Autonomic Imbalance as a Predictor of Metabolic Risks, Cardiovascular Disease, Diabetes, and Mortality

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Context: Identifying novel early predictors of metabolic disorders is essential to improving effective primary prevention.

Objectives: The objectives were to examine the contribution of two measures of autonomic imbalance, resting heart rate (RHR) and heart rate variability (HRV), on the development of five metabolic risk outcomes, and on cardiovascular disease, diabetes, and early mortality.

Design: This study was a secondary analysis of prospective data from Offspring Cohort participants (N = 1882) in the Framingham Heart Study (FHS).

Participants: Participants at FHS Exam 3 (1983–1987) with 1) age years 18 or older, and 2) data on RHR, HRV, and five measures of metabolic risk (blood pressure, fasting glucose, triglycerides, high-density lipoprotein [HDL] cholesterol, and body mass index [BMI]) at three follow-up visits over 12 years. We conducted a backward elimination variable selection procedure on a logistic regression model, using baseline RHR, HRV, age, sex, and smoking status to predict the odds of developing a specific metabolic risk.

Outcomes: Measures included hyperglycemia, high blood pressure, high triglycerides, low HDL cholesterol, and high BMI over 12 years; incident diabetes, cardiovascular disease, and early mortality over 20 years.

Results: RHR and HRV, along with sex, age, and smoking were significant predictors of high blood pressure, hyperglycemia, and a diagnosis of diabetes within 12 years. RHR and HRV also predicted the development of cardiovascular disease and early mortality for most of the sample.

Conclusions: In this community sample two measures of autonomic imbalance predicted multiple poor metabolic outcomes and mortality, making autonomic imbalance a potentially worthy target for intervention studies to reduce risks for cardiovascular disorders, diabetes, and early death. (J Clin Endocrinol Metab 100: 2443–2448, 2015)

The prevention of our most costly chronic conditions — obesity, diabetes, and heart disease — depends in part on the identification of early predictors of metabolic risk. One approach to establishing a threshold of risk for these conditions has focused on the common co-occurrence of multiple risk factors, such as high blood pressure (BP), high fasting blood glucose, and high lipids. Proponents of this approach have offered various definitions of the “metabolic syndrome” over the past 30 years to identify a group of people who have high risks of later developing...
type 2 diabetes (diabetes mellitus [DM]), coronary heart disease (CHD), and early death (1–4). Challenges to the public health value of the concept of metabolic syndrome have come from the authors of the multiple definitions, the American Diabetes Association, and the European Association for the Study of Diabetes (5), and most recently, from one of the earliest proponents of the metabolic syndrome concept (6).

The debate regarding the utility of the concept of metabolic syndrome exposes our lack of understanding about the pathophysiology of the process that leads to the co-occurrence of various metabolic risk factors. Insulin resistance plays a role in the early development of obesity, central adiposity, hyperglycemia, and hyperlipidemia (7); its role in the development of hypertension is less clear but may be related to compensatory hyperinsulinemia, which increases sympathetic nervous system activity (8).

Another factor that may contribute to the pathophysiology of these co-occuring metabolic risk factors is autonomic imbalance, which refers to excessive sympathetic activity and too little parasympathetic activity (9). Common measures of autonomic imbalance include resting heart rate, heart rate variability, and heart rate recovery (10). We recently found that autonomic imbalance, as measured by low heart rate variability and high resting heart rate, predicted the development of metabolic syndrome within 12 years in the Framingham Heart Study (FHS) offspring cohort, controlling for age and smoking (Wulsin, unpublished).

In a related analysis of the FHS, Franco and colleagues (11) examined the predictive value of first metabolic conditions on a range of metabolic outcomes and found that obesity conferred the highest risk of developing metabolic syndrome. In the other prospective study of predictors of metabolic risk, building on their findings of a cross-sectional association between autonomic imbalance and metabolic risk (12), Licht and colleagues (13) reported that in their 2-year followup of their Netherlands longitudinal sample four measures of autonomic imbalance predicted increases in the number of metabolic risks. Specific autonomic imbalance measures predicted increases in BP or decreases in high-density lipoprotein (HDL) cholesterol.

The first aim of this study was to examine in the FHS Offspring Cohort whether autonomic imbalance, measured by resting heart rate and heart rate variability, is an independent predictor of each of the five components of metabolic syndrome: 1) hyperglycemia, 2) high BP, 3) high triglycerides, 4) low HDL, and 5) high body mass index (BMI). The second aim was to examine whether autonomic imbalance predicts the development of cardiovascular disease, diabetes, and early mortality in this community sample. We hypothesized that autonomic imbalance would independently predict each of these eight outcomes.

Materials and Methods

Participants

The FHS Offspring Cohort was first examined in 1971–1975 and approximately every subsequent 4–8 years. We included subjects who met the following criteria at baseline (examination 3; 1983–1987): 1) age 18 years or older, and 2) had data on resting heart rate, heart rate variability, and five measures of metabolic risk (high BP, hyperglycemia, high triglycerides, low HDL, and high BMI).

From the initial sample of 1882, for each analysis examining the effect of autonomic imbalance on the incidence of each of the five metabolic factors, we selected that baseline subgroup that did not have the specific metabolic outcome of interest. For example, the size of the subgroup for the hyperglycemia regression (N = 1056) differed from the size of the subgroup for the high BP subgroup (N = 827).

Measures

Autonomic imbalance

Of the many available measures of autonomic imbalance (10), we focused on two measures: resting heart rate and heart rate variability. These measures appear commonly in the literature and are obtainable in primary care settings. For resting heart rate (RHR), we used the heart rate from the electrocardiogram, which was performed on each participant during the baseline clinic examination (1983–1987). For heart rate variability (HRV), we abstracted from the 2-hour Holter monitor data obtained during the baseline examination all available measures of heart

<table>
<thead>
<tr>
<th>Metabolic Factor</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Elevated triglycerides</td>
<td>≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides</td>
</tr>
<tr>
<td>Lowered LDL cholesterol</td>
<td>&lt;40 mg/dL (1.0 mmol/L)-Male; &lt;50 mg/dL (1.3 mmol/L)-Female or drug treatment for lowered HDL-C</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Systolic ≥130 mm Hg and/or diastolic &gt;85 mm Hg or antihypertensive drug treatment for hypertension</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>≥100 mg/dL or drug treatment for elevated glucose</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥25 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Because WC was not available at baseline, we substituted BMI for this component and used the cutoff of ≥25 kg/m<sup>2</sup>.
rate variability and focused our analyses on SDNN (the SD of beat-to-beat intervals), one of the most studied indices of HRV. The range of Pearson correlations between SDNN and the other common measures of heart rate variability in this sample was 0.60–0.82, all significant at <0.0001.

**Metabolic factors**

We classified metabolic factors as outcomes using the cutoffs from the consensus definition of metabolic syndrome (2). The metabolic factor criteria are listed in Table 1. Because waist circumference (WC) was not available at baseline, we substituted BMI for this component and used the cutoff of at least 25 kg/m². In our study, the correlations between WC and BMI at the follow-up time points were greater than 0.80 and, in another study (14), the correlation between WC and BMI was greater than 0.90.

**Other contributing factors**

To examine the relative contributions of other factors to metabolic risk, we selected covariates in our model for which reliable measures exist in the FHS Offspring database: sex, age, cigarette smoking (cigarettes/d or smoker vs nonsmoker), and current (past wk) depressive symptoms. (Data regarding depressive symptoms did not contribute to any of these models and so are not presented here.) Although potentially important, we did not include physical activity, insulin resistance, or C-reactive protein because these variables were not collected at baseline.

**Other outcomes**

For the second aim of this study, to examine the effect of autonomic imbalance on the development of diabetes (on diabetes medication or fasting glucose ≥126 mg/dL), cardiovascular disease (CVD), and early mortality we abstracted from the FHS Offspring data the consensus clinical diagnoses for CVD and data on death for the 20-year period following the baseline visit, that is 1987–2007. Incident CVD was assessed according to previously reported standardized criteria, including CHD (recognized or unrecognized myocardial infarction, angina pectoris, coronary insufficiency, or CHD death), cerebrovascular disease (stroke or transient ischemic attack), or CHF. Outcome events were adjudicated by a panel of three physicians after review of all available information, hospitalization records, and physician charts. A cause of death was obtained from death certificates, hospital admission records, medical records, and family members. All deaths were adjudicated by a panel of three investigators.

**Analyses**

For each metabolic syndrome factor, we conducted a logistic regression with backward elimination. The outcome variable was the dichotomous status of each metabolic syndrome factor at any follow-up time point within 12 years of baseline. We used the independent baseline variables of autonomic imbalance (RHR, HRV) and the covariates of age, sex, cigarette smoking, as well as their second-order interactions with autonomic imbalance, to predict the odds of developing each metabolic factor within 12 years. Thus, for this part of the analysis we conducted 10 separate logistic regressions. We considered models to be adequate if their Hosmer-Lemeshow GoF P ≥ .1 and the area under the receiver operating characteristic curve (AUR) was 0.65 or greater. Analyses were conducted with SAS v.9.2 (SAS Institute, Cary, NC) and the significance level retaining variables in the models was two-sided α = 0.05.

We followed a similar procedure to examine the effect of RHR and HRV on time to CVD and death, conducting Cox proportional hazards for the time to CVD and death and logistic regression for incident diabetes (diagnosis of diabetes within 12 years of baseline).

**Results**

The sample consisted of 1882 participants, nearly all of whom were Caucasian. The baseline age was 48 ± 10 years; there were more females than males (52% vs 48%); current smokers comprised 29% of the sample, and the baseline cigarettes smoked was 5.6 ± 11.5 cigarettes per day (median, 0 cigarettes/d). The baseline resting heart rate was 65.2 ± 10.6 beats per minute and the baseline heart rate variability (SDNN) was 0.094 ± 0.028 milliseconds. Tables 2 and 3 show the characteristics of the sample. Table 4 shows the sizes of each of the outcome variable subsamples at baseline, the number of cases identified for each outcome subsample during follow-up, and the number of subjects missing the outcome variable at some point in the follow-up. Sample characteristics of each of the eight outcome subgroups are available upon request.

Table 5 shows the models for predictors of the five metabolic factors. HRV and RHR, along with sex, age,

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**Table 2. Baseline Variables (n = 1882)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (sd)</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>48.0 (10.0)</td>
<td>21–76</td>
</tr>
<tr>
<td>Cigarettes, n/d</td>
<td>5.6 (11.5)</td>
<td>0–80</td>
</tr>
<tr>
<td>RHR, beats/min</td>
<td>65.2 (10.6)</td>
<td>36–117</td>
</tr>
<tr>
<td>HRV, msec</td>
<td>0.094 (0.028)</td>
<td>0.015–0.218</td>
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**Table 3. Baseline Variables (n = 1882)**

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>909</td>
<td>43</td>
</tr>
<tr>
<td>Female</td>
<td>973</td>
<td>57</td>
</tr>
<tr>
<td>Smokers</td>
<td>537</td>
<td>27</td>
</tr>
</tbody>
</table>

**Table 4. Outcome Variables (n = 1882)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (Excluding Participants with Baseline Prevalence of the Variable)</th>
<th>Positive Cases (%)</th>
<th>Missing Cases</th>
</tr>
</thead>
</table>
and smoking status were significant predictors of high BP and hyperglycemia within 12 years of baseline. None of the other logistic regression models yielded adequate coefficients for the AUR as well as the goodness of fit (GoF).

Table 6 shows the Cox proportional hazard models for the time to CVD and death. Along with various combinations of sex, age, and smoking status, HRV predicted CVD and death for males. RHR predicted CVD in the younger half of the sample and the sample for both sexes. Logistic regression for the prediction of a diagnosis of diabetes within 12 years showed that HRV and RHR, along with age, sex, and smoking status predicted incident diabetes (for HRV, odds ratio [OR] = 0.549; 95% confidence interval (CI), 0.429–0.701; \( P < .0001 \); AUR = 0.70; GoF P = .54; for RHR, OR = 1.638; 95% CI, 1.364–1.966; \( P < .0001 \); AUR = 0.70; GoF P = .14). Among nonsmokers HRV remained a significant predictor of CVD, diabetes, and death (data available upon request).

### Discussion

To our knowledge this is the first report to examine the effect of resting heart rate and heart rate variability on the development of each of the five metabolic factors of the metabolic syndrome, CVD, diabetes, and early mortality. Whereas both RHR and HRV significantly predicted hyperglycemia and high BP within 12 years, the evidence for the contribution of these autonomic imbalance variables to the development of the other three metabolic factors was not statistically as strong. In addition, in this sample HRV predicted the development of CVD and diabetes, as well as early death for males. RHR predicted CVD for the younger half of the sample, incident diabetes, and early death.

These findings elaborate on our recent analyses in this cohort of the role of RHR and HRV in the development of
metabolic syndrome (Wulsin, unpublished), in which both RHR and HRV significantly predicted the development of metabolic syndrome. In the current report our analyses of the role of RHR and HRV on individual components of the metabolic syndrome suggest that in this sample the bulk of the influence of RHR and HRV on metabolic syndrome may be exerted through their effects on high BP and hyperglycemia. It is not yet clear why these autonomic imbalance measures better predicted these two outcomes, compared with BMI, HDL, and triglycerides. It is possible that in our sample lipids were more influenced by insulin resistance or some other factor than by autonomic activity. Our findings contrast with those of Licht and colleagues (13), who found effects of autonomic imbalance on high BP and lipids but not on glycemic control. These differences in results may be attributed to differences in samples, measures of autonomic imbalance, and duration of followup (12 vs 2 y). These differences also reflect the complexity of the factors which contribute to metabolic risks.

The size of the effect of autonomic imbalance on metabolic disorders and early death in most of our analyses was comparable to the effects of age, sex, and smoking status. For example, one SD decrease in HRV was equivalent to an additional 16 years in age for the prediction of incident diabetes (further data available on request). This decrease in HRV could be the result of increased sympathetic tone, decreased parasympathetic tone, or both. Among nonsmokers as well as smokers, autonomic imbalance is a modifiable risk factor that could provide a novel target for interventions to reduce metabolic risk. Given that chronic stress has been associated with increased sympathetic tone and decreased parasympathetic tone (9), future research should examine whether autonomic imbalance may represent a useful early marker of stress-related risk for metabolic disorders.

In an effort to follow the example of the earlier analysis of this cohort by Franco and colleagues (11), we have shown that, like selected first conditions of metabolic syndrome, autonomic imbalance predicted metabolic risks, the development of CVD and DM, and early death. These findings lend support to the concept of metabolic syndrome by showing that it may represent a pathway from autonomic imbalance to CVD, DM, and early death.

However, these findings must be considered in the context of several limitations. The sample was Caucasian, middle aged, and mostly middle class, so our findings may not apply to other populations. We selected baseline measures of autonomic imbalance and do not yet know about the importance of the duration of autonomic imbalance for prediction of metabolic risks. Nor do we know the optimal frequency and set of measures of autonomic imbalance for identifying those with enduring risk. For example, we do not have data in this dataset on intraindividual variability for RHR or HRV measurements. Other variables for which we lacked reliable data, such as physical activity, inflammation, or insulin resistance, may also influence the relationship between autonomic imbalance and metabolic risk.

Future research should aim to address several questions, including refining the measures of autonomic imbalance for applications to clinical and epidemiologic studies, especially in primary care samples. The relationship between autonomic imbalance and insulin resistance during the development of metabolic risk deserves rigorous study. And these findings challenge others to reexamine in comparable existing longitudinal datasets the role of autonomic imbalance in the development of metabolic disorders and mortality.

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References