

## BACKGROUND

The widespread perception that tachycardia is a marker of transient and harmless anxiety. This stress-related increase of BP and heart rate reflects the beneficial and appropriate defense reaction.

This translated into practicing physician's "Go home , relax, don't worry" approach to the management of tachycardic prehypertension.

**WRONG, DEAD WRONG**

**The defense reaction is an appropriate response to imminent danger .**

**BUT!!!**

**Survival and longevity are two unrelated aspects of living.**

**(What might have once saved your life,  
could kill you later)**

**In this presentation I will demonstrate that in young people:**

**--Tachycardia is not transient**

**-- Tachycardia is a predictor of future hypertension**

**-- That in a large proportion of young and middle aged people tachycardia is a part of a distinct heritable syndrome which also includes high cardiac output, prehypertensive BP values and sympathetic overactivity.**

**-- Tachycardia is a predictor of negative cardiovascular outcomes**

**-- We understand mechanism of the deleterious effects of tachycardia**

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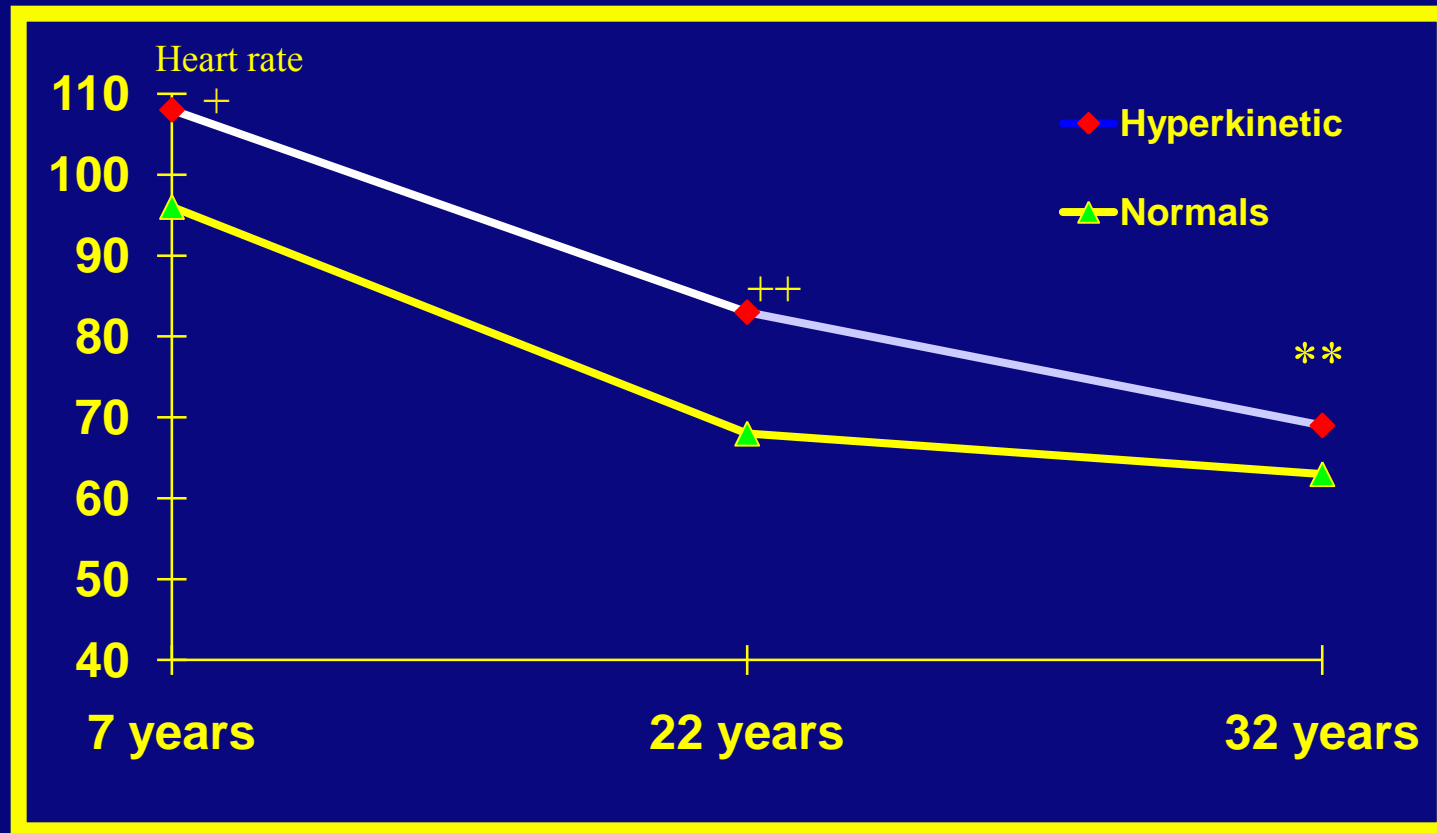
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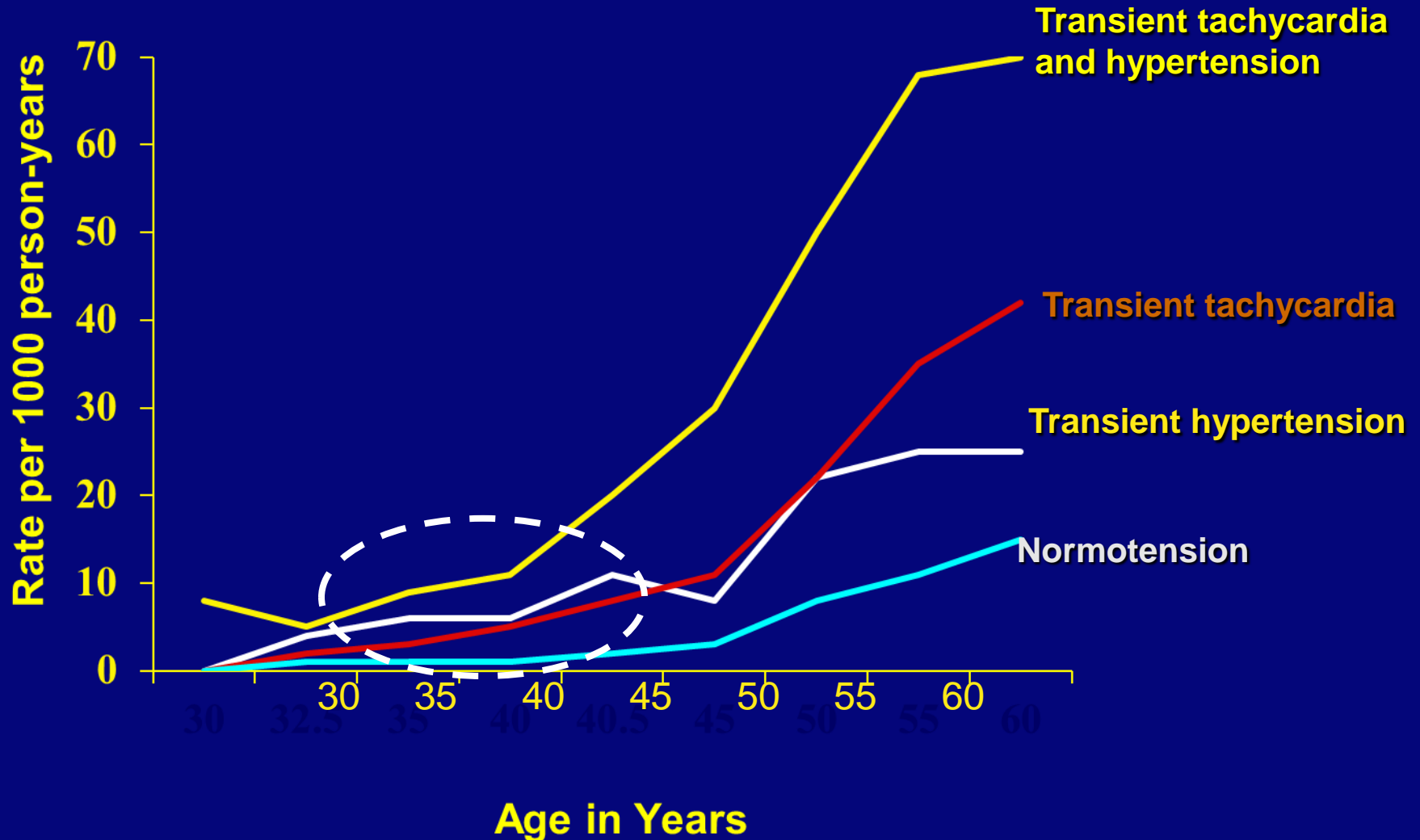
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# Heart rate trends in hyperkinetic hypertensives



From the Tecumseh Study

# Elevated HR: Long-Term Link to Hypertension



From Levy et al, JAMA 1945

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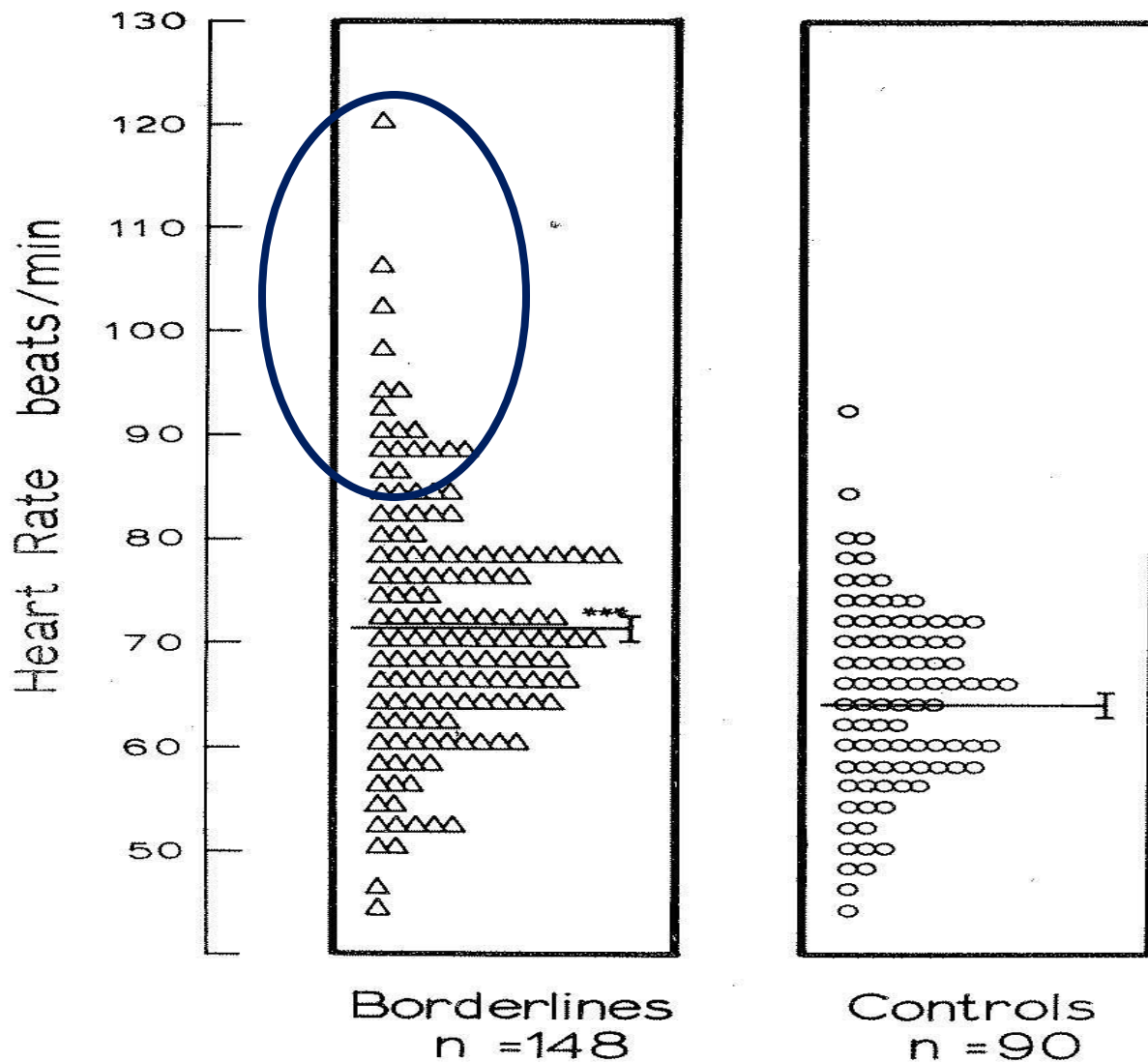
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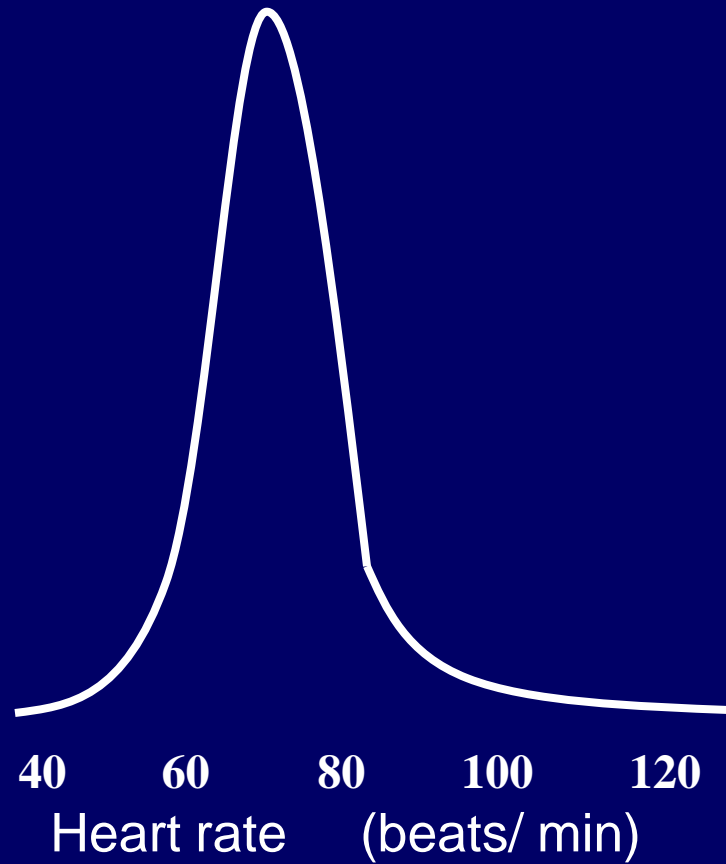
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# The root of the problem: how to develop an investigator - independent cut point ?





The problem: A “skewed” bell curve



# Pickering- Platt debate

(As described by Darwin Labarthe)

- Pickering's argument was that the clinician's habit of dividing people into two classes, "normal" and "abnormal", blinded them to the fundamental reality that blood pressure is a continuously distributed physiological trait. .. no "dividing line" to distinguish between abnormal and normal, or sick and healthy.
- Against Pickering's view, Robert Platt argued that the highest blood pressure values in a population distinguished a discrete group who represented the disease, hypertension, and that this fact could potentially be explained by specific **genetic** characteristics of this group.

# 1988 First attempt to objectively define the hyperkinetic state.

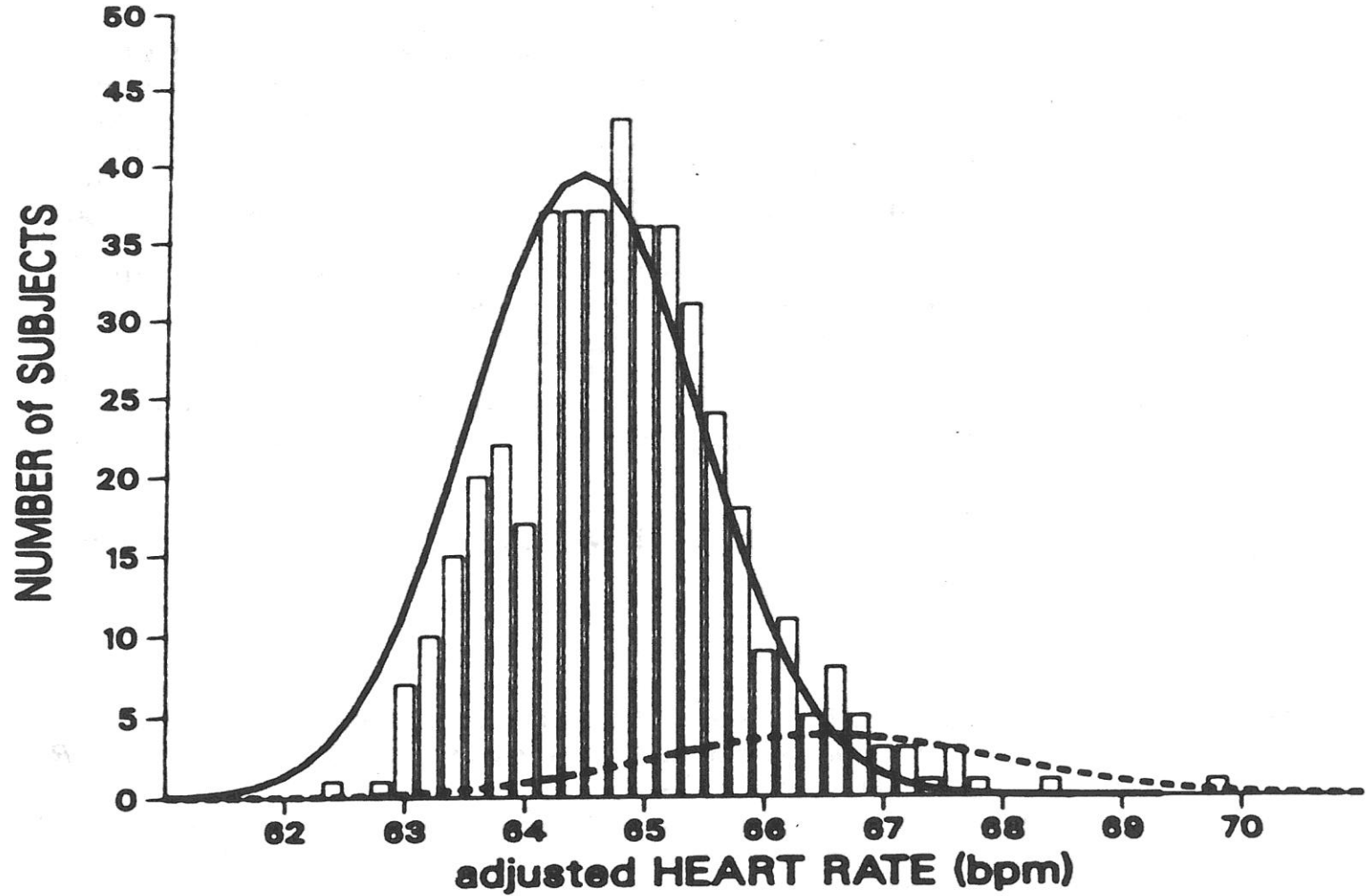
Population **195** prehypertension **243** normotensives  
Mainly young (18-24 ys) college male students .

Method Invasive hemodynamics: Intra-arterial BP,  
Cardiac output by dye dilution.

Objective : To find an investigator- independent  
definition of hyperkinetic state.

Statistical “mixture” analysis to determine whether one  
can detect two distinct subgroups in regards to BP,  
cardiac output and heart rate.

“This suggests that hyperkinetic state is an **abnormal** state of circulation uniquely characteristic of patients with borderline hypertension.”



# 1990 Mixture analysis applied to three different populations in the State of Michigan: Results

**Likelihood ratio that the bell shaped curve represents 2 mixed distributions .**

--Ann Arbor invasive studies (N= 444)  $p < 0.0000001$

--Hospital risk factor project (N = 1005)  $p < 0.0000001$

--State – wide population (N = 2633)  $p < 0.0000001$

***“At present we feel that our analyses described above strongly support the contention that the hyperkinetic state is a genuine disease entity .”***

## Results of the mixture analysis in three international populations

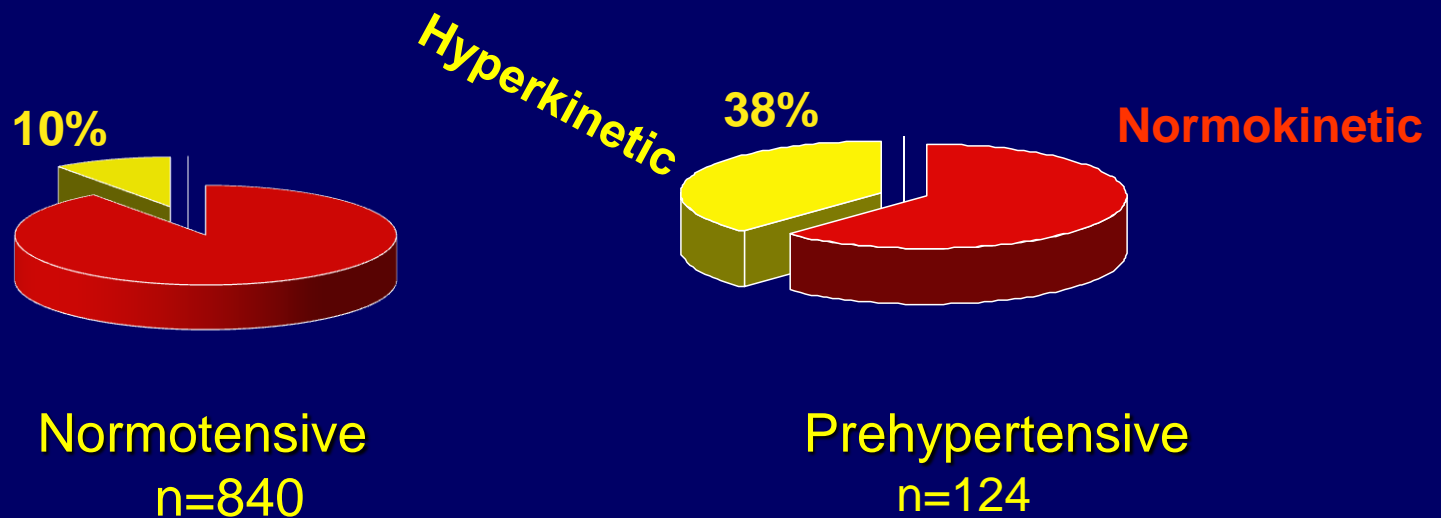
Belgian general population N= 514, Age 20-88

USA general population N= 680, Age 17-41

Italy Stage 1 hypertension N= 1098 Age 18-45

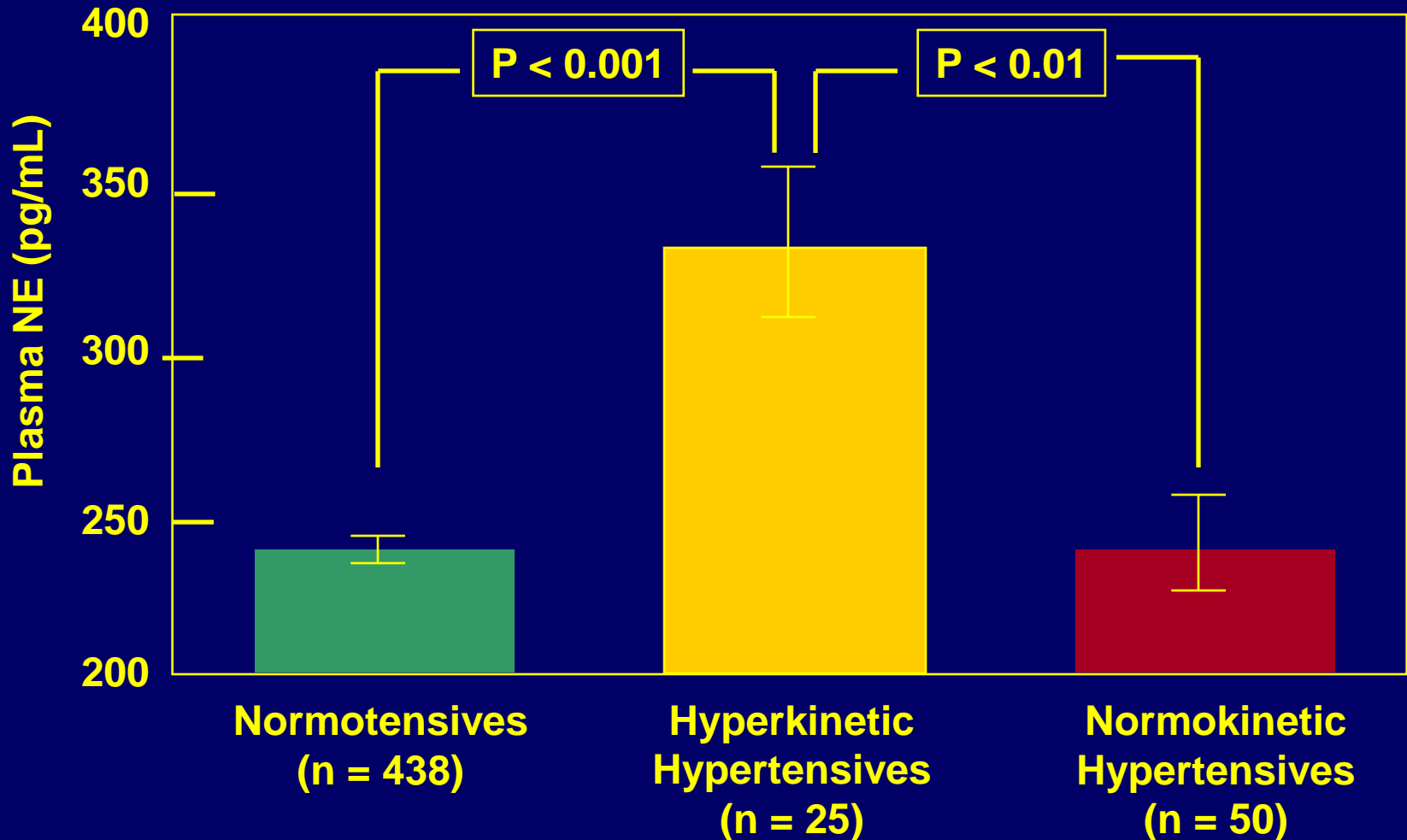
- Among men a subgroup with tachycardia had higher blood pressure and lipid levels.
- -Fasting insulin and post-load glucose levels were also elevated in men with tachycardia.
- In young women the results were less clear.

# Hemodynamic profiles using the mixture analysis in the Tecumseh study



The parents of hyperkinetic individuals also had elevated BP.

# Tecumseh Study Plasma Norepinephrine in All Normotensives vs. Hyperkinetic and Normokinetic Hypertensives

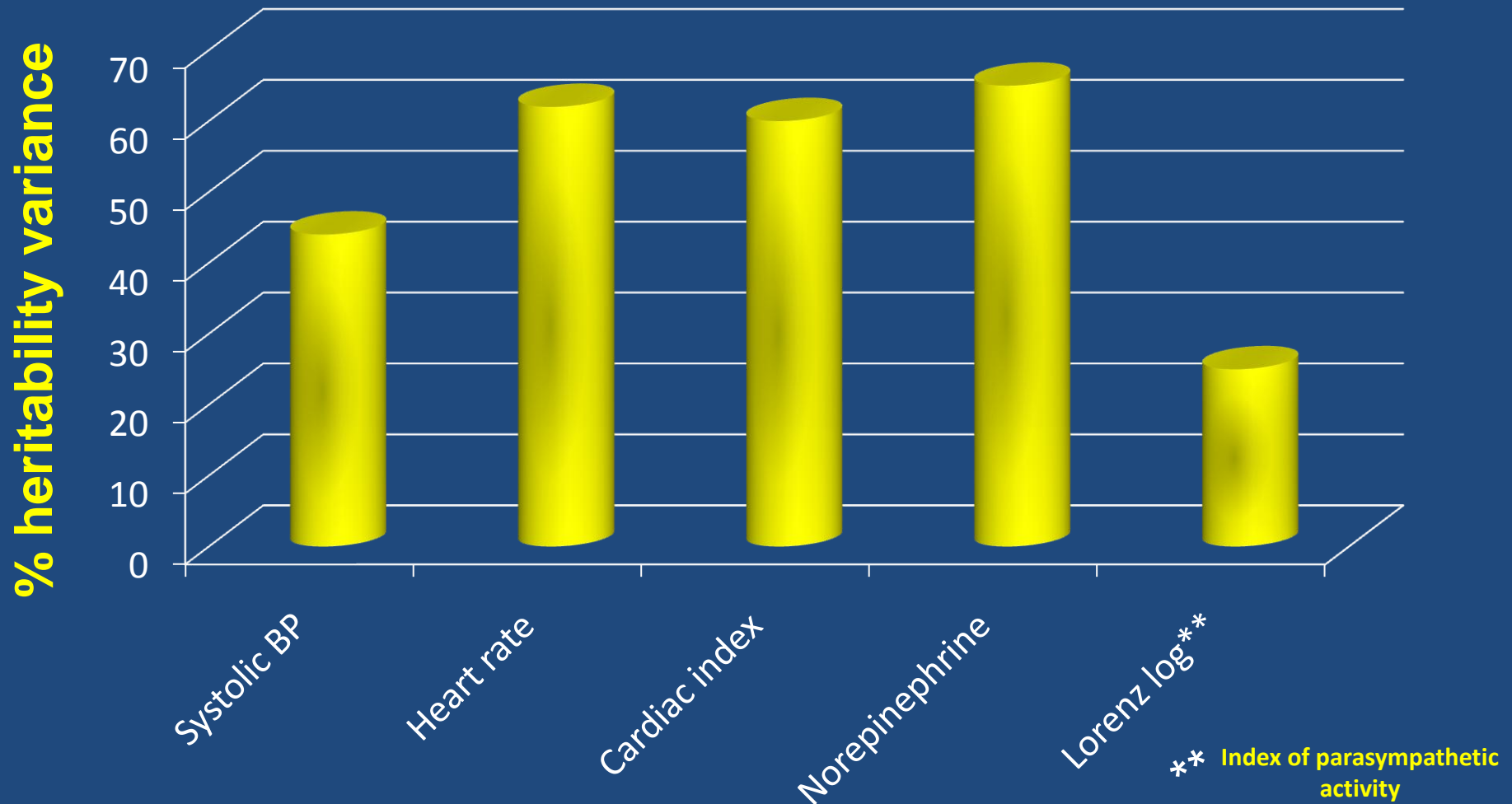




J.T. Davis, F. Rao, D. Naqshbandi et al  
J of Am. College of Cardiology v.59, No 24 2012  
(San Diego Study)

- “Eight hundred twelve individuals were evaluated in a sample of twin pairs, their siblings and other family members. They underwent noninvasive hemodynamic, autonomic and biochemical testing as well as estimates of trait heritability (the percentage of trait variance accounted for by heredity)”

# Assessment of heritability of hemodynamic and hormonal Factors in the San Diego Study



Adapted from J.T. Davis, et al JACC 2012

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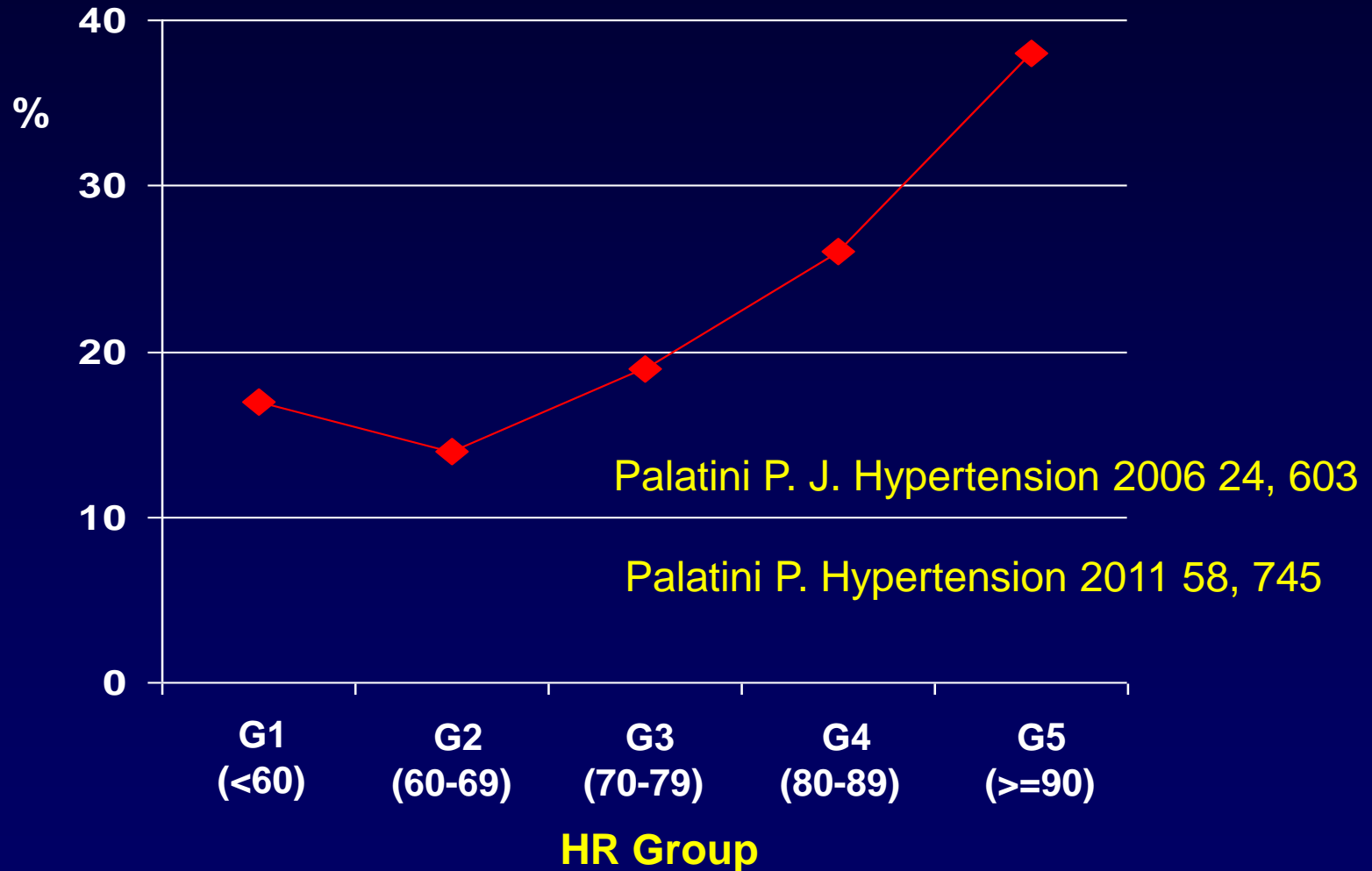
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# HR and Mortality in a Japanese General Population: an 18-year Follow-up Study



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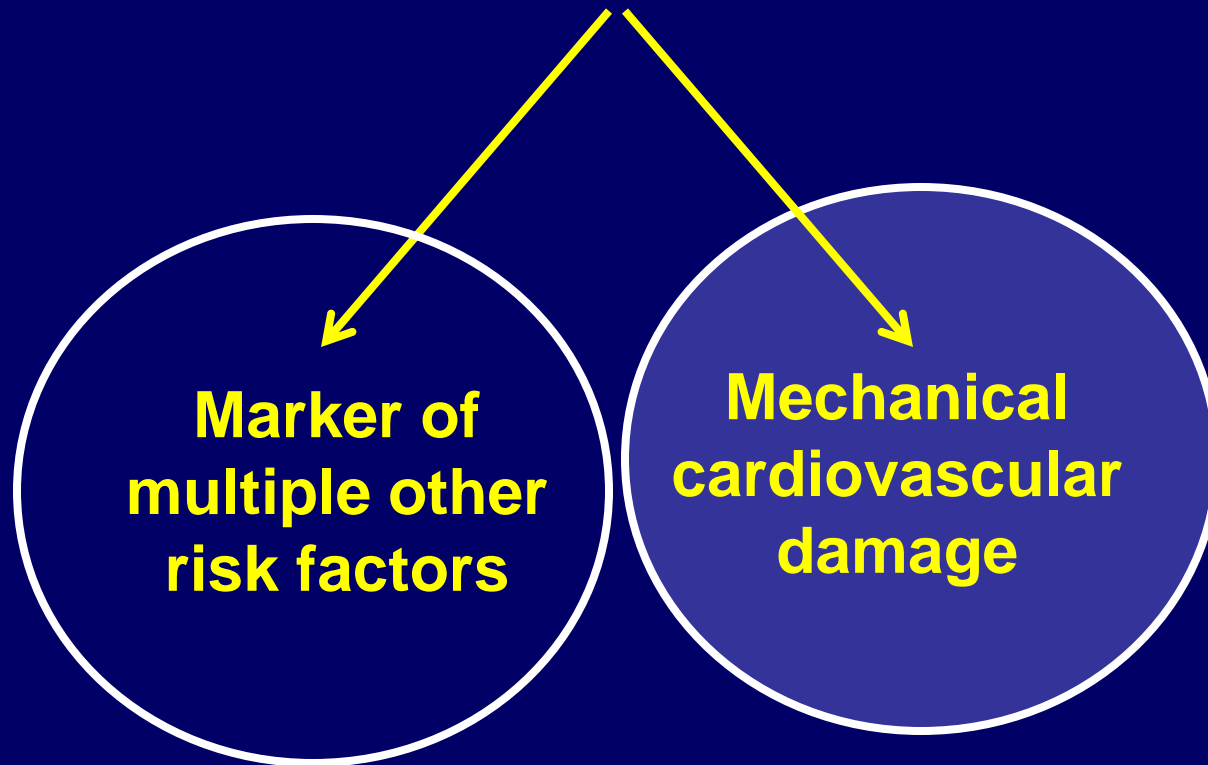
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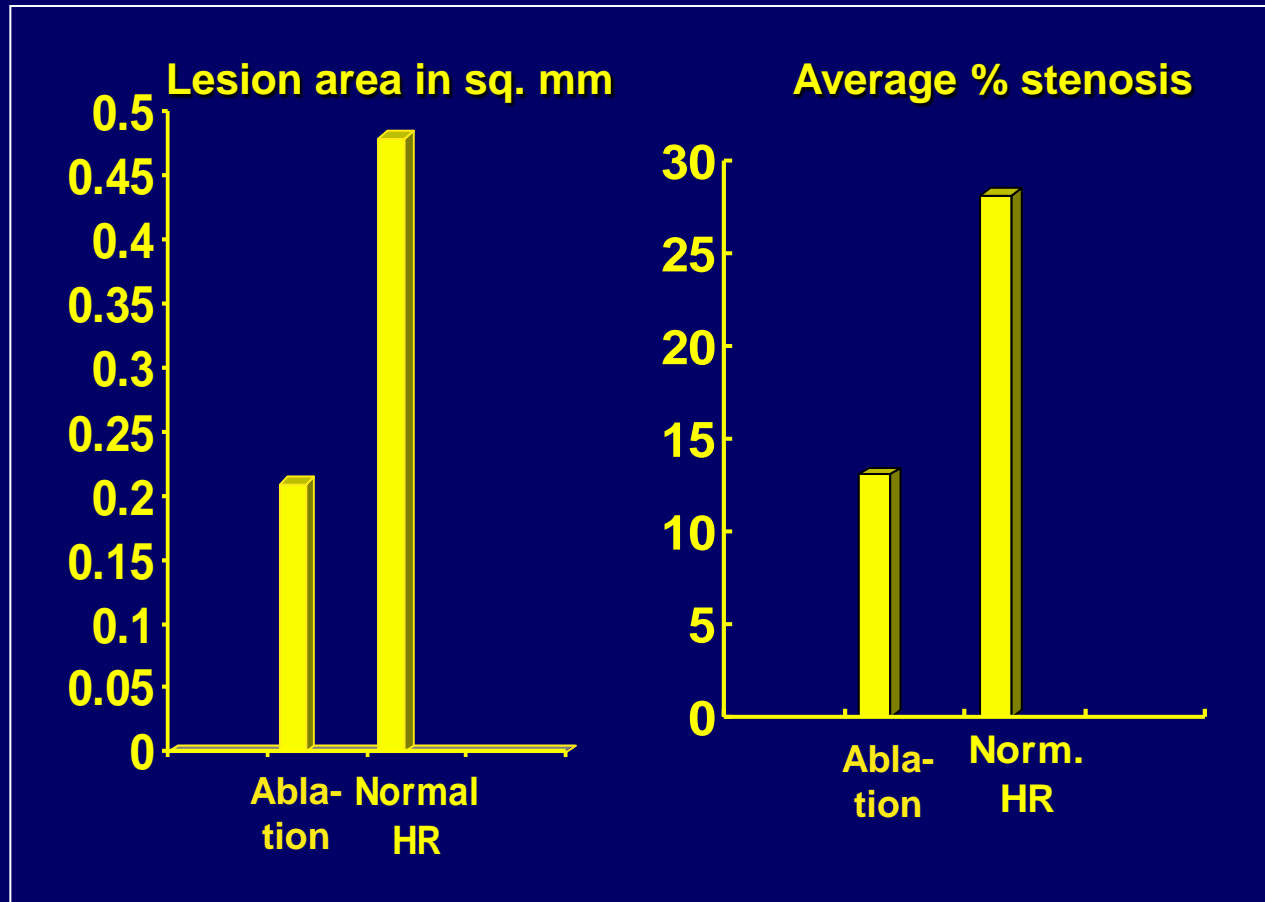
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## **Mechanism by which tachycardia increases cardiovascular risk**



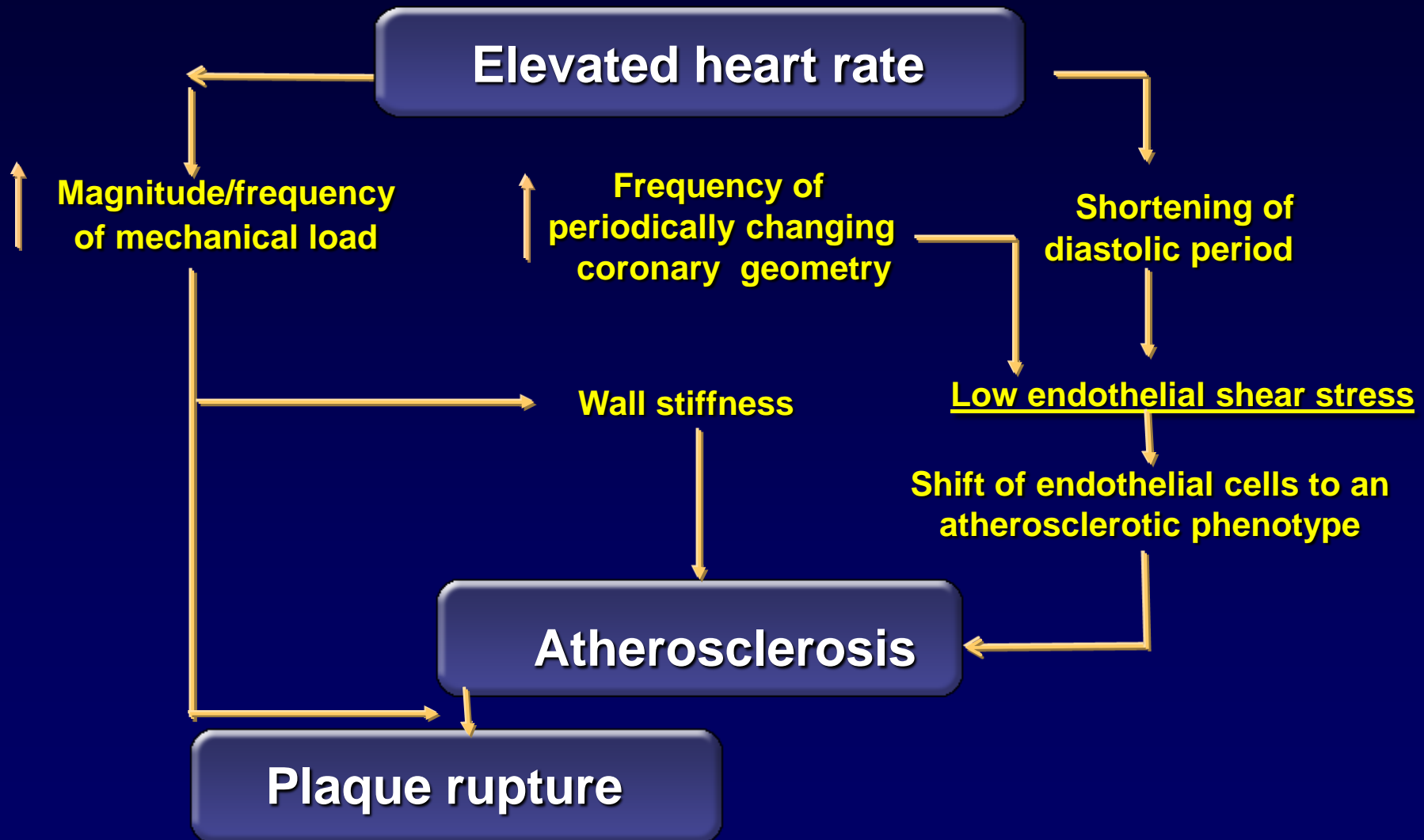
# Effect of low heart rate ( by ablating the SA node) on coronary lesions in cholesterol fed monkeys



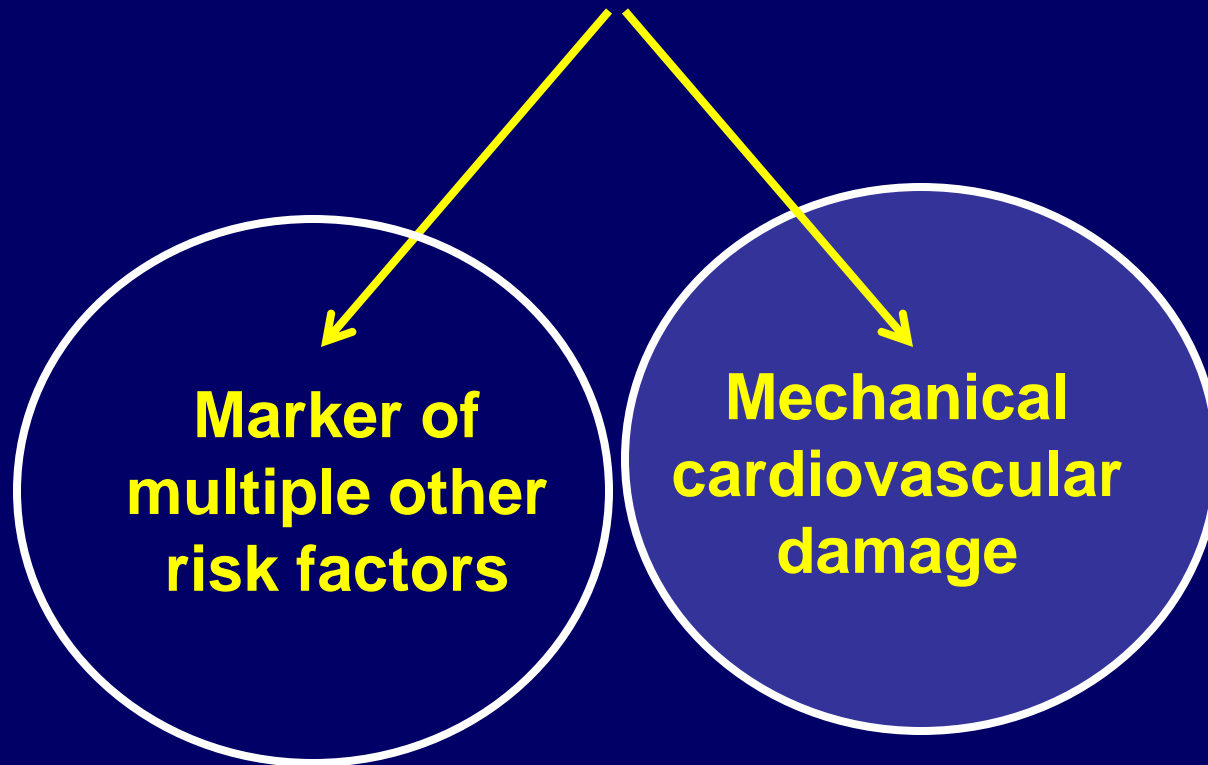
Adapted from Beere et al Science 1984



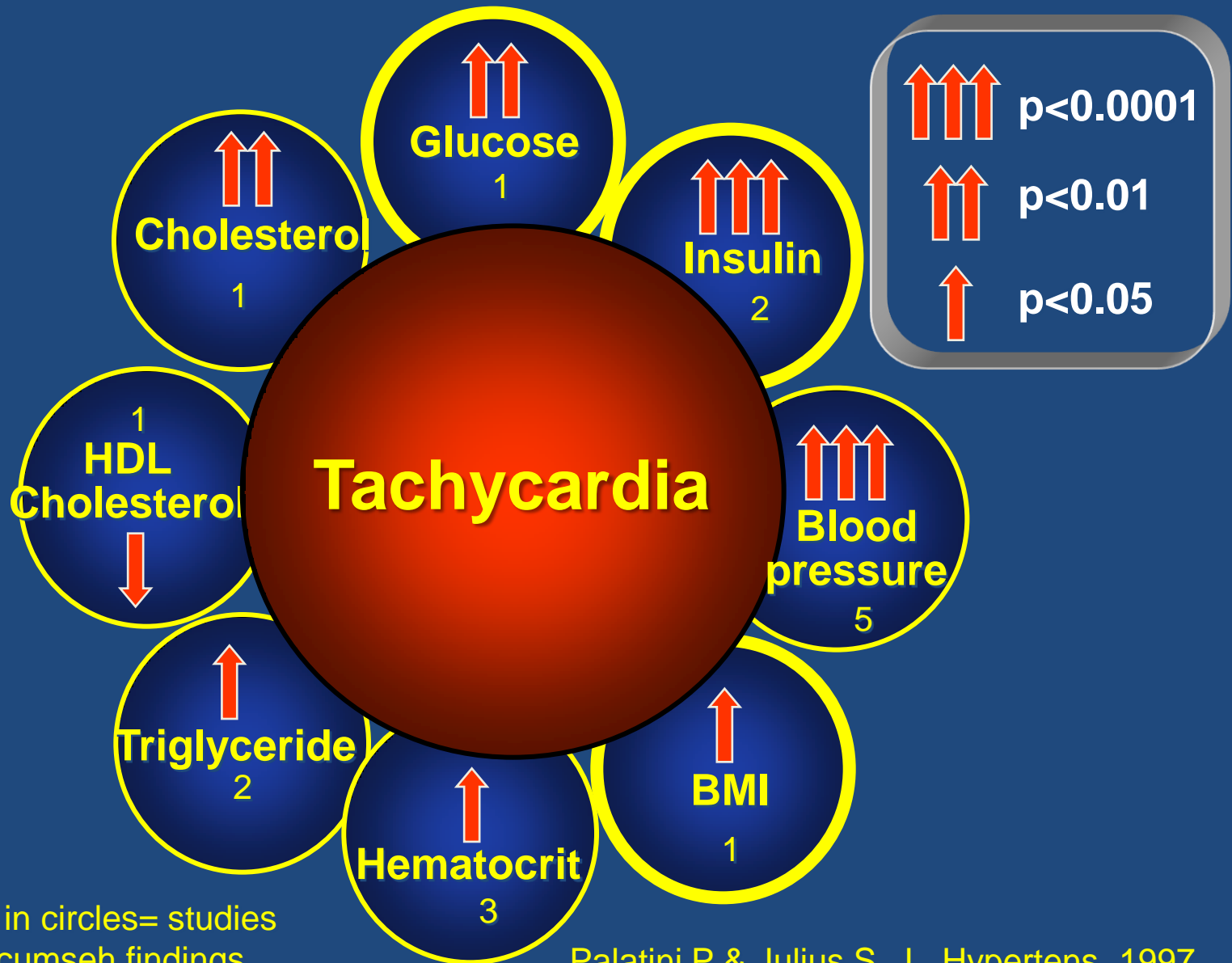
# Heart rate and atherosclerosis



## **Mechanism by which tachycardia increases cardiovascular risk**



# Tachycardia as a Marker of Other Risk Factors for Atherosclerosis in the Tecumseh Study and Other Studies



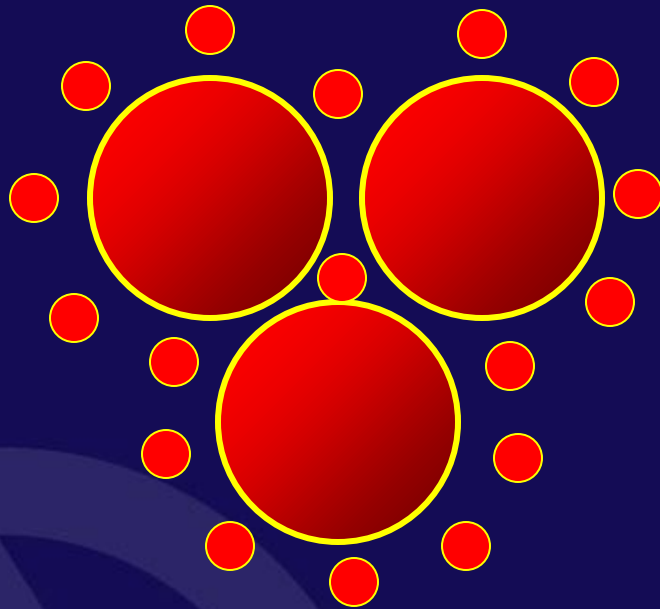
The numbers in circles= studies confirming Tecumseh findings

Palatini P & Julius S, J . Hypertens, 1997

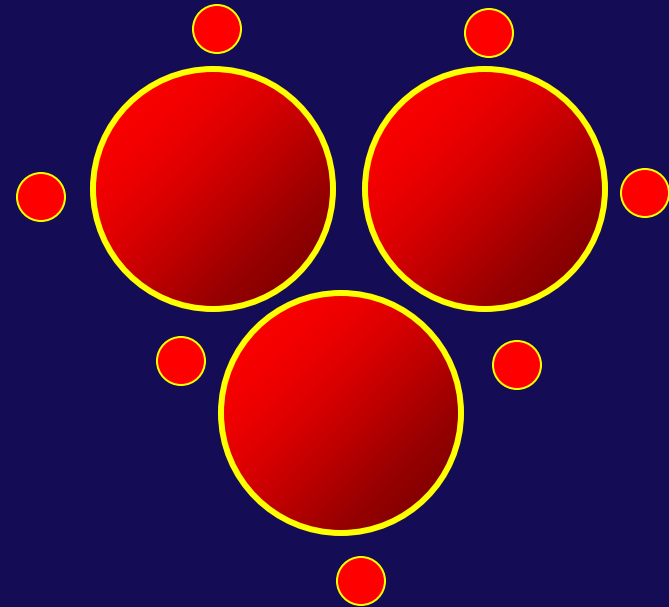
**The question:**  
**How could a hemodynamic abnormality (tachycardia) be associated with metabolic conditions (insulin resistance and obesity) ??**

**The answer:**  
**Because tachycardia is a marker of sympathetic overactivity**

# Schematic Presentation of the Nutritional Blood Flow



**Normal**

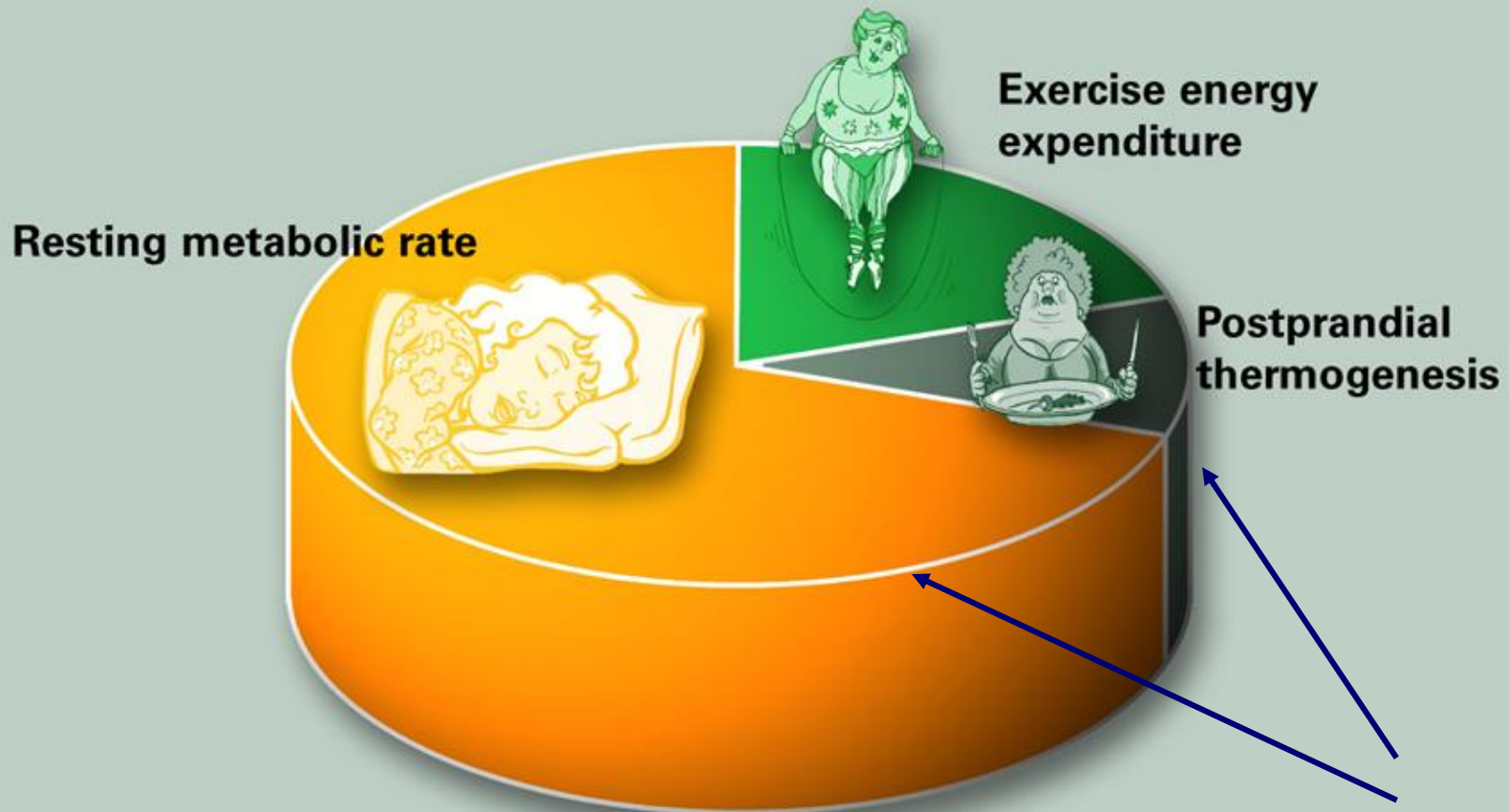


**Insulin Resistance**

Jamerson, Julius et al. Hypertension 1993. During intra-arterial insulin infusion a reflex vasoconstriction decreased glucose uptake in human forehands.

# Components of energy output

Valentini, Julius, Palatini et al J.Hypertension 2004: Energy expenditure response to isoproterenol infusion is decreased in hypertension. Since patients ability to dissipate calories is decreased they gain more weight.



Julius et al, Cir Research 1975; 36-37 (suppl): 199.

Kjeldsen SE, et al. Blood Pressure 5, 1996.

Valentini, Julius, Palatini et al J. Hypertension 2004

# CONCLUSION

**There is overwhelming evidence that tachycardia at youth (and at any point of human life cycle) is an ominous sign.**

**Tachycardia predicts cardiovascular morbidity/ mortality as well as all-cause mortality.**

**Despite of the evidence tachycardia is often ignored in clinical practice .**

**Cardiologists must become teachers and leaders in the effort to recognize the importance of tachycardia .**

**Early detection /treatment of the hyperkinetic syndrome and its metabolic components may have a positive effect on public health.**







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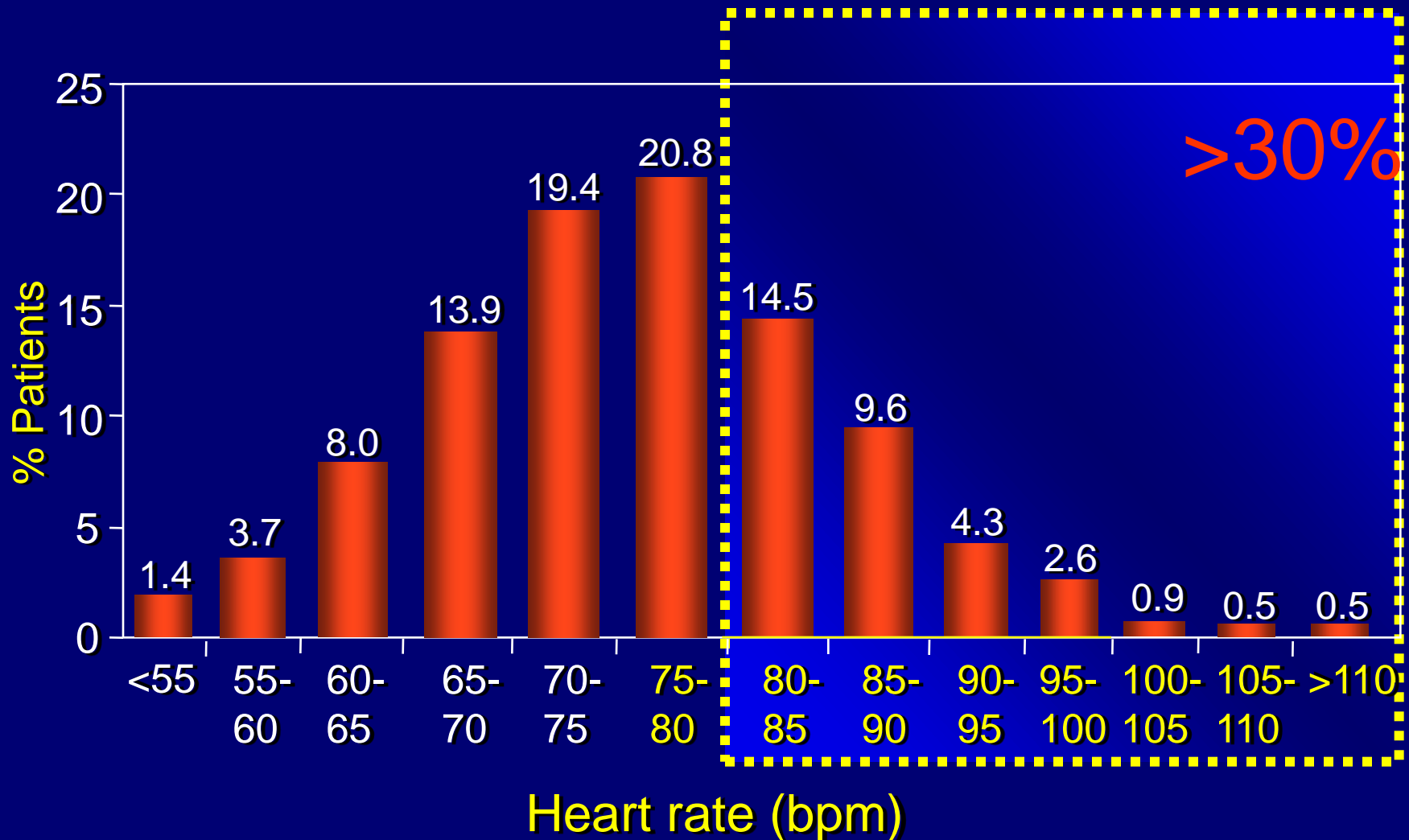
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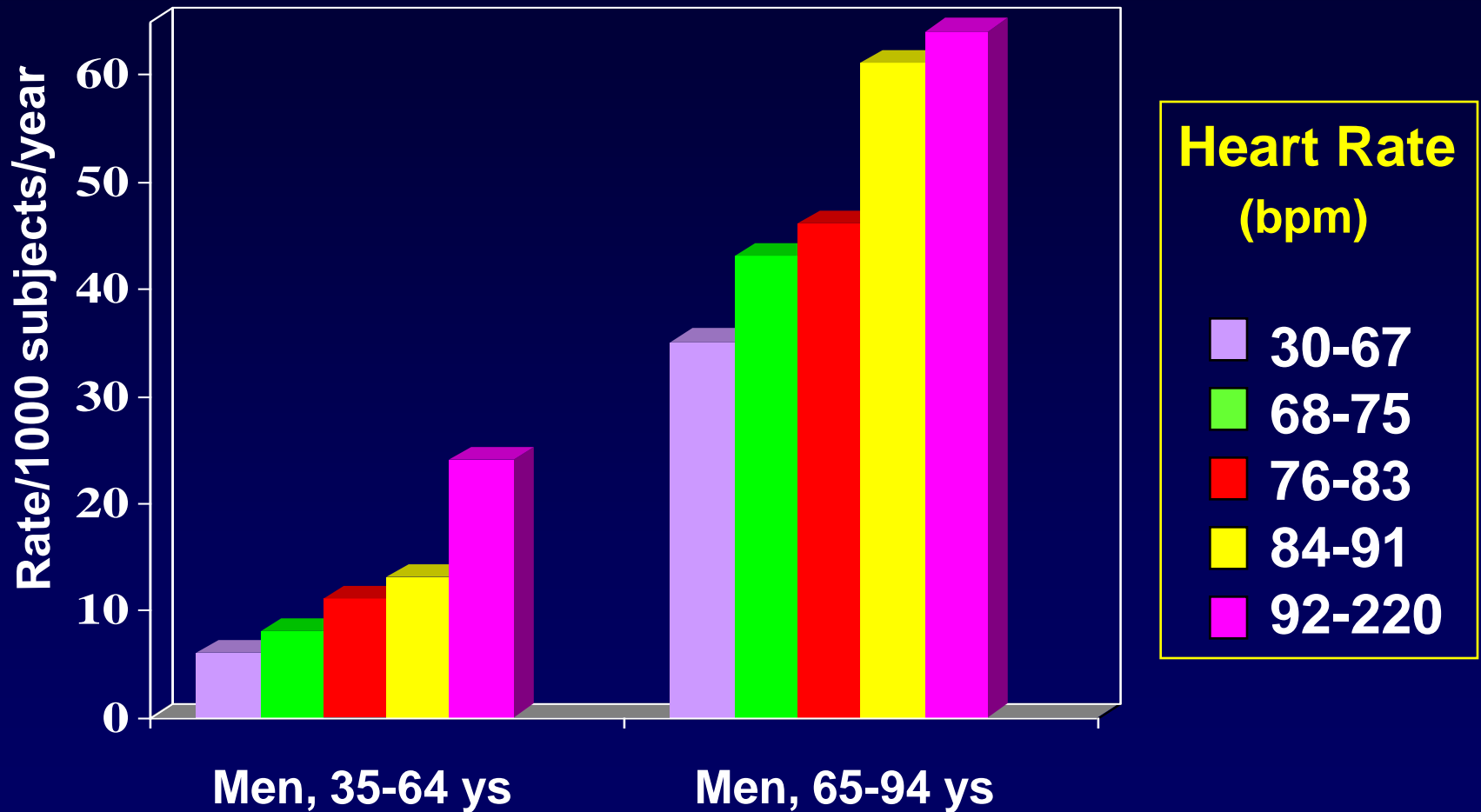
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# Heart Rate Distribution in Subjects With Hypertension (n=38,145)

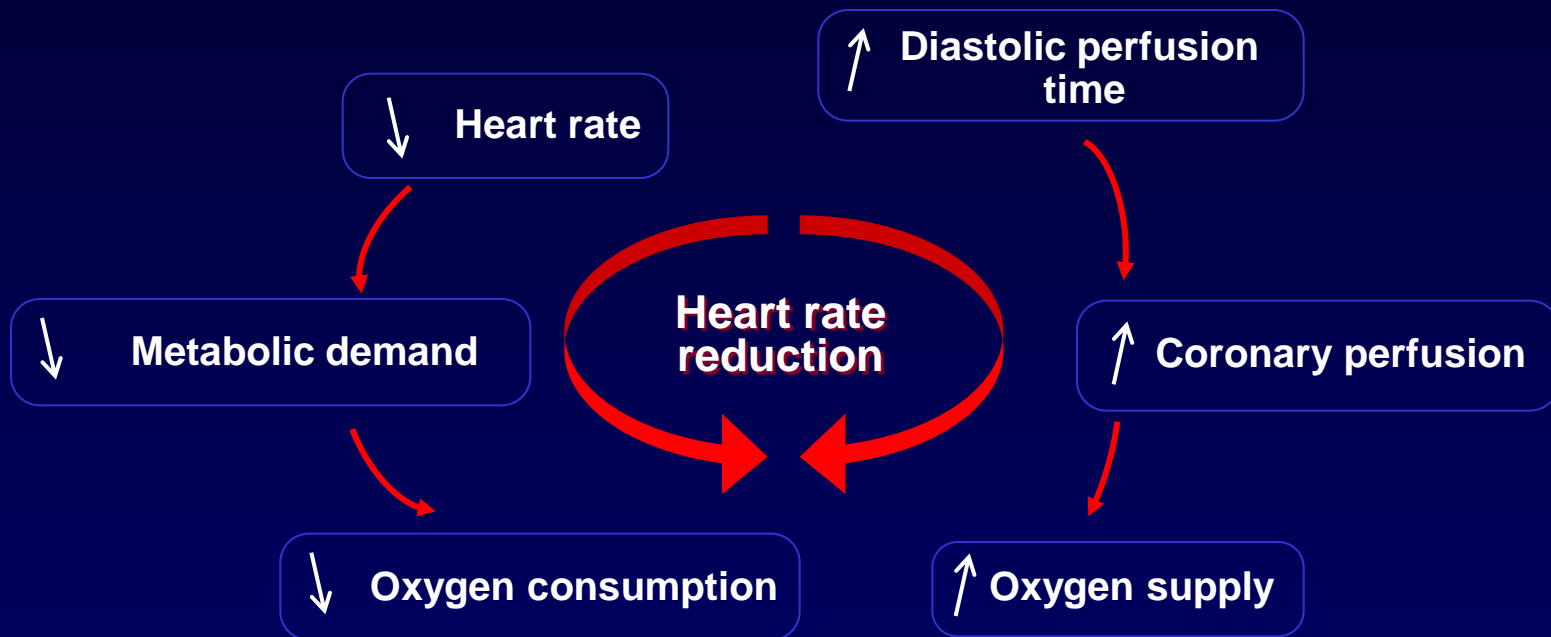


# Heart Rate and All-Cause Mortality

## *The Framingham Study*



# HEART RATE SLOWING IMPROVES MYOCARDIAL O<sub>2</sub> SUPPLY AND DEMAND BALANCE



Better balance  $\frac{\text{supply}}{\text{demand}}$  O<sub>2</sub> = Prevention of angina attacks

# CV Risk Factors and 10-yr Mortality in Elderly Men Living in Finland, Italy, and The Netherland

## *The FINE Study*

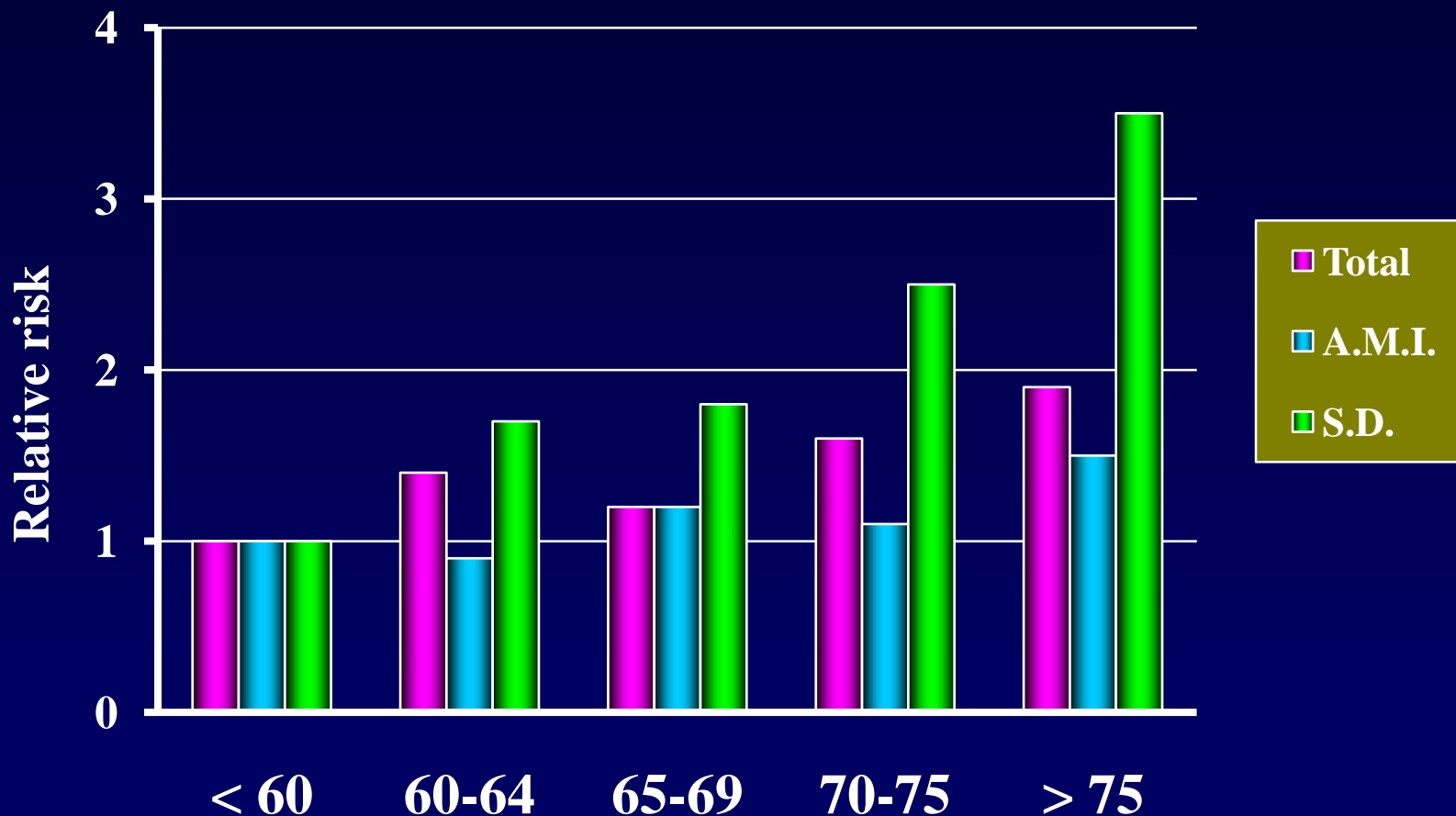
### 10-year mortality

Age (+)	p=0.0001
Smoking (+)	p=0.0001
Heart rate (+)	p=0.0001
BMI (-)	p=0.0006
HDL-chol. (-)	p=0.002

### 6-to-10-year mortality

Age (+)	p=0.0001
Smoking (+)	p=0.0001
Heart rate (+)	p=0.0001
Systolic BP (+)	p=0.01

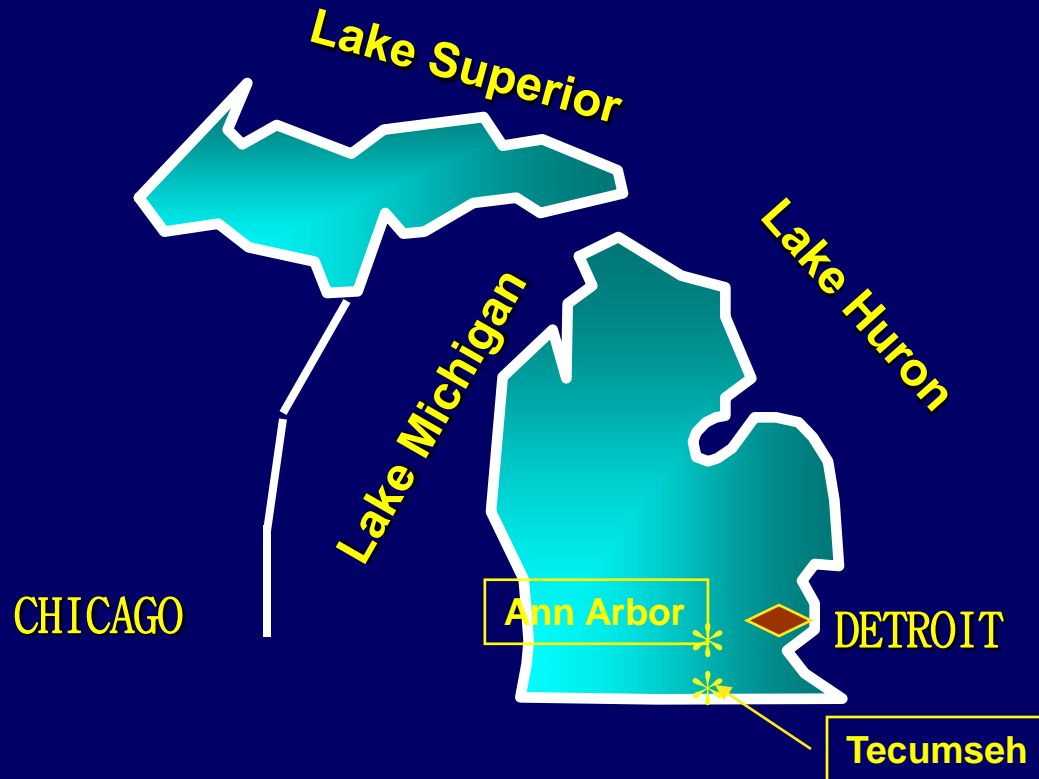
# Risk of Total Mortality, Non Sudden Death from AMI, and Sudden Death from AMI in 5713 Asymptomatic Men by Quintile of Resting Heart Rate



# The Tecumseh Blood Pressure Study

## N= 946

- A prospective epidemiologic study of antecedents of hypertension in a general population of young adults.





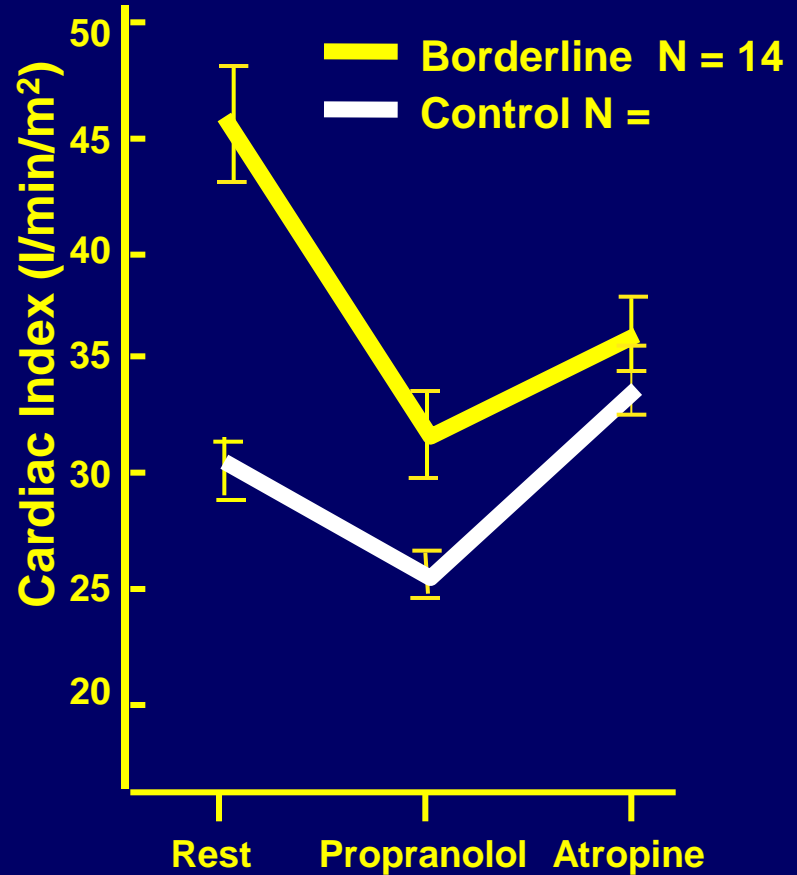
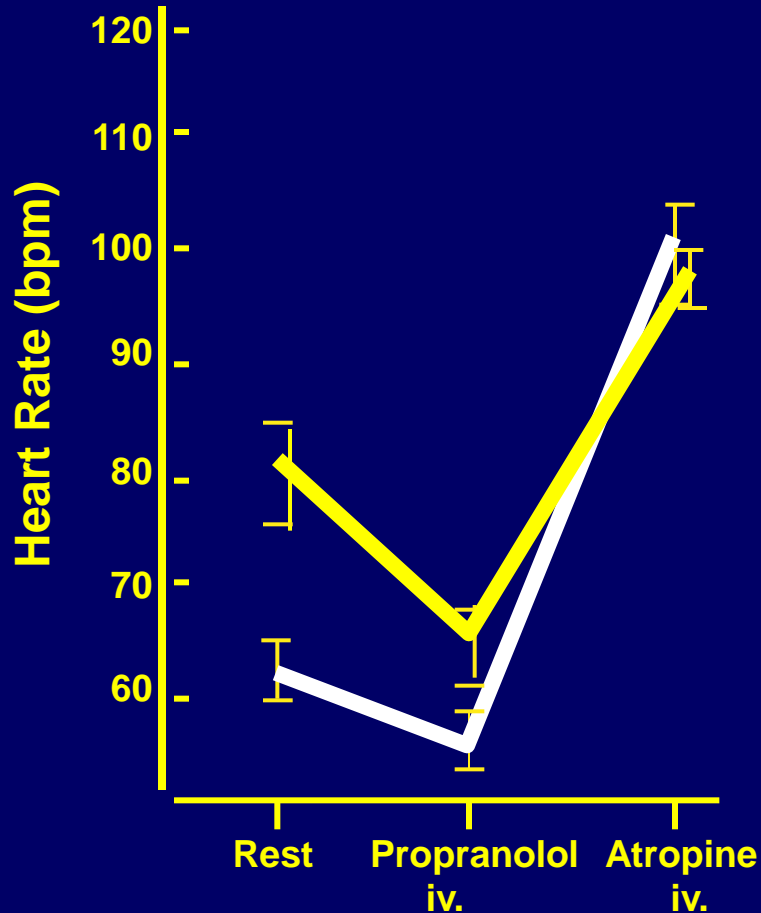
# 1990 Mixture analysis applied to three different populations in the State of Michigan

Invasive measurements in the Ann Arbor laboratory N = 444

University of Michigan Hospital risk factor detection program N = 1005

Random selection from the State-Wide home BP survey N = 2633

# Sympathetic and Parasympathetic Aberrations; an evidence that the Abnormality Emanates from the Brain.



Julius et al, Circulation 1971

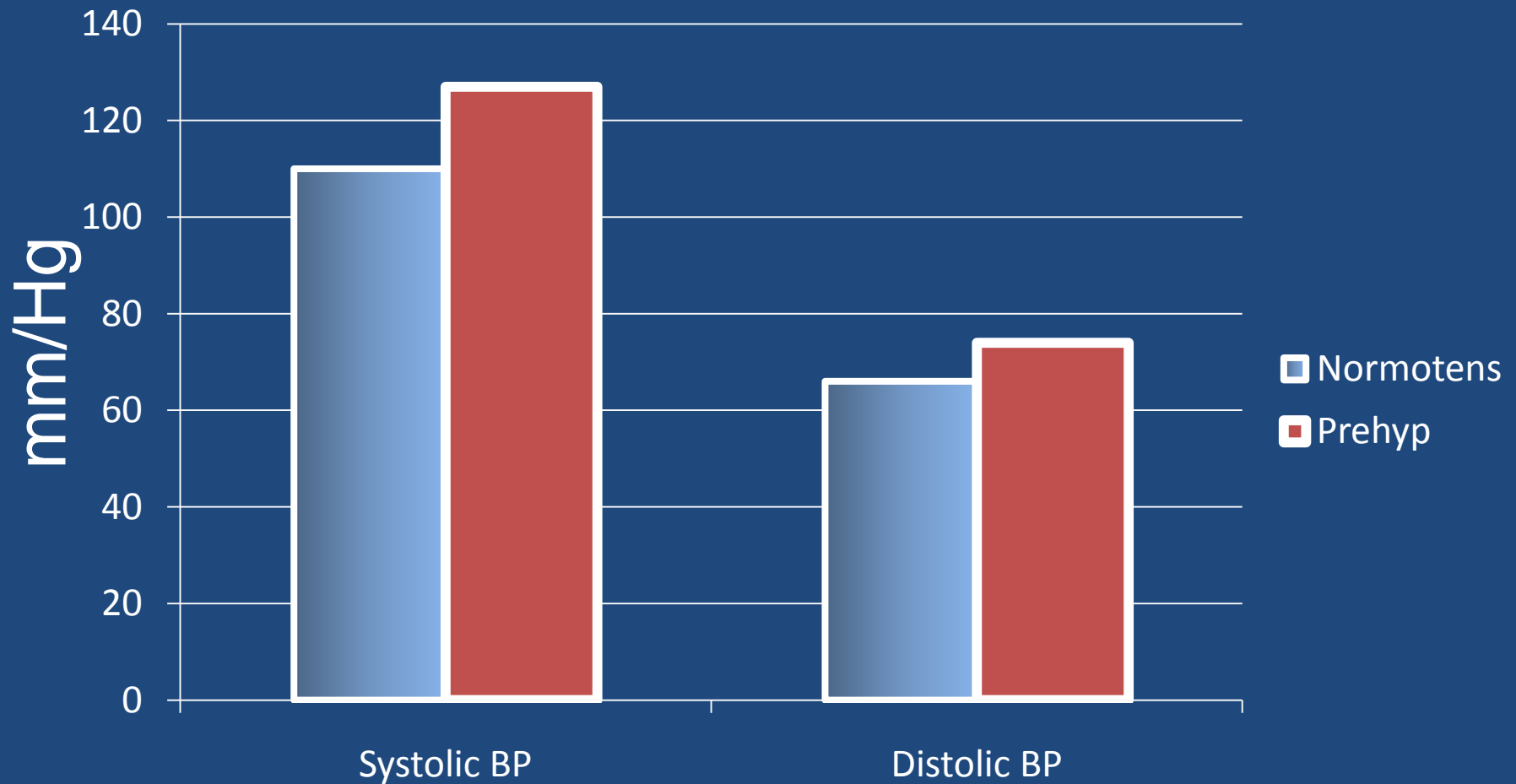
**1990 a change of the objective: Is hyperkinetic state a  
disease entity ?**  
**(A revisit of the Pickering-Platt debate)**

**Disease Entities, Mixed Multi-normal Distributions And  
The Role Of The Hyperkinetic State In The Pathogenesis  
Of Hypertension**

**N.J Schork, A.B. Weder, M.A. Schork, D.R. Bassett and S. Julius**

**STATISTICS IN MEDICINE VOL.9 1990**

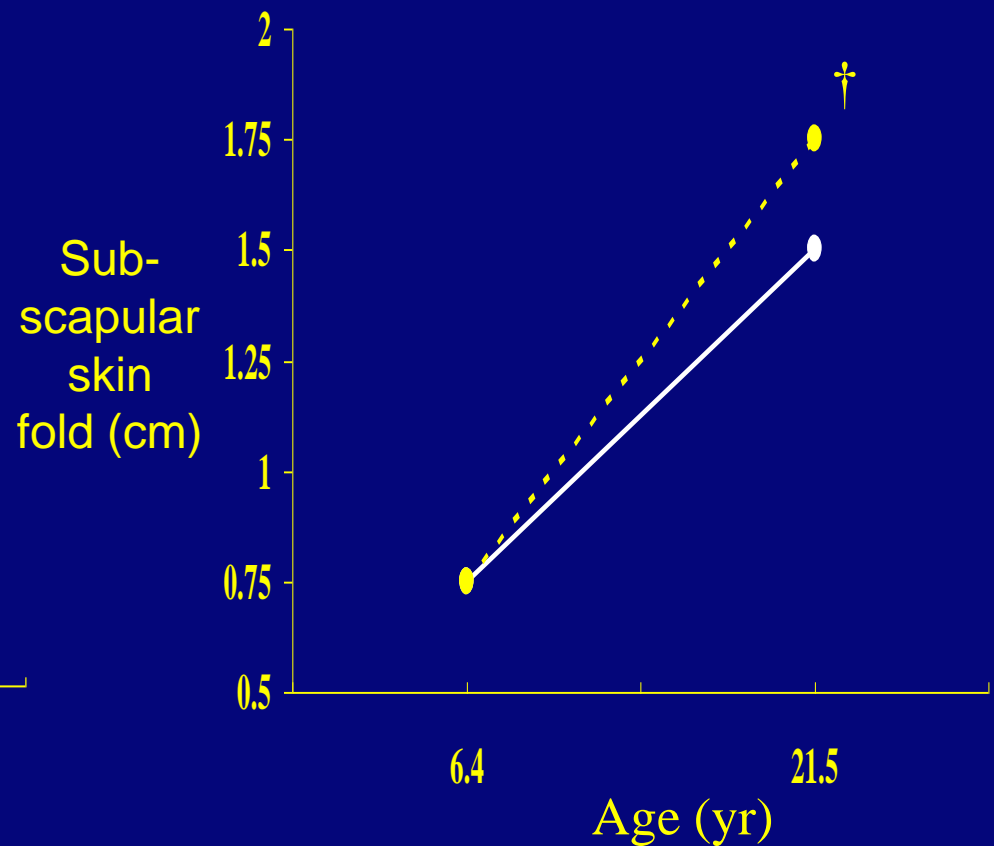
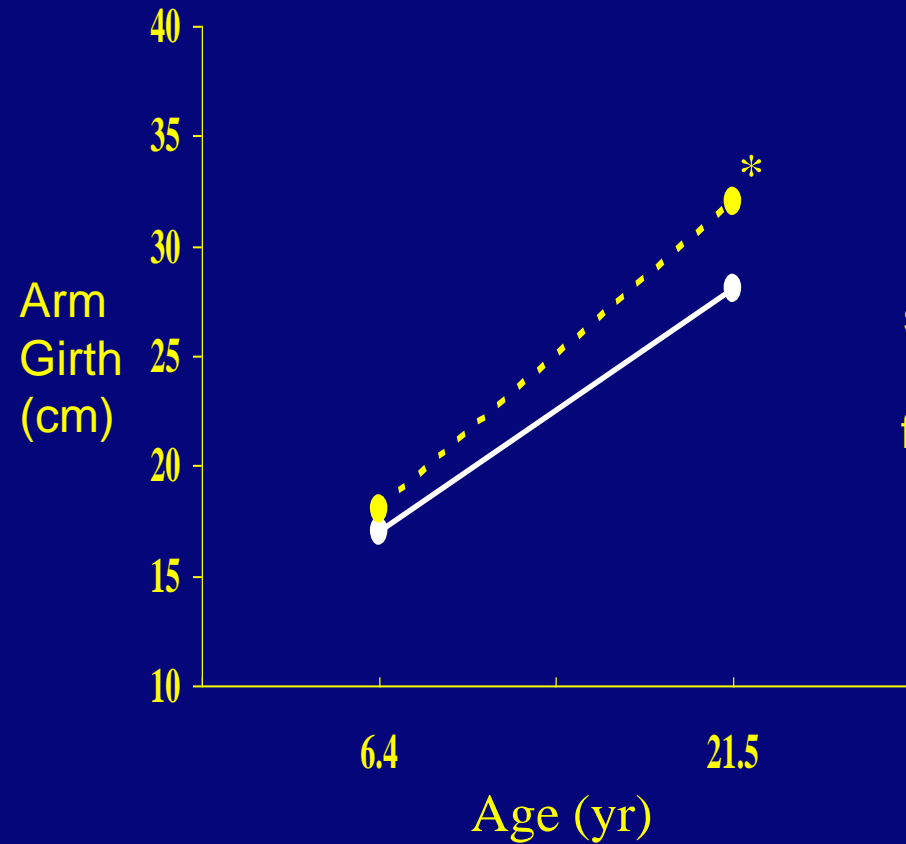
# BP levels in the normotension and prehypertension groups in the San Diego study



Adapted from J.T. Davis, et al JACC 2012

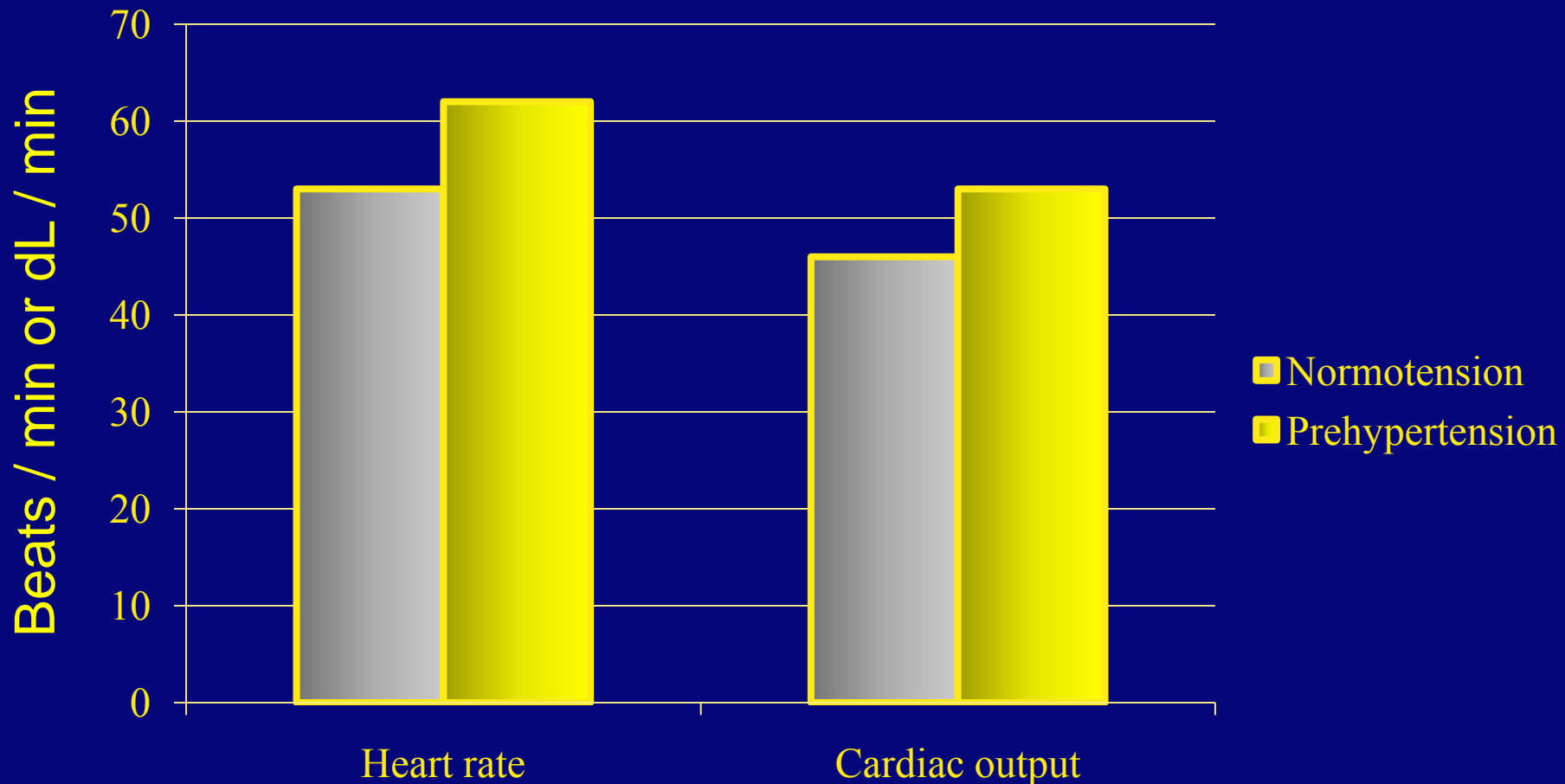
# Sympathetic overactivity and high BP first, overweight later !

Arm Girth and Subscapular Skin folds in Normotensives (●—●) and Borderline Hypertensives (●-----●) at 32 ys. of age



\*P<0.0015; † P<0.001

# Hemodynamic data in the normotension and prehypertension groups in the San Diego Study

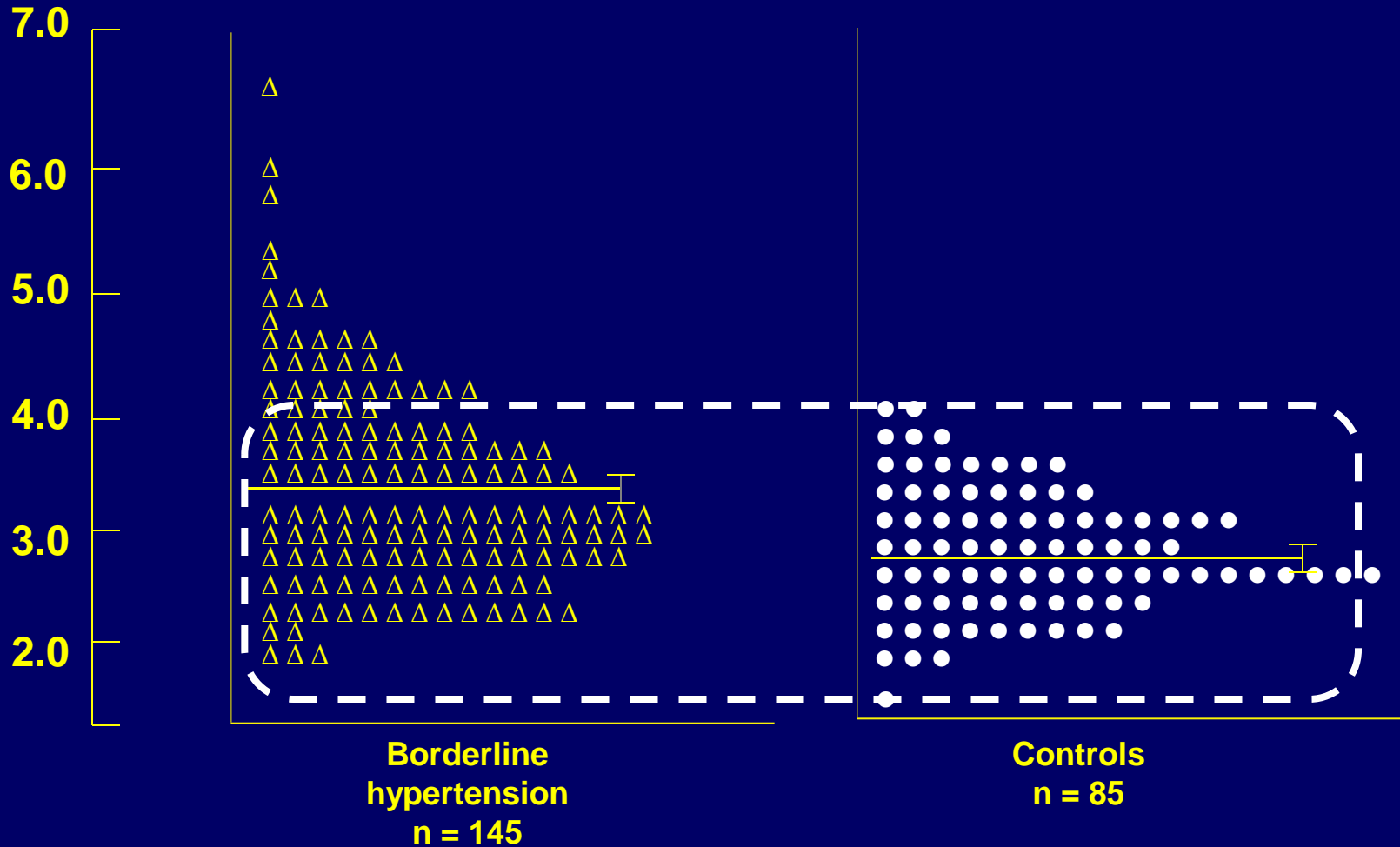


In Western societies, high heart rate pertains to a distinct subgroup of subjects, who are more frequently men and exhibit the characteristic features of the insulin resistance syndrome. Sympathetic overactivity is likely to be the mechanism underlying this clinical condition.

# 1976

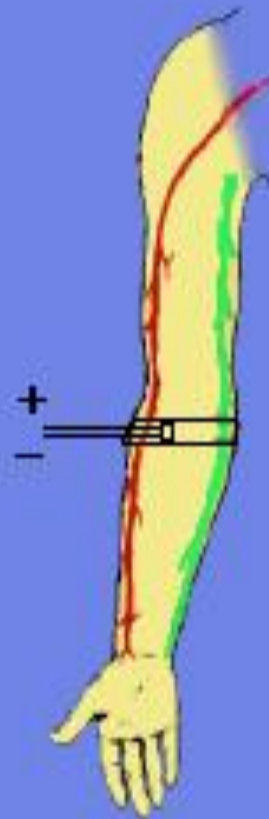
(cardiac index by dye dilution method)

L/min/m<sup>2</sup>





# The Isolated Perfused Human Forearm

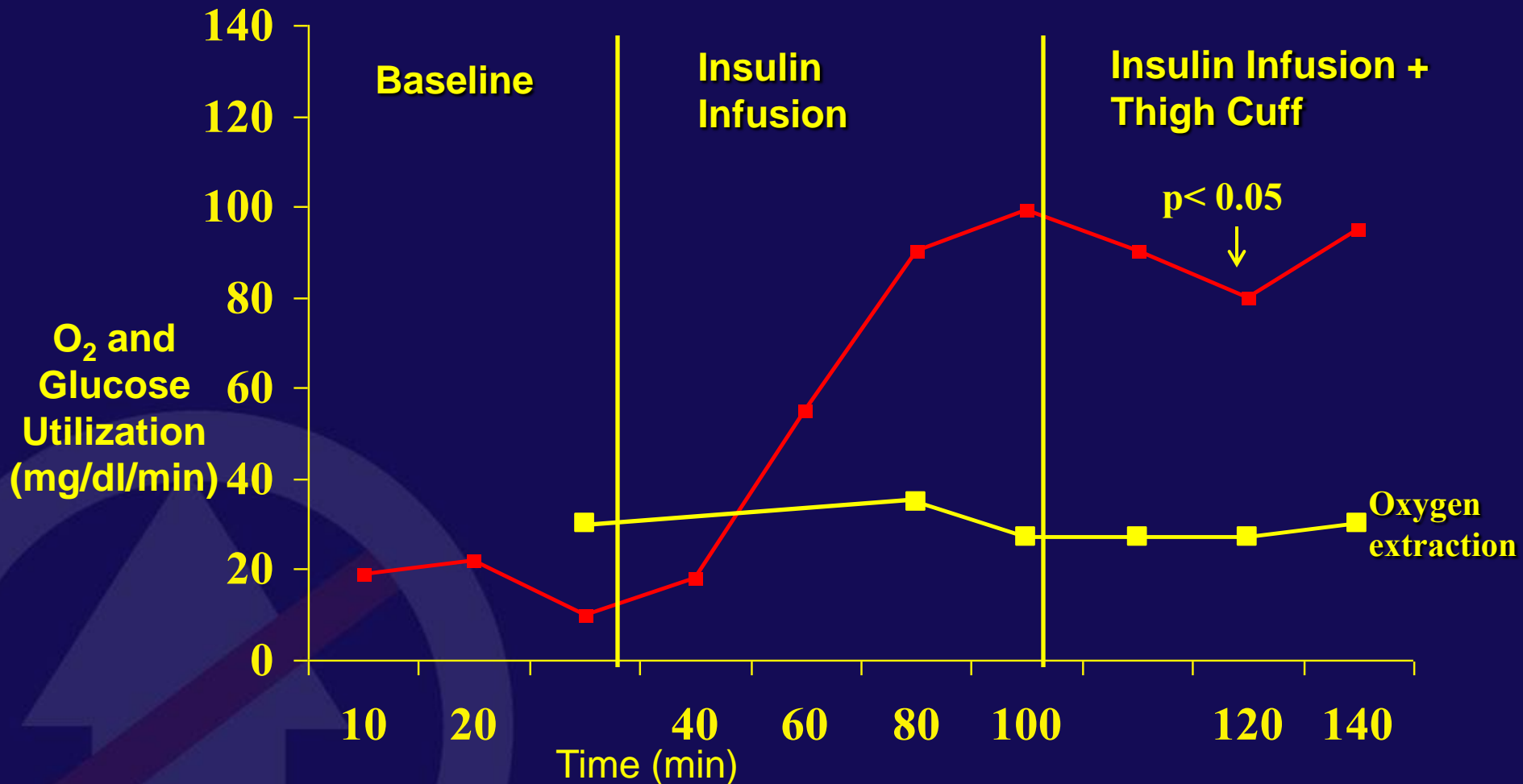




OUTPATIENT

OUTPATIENT

# The Effect of Insulin Infusion and Reflex Vasoconstriction on Glucose and Oxygen Extraction in the Forearm of 14 Healthy Volunteers



Over a period of 35 years the Ann Arbor group investigate the heart rate response to isoproterenol in 3 separate experiments on 3 different hypertensive populations.

In each study hypertensive patients had a suppressed heart rate increase to isoproterenol.

The decreased sensitivity of beta adrenergic receptors is due to a receptor downregulation in response to a persistently increased sympathetic tone.

We believe that this downregulation plays a role in the excessive gain of weight in hypertension.