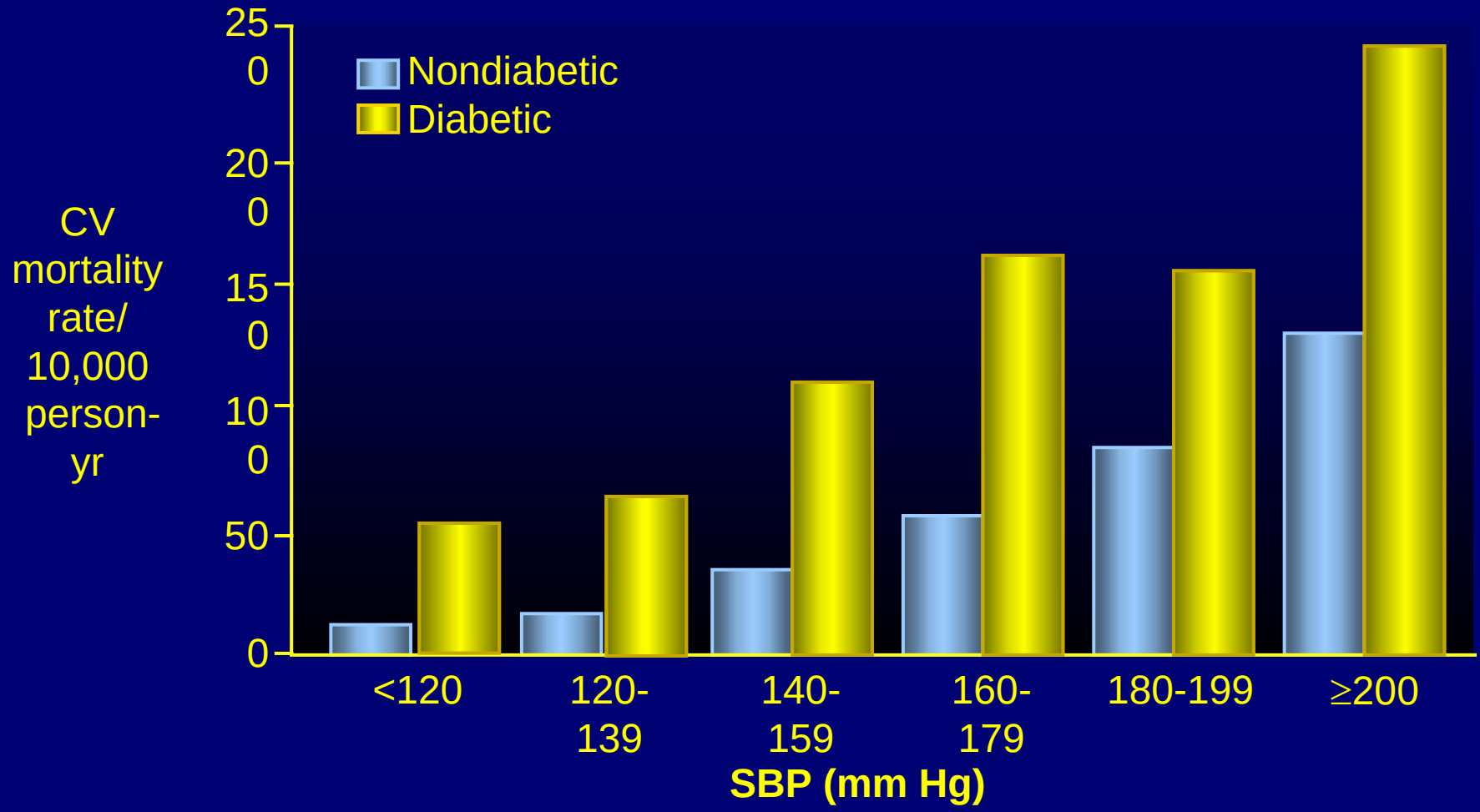
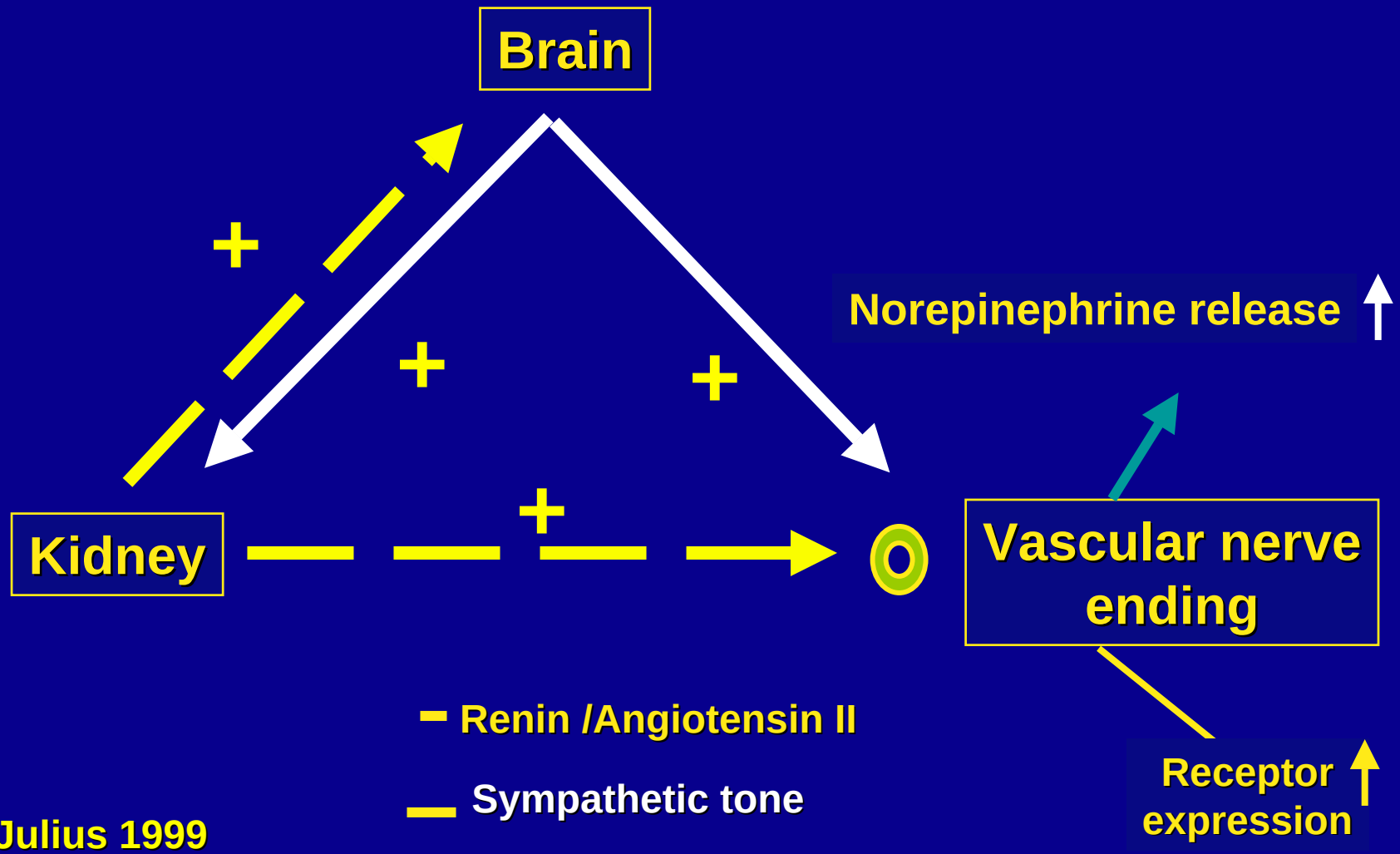
Association of SBP and CV Mortality in Type 2 Diabetes



Stamler J et al. *Diabetes Care.* 1993;16:434-444.

The very early appearance of glucose abnormalities and obesity in the course of natural history of hypertension.

Feedback between angiotensin and sympathetic tone



S. Julius 1999

Patient Characteristics - Tecumseh BP Study

	Normo-tensive (n=882)	Border-line (n=124)	p
Sex (M/F)	402/420	93/31	<.0001
Age (years)	30.6	31.4	NS
Clinic BP-Systolic Diastolic	112.4 75.4	130.7 93.8	<.0001 <.0001
Home BP-Systolic Diastolic	114.0 71.4	126.2 79.5	<.0001 <.0001
Resting Heart Rate	68.7	72.6	<.0001

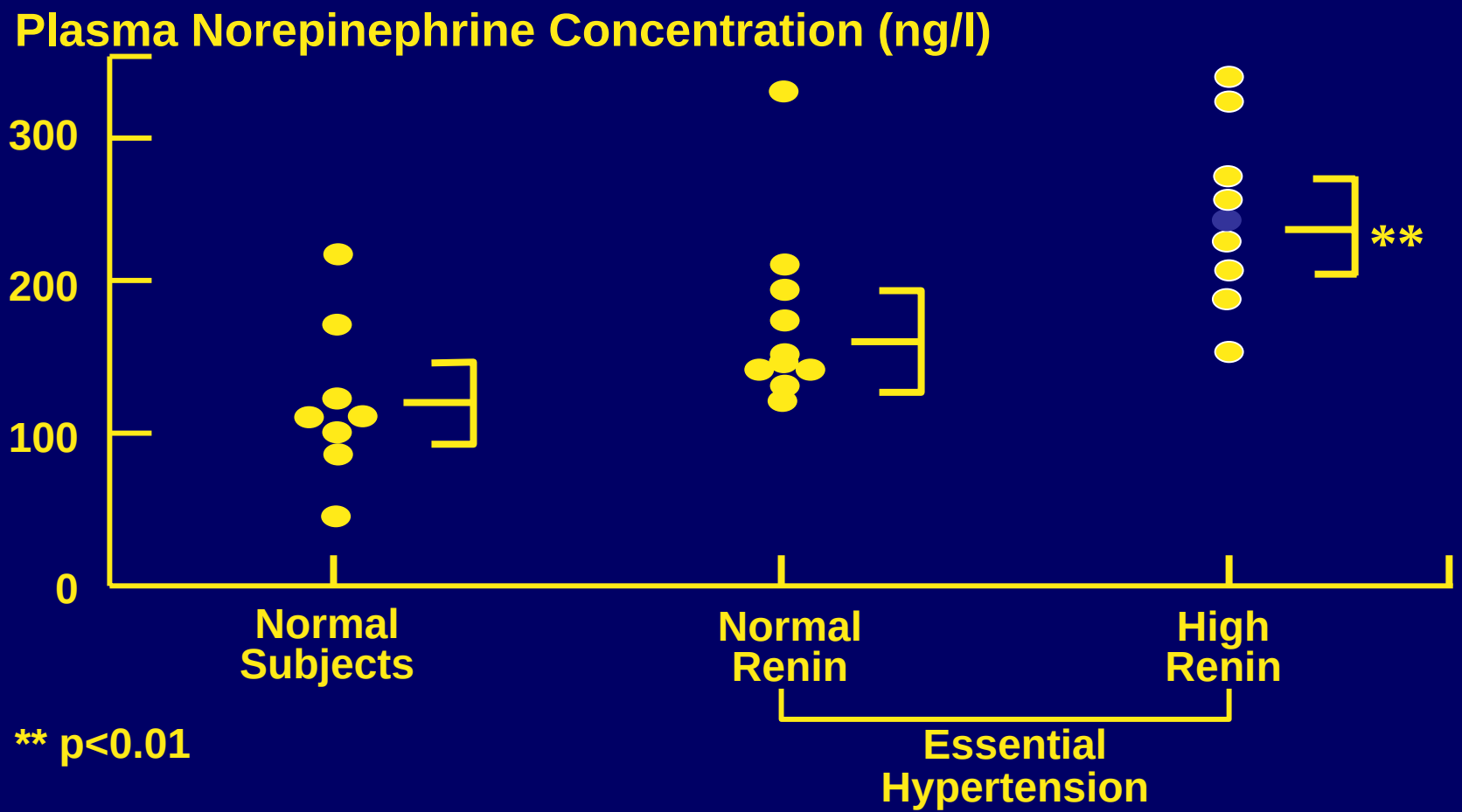
Julius S, et al; JAMA 1990, 264:354-358.

Risk Factors - Tecumseh BP Study

	Normotensive (n=822)	Borderline (n=124)	p
Cholesterol (mg/dL)	176	190	<.0001
HDL (mg/dL)	43	40	<.001
Triglycerides (mg/dL)	95	135	<.0001
Insulin (μU/dL)	12	18	<.0001
Glucose (mg/dL)	92	95	<.001
Insulin-glucose ratio	0.155	0.200	<.0001
Percent overweight	13.6	30.1	<.0001

Julius S, et al: JAMA 1990; 264: 354-358.

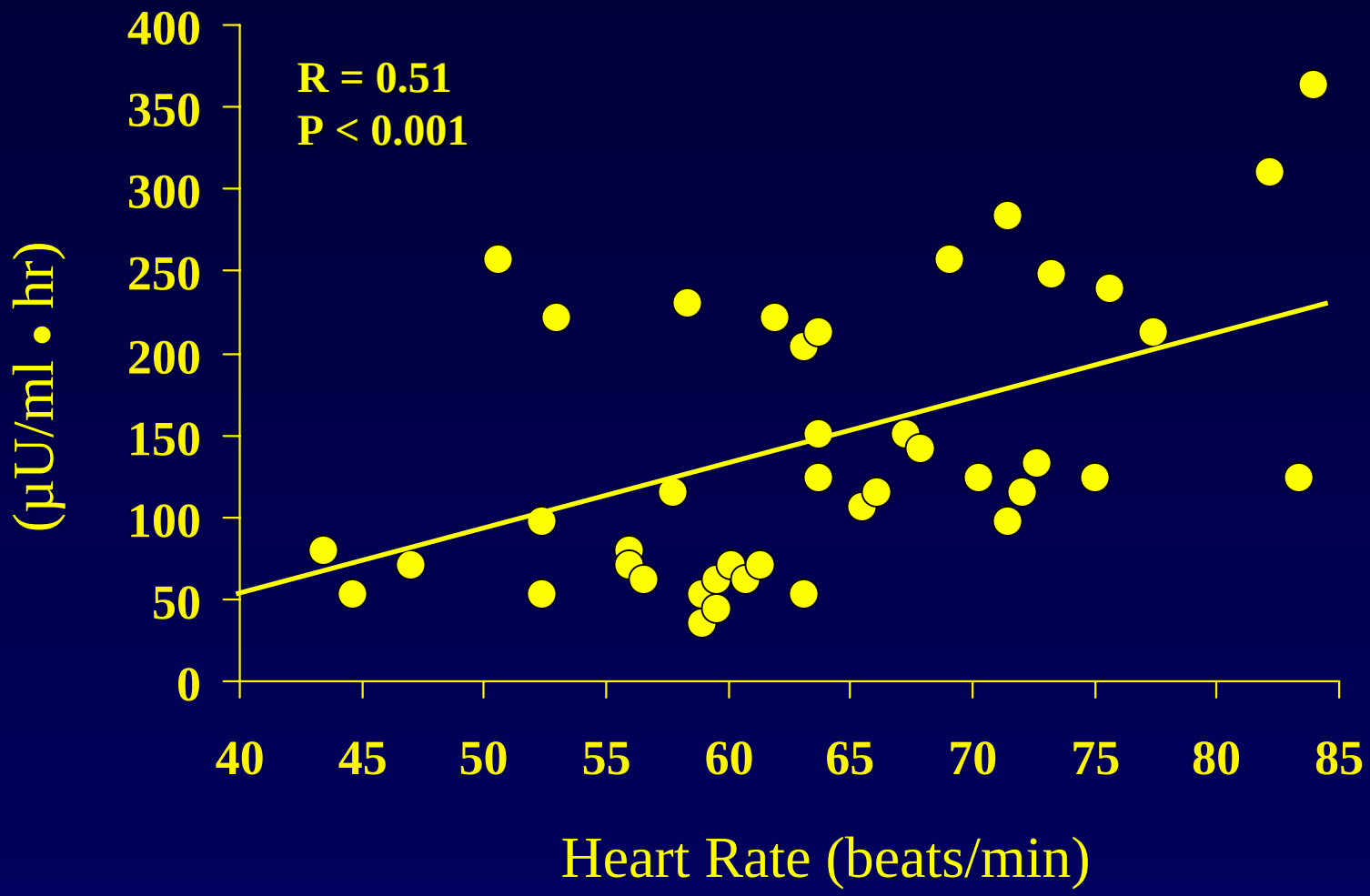
Norepinephrine and renin in mild hypertension



Esler et al. N Engl J Med 1977;296-405

Evidence for association of sympathetic and renin / angiotensine over-activity with hypertension, insulin resistance, and obesity.

Night-time heart rate correlates with insulin insensitivity

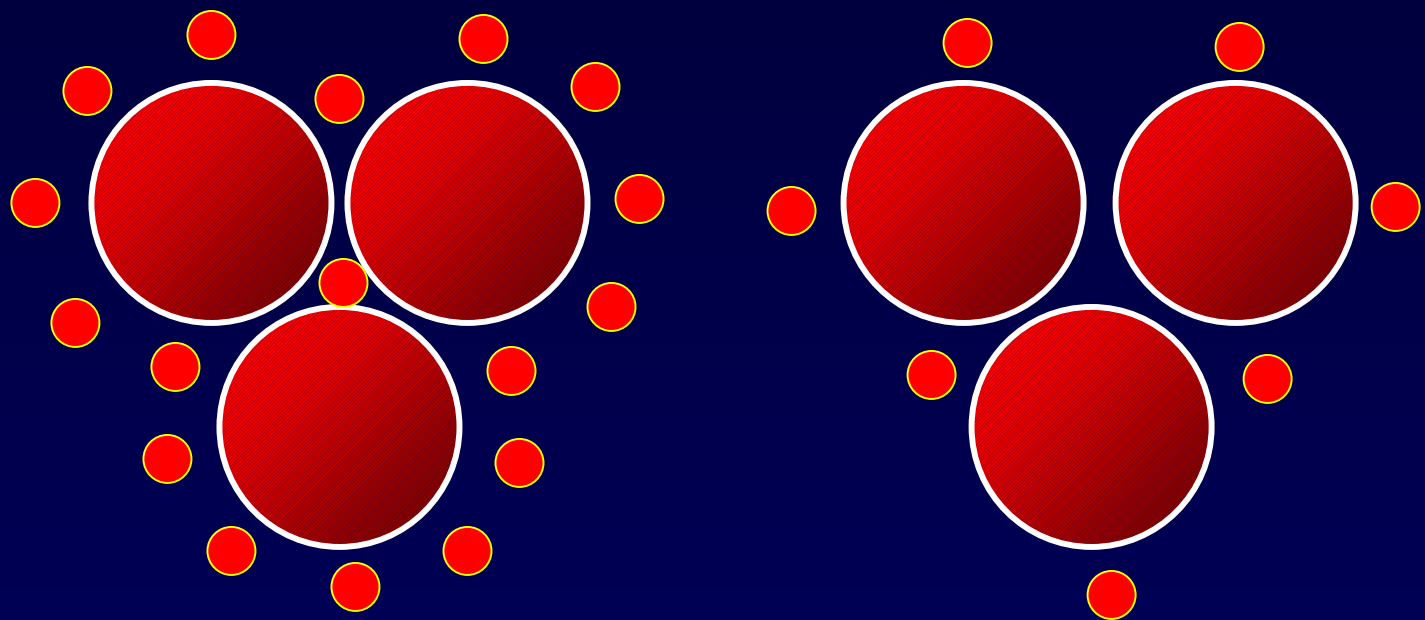


Facchini FS et al. AJH 1996; 9:1013-17

How could sympathetic overactivity cause both a hemodynamic condition (hypertension) and multiple metabolic abnormalities (insulin resistance, hyperlipidemia and obesity)?

1. Glucose and lipid abnormalities
2. Obesity

Schematic Presentation of the Nutritional Blood Flow

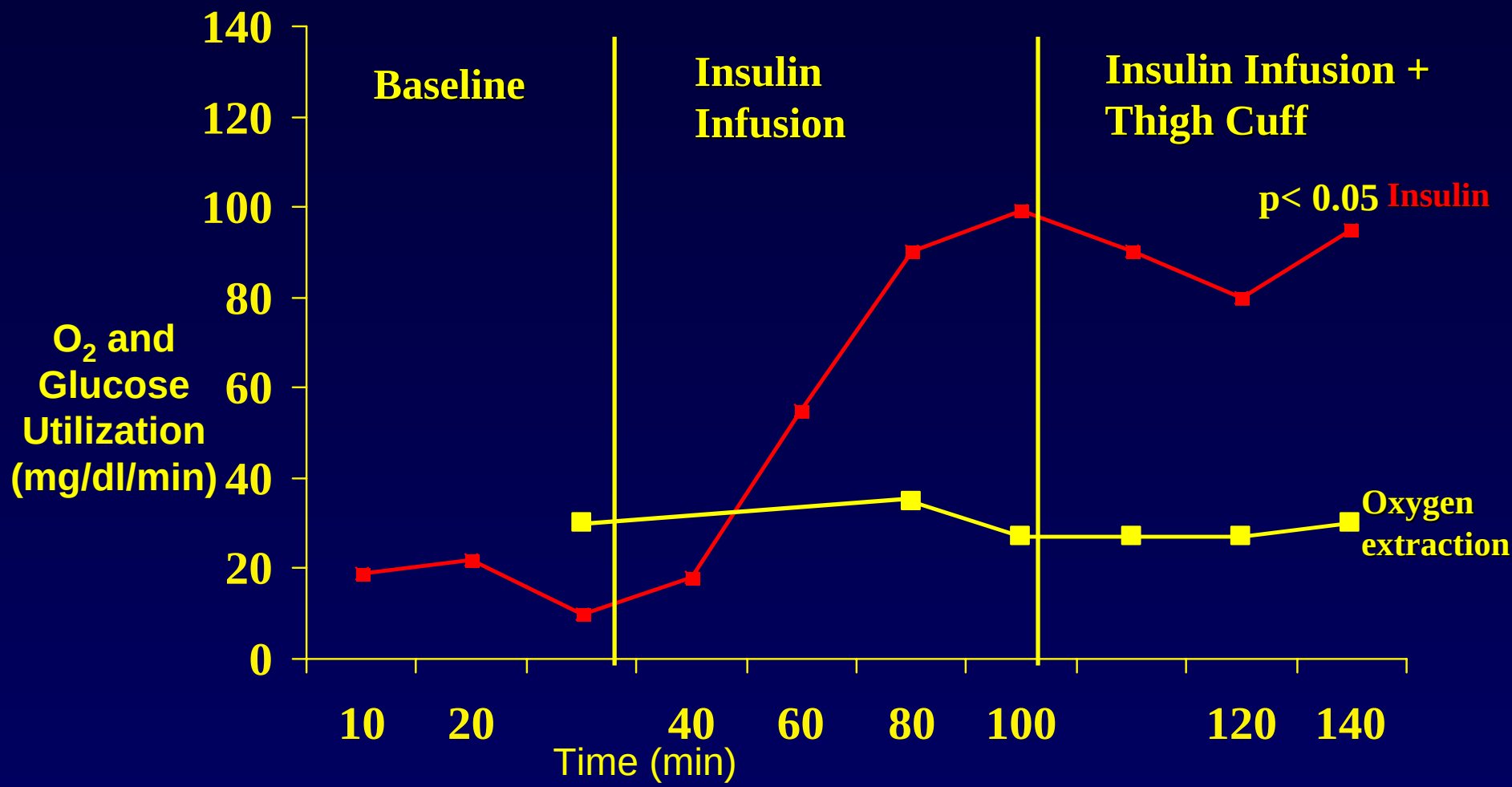


Normal

Insulin Resistance

S. Julius, 2001

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



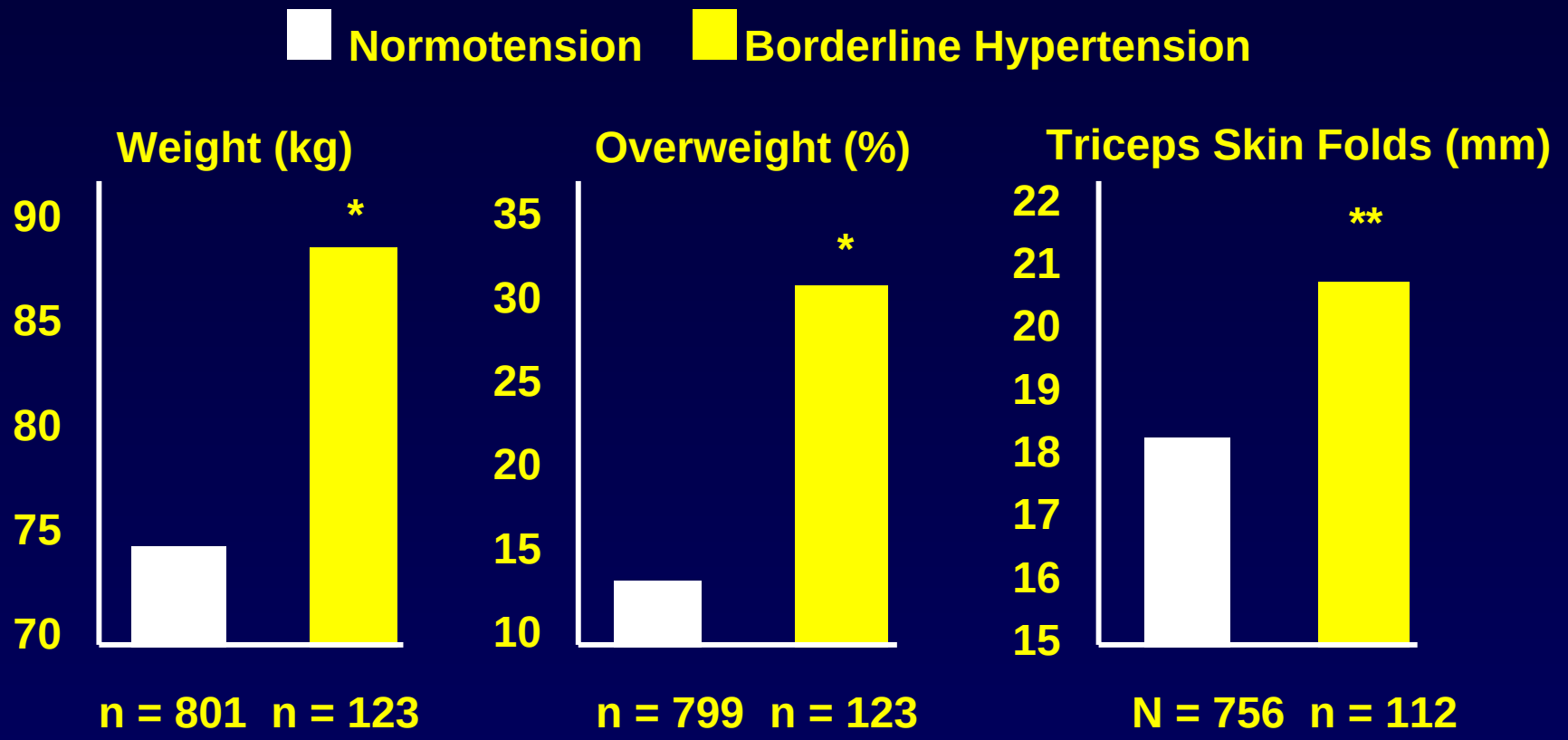
Jamerson KA, Julius S et al. Hypertension 1993;21:618-23.

“Proof” of a relationship of sympathetic overactivity to insulin resistance

1. Vasoconstriction causes insulin resistance

2. Vasodilatation improves insulin sensitivity

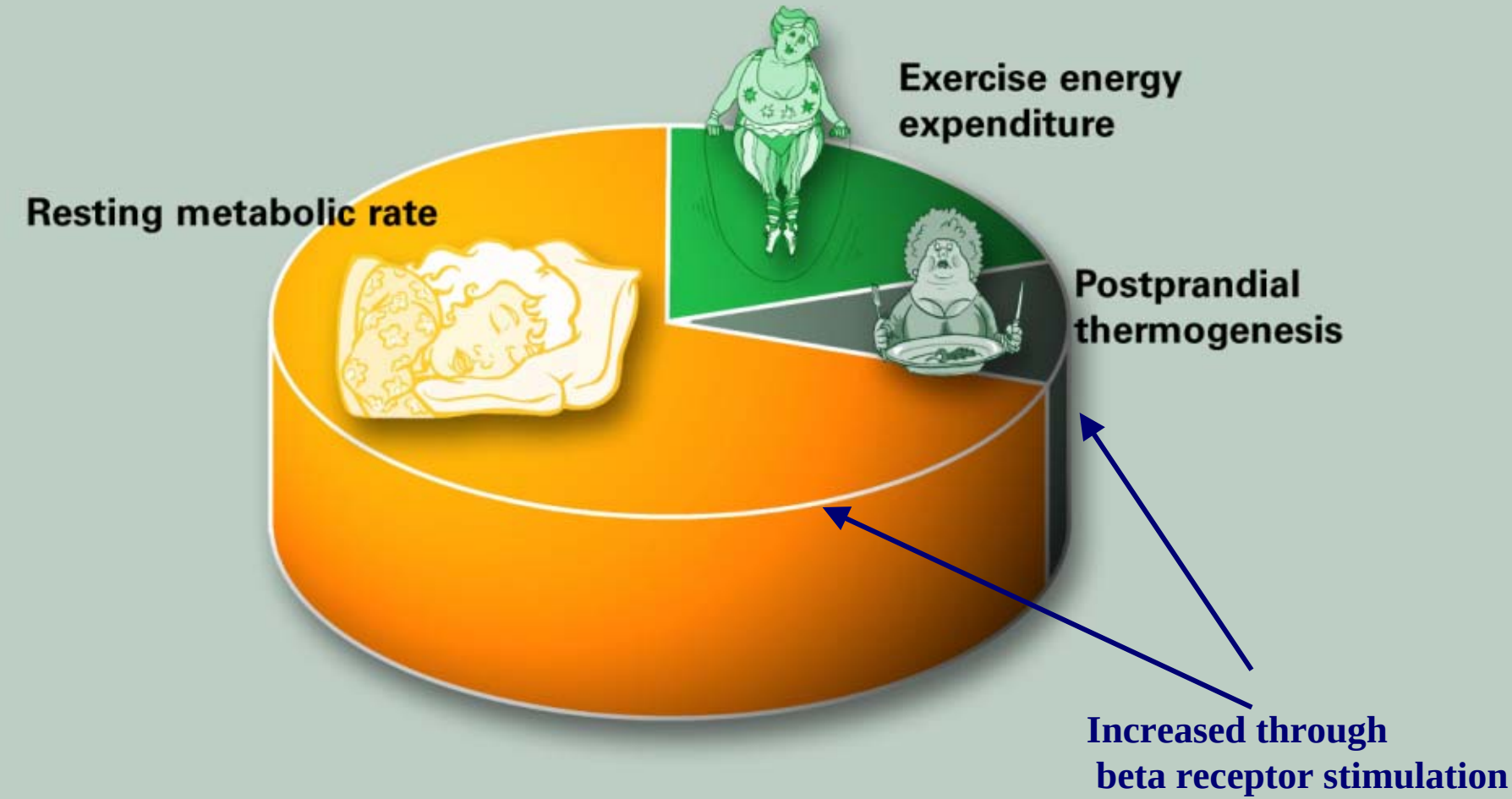
Indices of Body Size: Tecumseh Study



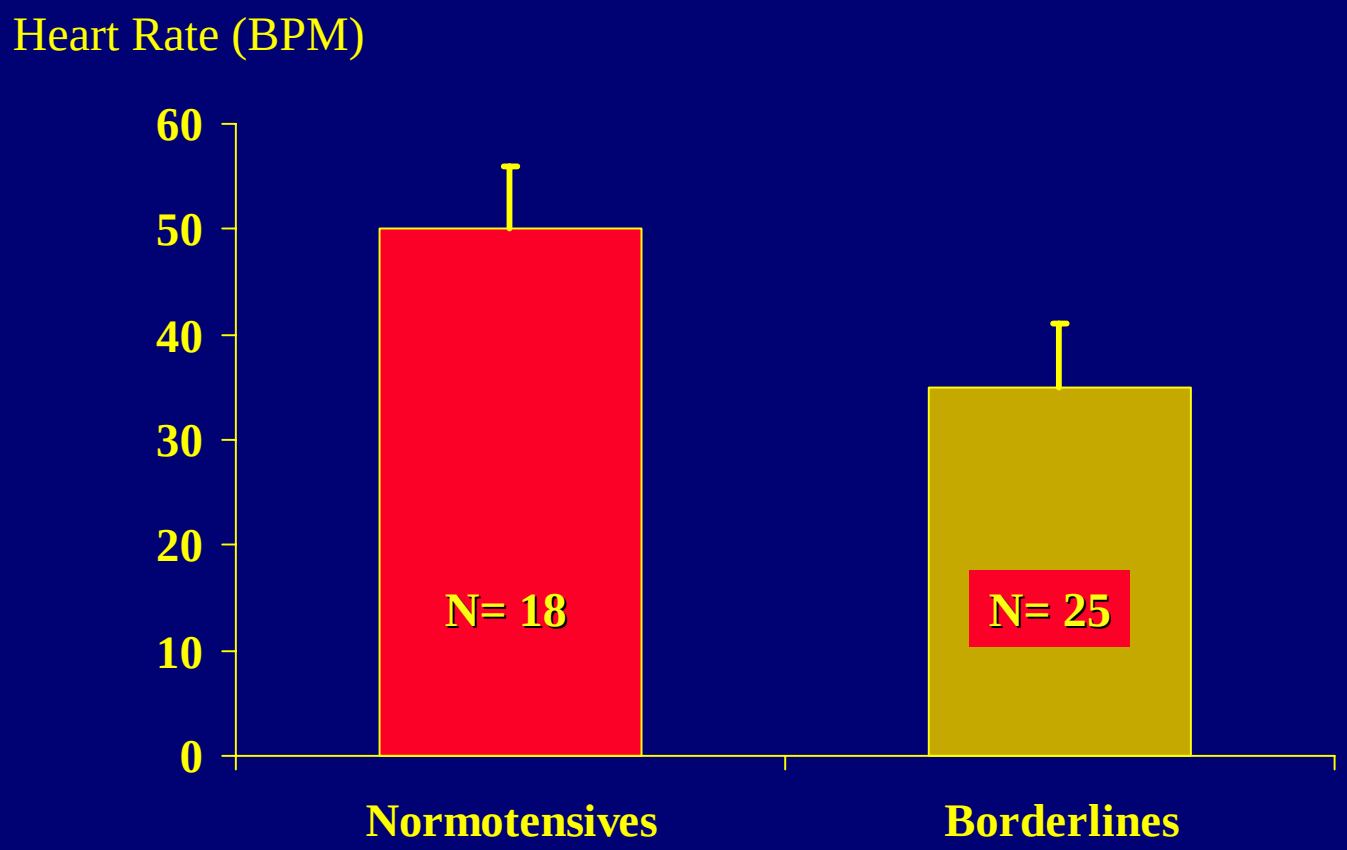
* P<0.001; ** P<0.005

Julius S, et al: JAMA 1990-264:354-358

Components of energy output



CHANGE IN HEART RATE RESPONSE TO ISOPROTERENOL (3 µg/min IV) FROM RESTING MEASUREMENT

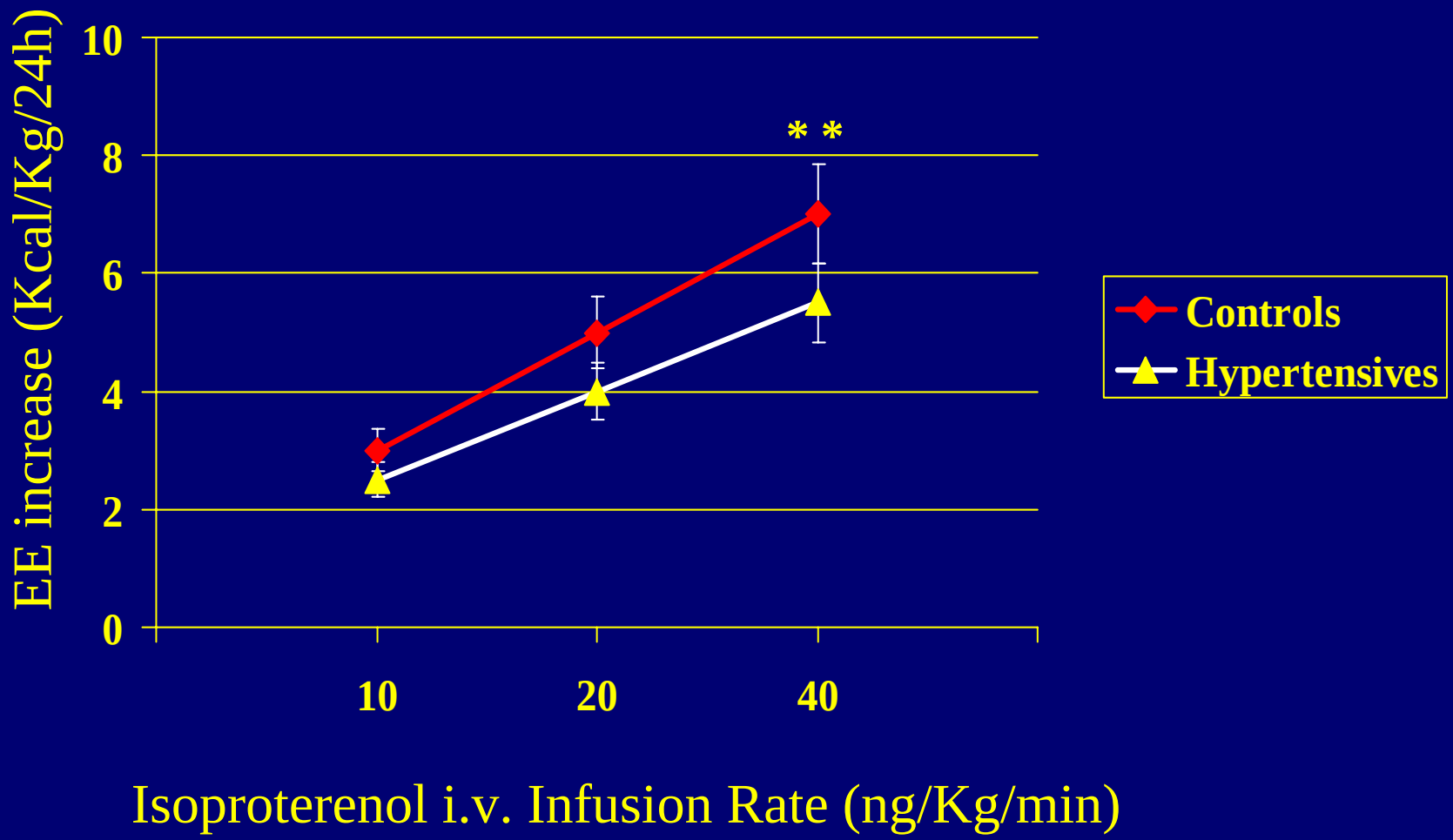


Julius et al, Cir Research 1975; 36-37 (suppl): 199.

HYPOTHESIS

If in addition to cardiovascular responses, the metabolic responses were also decreased in hypertension, the patient's ability to dissipate calories would be diminished and they would gain more weight.

Energy expenditure response to isoproterenolol is decreased in hypertension.



Valentini, Julius, Palatini et al J. Hypertension 2004

2- and 3-Adrenergic Receptor Polymorphisms Are Related to the Onset of Weight Gain and Blood PressureElevation Over 5 Years

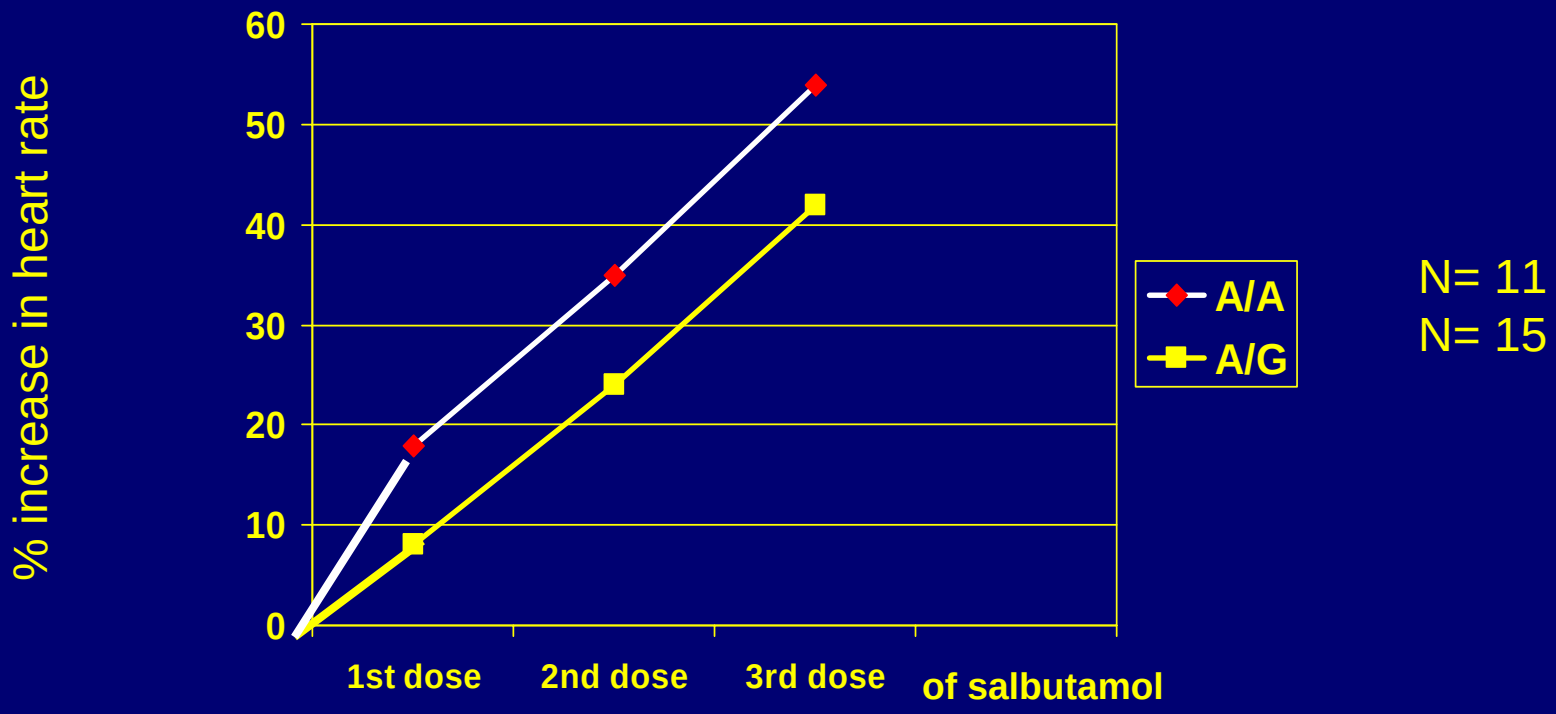
Kazuko Masuo, MD, PhD; Tomohiro Katsuya, MD, PhD; Yuxiao Fu, MD; et al

***Methods and Results*—To longitudinally clarify the relevance to alterations in -adrenergic receptor polymorphisms related to weight gain, blood pressure (BP) elevation, and sympathetic nerve activity as measured by plasma norepinephrine level, we studied 160 young, nonobese, normotensive men**. Changes in body weight, BP, plasma norepinephrine levels, and 2-adrenergic (Arg16Gly, Gln27Glu) and 3-adrenergic (Trp64Arg) receptor polymorphisms were measured periodically over a 5-year period. Weight gain and BP elevation were defined as 10% increases from entry levels over 5 years in body mass index or mean BP. The presence of the Gly16 allele of Arg16Gly was associated with a higher frequency of weight gain and BP elevation over the **5-year period**. The subjects carrying the Glu27 allele of Gln27Glu and the Trp64 allele of Trp64Arg had a higher frequency of BP elevation. Significantly higher levels of plasma norepinephrine at entry and at year 5 were observed in the subjects with the Gly16 allele of Arg16Gly and the Glu27 allele of Gln27Glu compared with those without the Gly16 or the Glu27 alleles.

Conclusions—These results demonstrate that the **Gly16 allele is related to greater weight gain and BP elevation.** Additionally, Glu27 and Trp64 alleles are linked to BP elevation. **The subjects carrying the 2-polymorphisms linked to weight gain and BP elevation also have higher plasma norepinephrine levels that are present at entry before weight gain and BP elevation**. **These findings suggest that 2-adrenergic receptor polymorphisms in association with a heightened sympathetic nerve activity could predict the future onset of obesity and hypertension, as shown in the 5-year longitudinal study.**

(*Circulation*. 2005;111:3429-3434.)

Beta 2 receptor polymorphism and heart rate response of young healthy subjects to infusions (8 min) of increasing doses of beta agonist.



AA= arginine 16 arginine 16
A/G arginine 16 glycine 16

Adapted from Gratze et al Hypertension 1999.