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Modeling Preclinical Cardiovascular Risk for Use in Epidemiologic Studies

Miami Community Health Study

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To develop a method for assessing preclinical cardiovascular disease risk, models of resting cardiovascular regulation and of insulin metabolic syndrome were derived from information collected from 1991 to 1996 in a culturally heterogeneous sample of 319 healthy men and women (aged 25–44 years) from Miami-Dade County, Florida. The model of resting cardiovascular regulation used 8 noninvasive measures of autonomic and cardiovascular function. Three factors were derived: 1) parasympathetic, 2) inotropy, and 3) systemic vascular resistance. The model of insulin metabolic syndrome used 12 measures assessing body mass, insulin, glucose, and lipid metabolism. Four factors were derived: 1) body mass and fat distribution, 2) glucose level and regulation, 3) insulin level and regulation, and 4) plasma lipid levels. Analyses of the association of the two models revealed that subjects with lower cardiac contractility had greater body mass, higher fasting and postload insulin and glucose levels, and lower insulin sensitivity. Subjects with greater vascular resistance had greater body mass, higher total cholesterol and triglyceride levels, and lower high density lipoprotein cholesterol levels. These findings indicate that preclinical cardiovascular disease risk may involve pathophysiologic processes in which cardiac inotropic and vasodilatory functions are linked to specific aspects of insulin metabolic syndrome. *Am J Epidemiol* 2001;154:765–76.

blacks; cardiovascular system; factor analysis, statistical; Hispanic Americans; insulin resistance; models, cardiovascular; sex; whites

Preclinical cardiovascular disease (CVD) describes the pathologic changes in the heart and arteries that develop early in the course of hypertensive and atherosclerotic disease prior to the occurrence of symptoms or morbid events (1). It has long been recognized that CVD risk factors tend to cluster within persons, such that their co-occurrence is greater than expected by chance (2–5). For example, the presence of unfavorable levels of blood pressure, lipids, insulin, and obesity is highly prevalent in persons who have type II diabetes mellitus (6), an illness that predisposes to atherosclerosis. The clustering of these risk factors is considered to reflect a dysfunction of insulin metabolism in interaction with cardiovascular regulation and has come to be known as the deadly quartet, syndrome X, or the insulin metabolic syndrome (7–9).

A highly relevant clustering of CVD risk variables is represented by measures of resting cardiovascular regulation. One characteristic hemodynamic pattern denoting risk has been termed low-flow circulatory state, in which systemic vascular resistance is elevated and cardiac output is reduced (10). In persons with this circulatory state, left ventricular systolic and diastolic functions typically are impaired, with reductions in left ventricular end-diastolic filling, ejection fraction, cardiac contractility, and stroke volume (11–16). This hemodynamic pattern has been observed in persons with coronary artery disease, hypertension, and type I and II diabetes mellitus and among healthy persons with a family history of hypertension (11, 17–21). The transition to a low-flow circulatory state in CVD progression has been documented and may precede the appearance of clinically diagnosable athero- and arteriosclerotic structural changes (17–19).

Despite the fact that both cardiovascular- and insulin-metabolic regulatory processes have been firmly associated with atherosclerosis, studies of the relations between these processes are limited. Moreover, because single measures are primarily used, the multidimensionality of these processes commonly has been neglected. To better understand preclinical CVD pathophysiology, the present study used multidimensional quantitative techniques to examine the complex nature and interrelation of both regulatory processes in a culturally heterogeneous sample of healthy men and women.

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Abbreviations: BMI, body mass index; CVD, cardiovascular disease; TPEV, time to peak ejection velocity.

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MATERIALS AND METHODS

Subjects

Subjects were participants in the Miami Community Health Study, designed to assess the correlates of blood pressure and other CVD risk factors in African Americans, Cuban Americans, and non-Hispanic Whites living in Miami-Dade County, Florida. The recruitment methodology for this study has been described previously (22, 23). In brief, the study cohort was selected from census tracts (1990 US Census) located within 10 miles (16.09 km) of the University of Miami, with populations composed of at least 80 percent of the targeted ethnic group. Different census tracts were selected from which to recruit all three ethnic groups included in this study.

Subjects were included if they were 25–44 years of age, were healthy, and had no current or past history of hypertension, diabetes mellitus, or other CVD. This status was confirmed by physical examination, medical history, fasting blood chemistry analysis, and 12-lead electrocardiogram. The overall participation rate was 53 percent (23); of the 15,159 people consenting to a telephone interview, 980 met all eligibility criteria. Of these subjects, 2 percent were found medically ineligible upon examination, and 45.6 percent declined to participate. From the 514 subjects enrolled in the Miami Community Health Study, 372 completed the entire protocol. Of these, 53 were excluded for various reasons that precluded use of their data. Thus, data were available for 319 normotensive healthy men (72 non-Hispanic White, 52 African American, 38 Cuban American) and women (57 non-Hispanic White, 64 African American, 36 Cuban American), whose mean age was 35.2 (standard deviation, 5.7) years.

Experimental protocol, procedures, and physiologic measures

Informed consent was obtained, and subjects participated in two testing sessions on different days; a subset of subjects returned for a third session. Prior to the first testing session, subjects were instructed to fast and to refrain from smoking and exercising for 10–12 hours. Prior to the second testing session, subjects refrained from smoking, exercising (for 2 hours), and consuming caffeinated beverages (for 6 hours). When they arrived at the Behavioral Medicine Research Center in Miami, their compliance with these restrictions was determined from self-report, and urinary toxicology screens were performed for illicit drugs and alcohol. Noncompliance resulted in rescheduling or exclusion.

Session 1. An oral glucose tolerance test was administered (24). Plasma lipids, glucose, and insulin levels were determined 15 and 0 minutes before glucose was consumed. Plasma glucose and insulin levels were then obtained 1 and 2 hours postload. During this session, triceps and subscapular skinfold thicknesses, waist and hip girth, and height and weight were measured by using standard methods (22, 25). The ratios of waist-to-hip girth and body mass index (BMI; kg/m^2) were calculated.

Session 2. Cardiovascular and autonomic measures were obtained by using electrocardiogram, impedance cardiogram, phonocardiogram, and respiration signals (26). Systolic, diastolic, and mean arterial blood pressure measurements were obtained by using a Critikon Dinamap Monitor (model 1846SX; Johnson & Johnson, Tampa, Florida). The cardiovascular and autonomic measures were recorded while subjects were at rest or engaged in stressful behavioral challenges, which included the mirror tracing, speech, and foot cold pressor tests (27). The cardiovascular data used in this study were collected during the 3 minutes prior to the end of the initial 30-minute baseline period. Blood pressure was sampled at 1.5-minute intervals. The electrocardiogram, impedance cardiogram, phonocardiogram, and respiration signals were collected temporally proximal to the blood pressure readings. These samples were assessed by using computer signal processing procedures developed previously (28, 29).

Session 3. A subset of the subjects ($n = 52$; 28 men and 24 women; 28 non-Hispanic White and 24 African American) returned for a third session to receive a euglycemic hyperinsulinemia clamp to assess insulin sensitivity (30). Insulin sensitivity was defined as mean exogenous glucose disposal rate in milligrams/kilograms•minutes by calculating the steady-state glucose infusion rate over consecutive 20-minute periods and applying a space correction factor (31).

Cardiovascular and autonomic variables

The following noninvasive indices of cardiac inotropy and cardiovascular performance were derived (27): 1) heart rate; 2) stroke volume; 3) cardiac output; 4) preejection period; 5) time from ejection onset to peak ejection velocity (TPEV); 6) acceleration index of cardiac contractility; 7) total peripheral resistance (mean arterial pressure/cardiac output/16.67); and 8) systolic blood pressure, diastolic blood pressure, and mean arterial pressure. Three variables were used as the parasympathetic-cardiac indices: 1) respiratory sinus arrhythmia, derived by decomposing the heart rate signal using a time-domain adaptive filtering technique and partitioning the signal variance due to respiratory and nonrespiratory factors (i.e., that variation associated with sympathetic and nonneural influences) (32, 33); 2) high-frequency power in the heart rate spectrum (0.15–0.50 Hz), derived from a power spectral analysis of both heart rate and respiration (20), with a resolution of 0.0078 Hz; and 3) heart rate max-min, calculated as the difference between the maximum and the minimum heart rates (34).

Assays for glucose, insulin, and lipid levels

Plasma glucose was measured by using an enzymatic glucose oxidase method (35), and plasma insulin was determined by radioimmunoassay using an insulin-specific kit (Linco Research, Inc., St. Charles, Missouri (36)). Lipid profiles (serum cholesterol, triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol) were determined in the Smith-Kline Laboratory (Miramar, Florida).

Statistical analysis

Modeling insulin metabolic syndrome. The following 12 insulin metabolism and lipid profile variables were included in a factor analysis (SAS Factor procedure (37)) by using the principal component method: 1) BMI, 2) triceps skinfold thickness, 3) subscapular skinfold thickness, 4) fasting glucose, 5) 1-hour postload glucose, 6) 2-hour postload glucose, 7) fasting insulin, 8) 1-hour postload insulin, 9) 2-hour postload insulin, 10) total cholesterol, 11) triglycerides, and 12) high density lipoprotein cholesterol. Variables that were linear combinations or were included in the computation of other variables were not included (e.g., low density lipoprotein cholesterol). The composite variables (e.g., BMI) were used instead of their constituents, permitting a larger sample-to-variable ratio and increasing model stability. Four components with eigenvalues of >1 were extracted and were retained for varimax rotation. Only variables sharing at least 15 percent of the variance with the factor (factor loading ≥ |0.40|) were used for interpretation (38). The waist-to-hip ratio was not included based on an inspection of the correlation matrix, which indicated it did not correlate satisfactorily with the other measures of body fat (i.e., $r < 0.30$). This finding could indicate that waist-to-hip ratio contains information about fat distribution that the other variables do not.

Modeling resting cardiovascular regulation. Confirmatory factor analysis was performed by using maximum likelihood estimation (SAS CALIS procedure (37)). Goodness-of-fit indices were used to assess the overall fit of each model to the data (39), and use of multiple fit measures protected against the possibility of model misspecification and sampling error (40). The following five indices were used: 1) chi-square (χ^2) statistic, 2) goodness-of-fit index, 3) root mean square residual, 4) squared multiple correlation, and 5) *t* tests (41).

Predictive association of the cardiovascular and insulin metabolic syndrome models. After deriving factor scores from the models, a multiple regression analysis was conducted (SAS GLM procedure (37)) to derive the unique contribution of the predictors (cardiovascular model factor scores) to the dependent variables (insulin metabolic syndrome model factor scores). Age, ethnicity, and gender were used as covariates. By using the specified covariates, an additional multiple regression analysis was conducted with insulin sensitivity as the dependent variable and factor scores from both models as the predictors.

RESULTS

Modeling insulin metabolic syndrome

Table 1 summarizes the sample values of measures of insulin metabolism, lipidemia, and body size and fat distribution for the 257 subjects for whom data were complete. All but three variables (1-hour postload glucose, total cholesterol, triceps skinfold thickness) were transformed by taking their natural log due to positively skewed distributions. Variables were standardized to have unit variance. Table 2 displays the correlations among these measures. The following standard definitions were used: obesity = BMI ≥27.3 kg/m^2 in women and ≥27.8 kg/m^2 in men, corresponding to about 120 percent of ideal body weight; impaired glucose tolerance = 2-hour oral glucose tolerance test glucose >140 mg/dl; hyperinsulinemia = fasting insulin level >90th percentile (i.e., >15 μU/ml); and hypertriglyceridemia = triglycerides >90th percentile (i.e., >200 mg/dl).

TABLE 1. Values of insulin metabolic syndrome and cardiovascular measures for study subjects (*n* = 319), Miami-Dade County, Florida, 1991–1996

Variable (unit)*	Mean (standard deviation)
Insulin sensitivity (mg/kg•minute)†	8.0 (3.1)
Body mass index (kg/m^2)	26.7 (5.3)
Triceps skinfold thickness (mm)	24.8 (11.4)
Subscapular skinfold thickness (mm)	26.5 (13.9)
Fasting glucose (mg/dl)	87.6 (10.0)
1-hour postload glucose (mg/dl)	139.7 (34.5)
2-hour postload glucose (mg/dl)	115.3 (31.2)
Fasting insulin (μU/ml)	8.7 (9.2)
1-hour postload insulin (μU/ml)	66.1 (51.5)
2-hour postload insulin (μU/ml)	66.5 (65.1)
High density lipoprotein cholesterol (mg/dl)	47.9 (13.6)
Total cholesterol (mg/dl)	197.9 (43.9)
Triglycerides (mg/dl)	119.7 (66.8)
Waist-to-hip ratio	0.82 (0.1)
Systolic blood pressure (mmHg)	107.6 (11.8)
Diastolic blood pressure (mmHg)	63.1 (7.7)
Total peripheral resistance (pru)‡	1.07 (0.3)
Heart rate (beats/minute)	70.7 (9.3)
Stroke volume (ml)	67.8 (17.5)
Cardiac output (liters/minute)	4.7 (1.1)
Preejection period (msecond)	93.2 (20.3)
Time to peak ejection velocity (msecond)	76.9 (19.3)
Acceleration index (Ω/second^2)	28.1 (14.5)
Heart rate high-frequency power	3.9 (4.0)
Respiratory sinus arrhythmia (beats/minute)^2	2.7 (2.9)
Heart rate maximum – minimum (beats/minute)	12.7 (5.1)

* For 62 subjects, data were missing on at least one of the variables in the insulin metabolic syndrome model: fasting (glucose (*n* = 11); 1-hour postload glucose (*n* = 21); 2-hour postload glucose (*n* = 22); fasting insulin (*n* = 17); 1-hour postload insulin (*n* = 51); 2-hour postload insulin (*n* = 40); cholesterol and lipid profile (*n* = 8); heart rate high-frequency power, respiratory sinus arrhythmia, and heart rate maximum minus minimum (*n* = 4); and systolic blood pressure, diastolic blood pressure, and total peripheral resistance (*n* = 3).

† Assessed for only 52 subjects.

‡ Total peripheral resistance is measured in peripheral resistance units (pru).

TABLE 2. Correlations* among body mass, fat distribution, insulin, glucose, and lipid variables for study subjects (*n* = 257), Miami-Dade County, Florida, 1991–1996

	Body mass index	Triceps skinfold thickness	Sub-scapular skinfold thickness	Fasting glucose	1-hour postload glucose	2-hour postload glucose	Fasting insulin	1-hour postload insulin	2-hour postload insulin	High density lipoprotein cholesterol	Total cholesterol
Body mass index											
Triceps skinfold thickness	0.64										
Subscapular skinfold thickness	0.76	0.71									
Fasting glucose	0.23	0.15	0.14								
1-hour postload glucose	0.03	0.03	0.03	0.42							
2-hour postload glucose	0.18	0.23	0.25	0.32	0.58						
Fasting insulin	0.17	0.12	0.14	0.10	0.03	0.09					
1-hour postload insulin	0.24	0.16	0.22	0.16	0.20	0.08	0.29				
2-hour postload insulin	0.34	0.32	0.41	0.16	0.19	0.42	0.35	0.68			
High density lipoprotein cholesterol	–0.29	–0.12	–0.23	–0.18	–0.14	–0.17	–0.12	–0.18	–0.26		
Total cholesterol	0.14	–0.00	0.02	0.13	0.15	0.17	0.07	0.18	0.18	0.02	
Triglycerides	0.24	0.04	0.11	0.19	0.16	0.18	0.15	0.24	0.21	–0.39	0.44

* $r \geq |0.11|$ were significant at or below $\alpha = 0.05$.

On the basis of these definitions, 33.9 percent of the sample was obese, 18.8 percent had impaired glucose tolerance, 8.5 percent evidenced hyperinsulinemia, and 9.7 percent had hypertriglyceridemia, comparable with a similar sample reported previously (9).

Factor patterns, after principal component method and orthogonal rotation of the correlation matrix, loadings, communalities, and percentages of variance and covariance, are displayed in table 3. In this table, variables are ordered and grouped by size of loading to facilitate interpretation. Loadings of less than 0.30 were replaced by zeros. The four factors accounted for 65 percent of the total variance. All factors were internally consistent and were defined by at least three variables with absolute factor loadings of more than 0.5. Factor 1 (BMASS) was dominated by positive loadings of two body fat skinfold measures and body mass index. Factor 2 (GLUCOSE) was characterized by the clustering of fasting and postload plasma glucose levels. Factor 3 (INSULIN) was characterized by the clustering of fasting and postload plasma insulin levels, and factor 4 (LIPID) was characterized by positive loadings for triglyceride and cholesterol levels and a negative loading for high density lipoprotein cholesterol.

Modeling resting cardiovascular regulation

Table 1 displays the means (standard deviations) and table 4 presents the correlations for the eight resting cardiovascular variables used in this model. An initial validation test of a three-dimensional factor structure previously developed in an independent sample in our laboratory (10) was conducted. This model included the parasympathetic-cardiac (PNS) factor, the sympathetic-cardiac contractility (INOTROPY) factor, and the blood pressure/vascular (VAS) factor. The analysis was performed with the following three modifications: 1) heart rate variance was replaced by heart rate high-frequency spectral power; 2) total peripheral resistance was replaced by heart rate, a constituent of cardiac output, which, together with the existing stroke volume and blood pressure measures, are the constituents from which total peripheral resistance is derived; and 3) acceleration index was dropped in favor of its constituent, the TPEV interval. This modification had the advantage of keeping the factor uniform in measurement units and preventing dependencies communicated by the numerator of the acceleration index measure. To avoid model underidentification, each variable was allowed to define only one factor, resulting in a factor complexity of one for each indicator. Factor parameter estimates (lambda matrix) were used from previous runs, providing a scale for each factor. The covariances in the phi matrix were free to be estimated. Within the theta-delta matrix, two pairs of correlated errors (heart rate max-min/heart rate; diastolic blood pressure/TPEV) were freed to be estimated, while all others were constrained to zero, in accordance with previous model runs. The independence model that tests the hypothesis that all variables are uncorrelated was easily rejected; χ^2 (28 df, $n = 319$) = 1,199.29, $p < 0.01$. The hypothesized model

TABLE 3. Factor loadings, communalities (h^2), percentages of variance and covariance for principal factors extraction, and varimax rotation for study subjects ($n = 257$), Miami-Dade County, Florida, 1991–1996

Variable	Factors*				h^2
	F1	F2	F3	F4	
Subscapular skinfold thickness	0.88	0.00	0.00	0.00	0.83
Triceps skinfold thickness	0.86	0.00	0.00	0.00	0.76
Body mass index	0.82	0.00	0.00	0.31	0.78
Postload glucose at 1 hour	0.00	0.86	0.00	0.00	0.76
Postload glucose at 2 hours	0.00	0.80	0.00	0.00	0.69
Fasting glucose	0.00	0.62	0.00	0.00	0.43
Postload insulin at 1 hour	0.00	0.00	0.84	0.00	0.71
Postload insulin at 2 hours	0.00	0.34	0.73	0.00	0.73
Fasting insulin	0.00	0.00	0.65	0.00	0.48
Triglycerides	0.00	0.00	0.00	0.89	0.82
Total cholesterol	0.00	0.00	0.00	0.65	0.43
High density lipoprotein cholesterol	0.00	0.00	0.00	–0.53	0.37
% of variance	19.8	16.1	15.1	14.1	
% of covariance	30.5	24.7	23.2	21.8	

* F1, BMASS (body mass/fat distribution); F2, GLUCOSE (glucose level and metabolism); F3, INSULIN (insulin level and metabolism); F4, LIPID (lipidemia).

TABLE 4. Correlations* among selected resting cardiovascular regulation measures for study subjects (*n* = 319), Miami-Dade County, Florida, 1991–1996

	Respiratory sinus arrhythmia	Heart rate maximum minus minimum	Heart rate high-frequency power	Diastolic blood pressure	Heart rate	Stroke volume	Preejection period
Respiratory sinus arrhythmia							
Heart rate maximum minus minimum	0.68						
Heart rate high-frequency power	0.84	0.80					
Diastolic blood pressure	–0.08	–0.01	–0.09				
Heart rate	–0.03	0.05	–0.03	0.14			
Stroke volume	0.05	0.14	0.09	–0.26	–0.47		
Preejection period	0.07	0.06	0.08	–0.10	–0.15	0.04	
Time to peak ejection velocity	–0.15	–0.11	–0.16	0.23	0.09	–0.06	–0.69

* $r \geq |0.12|$ were significant at or below $\alpha = 0.05$.

was tested next, and support for it was found; χ^2 (20 df, n = 319) = 45.02, $p = 0.001$, goodness-of-fit index = 0.97, root mean square residual = 0.04. A χ^2 difference test indicated a significant improvement in fit between the independent and the hypothesized model.

Factor uniqueness refers to the theta-delta matrix that includes a combination of specific variance and measurement error associated with each measured variable or indicator. These uniqueness terms are often hypothesized to be uncorrelated, but it is also possible to fit correlated uniquenesses to reflect relations between individual indicators that cannot be explained in terms of the a priori factors (42). Post-hoc model modifications were performed in an attempt to develop a better fitting model. As per the Lagrangean multiplier test, the correlated error term between heart rate max-min and stroke volume was freed to be estimated. Such alterations were theoretically justified, given that the correlated uniquenesses for heart rate max-min/heart rate and heart rate max-min/stroke volume are consistent with a heart rate variance factor and the correlated uniqueness for diastolic blood pressure/TPEV is consistent with a mechanical factor. Both factors were not fully incorporated into the model because of the constraints on model identification described above, introducing extraneous noise in the form of the correlated uniquenesses.

This modified three-factor model, including all three correlated uniqueness terms, was consistent with the data; χ^2 (19 df, n = 319) = 36.96, $p = 0.008$, goodness-of-fit index = 0.98, root mean square residual = 0.04. The three factors (latent variables) accounted for significant variance in the model (PNS, $t = 12.21$; INOTROPY, $t = 10.16$; VAS, $t = 7.63$). When this model was compared with the hypothesized model (without the added correlated error), a significant $\chi^2(1)$ value of 8.06, $p = 0.01$, was obtained. Therefore, the previous model was rejected in favor of the modified model. All goodness-of-fit indices were improved, while inclusion of the additional parameter had a negligible effect on the results for the remaining estimates (table 5). The three factors in the model were again allowed to covary. The associations between the PNS and INOTROPY factors, the PNS and VAS factors, and the INOTROPY and VAS factors were $r = 0.15$ ($t = 2.43$), $r = –0.13$ ($t = –1.79$), and $r = –0.18$ ($t = –2.25$), respectively.

The Shapiro-Wilk test of departure from normality was inspected for all derived model factors. The normality hypothesis was retained for the VAS, INSULIN, and GLUCOSE factors, but it was rejected for all other factors. Nevertheless, because even minor departures from normality lead to significant results on the Shapiro-Wilk test, factors were considered normally distributed on the basis of visual inspection of their distribution. Acceptable levels of skewness (0.42 to 0.62), kurtosis (–0.35 to 0.57), and W values (all >0.97) were noted for all factors except INOTROPY, which had a bimodal distribution (skewness = 0.21, kurtosis = –1.22, $W = 0.92$).

Analyses conducted to further clarify the VAS factor indicated that subjects in the top quartile of this factor had greater systolic blood pressure (111.9 vs. 105.1 mmHg, $p < 0.001$), diastolic blood pressure (67.6 vs. 59.2 mmHg, $p < 0.001$), and total peripheral resistance (1.3 vs. 0.9 peripheral resistance units, $p < 0.001$) than subjects in the bottom quartile. Upper-quartile subjects also had lower cardiac output (4.1 vs. 5.4 liters/minute, $p < 0.001$) than lower-quartile subjects because of lower stroke volume (50.9 vs. 88.7 ml, $p < 0.001$). Therefore, higher scores on this factor reflected elevated blood pressure and afterload; thus, this factor was renamed the systemic vascular resistance (SVR) factor. Figure 1 depicts the final resting cardiovascular regulation model.

Predictive association of the two models

The results of the multiple regression analyses are presented in table 6, including R^2 values for the regression equations, significance levels, and parameter estimates for the individual predictors, standard errors, percentage of

TABLE 5. Factor loadings, squared multiple correlations, standard errors, and *t*-test values for the cardiovascular regulation models tested* for study subjects (*n* = 319), Miami-Dade County, Florida, 1991–1996

Factor†	Measure‡	λ§	R^2¶	Standard error	*t*-test value
		Model I			
F1	Heart rate high-frequency power	0.9582	0.98	0.057	16.84
F1	Respiratory sinus arrhythmia	0.8508	0.76	0.064	13.31
F1	Heart rate maximum minus minimum	0.8162	0.72	0.064	12.81
F2	Heart rate	0.7134	0.42	0.098	7.24
F2	Stroke volume	–0.6987	0.46	0.097	–7.20
F2	Diastolic blood pressure	0.5058	0.18	0.083	6.11
F3	Time to peak ejection velocity	–0.8298	0.64	0.139	–5.95
F3	Preejection period	0.7688	0.73	0.134	5.75
		Model II			
F1	Heart rate high-frequency power	0.9531	0.98	0.057	16.75
F1	Respiratory sinus arrhythmia	0.8553	0.76	0.064	13.45
F1	Heart rate maximum minus minimum	0.8186	0.72	0.062	13.16
F2	Heart rate	–0.7227	0.45	0.098	–7.36
F2	Stroke volume	0.7119	0.41	0.096	7.40
F2	Diastolic blood pressure	0.4761	0.17	0.082	5.82
F3	Time to peak ejection velocity	0.8196	0.73	0.164	4.99
F3	Preejection period	–0.7563	0.64	0.152	–4.98

* Model II is model I plus one correlated error.

† F1, PNS (parasympathetic-cardiac/respiratory sinus arrhythmia); F2, SVR (systemic vascular resistance); F3, INOTROPY (sympathetic-cardiac/inotropy).

‡ The high-frequency, respiratory sinus arrhythmia, heart rate maximum minus minimum, and diastolic blood pressure measures were natural log-transformed prior to factor analysis. Preejection period and time to peak ejection velocity had a binormal distribution, for which a χ^2 value, corrected for kurtosis (78), was examined. As an additional measure to defend against error due to asymmetric distributions, the parameters derived by the unweighted least-squares methods were used (79). One univariate outlier and a total of seven missing values were replaced by the respective gender group mean (80). Then, variables within each gender group were standardized to have unit variance. These data management procedures did not appreciably alter the correlations among the variables, changing the correlation coefficients by only –0.04 to 0.04 (mean, 0.005).

§ Factor loading.

¶ Squared multiple correlation.

unique variance, and covariate effects. The INOTROPY factor was a significant predictor of BMASS, GLUCOSE, INSULIN, and insulin sensitivity. The SVR factor was a significant predictor of BMASS and LIPID. In addition, the BMASS, INSULIN, and LIPID factors were all significant predictors of insulin sensitivity.

DISCUSSION

The main objective of this study was to develop quantitative techniques that could be used in epidemiologic studies to examine the association between multiple preclinical processes reflecting risk for developing insulin metabolic syndrome and CVD. The present study 1) developed a model of insulin metabolic syndrome from measures of insulin and glucose metabolism, body mass, and lipidemia; 2) validated a model of cardiovascular regulation from resting measures; 3) examined the predictive association of the two models; and 4) assessed the association of the two models with insulin sensitivity, a measure central to insulin metabolic syndrome and the assessment of CVD risk.

Modeling insulin metabolic syndrome

In modeling insulin metabolic syndrome, the factor analysis reduced 12 variables to four newly defined factors. Factor 1, the body mass and fat distribution (BMASS) factor, was characterized by subscapular and triceps skinfold thicknesses and by BMI. Factor 2, the glucose (GLUCOSE) factor, was characterized by oral glucose tolerance test postload glucose levels and fasting glucose. Factor 3, the insulin (INSULIN) factor, was characterized by oral glucose toler-

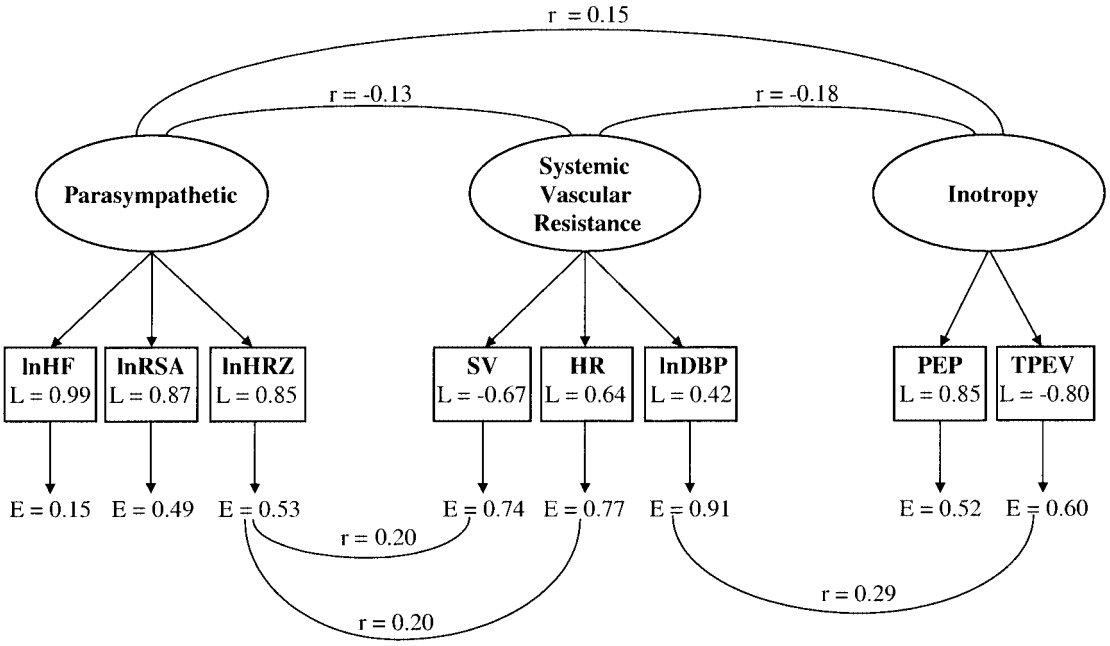

FIGURE 1. Model of cardiovascular regulation ($n = 319$), Miami-Dade County, Florida, 1991–1996. r, correlation; ln, natural log; HF, heart rate high-frequency spectral power; RSA, respiratory sinus arrhythmia; HRZ, heart rate maximum minus minimum; SV, stroke volume; HR, heart rate; DBP, diastolic blood pressure; PEP, preejection period; TPEV, time to peak ejection velocity; L, standardized factor loading; E, error term.

ance test postload insulin levels and fasting insulin; factor 4, the lipidemia (LIPID) factor, was characterized by positive loadings for total cholesterol and triglyceride levels and a negative loading for high density lipoprotein cholesterol level. Overall, these four factors are consistent with several well-characterized aspects of insulin metabolic syndrome, including excess body mass and body fat, hyperinsulinemia, and hyperglycemia and with elevated levels of cholesterol and triglycerides accompanied by reduced high density lipoprotein cholesterol levels (6, 43, 44).

Recently, factor analytical methods have been used to identify major factors associated with insulin metabolic regulation. A body weight/fat distribution factor, an insulin/glucose factor, and a lipid factor were identified in a study of middle-aged women (45). In a study of nondiabetic children and spouses of subjects from the original Framingham Heart Study cohort, a general metabolic factor, an impaired glucose tolerance factor, and a hypertension factor were obtained (46). Similar results were obtained in the Rancho Bernardo Study (47). Compared with these studies, the present strategy yielded more factors to constitute the insulin metabolic syndrome model, which can be attributed to more comprehensive inclusion of related measures of the processes selected. Consequently, a more precise description of these separate processes was possible. Theoretically, however, an even more comprehensive insulin metabolic syndrome model would have included insulin sensitivity, which is clearly central to the syndrome. Unfortunately, this measure was available for only a subset of study participants. However, when the association of the present model with insulin sensitivity was examined for these subjects, the BMASS, INSULIN, and LIPID factors were significant predictors of insulin sensitivity, providing evidence of the model's validity.

Modeling resting cardiovascular regulation

The present study also validated a three-dimensional model of resting cardiovascular regulation that our laboratory identified previously in an independent sample of 206 non-Hispanic White and African-American men (10). In the present study, the first factor was defined by the heart rate power in the high-frequency spectral band, respiratory sinus arrhythmia, and heart rate max-min measures obtained during an epoch of resting, spontaneous breathing. Because these indices are all cardiovagal estimates, this factor was termed the parasympathetic-cardiac factor (PNS). Higher PNS scores were interpreted as reflecting greater parasympathetic-cardiac input.

The second factor was positively defined by preejection period and negatively defined by TPEV. Because these measures reflect preejection- and ejection-phase contractile function, this factor was termed the sympathetic-cardiac/inotropic factor (INOTROPY). Higher INOTROPY scores were indicative of greater myocardial contractility, wherein as inotropy increases, venous return increases, resulting in a longer preejection period and shorter time to reach peak ejection velocity.

The third factor included a positive loading of diastolic blood pressure and heart rate and a negative loading of stroke volume. The positive loading of heart rate on this factor may be interpreted as a consequence of the inverse compensatory

TABLE 6. Results of multiple regression analysis† examining the predictive association of insulin metabolic syndrome factors,‡ insulin sensitivity, and cardiovascular regulation factors,§ after control for gender, age, and ethnicity, Miami-Dade County, Florida, 1991–1996

Dependent variable¶	*F* test value (df)	R^2	*p* value	Significant predictors				Significant covariates			
				Factor	β	Standard error	% unique variance#	Factor	β	Standard error	% unique variance#
BMASS	6.58 (7,249)	0.16	<0.0001	INOTROPY	–0.2	0.1	2.8	Gender††	–6.3	1.8	4.2
				SVR	0.2	0.1	2.8	Ethnicity‡‡			
								White	–2.7	2.2	3.2
								Black	3.6	2.4	
GLUCOSE	2.53 (7,249)	0.07	<0.0160	INOTROPY	–0.2	0.1	1.9	Age*	0.3	0.2	1.4
INSULIN	4.34 (7,249)	0.11	<0.0001	INOTROPY	–0.1	0.1	1.7	Age	–0.4	0.2	1.7
								Ethnicity			
								White	–1.6	2.3	5.4
								Black	6.5	2.5	
LIPID	15.23 (7,249)	0.30	<0.0001	SVR	0.2	0.1	3.8	Gender	14.9	1.6	23.4
								Ethnicity			
								White	–3.3	2.0	2.9
								Black	–7.0	2.2	
Insulin sensitivity	9.22 (10,39)	0.70	<0.0001	BMASS	–0.1	0.02	33.3	Age	–0.1	0.1	3.3
				INSULIN	–0.1	0.02	5.8				
				INOTROPY	0.1	0.02	4.3				
				LIPID	–0.1	0.03	4.3				

* $p = 0.052$.

† The beta coefficients represent change in the outcome measure (dependent variable) per unit change in the predictor (independent variable) for the continuous predictors. For the categorical predictors (sex, ethnicity), the coefficients represent the differences between the groups (men vs. women; White vs. African American vs. Cuban American).

‡ Insulin metabolic syndrome factors: BMASS (body mass/fat distribution); GLUCOSE (glucose level and metabolism; INSULIN (insulin level and metabolism); LIPID (lipidemia).

§ Cardiovascular regulation factors: PNS (parasympathetic-cardiac/respiratory sinus arrhythmia); SVR (systemic vascular resistance); INOTROPY (sympathetic-cardiac/inotropy).

¶ Factor scores were calculated by using the Score option in the CALIS procedure (37), standardizing each factor to produce a mean of 100 and a standard deviation of 15.

\# Calculated as type III sums of squares divided by corrected total sums of squares.

†† Contrast for gender: 1 = men, 0 = women.

‡‡ Contrasts for ethnicity: 1 = non-Hispanic White, 0 = Cuban American for the first contrast; 0 = Cuban American, 1 = African American for the second contrast.

relation of heart rate and stroke volume in homeostatically regulating cardiac output. Higher scores on this factor indicated elevated blood pressure and vascular resistance; hence, this factor was termed systemic vascular resistance (SVR).

Association of the two models

When the present study controlled for age, ethnicity, and gender, the factors derived from the resting cardiovascular regulation model were significantly associated with factors derived from the insulin metabolic syndrome model. A most intriguing finding was the dissociation between the INOTROPY and SVR factors. Specifically, INOTROPY was a predictor of INSULIN, GLUCOSE, and insulin sensitivity but not of LIPID. In contrast, vasodilatory status as reflected by the SVR factor was a predictor of LIPID but not of INSULIN, GLUCOSE, or insulin sensitivity.

These findings are consistent with reports that impaired myocardial contractility is associated with hyperglycemia and glucose intolerance (48, 49). They are also consistent with the fact that insulin levels are positively related to left ventricular hypertrophy and mass (50–52), which in turn are linked with diminished contractile status (53–56). The association between insulin sensitivity and inotropy has been less well studied, but the present results are consonant with a cardiology literature indicating that with CVD progression, there is increasing insulin resistance and a progression toward a low-flow circulatory state (10, 11, 57). The association between the SVR and LIPID factors is consistent with the high comorbidity of hypertension and hyperlipidemia in the general population, which is related to development of atherosclerosis (58). Many other studies have demonstrated an association between increased blood pressure and altered lipid profiles in normotensive and hypertensive adults (59–62).

The finding that SVR was not a significant predictor of insulin sensitivity appears to contradict the literature, which reports that hyperinsulinemia during the euglycemic-hyperinsulinemia clamp increases skeletal muscle perfusion (63, 64) and that insulin-mediated vasodilation is defective in insulin-resistant states such as obesity, type II diabetes mellitus, and essential hypertension (64–66). However, recent studies clearly show that systemic and not local hyperinsulinemia facilitates endothelial-dependent vasodilatory mechanisms (67, 68); this finding indicates that insulin-mediated vasodilatory function involves alternative mechanisms (e.g., the sympathetic nervous system) activated during systemic hyperinsulinemia that would not be impacted by diminished insulin sensitivity per se. Therefore, the observation of diminished vasodilatory function in insulin-resistant states may be secondary to a dysfunction within these alternative mechanisms and not directly related to insulin sensitivity. This conclusion is further supported by the lack of correlation between insulin sensitivity and diastolic blood pressure, reported previously (57).

The present study also documented an association between BMASS and both INOTROPY and SVR such that subjects with increased body mass and fat distribution had decreased contractility and elevated vascular resistance. The BMASS factor was related positively to total peripheral resistance ($r = 0.26$, $p < 0.001$) and negatively to cardiac output ($r = -0.21$, $p < 0.001$). These results are consistent with previous findings, in which central obesity, as indicated by waist-to-hip ratio, has been associated with the low-flow circulatory profile (69). The present findings are also consistent with other reports showing that body mass and obesity are strongly associated with elevated blood pressure and hypertension (9) and with compromised myocardial contractility (70–75). In contrast, the PNS factor was not a significant predictor of any of the insulin metabolic syndrome factors, which may be a function of the fact that the present sample comprised healthy normotensive adults. Indeed, reduced parasympathetic outflow is generally observed in clinical populations with advanced disease processes that confer increased CVD risk (e.g., type II diabetes mellitus and hypertension (76, 77)).

In this study, the cardiovascular and the insulin metabolic syndrome factor scores and covariates accounted for up to 70 percent of the variance in insulin sensitivity. The BMASS, INSULIN, INOTROPY, and LIPID factors were significant predictors in this equation that included age as a significant covariate. The BMASS factor accounted for the largest portion of the variance, predicting, within the context of the other predictors, 33 percent of the unique variance in insulin sensitivity. When the three variables that comprise BMASS (BMI, triceps and subscapular skinfold thicknesses) were used instead of the BMASS factor itself, the largest unique variance was only 5 percent, providing support for the superiority of using factors over individual variables. Therefore, by using factors that represent a weighted combination of several variables, a sensitive method for identifying stable but insidious processes was provided in the present study that would not have been discovered by evaluating the measures individually.

In conclusion, the associations between the cardiovascular and insulin metabolic syndrome factor scores and insulin sensitivity indicate that preclinical CVD risk may involve pathophysiologic processes in which cardiac inotropic and vascular functions are linked to specific aspects of insulin metabolic syndrome. Additional examination of the relation of the models in at-risk and CVD-diagnosed persons is required to further assess the possible dissociation of pathogenic CVD pathways suggested in this study and to determine the prognostic utility of the measures of resting inotropic and vascular function in predicting CVD.

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