Autonomic Imbalance Predicts the Development of Metabolic Syndrome

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Background

- obesity, diabetes, CAD share common (rarely treated) mechanism: autonomic imbalance

**autonomic imbalance:**
- too much sympathetic tone
- too little parasympathetic tone

- metabolic syndrome is a precursor condition for obesity, diabetes, and CAD
Background

- **metabolic syndrome (MetS) definition:**
  - high fasting glucose
  - high triglycerides
  - low HDL
  - high blood pressure
  - high waist circumference

- affects 1/3 of U.S. population
- increased rates of CAD, DM II, mortality
- avg annual cost increase of 24% per MetS component
Debate

- Does “metabolic syndrome” add any public health value beyond the sum of its parts?
- Reaven (2010), one of the early definers of the syndrome, does not think so...
Autonomic Imbalance

- sympathetic overactivity, parasympathetic underactivity
- only mechanism associated with all 8 major CAD risk factors
- measurable, treatable
- predictive?
Associational Evidence

- Licht, CM (2010):
  - in large Dutch community sample, baseline autonomic imbalance (HR and HRV), but not HPA axis, related to MetS
  - dose-response relationship relative to number of components of MetS

- Gehi, AK (2009): Twins Heart Study
  - in 288 twins, controlling for genes and environment, MetS associated with low HRV
  - each additional component of MetS assoc with lower HRV
Predictors of MetS

Franco, OH (2009): Framingham Heart Study

- FHS Offspring (N=3078)
- 1980’s, 10 yr f/u
- prevalence of MetS doubled: 23.5% to 40.6%
- Does first condition predict development of MetS?
  - central obesity conferred the highest risk (OR 4.75)
  - in women, HBP tended to be first condition
  - in men, low HDL tended to be first condition
Hypothesis

- Autonomic imbalance at baseline will significantly increase the odds of developing MetS within 12 years.
Participants

- FHS Offspring cohort (first enrolled 1971-75)
- complete “baseline” visit 3 data (1983-87) for
  - EKG (resting heart rate/RHR)
  - 2-hour Holter monitor (heart rate variability/HRV)
  - MetS measures
- 18 or older at baseline
- N=1882
- excluded: MetS at baseline (539), incomplete f/u (197)
- final sample N=1143
Participant Selection

Offspring cohort
N=1882

Baseline MetS?

Yes
N=539

No
N=1342

Unknown
N=1

MetS at 4-, 8- and/or 12-Year Follow-Up?

"Ever"
N=504

"Never"
N=641

Unknown
N=197

N=1145

*Sample Used*
N=1143

Baseline smoking data missing
N=2
Measures

- autonomic imbalance
  - RHR from EKG
  - HRV from 2-hr Holter monitor, the SD of beat-to-beat interval (SDNN)
### Measures

<table>
<thead>
<tr>
<th>Metabolic Syndrome Component</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>(1) Elevated triglycerides</td>
<td>$\geq 150\text{mg/dL (1.7 mmol/L)}$ or drug treatment for elevated triglycerides</td>
</tr>
<tr>
<td>(2) Lowered high-density lipoprotein</td>
<td>$&lt; 40\text{mg/dL (1.0 mmol/L)}$-Male / $&lt; 50\text{mg/dL (1.3 mmol/L)}$-Female</td>
</tr>
<tr>
<td>cholesterol (HDL-C)</td>
<td>or drug treatment for lowered HDL-C</td>
</tr>
<tr>
<td>(3) Elevated blood pressure</td>
<td>systolic $\geq 130\text{mm Hg}$ and/or diastolic $\geq 85\text{mm Hg}$ or antihypertensive drug treatment for hypertension</td>
</tr>
<tr>
<td>(4) Elevated fasting glucose</td>
<td>$\geq 100\text{mg/dL}$ or drug treatment for elevated glucose</td>
</tr>
</tbody>
</table>
| (5) Increased waist circumference*           | $> 102\text{cm – males}$  
                                 | $> 88\text{cm – females}$                                                 |

*Because waist circumference (WC) was not available at baseline, we substituted Body Mass Index (BMI) for this component and used the cutoff of $\geq 25$. 
### Analyses

- secondary analysis
- logistic regression model
  - [backward elimination variable selection](#)
- predictor variables: RHR, HRV
- covariates: age, gender, cigarettes/day, depressive sx (CESD)
- outcome variables: MetS status at any time after baseline (4-, 8-, 12- yr f/u)
Results

- sample characteristics at baseline (N = 1143)
  - mean age 46.6 ± 9.9
  - females 57%
  - cigarettes/day 5.6 ± 11.5
  - RHR (bpm) 64.4 ± 9.9
  - SDNN (msec) 0.099 ± 0.027
Results

- best model:
  - MetS predicted by HRV (SDNN)
    - age
    - gender
    - smoking
  
  AUR = 0.665
  Hosmer Lemeshow Goodness-of-fit p value = 0.73
Results

- 1 SD of decrease in HRV increased the odds of developing MetS within 12 yrs by 43% (95% CI 30%-57%, p<0.001)
- for each 1 yr increase in age, the odds of MetS increased by 2.2% (95% CI 1.4%-2.9%, p<0.001)
Results

- for each additional cigarette smoked per day, the odds of MetS increased by
  
  **1.8%** (95% CI 0.8%-3.0%, p<0.005)

- for males (vs. females) the odds of MetS was higher by
  
  **2.2x** (95% CI 1.73-2.83., p<0.001)
Results

Predicted Probability of Metabolic Syndrome
mean age=46.59  mean cigarettes=5.62

Probability

HRV SDNN

Gender  Female  Male
Results

- without HRV, RHR was significant predictor:
- for each increase in RHR by 10 bpm, the odds of MetS increased by

  24% (95% CI 9.4%-42%, p<0.001)

- effect of gender and smoking similar to HRV model, but effect of age in RHR model was somewhat greater
Discussion

- first report of evidence that autonomic imbalance predicts the development of MetS in a community sample
- as HRV drops by half, risk for MetS doubles
- 1 SD decrease in HRV is equal to the effect of
  - 16 additional years
  - nearly 1 ppd of cigarettes
- effect of HRV on risk for MetS may be as important as age and smoking
Discussion

- RHR also proved to be an independent predictor of MetS, though not as strong as HRV
  - not yet clear why

- Limitations
  - sample Caucasian, middle aged, middle class
  - no analyses yet on duration of autonomic imbalance
  - HRV based on 2-hr Holter (not 24-hr)
  - no data on insulin resistance, physical activity, inflammation, which may influence this relationship
Implications

- initial proof of concept
- support for prospective observational study of new high risk group:
  - high RHR, low HRV
  - 1-2 metabolic risks
- support for potential prevention intervention trials:
  - Does correcting autonomic imbalance reduce the risk for MetS?