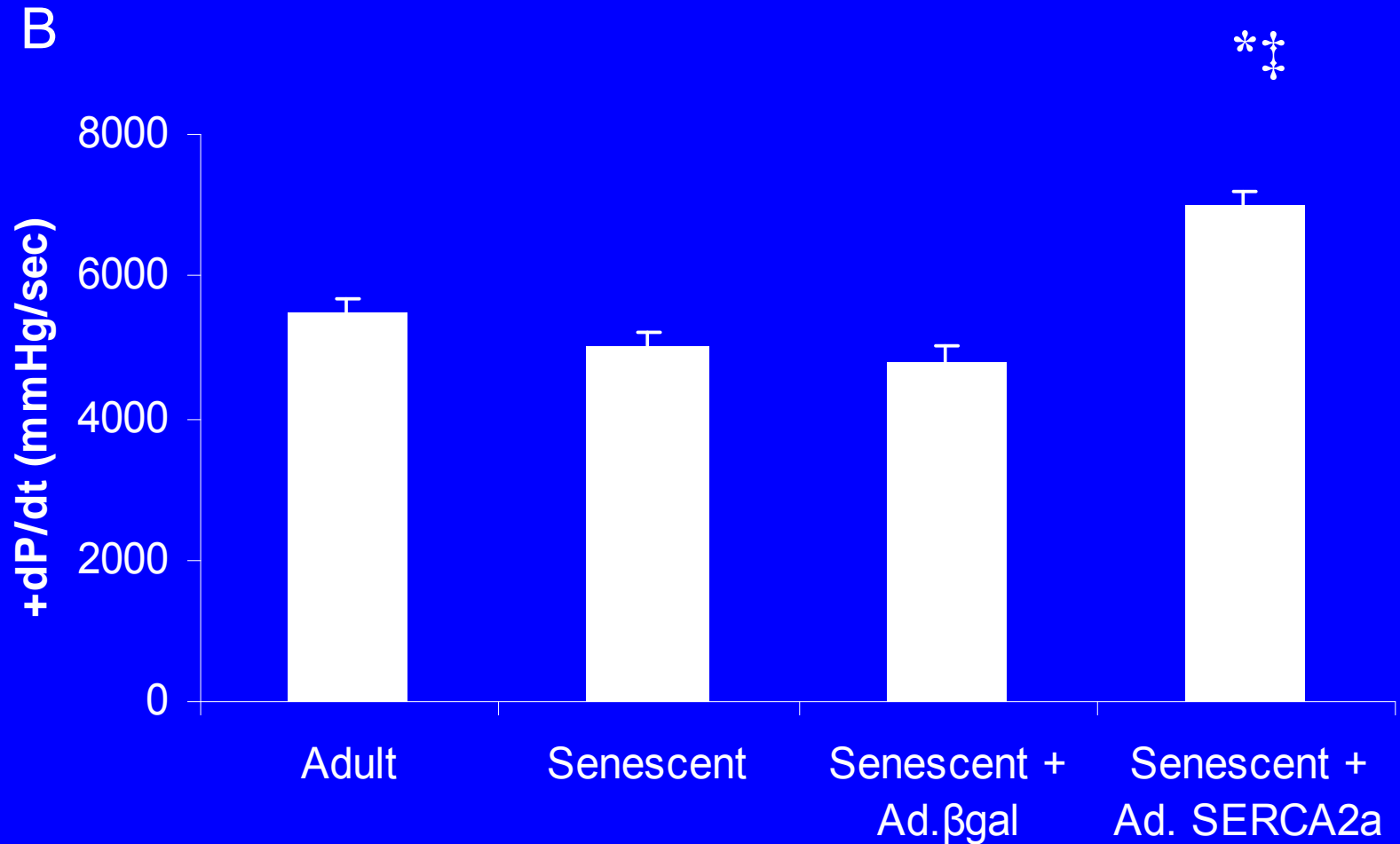
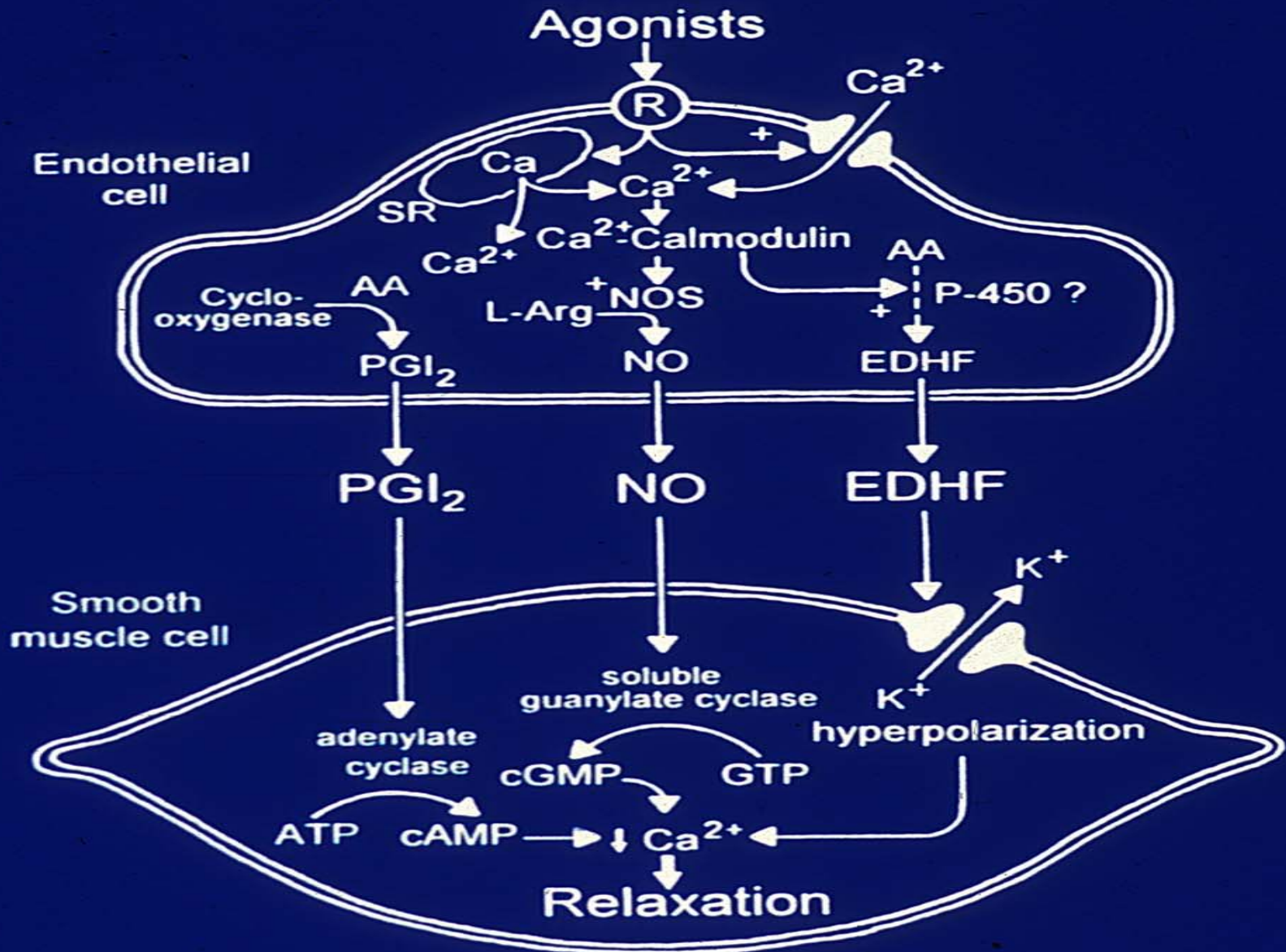
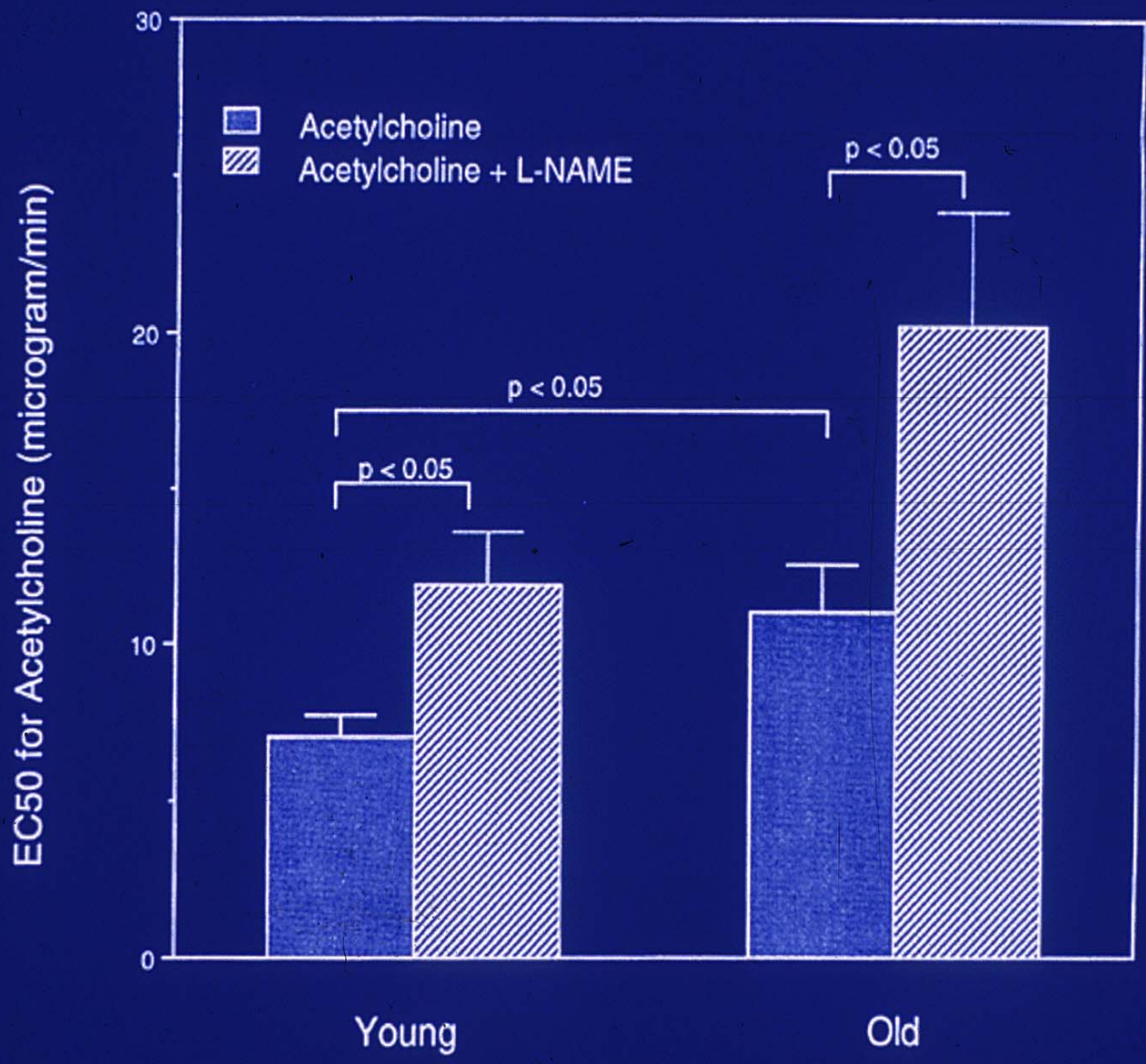


Figure 5. Measurements of systolic parameters **+dP/dt (B)** in adult uninfected rat hearts (n=6), senescent uninfected rat hearts (n=8), senescent hearts infected with Ad.β-Gal at day 2 (n=6), and senescent hearts infected with Ad.SERCA2a at day 2 (n=6). *P<0.05 compared with adult. ‡P<0.05 compared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





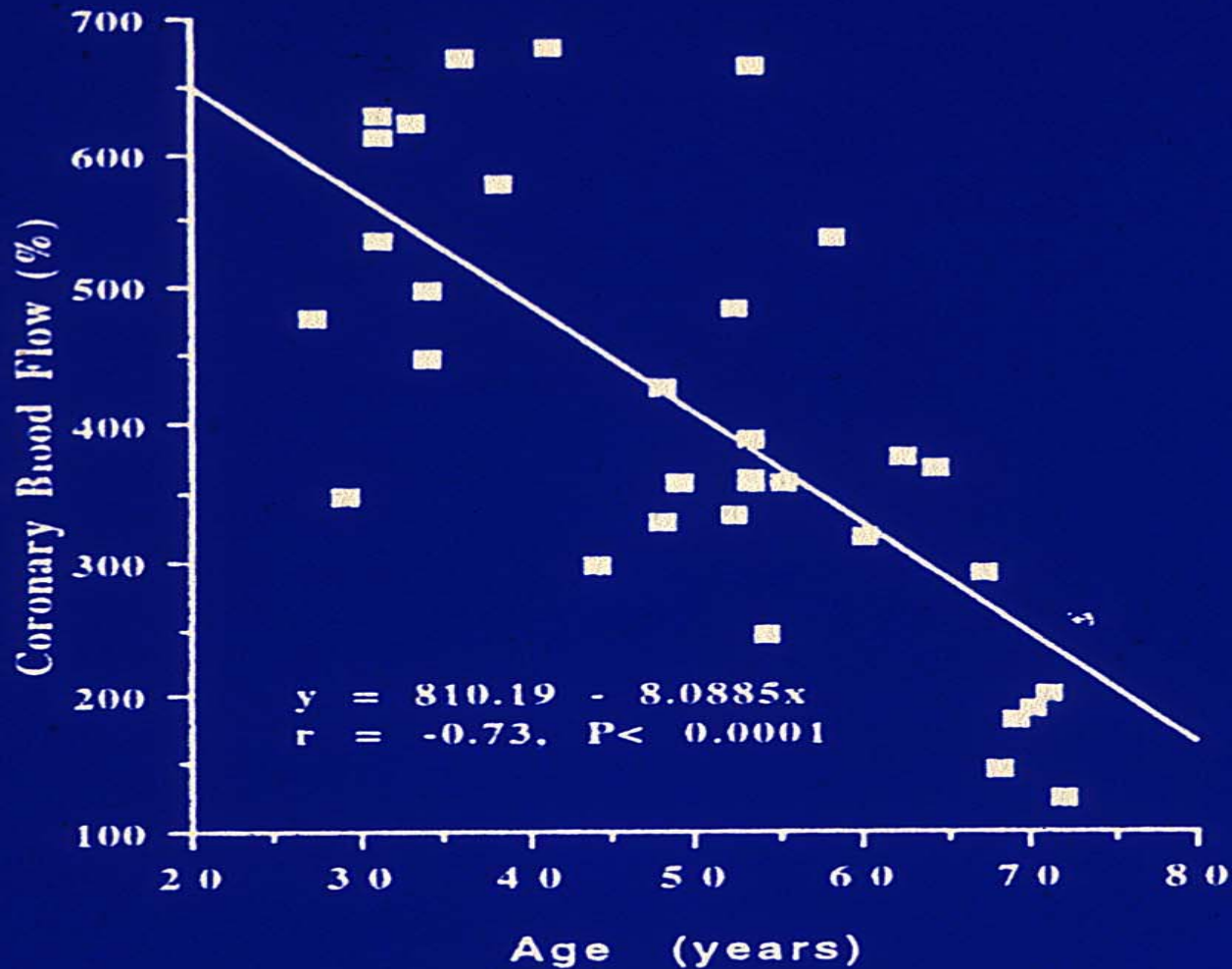
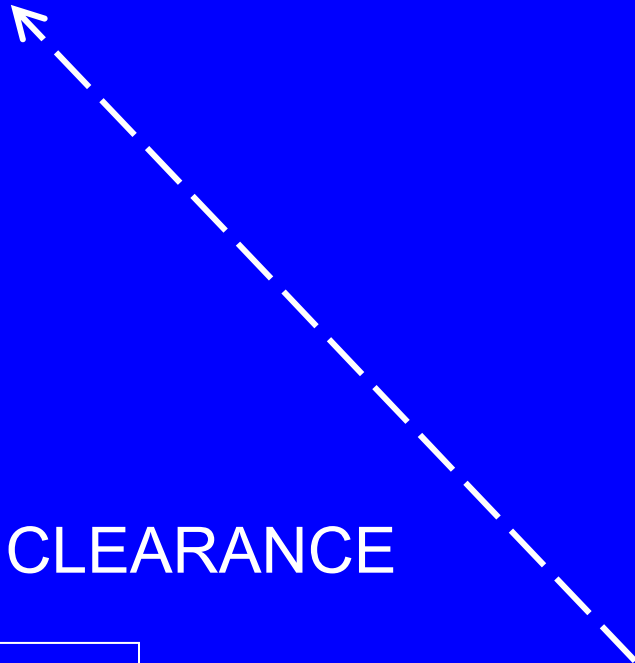
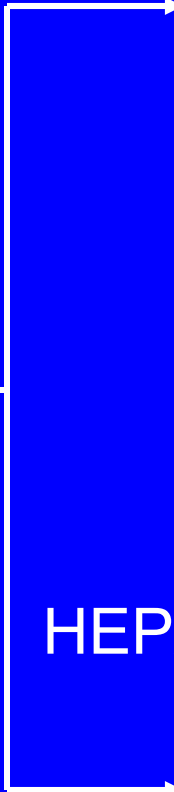


Figure 2. Scatterplot of correlation of age and peak (percent of control values) coronary blood flow response to acetylcholine.

RENAL CLEARANCE



PARENT DRUG



HEPATIC CLEARANCE



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

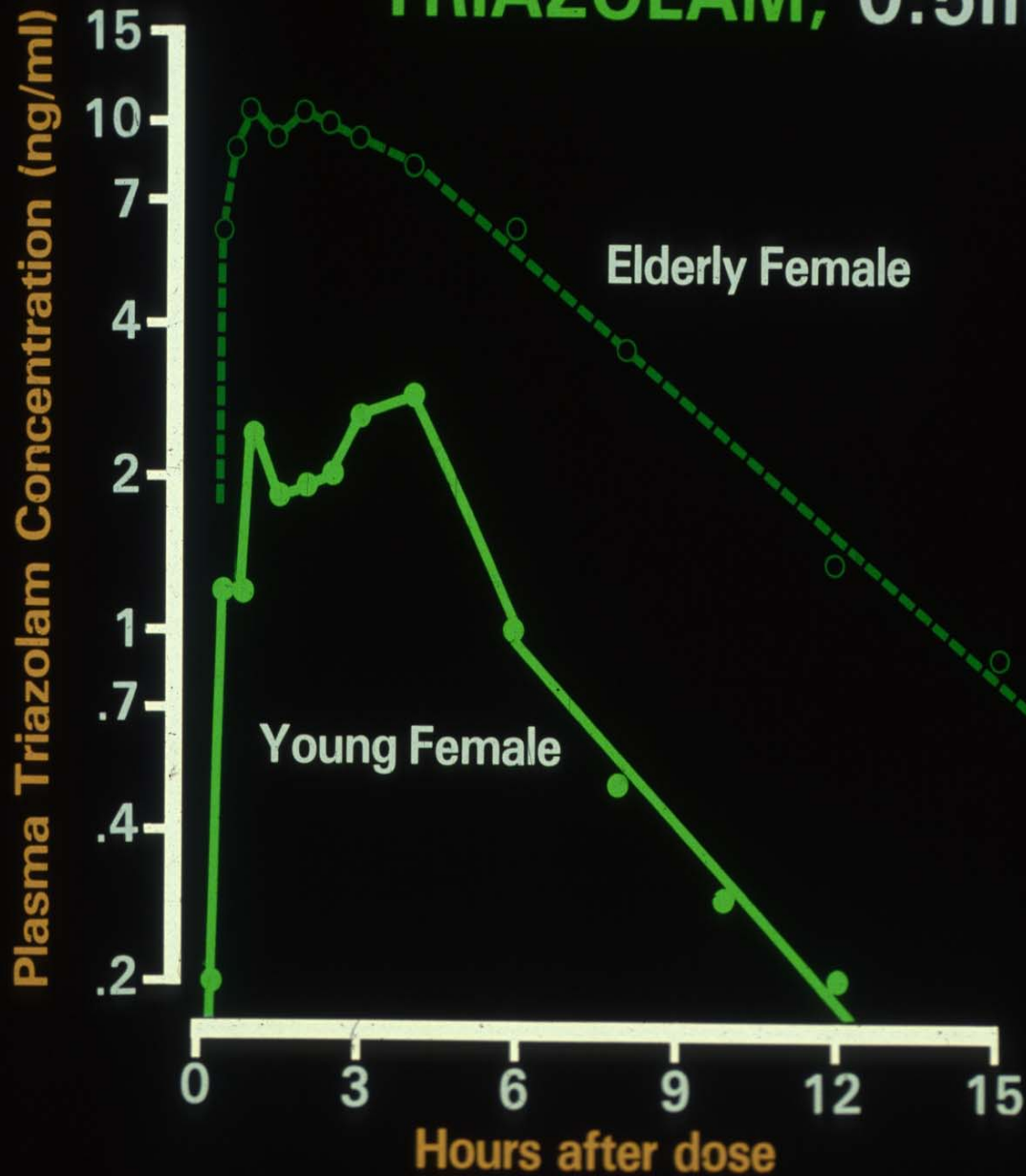
 - Verapamil
 - Nifedipine
 - Diltiazem
 - Felodipine
 - Nimodipine

 - Diazepam
 - Midazolam
 - Triazolam

 - Cyclosporine
 - Tacrolimus
 - Lovastatin
 - Progesterone
 - Testosterone
 - Cisapride
 - Lansoprazole

Modified from Flockart. *J Psychopharm.*

TRIAZOLAM, 0.5mg



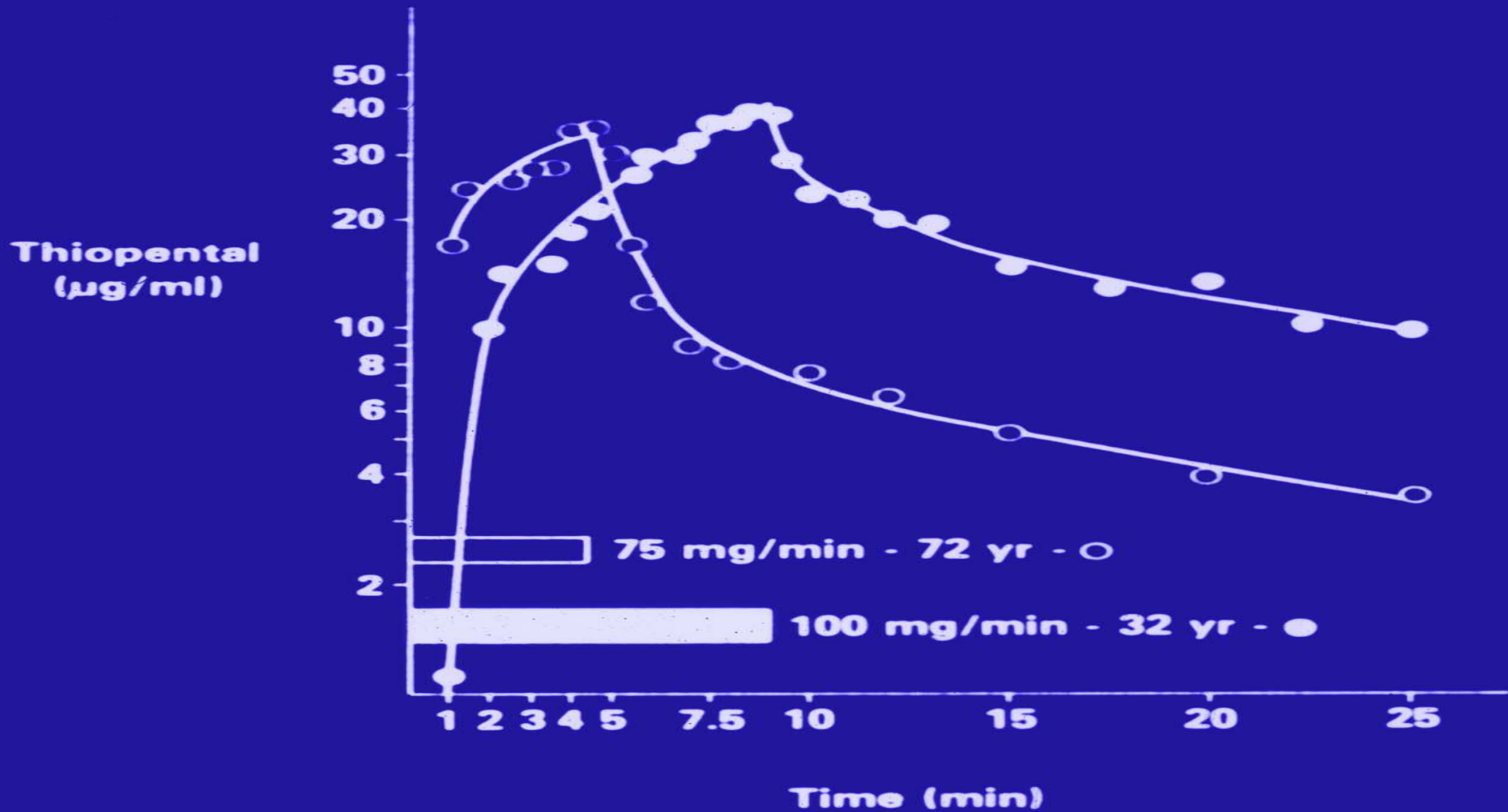


FIG. 5. Serum thiopental concentration (log scale) versus time for the young (filled circles and bars) and the elderly (unfilled circles and bars) patients shown in figure 3. All of the measured thiopental concentrations for the patients are indicated in this figure, whereas all data could not be displayed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

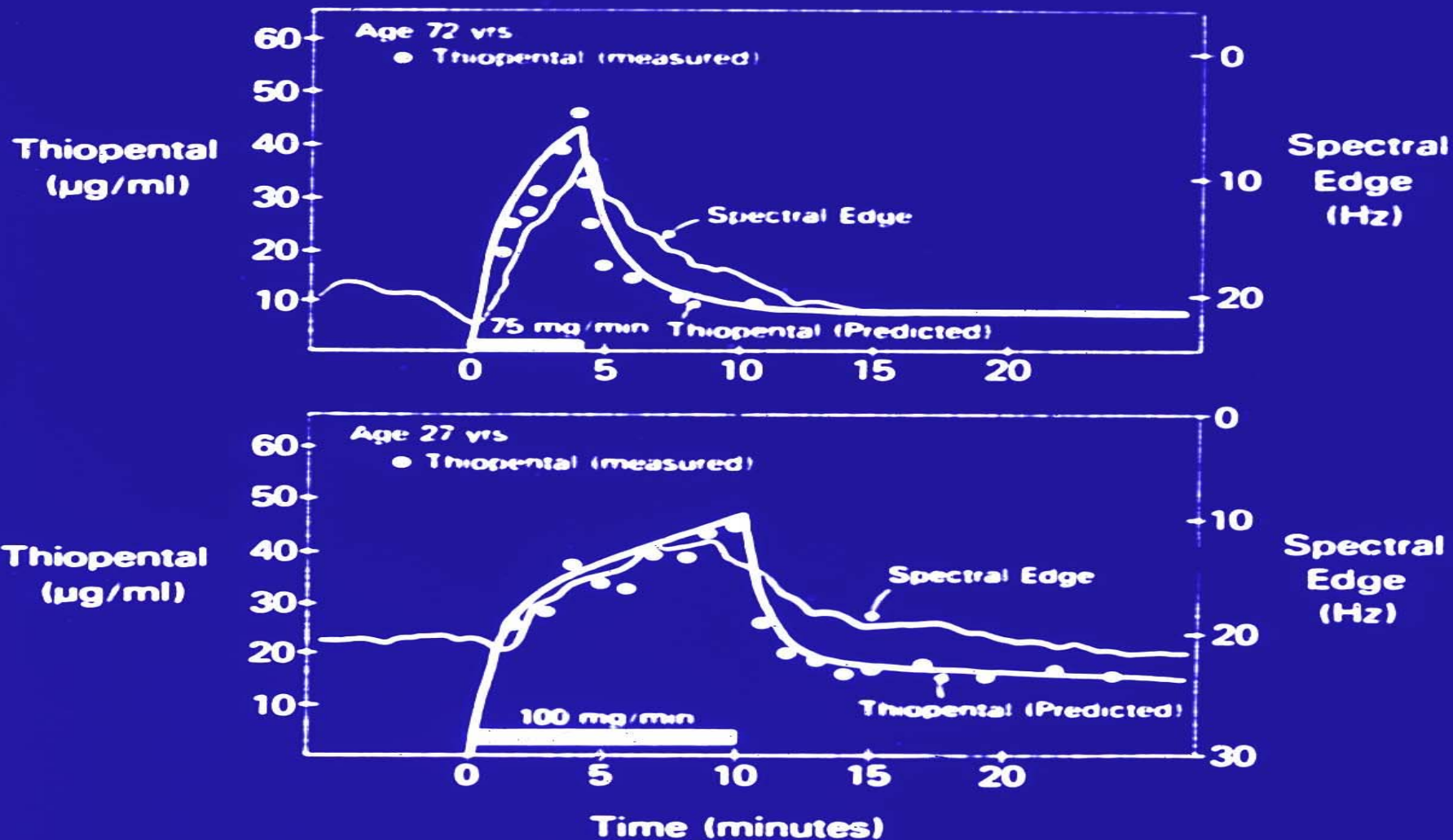


FIG. 3. The concentration of thiopental *versus* 1) time and 2) spectral edge in an elderly patient (top figure) and in a younger patient (bottom figure). Solid horizontal bars represent the length of thiopental infusion. Dots represent the measured thiopental concentration (linear scale), and the solid line next to them, the fitted data. Homer and Stanski, *Anesthesiology*, 1985;62:714-724.

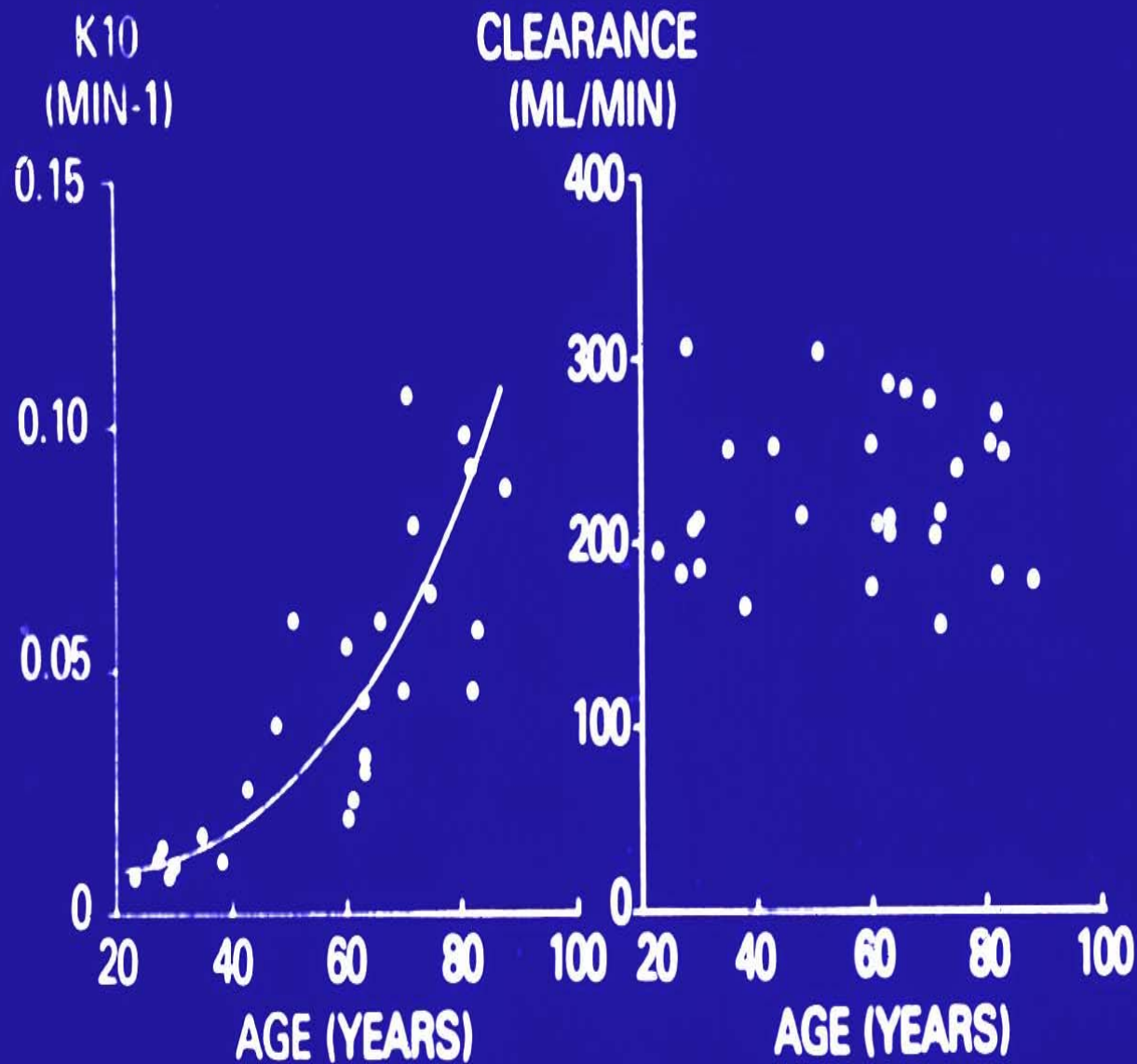


FIG. 8. K_{10} and clearance versus age. Dots represent the rate constants or clearance derived from the pharmacokinetic analysis derived for each patient. K_{10} , the first-order rate constant of drug elimination (metabolism) from the body, has an exponential relationship with age. This relationship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

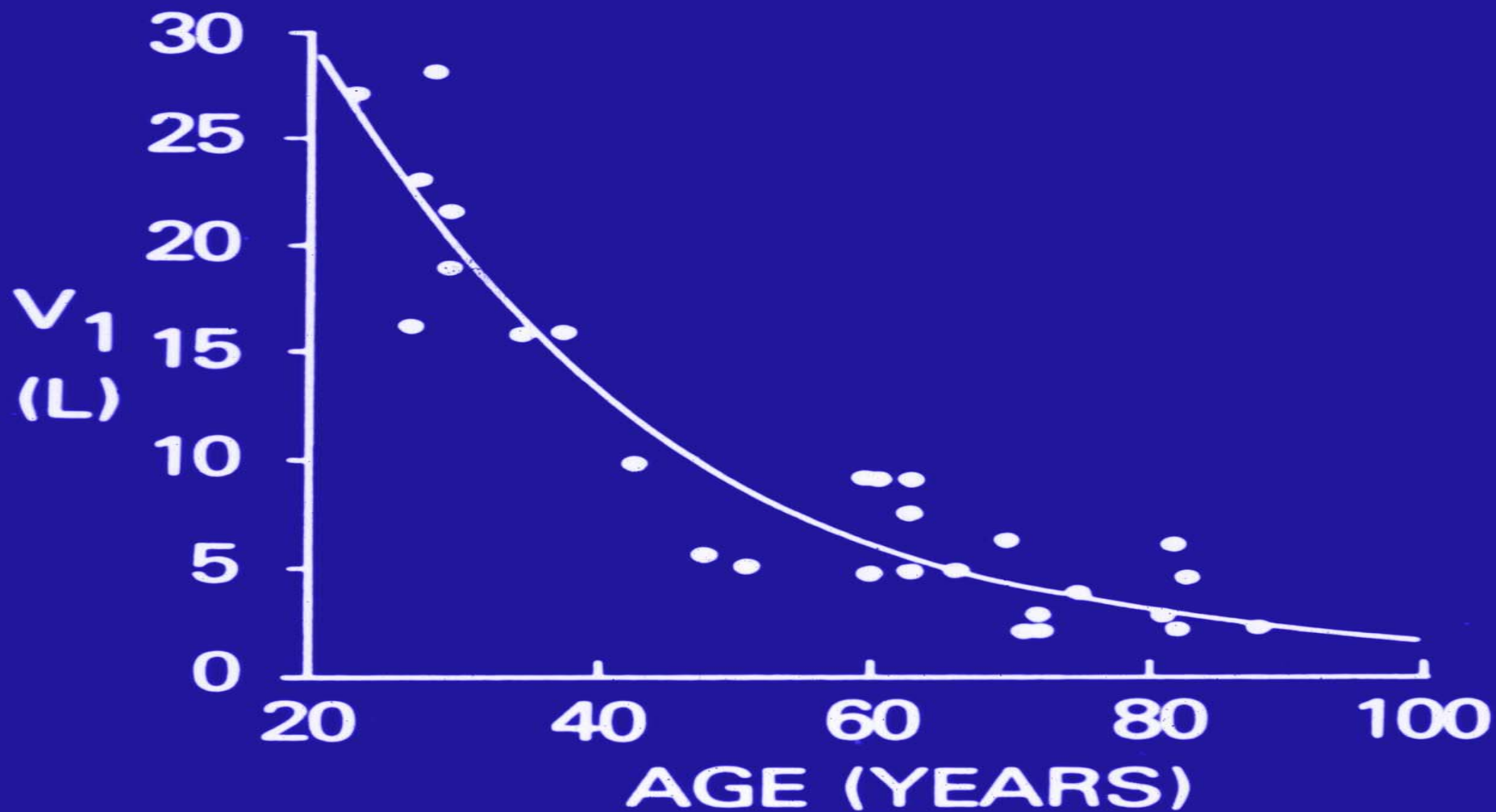
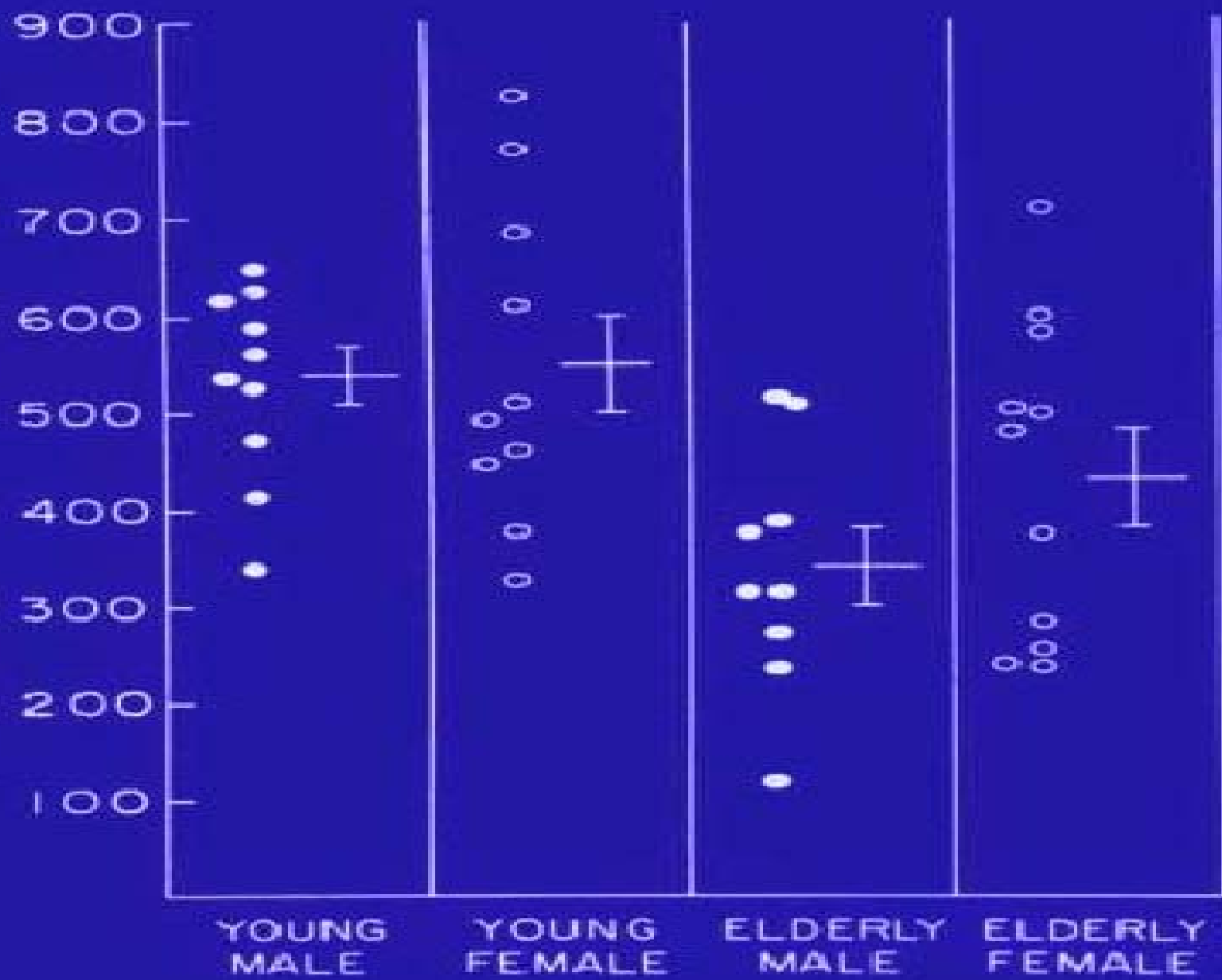


FIG. 6. Volume of the central compartment (V_1) *versus* age. The dots represent the V_1 , derived from the pharmacokinetic analysis for each patient. The solid curve was derived using nonlinear regression of V_1 *versus* age to an exponential equation (see table 2).

MIDAZOLAM CLEARANCE (ml/min)



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 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)