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
Survival and longevity are two unrelated aspects of living.

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

S. Julius, 2000
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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Heart rate trends in hyperkinetic hypertensives

From the Tecumseh Study
Elevated HR: Long-Term Link to Hypertension

- Transient tachycardia and hypertension
- Transient tachycardia
- Transient hypertension
- Normotension

From Levy et al, JAMA 1945
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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.”

Schork et al; Statistics In Medicine v.9 1990
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.

Palatini P et al, Hypertension 1997; 30: 1267
Hemodynamic profiles using the mixture analysis in the Tecumseh study

The parents of hyperkinetic individuals also had elevated BP.

Julius et al J of Hypertension 1991, v 9
Tecumseh Study Plasma Norepinephrine in All Normotensives vs. Hyperkinetic and Normokinetic Hypertensives

Julius et al., J. Hypertension, 1991
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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HR and Mortality in a Japanese General Population: an 18-year Follow-up Study

Palatini P. J. Hypertension 2006 24, 603
Palatini P. Hypertension 2011 58, 745

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Mechanism by which tachycardia increases cardiovascular risk

- Marker of multiple other risk factors
- Mechanical cardiovascular damage
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

Adapted from Giannoglou G et al. *Int J Cardiol*. 2008;126:302-312

- **Magnitude/frequency of mechanical load**
- **Frequency of periodically changing coronary geometry**
- **Shortening of diastolic period**
- **Low endothelial shear stress**
- **Shift of endothelial cells to an atherosclerotic phenotype**

**Atherosclerosis**

- **Elevated heart rate**
- **Wall stiffness**

**Plaque rupture**
Mechanism by which tachycardia increases cardiovascular risk

Marker of multiple other risk factors

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

- Cholesterol
- HDL Cholesterol
- Triglyceride
- Insulin
- Glucose
- Hematocrit
- Blood pressure
- BMI

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

Increased through beta receptor stimulation.

Valentini, Julius, Palatini et al J.Hypertension 2004: Energy expenditure response to isoproterenolol 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.

Valentini, Julius, Palatini et al J. Hypertension 2004
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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-- We understand mechanism of the deleterious effects of tachycardia
Heart Rate Distribution in Subjects With Hypertension (n=38,145)

Farinaro E et al, Nutr Metab Cardiovasc Dis 1999:9;196
Heart Rate and All-Cause Mortality

The Framingham Study

Kannel WB et al 1987;113:1489
HEART RATE SLOWING IMPROVES MYOCARDIAL O₂ SUPPLY AND DEMAND BALANCE

Heart rate reduction

↓ Heart rate

↓ Metabolic demand

↓ Oxygen consumption

↑ Diastolic perfusion time

↑ Coronary perfusion

↑ Oxygen supply

Better balance demand supply O₂ = 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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sign</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>+</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>+</td>
<td>0.0001</td>
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<tr>
<td>BMI</td>
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<tr>
<td>HDL-chol.</td>
<td>-</td>
<td>0.002</td>
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</table>

### 6-to-10-year mortality

<table>
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<tr>
<td>Heart rate</td>
<td>+</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>+</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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Menotti A et al, Eur Heart J 2001;22:573
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

Schork et al; Statistics In Medicine v.9 1990
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

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

Palatini P et al, Hypertension 1997; 30: 1267
1976
(cardiac index by dye dilution method)

L/min/m²

Borderline hypertension
n = 145

Controls
n = 85

S. Julius in “Nervous System in Hypertension” C.S. Thomas 1976
The Isolated Perfused Human Forearm
The Effect of Insulin Infusion and Reflex Vasoconstriction on Glucose and Oxygen Extraction in the Forearm of 14 Healthy Volunteers

O$_2$ and Glucose Utilization (mg/dl/min)

Time (min)

Baseline
Insulin Infusion
Insulin Infusion + Thigh Cuff

Oxygen extraction

p < 0.05

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.