Sympathetic overdrive and the metabolic syndrome in prehypertension. Pathophysiology of obesity and insulin resistance.

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Tachycardia is reliable and practical marker of sympathetic overactivity.

Modified from Grassi G et al, J Hypertens 1998 and 1999
Tecumseh Study Plasma Norepinephrine in All Normotensives vs. Hyperkinetic and Normokinetic Hypertensives

Plasma NE (pg/mL)

400
350
300
250
200

Normotensives (n = 438)

Hyperkinetic Hypertensives (n = 25)

Normokinetic Hypertensives (n = 50)

P < 0.001

P < 0.01

Julius et al., J. Hypertension, 1991
Association of tachycardia with other cardiovascular risk factors in the Tecumseh study

Glucose
Cholesterol
HDL Cholesterol
Insulin
Blood pressure
Hematocrit
BMI
Triglyceride

Heart Rate

Adjusted from Palatini P & Julius S, J Hypertens, 1997
A PERENNIAL SCIENTIFIC PROBLEM

Association ??

A  D
B  C

Causation ??

A  B  C  D
RELATIONSHIP OF TACHYCARDIA AND SYMPATHETIC OVERDRIVE TO OBESITY AND INSULIN RESISTANCE.

--- Is there a plausible mechanism by which the overdrive could cause metabolic syndrome?

--- Did the overdrive precede the metabolic syndrome?
Sympathetic overactivity and insulin resistance - diabetes
A large proportion of subjects with prehypertension has hyperkinetic circulation

The prevalence of hyperkinetic prehypertension determined by noninvasive measurement in an unselected general population of the village of Tecumseh.

Normotensive $n=840$
Prehypertensive $n=124$

Julius et al J of Hypertension 1991, v 9
Heart rate trends in two subpopulations of prehypertension in Tecumseh

Julius et al., J. Hypertension, 1991
HYPOTHESIS

The hemodynamic link between insulin resistance and hypertension.


The question:
How could a hemodynamic abnormality (hypertension) be associated with a metabolic condition (insulin resistance) ??

The answer:
Through changes in microcirculation facilitated by increased sympathetic tone
Schematic Presentation of the Nutritional Blood Flow

Normal

Insulin Resistance

S. Julius, 2001
The Isolated Perfused Human Forearm

Testing the hypothesis Jamerson KA,
Julius S et al. Hypertension
1993;21:618-23
The Effect of Insulin Infusion and Reflex Vasoconstriction on Glucose and Oxygen Extraction in the Forearm of 14 Healthy Volunteers

The chart shows the change in glucose and oxygen utilization with time during baseline, insulin infusion, and insulin infusion with thigh cuff. The y-axis represents O₂ and glucose utilization (mg/dl/min) ranging from 0 to 140. The x-axis represents time in minutes from 10 to 140.

- **Baseline**: Glucose and oxygen utilization remain relatively stable.
- **Insulin Infusion**: There is a significant increase in glucose and oxygen utilization, peaking at around 80 minutes.
- **Insulin Infusion + Thigh Cuff**: Utilization decreases after the peak, with a noted decrease in O₂ extraction marked by "p<0.05".

References:
Effects of antihypertensive agents on insulin sensitivity

Index another argument supporting the concept that vasoconstriction causes insulin resistance.

*Data derived from various double-blind and open studies
FASTING PLASMA INSULIN ADJUSTED FOR CONFOUNDERS IN THE SUBJECTS CLASSIFIED AS HAVING NORMAL HR OR HIGH HR ACCORDING TO MIXTURE ANALYSIS (The Tecumseh Study)

Palatini P et al, Hypertension 1997; 30: 1267
Stratified resting Heart Rate and OR (95% CI)* of developing Metabolic Syndrome in 4 years in 89,860 Chinese People

0.80(0.66-0.98)

1.08(1.01-1.16)

1.17(1.09-1.25)

1.22(1.10-1.35)

1.41(1.21-1.65)

*adjusted for other risk factors and confounders

Sympathetic overactivity and overweight- obesity
Indices of Body Size at 32 years of age in the Tecumseh Study


* P<0.001; ** P<0.005
Heart rate trends in "pure hyperkinetic prehypertension" (n = 24, &) and normotensives (n = 787) in the Tecumseh study.

Prehypertension vs Normotension:
- P < 0.0001

Prehypertensive with elevated Li–Na counter-transport eliminated

S. Julius K. Jamerson, J. Hypertension, 1994
Arm Girth and Subscapular Skin folds at 6 years of age and 21 years in subjects classified at 32 yrs of age as normotensives (●) and Borderline hypertensives (○).

High BP and tachycardia first obesity later. How come?

*P<0.0015; †P<0.001

Increased through beta receptor stimulation
Over a period of 30 years the Ann Arbor group investigate the heart rate response to beta adrenergic agonist in 3 separate experiments on 3 different hypertensive populations.

Valentini, Julius, Palatini et al J. Hypertension 2004

In each study hypertensive patients had a suppressed heart rate increase to beta adrenergic agonists.

HYPOTHESIS:
If in addition to cardiovascular responses, metabolic responses to isoproterenol were also decreased in hypertension, patient’s ability to dissipate calories would be diminished.
Material.
13 patients with stage I hypertension
25 normal controls (similar age and gender)

Design.
Day one. Lab tests, Heart rate response to increasing doses of isoproterenol (bolus)

Day two: Hemodynamic, electrolyte, glucose and energy expenditure responses to increasing doses of isoproterenol (infusion)

Valentini, Julius, Palatini et al J. Hypertension 2004
Heart rate response to graded increase of beta adrenergic stimulation

Valentini, Julius, Palatini et al J. Hypertension 2004
Energy expenditure response to isoproterenol is decreased in hypertension.

Valentini, Julius, Palatini et al. J. Hypertension 2004
Correlations of 24h Urinary Norepinephrine With *Heart Rate* Responsiveness and *Energy Expenditure (EE)* Responsiveness at the Highest Isoproterenol Dose in the Whole Study Population

Long term sympathetic stimulation in hypertension elicits down regulation of beta adrenergic receptors. This decreases patients' ability to “burn off” excessive calories and favors gain of weight.

In most patients the weight gain is not due to insufficient willpower or lack of motivation for life style modification; rather it reflects a physiologic imperative.