Impact of Cardiorespiratory Fitness and Risk of Systemic Hypertension in Nonobese Versus Obese Men Who Are Metabolically Healthy or Unhealthy

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Few data are available regarding the influence of body phenotype on systemic hypertension (SH) and whether cardiorespiratory fitness (CRF) attenuates this relation. We tested the hypothesis that obesity phenotypes and CRF would predict incident hypertension, evaluating 3,800 Korean men who participated in 2 health examinations in1998 to 2009. All participants were normotensive at baseline and were divided into 4 groups based on body mass index using the Asia-Pacific descriptors for obesity and metabolic health status and the National Cholesterol Education Program's adult treatment panel III (ATP-III) criteria. A metabolically healthy obese (MHO) phenotype was defined as a body mass index of ≥25 kg/m^2 with <2 metabolic abnormalities. CRF was directly measured by peak oxygen uptake, and the participants were divided into unfit and fit categories based on age-specific peak oxygen uptake percentiles. Compared with the metabolically healthy nonobese phenotype, MHO and metabolically unhealthy nonobese (MUNO) phenotypes were at increased risk of SH (relative risk [RR] = 1.47; 95% confidence interval [CI], 1.07 to 2.02 and 1.62, 1.21 to 2.16) after adjusting for potential confounders. Joint analysis showed that MHO or MUNO unfit men had 1.91 and 2.27 greater risk of incident SH, respectively. However, MHO fit men had no significant RR of incident SH (RR 1.37; 95% CI, 0.93 to 2.03), whereas MUNO fit men remained at increased risk (RR 1.48; 95% CI, 1.04 to 2.11) compared with their metabolically healthy nonobese fit counterparts. In conclusion, MHO and MUNO men were at increased risk of SH, but these risks were attenuated by fitness. **(Am J Cardiol 2017;120:765–768)**

Metabolically healthy obese (MHO) subjects are included in a cohort of the obese population who do not have metabolic abnormalities and are at relatively low risk of cardiovascular disease (CVD).[1] Metabolically unhealthy nonobese (MUNO) subjects, who are of normal weight but with abnormal metabolic profiles, appear to be at greater risk of CVD.[2–4] Some studies have suggested that MHO and/or MUNO are at increased risk of incident systemic hypertension (SH),[5–8] but potential confounding variables have not been adequately accounted for in these reports. Cardiorespiratory fitness (CRF), an important confounding variable in body phenotype cohorts,[9,10] is inversely associated with obesity and metabolic risk factors.[11] Although high fitness may favorably modify the prognosis of MHO and MUNO patients,[10,12,13] the inclusion of CRF, along with metabolic parameters and body habitus, may help to clarify the relative contribution of fitness to long-term health outcomes.[14] Because fitness reduces the risk of SH independent of obesity and metabolic abnormalities,[15,16] the impact of CRF on the association between body phenotype and risk of SH needs clarification. We tested the hypothesis that body phenotype is associated with the risk of incident SH, but that CRF modifies these associations.

Methods

A total of 5,616 men participated in 2 general health examinations in 1998 to 2009 at the Samsung Medical Center, Seoul, South Korea. Among these participants, those with a diagnosis of SH (i.e., systolic and/or diastolic blood pressure at rest [SBP/DBP] ≥140 or ≥90 mm Hg), type 2 diabetes mellitus (i.e., fasting glucose >126 mg/ml), history of CVD, and the use of antihypertensive or oral hypoglycemic medications were excluded. After applying these exclusion criteria, 3,800 men (mean age 48 ± 6 years, range 20 to 76 years) remained for analyses. Written informed consent was obtained from all participants before the health screening program, and the study was approved by the medical center institutional review board.

All participants underwent progressive cardiopulmonary exercise testing to determine the peak oxygen uptake (VO_{2peak}) (Jaeger Oxycon Delta; Eric Jaeger, Hoechberq, Germany) using the methods previously described.[17] The metabolic profile was partially obtained from blood samples collected after a 12-hour overnight fasting state.[17] Blood pressure was measured

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See page 768 for disclosure information.

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0002-9149/
http://dx.doi.org/10.1016/j.amjcard.2017.05.054

during seated rest using an automated blood pressure monitor after 5 minutes of quiet rest (Dinamap PRO 100, Milwaukee, WI). Incident SH was defined as an SBP/DBP of ≥140/90 mm Hg and/or diagnosed by a physician at the second examination. Body composition (relative body fatness in percentage) was measured using bioelectrical impedance, and body mass index (BMI) was calculated as weight (in kilogram) divided by height squared (in square meter). Smoking habits and alcohol intake were evaluated through self-reported questionnaires.

All participants were divided into 4 groups based on their BMI by the Asia-Pacific criteria for obesity and metabolically unhealthy categorization using the ATP-III criteria (i.e., blood pressure >130/85 mm Hg, high-density lipoprotein cholesterol [HDL-C] <40 mg/ml, triglyceride [TG] >150 mg/ml, and glucose >100 mg/ml). Definitions of metabolically healthy or unhealthy in nonobese and obese cohorts were metabolically healthy nonobese (MHNO)—BMI <25 kg/m^2 with ≤1 metabolic abnormality, MUNO—BMI <25 kg/m^2 with ≥2 metabolic abnormalities, MHO—BMI ≥25 kg/m^2 with ≤1 metabolic abnormality, and metabolically unhealthy obese (MUO)—BMI ≥25 kg/m^2 with ≥2 metabolic abnormalities. The VO_{2peak} was divided into tertiles and classified into unfit (lowest tertile) and fit (middle and upper tertiles) categories based on age-specific VO_{2peak} percentiles as previously described.[18] We further divided our study population into 8 groups based on cross-classification of metabolic health, body habitus phenotypes, and CRF.

Data are presented as mean ± SD or median interquartile range for continuous variables and as proportions for categorical variables. For group comparisons by body habitus phenotypes, the variables were assessed using analysis of variance with Scheffe's post hoc and chi-square tests for continuous and categorical variables, respectively. To determine the associations of body habitus phenotypes and fitness status with incident SH, relative risks (RRs) and 95% confidence intervals (95% CIs) from the Cox proportional hazards regression models were calculated after adjusting for age, percent body fat, low-density lipoprotein cholesterol, white blood cell, uric acid, smoking, alcohol consumption, and fitness (when the body habitus phenotype was considered) or body habitus phenotype (when fitness was considered). The joint effects of body habitus and fitness on the risk of SH were examined using combined groups. The participants were divided into groups based on metabolic health and body habitus phenotypes (MHNO, MUNO, MHO, and MUO) and CRF (fit and unfit). Fit MHNO was used as the reference group. Statistical significance was set at $p < 0.05$, and analyses were conducted using SPSS 22.0 (SPSS, Armonk, NY).

Results

Table 1 lists the characteristics of participants by metabolic health (i.e., healthy or unhealthy), with the prevalence of nonobese and obese phenotypes. We found that 21.1% and 17.8% of the participants were classified as MHO and MUNO, respectively. Patients with MHO or MUNO had greater relative BMI, waist circumference, body fatness, SBP/DBP, total cholesterol, TG, glucose, white blood cell, and uric acid, but lower HDL-C and CRF than patients who were categorized as MHNO. Compared with the MUO patients, the MHO patients had lower relative SBP/DBP, TG, glucose, and uric acid, but greater HDL-C.

During an average follow-up of 5 years, 371 (9.8%) men developed SH. Compared with MHNO patients, MHO and MUNO patients demonstrated 1.47-fold and 1.62-fold increased risks of SH, respectively, after adjusting for potential confounders. In addition, fit men had a 21% reduced risk of incident SH compared with unfit men in our multivariable adjusted model (Table 2).

Combined analysis showed that unfit MHO or MUNO men had a greater risk of incident SH compared with their fit MHNO counterparts (reference group) after adjusting for potential confounders (RR 1.91, 95% CI, 1.25 to 2.92 and RR:

Table 1
Baseline characteristics of participants by metabolic health and body habitus phenotypes (n = 3800)

Variables	MHNO (n = 1726)	MUNO (n = 677)	MHO (n = 803)	MUO (n = 594)	p-value
Age (years)	47.7 ± 6.5	48.3 ± 6.1	47.8 ± 6.2	47.5 ± 6.2	0.146
Body mass index (kg/m^2)	22.8 ± 1.7	23.3 ± 1.3*	26.7 ± 1.5*,†	26.8 ± 1.4*,†	<0.001
Waist girth (cm)	82.5 ± 5.5	84.5 ± 4.2*	91.2 ± 5.1*,†	91.6 ± 4.4*,†	<0.001
Body fat (%)	19.7 ± 3.9	21.1 ± 3.5*	24.8 ± 3.6*,†	24.8 ± 3.5*,†	<0.001
Current smokers	24.8%	21.1%	30.0%	29.1%	0.102
Alcohol intake (3d/wk)	5.2%	4.4%	6.1%	5.2%	0.390
Systolic blood pressure (mmHg)	114 ± 11	122 ± 12*	116 ± 10*,†	121 ± 12*,‡	<0.001
Diastolic blood pressure (mmHg)	73 ± 8	79 ± 8*	74 ± 8*,†	78 ± 9*,‡	<0.001
Total cholesterol (mg/dl)	197 ± 33	205 ± 34*	204 ± 33*	207 ± 34*	<0.000
High density lipoprotein cholesterol (mg/dl)	53 ± 11	46 ± 11*	50 ± 10*,†	42 ± 9*,†,‡	<0.001
Low density lipoprotein cholesterol (mg/dl)	124 ± 30	126 ± 32	131 ± 30*,†	129 ± 32*	<0.001
Triglyceride (mg/dl)	116 ± 52	195 ± 93*	133 ± 64*,†	210 ± 98*,†,‡	<0.001
Glucose (mg/dl)	92 ± 9	100 ± 10*	94 ± 9*,†	101 ± 10*,‡	<0.001
White blood cell (×10^{9}cells/l)	5.8 ± 1.6	6.2 ± 1.6*	6.1 ± 1.5*	6.3 ± 1.5*	<0.001
Uric acid (mg/dl)	5.6 ± 1.1	5.9 ± 1.1*	5.9 ± 1.1*	6.2 ± 1.3*,†,‡	<0.001
Peak oxygen consumption (ml/kg/min)	35.9 ± 5.1	34.9 ± 5.1*	34.0 ± 4.8*,†	33.5 ± 4.5*,†	<0.001

MHNO = metabolically healthy nonobese; MUNO = metabolically unhealthy nonobese; MHO = metabolically healthy obese; MUO = metabolically unhealthy obese.

* p <0.05 vs. MHNO, †p <0.05 vs. MUNO, ‡p <0.05 vs. MHO.