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Cardiovascular correlates of insulin resistance in normotensive and hypertensive African Americans

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Abstract

Insulin resistance (IR) is associated with obesity and predisposes to diabetes mellitus (DM) and cardiovascular disease. The purpose of this study is to determine if IR is related to cardiovascular function independent of DM or hypertension among African Americans (AA). Four hundred sixty-two nondiabetic AA (50% hypertensive and 51% women) were studied on an inpatient General Clinical Research Center. Measurements included anthropometrics and 24-hour blood pressure (BP), heart rate (HR), fasting blood glucose, plasma aldosterone, and insulin. Stroke volume (SV) and cardiac output (CO) were measured by impedance plethysmography; peripheral vascular resistance (PVRI) and vascular compliance indices (VCI) were computed. These measurements were also obtained in response to mental (computerized math testing) and pharmacologic (graded norepinephrine infusion) stress. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR). SV, CO, and VCI decreased with increasing HOMA-IR, whereas HR and PVRI increased. Overall, BP, HR, and PVRI were positively correlated with HOMA-IR ($P < .01$); and SV index, cardiac index, and VCI were negatively correlated with HOMA-IR ($P < .0001$). The correlations persisted after adjustment for BP, age, sex, plasma aldosterone, total cholesterol, or low-density lipoprotein and high-density lipoprotein cholesterol. In addition, multiple linear regression analyses showed that HOMA-IR contributes to the maximum variability of all the hemodynamic variables. Blood pressure responses to math stress and norepinephrine infusion did not correlate with HOMA-IR. Unrelated to DM and BP, IR is associated with increased PVRI and decreased CO in AA. These observations suggest that an exclusive focus on effects of IR on DM or BP may ignore independent pathophysiologic contributions of IR to cardiovascular disease.

1. Introduction

Obesity and insulin resistance may contribute to cardiovascular disease in both African Americans and whites through their association with type 2 diabetes mellitus, hypertension, and dyslipidemia [1]. African Americans have a high prevalence of obesity, hypertension, and type 2 diabetes mellitus and an even higher degree of insulin resistance and cardiovascular disease than whites [2]. However, the relationship of insulin resistance with hypertension or dyslipidemia is less consistent among African Americans than in whites [3,4].

Several observations suggest that insulin resistance has direct effects on cardiac and vascular function. Insulin has key physiologic functions in the heart and vasculature apart from classic insulin targets for regulating glucose homeostasis such as skeletal muscle, liver, and adipose tissue [5]. Insulin resistance is associated with impaired selective signaling pathways that result in structural and functional alterations in both the peripheral vasculature and myocardium in experimental animals and in humans [6-11]. In addition, insulin resistance is associated with acceleration of atherosclerosis and impaired endothelium-dependent vasodilation [12-15].

In conjunction with our ongoing studies of hypertension mechanisms in African Americans [4,16-18], the present study was undertaken to evaluate the hypothesis that insulin resistance is related to cardiac and vascular function independent of blood pressure, obesity, or type 2 diabetes

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mellitus because of its direct actions on cardiac and vascular functions among African Americans. Specifically, we evaluated the relationship of insulin resistance to the physiologic determinants of cardiovascular function in nondiabetic, normotensive, and hypertensive African Americans.

2. Methods

African American subjects between the ages of 18 and 55 years were recruited from a variety of community resources and health care providers within the Milwaukee area. Subjects were defined as African American based on self-identification, birth in the continental United States, both parents reported as being African American, and English as the native language. All subjects were initially evaluated during a screening outpatient visit and were considered to have hypertension if standardized outpatient measurement of systolic blood pressure was at least 140 mm Hg, if diastolic blood pressure was at least 90 mm Hg, or if they were taking antihypertensive medications. Pregnant subjects and subjects with secondary hypertension, myocardial infarction, stroke within 6 months of study onset, and substance abuse were excluded. Eight of 3870 screened subjects (0.21%) had serum creatinine greater than 2.2 mg/dL (194.48 μmol/L), and these subjects were excluded to eliminate potential confounding effects of renal hypertension. Subjects with diabetes mellitus (fasting blood glucose >126 mg/dL [6.99 mmol/L]) were excluded to eliminate the effect of preexisting diabetes mellitus on cardiovascular function. Because of the difficulty of measuring cardiac output by impedance plethysmography in the very obese, subjects with body mass index (BMI) greater than 36 kg/m^2 were also excluded. Before further study, subjects taking antihypertensive and lipid-lowering medications discontinued these agents for at least 1 and 4 weeks, respectively. Subjects were then admitted to an inpatient General Clinical Research Center for 2 days and placed on a weight-maintaining diet containing 150 mEq sodium and 80 mEq potassium per day. The Froedtert Memorial Lutheran Hospital/Medical College of Wisconsin Institutional Review Board approved the protocol.

After subjects provided informed consent, standardized anthropometric measurements including height, weight, and waist circumference were acquired. Waist circumference was taken at a narrowest point between the umbilicus and superior iliac spine. On day 1, peripheral venous blood was collected after an overnight fast for measurement of serum concentrations of total cholesterol, glucose, and insulin. Plasma aldosterone was measured after 10 minutes of standing. Subsequently, cardiac output, stroke volume, blood pressure, and heart rate were measured before and after 2-minute computerized math testing. In addition, blood pressures were measured over a 24-hour period with an Accutracker (Suntech Medical Instruments) every 30 minutes during the day (6:00 AM to 8:00 PM) and every 60 minutes during the night (8:00 PM to 6:00 AM).

On day 2, cardiac output, stroke volume, blood pressure, and heart rate were measured in response to graded infusions of norepinephrine. Automated blood pressure and heart rate (Accutracker) were measured, and the average of the 3 readings obtained at 5-minute intervals before norepinephrine infusion served as the baseline value. Norepinephrine was infused at progressively higher doses (0.01, 0.025, and 0.05 g/[kg min]) for 30 minutes each. Blood pressure, heart rate, cardiac output, and stroke volume were measured at 5-minute intervals. The protocol was discontinued for a greater than 30 mm Hg increase of systolic blood pressure over baseline or a greater than 20 mm Hg increase of diastolic blood pressure.

Cardiac output and stroke volume were measured by impedance plethysmography (Sorba Medical Systems, Milwaukee, WI). Cardiac index was computed as cardiac output/body surface area; stroke volume index was computed as stroke volume/body surface area; peripheral vascular resistance index was computed as (mean arterial pressure − central venous pressure/cardiac index) × 80; vascular compliance index was computed as stroke volume index/pulse pressure. In the computation of peripheral vascular resistance index, central venous pressure was estimated to be 4 mm Hg. Reported values are the average of 3 measurements obtained 5 to 10 minutes apart. Average values for each of the baseline hemodynamic measurements in the same subjects did not differ on day 1 and day 2; and comparing measurements on day 1 and day 2, correlation coefficients ranged from 0.80 to 0.90 ($P < .0001$).

Serum glucose was measured with an automated glucose oxidase enzymatic assay. Insulin was measured by using a commercially available double-antibody, equilibrium radioimmunoassay. Insulin resistance was calculated with the homeostasis model assessment (HOMA-IR) index, a Web-based program made available by Oxford University [19]. The degree of insulin resistance is related to the height of the index. Subjects were subsequently divided by HOMA-IR tertiles. Serum cholesterol was measured using a colorimetric enzymatic procedure. Plasma aldosterone concentrations were measured by radioimmunoassay with a commercially available assay kit. Glomerular filtration rate was calculated using Modification of Diet in Renal Disease formula adjusted for age, sex, and race [20].

3. Statistical methods

Continuous variables were reported as means ± SEM. Differences in the distributions of all selected phenotypes between hypertensives and normotensives were determined either by Student t test or by Wilcoxon rank sum test, depending upon the distribution of variables. Age- and sex-adjusted partial correlations of HOMA-IR with hemodynamic variables were identified by Spearman correlation analysis. To elicit the difference in the distribution of selected phenotypes among the insulin resistance tertile

groups, one-way analysis of variance was used with a Bonferroni correction for the pairwise insulin resistance tertile comparisons of the selected variables. Significance of the change in hemodynamic variables to stressors was elicited using sign test. A stepwise backward multiple regression analysis was performed for each dependent characteristic beginning with age, sex, HOMA-IR, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and plasma aldosterone. In addition, systolic blood pressure was included in the model for stroke volume and cardiac indices, although it was eliminated for peripheral vascular resistance and vascular compliance indices because it was included in the formula to compute these 2 parameters. Independent variables with P value < .05 were left in the model. All analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

Table 2
Age- and sex-adjusted Spearman correlation coefficients of HOMA-IR with anthropometric and hemodynamic characteristics

Variable	Overall (N = 462)	Normotensive (n = 231)	Hypertensive (n = 231)
24-h blood pressure (SBP/DBP)	0.15†/0.14†	0.09/0.06	0.07/0.03
Average 24-h heart rate	0.28‡	0.18†	0.34‡
Body surface area	0.35‡	0.36‡	0.29‡
BMI	0.44‡	0.47‡	0.37‡
Waist circumference	0.43‡	0.43‡	0.36‡
Stroke volume index	−0.28‡	−0.28‡	−0.25‡
Cardiac index	−0.22‡	−0.25‡	−0.17*
Peripheral vascular resistance index	0.25‡	0.24‡	0.19*
Vascular compliance index	−0.25‡	−0.25‡	−0.20†

P value *≤ .05, †≤ .01, and ‡≤ .001.

4. Results

Overall, 462 subjects were studied (50% hypertensive and 51% female). Fifty-one percent of normotensive subjects and 51.5% of hypertensives were female (Table 1). Hypertensives were older and had higher BMI, waist circumference, body surface area (P < .0001), and insulin resistance (P = .01). In addition, hypertensives had higher peripheral vascular resistance index (P < .0001), lower stroke volume index (P = .05), and lower vascular compliance index (P < .0001). Although average 24-hour heart rate and cardiac index did not differ in the 2 groups, average nighttime heart rate was faster in hypertensives than in normotensives (67 vs 65 beats per minute, P = .03).

Overall, combining normotensive and hypertensive subjects, HOMA-IR was correlated positively (P < .01) with average 24-hour systolic and diastolic blood pressures (Table 2). However, insulin resistance was not correlated with blood pressure in either normotensive or hypertensive subject groups considered separately. In both overall and within the normotensive and hypertensive subject groups, insulin resistance was positively correlated with anthropometric measures and with 24-hour heart rate and peripheral vascular resistance index and inversely correlated with cardiac index, stroke volume index, and vascular compliance index (Fig. 1). The statistical significance of these associations was not appreciably affected after statistical adjustment for age, sex, blood pressure, serum total cholesterol or LDL and HDL cholesterol, and plasma aldosterone. However, when adjusted for heart rate along with above variables, the correlations were no longer significant among normotensives but still persisted among hypertensives and overall subjects.

The results of the stepwise multiple linear regression analyses to identify the independent predictors of hemodynamic variables are shown in Table 5. HOMA-IR contributed the most to the variability of all the dependent variables (P < .0001). In addition, age also influenced them, particularly peripheral vascular resistance index (P < .0001). Plasma aldosterone had no effect on stroke volume or vascular compliance after adjustment for HOMA-IR.

To further evaluate the relationship of insulin resistance with blood pressure and its physiologic determinants, all

Table 1
Baseline characteristics (mean ± SEM)

Variable	Overall (N = 462)	Normotensive (n = 231)	Hypertensive (n = 231)
Age (y)	43.4 ± 0.3	41.7 ± 0.4	45.1 ± 0.5‡
Average 24-h SBP/DBP (mm Hg)	129 ± 1/78 ± 1	116 ± 1/69 ± 1	142 ± 1/86 ± 1
Average 24-h heart rate (beats/min)	70.3 ± 0.4	69.7 ± 0.6	70.9 ± 0.6
Body surface area (m^2)	1.70 ± 0.01	1.62 ± 0.02	1.77 ± 0.02‡
BMI (kg/m^2)	28.2 ± 0.2	27.5 ± 0.3	28.98 ± 0.3‡
Waist circumference (cm)	90 ± 1	87 ± 1	93 ± 1‡
Insulin resistance index (HOMA-IR)	1.53 ± 0.04	1.45 ± 0.05	1.61 ± 0.05†
Stroke volume index (mL/m^2)	36.4 ± 0.9	37.2 ± 1.2	35.5 ± 1.4*
Cardiac index ($L/[min\ m^2]$)	2.22 ± 0.05	2.22 ± 0.07	2.23 ± 0.09
Peripheral vascular resistance index ($dyne.s.cm^{-5}/m^2$)	4229 ± 127	3556 ± 144	4933 ± 199‡
Vascular compliance index ($mL/[m^2\ mm\ Hg]$)	0.77 ± 0.02	0.91 ± 0.03	0.62 ± 0.03‡
Glomerular filtration rate (mL/min)	113.4 ± 1.1	116.2 ± 1.5	110.7 ± 1.5†

P value *≤ .05, †≤. 01, and ‡≤ .001 comparing normotensives with hypertensives. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

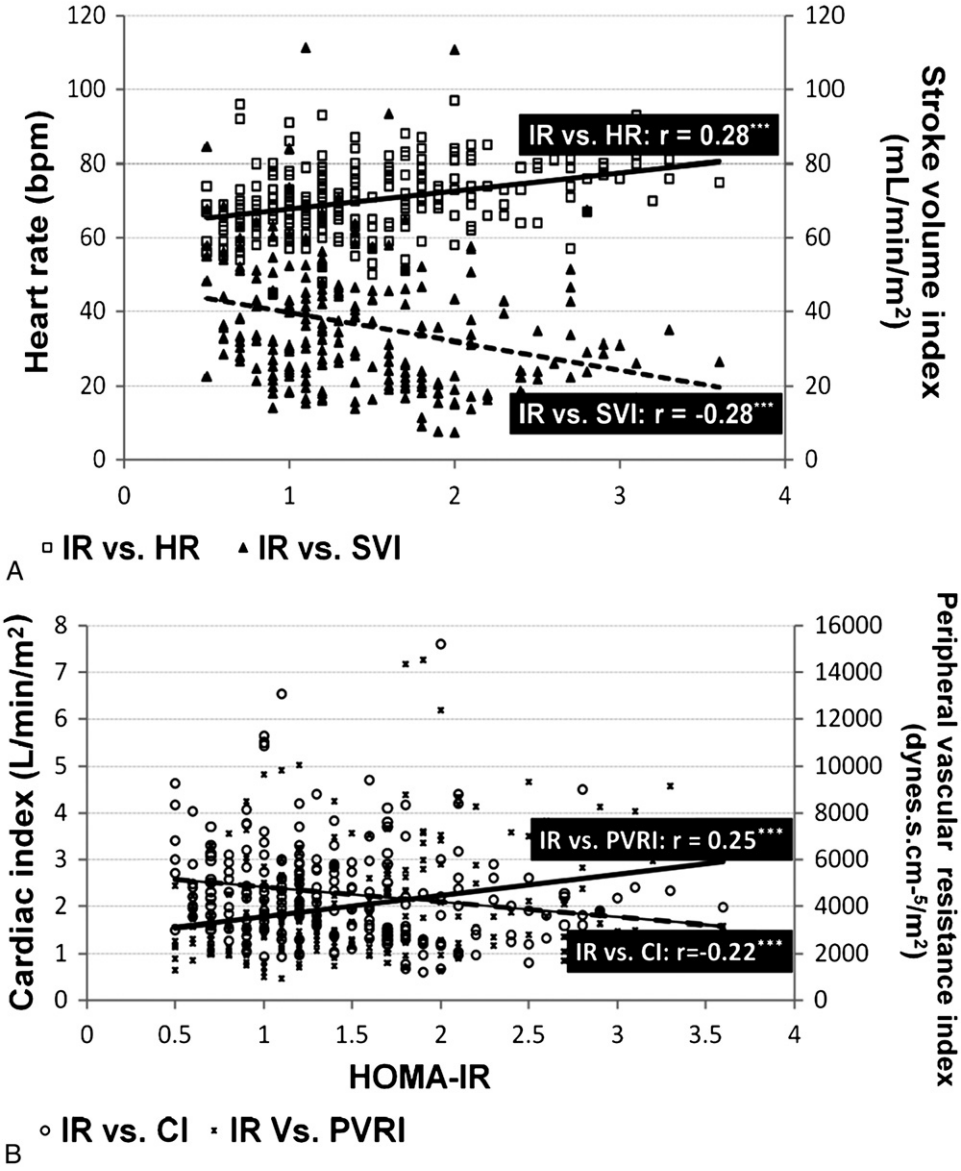

Fig. 1. Scatter plot depicting the relationship between insulin resistance and hemodynamic variables. A, The positive correlation between insulin resistance (HOMA-IR) and heart rate and the negative relationship between HOMA-IR and stroke volume index. B, The positive correlation between HOMA-IR and peripheral vascular resistance index and the negative relationship between HOMA-IR and cardiac index). *P* value *≤ .05, **≤ .01, and ***≤ .001. HR indicates heart rate; SVI, stroke volume index; PVRI, peripheral vascular resistance index; CI, cardiac index.

subjects were grouped by tertiles of HOMA-IR (Table 3). Subjects in the highest tertile of insulin resistance had higher heart rate and waist circumference than the other 2 groups ($P \leq .01$). Peripheral vascular resistance index was also increased, whereas cardiac index, stroke volume index, and vascular compliance index were decreased, in the highest insulin resistance tertile compared with the lower 2 tertile groups ($P \leq .01$). Plasma aldosterone concentrations did not differ significantly among the 3 insulin resistance tertiles.

In response both to mental stress and to graded norepinephrine infusions, the increases of blood pressure in hypertensive subjects were greater than the increases in normotensive subjects ($P < .05$). Overall, combining subject groups, heart rate and cardiac index increased in response to mental stress ($P < .001$). In response to norepinephrine infusions, systolic and diastolic blood pressures and peripheral vascular resistance increased at each infusion rate ($P < .001$), whereas heart rate and vascular compliance index decreased ($P < .001$) (Table 4). Cardiac index and the stroke volume index increased only at the highest infusion rate ($P < .001$). At the highest norepinephrine infusion rate, HOMA-IR was inversely correlated with the increment of stroke volume, i.e., the greater the degree of insulin resistance, the lesser the increase of stroke volume. In contrast to baseline

Table 3
Baseline characteristics of the overall sample by tertiles of insulin resistance

Variable	Lower tertile (n = 166)	Mid tertile (n = 140)	Upper tertile (n = 156)
HOMA-IR	0.88 ± 0.01	1.37 ± 0.01‡	2.38 ± 0.06‡¶
Age (y)	43 ± 1	43 ± 1	43 ± 1
% Female	43	59†	53
% Hypertensive	31	32	37
Plasma aldosterone (ng/dL)[a]	7.0 ± 0.5	6.8 ± 0.4	7.8 ± 0.5
Waist circumference (cm)	85 ± 1	91 ± 1‡	95 ± 1‡‖
Body surface area (m^2)	1.59 ± 0.02	1.71 ± 0.02‡	1.79 ± 0.02‡
BMI (kg/m^2)	25.97 ± 0.31	28.68 ± 0.34‡	30.19 ± 0.28‡‖
240h blood pressure (SBP/DBP) (mm Hg)	126 ± 1/76 ± 1	130 ± 2/78 ± 1	131 ± 1/79 ± 1
Average 24-h heart rate (bpm)	67 ± 1	71 ± 1†	73 ± 1‡
Stroke volume index[a] (mL/m^2)	40.3 ± 1.6	37.5 ± 1.5	31.1 ± 1.5‡¶
Cardiac index[a] ($mL/min/m^2$)	2.4 ± 0.1	2.3 ± 0.9	2.0 ± 0.1†‖
Peripheral vascular resistance index ($dyne.s.cm^{-5}/m^2$)	3800 ± 201	4027 ± 212	4884 ± 236‡
Vascular compliance index[a] ($mL/[m^2$ mm Hg])	0.88 ± 0.04	0.77 ± 0.04	0.65 ± 0.03‡

For pairwise comparisons, Bonferroni correction was applied; only P values < .016 were considered significant.
P value *≤ .05, †≤ .01, and ‡≤ .001 comparing lower tertile to mid and upper tertile.
P value §≤ .05, ‖≤ .01, and ¶≤ .001 comparing mid and upper tertile.
[a] To convert plasma aldosterone into SI units (nanomoles per liter), multiply by 0.0277.

correlations, HOMA-IR was not correlated with changes in any of the other hemodynamic responses to norepinephrine infusion or mental stress (Table 5).

5. Discussion

To better understand the potential consequences of insulin resistance, in the present study, we evaluated the relationship of insulin resistance to blood pressure and other hemodynamic indicators of cardiovascular function, both at rest and in response to mental stress and norepinephrine infusion. We observed correlations between blood pressure and insulin resistance, albeit weak, in the combined group of nondiabetic hypertensive and normotensive subjects; but no correlation was observed when the 2 groups were considered separately. More robust and consistent correlations were observed between insulin resistance and indicators of cardiovascular function. As summarized in Fig. 2, independent of body surface area, insulin resistance is positively associated with peripheral vascular resistance and heart rate, and negatively associated with cardiac output and stroke volume. These relations persisted after statistical adjustment for age, sex, dyslipidemia, plasma aldosterone, and blood pressure. These observations suggest that the insulin resistance has independent effects on cardiovascular function and is perhaps an independent cardiovascular disease risk factor in African Americans. However, in contrast to baseline measures, insulin resistance was not associated with hemodynamic responses to mental stress or to norepinephrine infusion.

We have previously reported that plasma aldosterone is higher in hypertensive African Americans than in either normotensive African Americans or hypertensive whites [4,21]. Furthermore, among African Americans, aldosterone is positively correlated with blood pressure and negatively correlated with vascular compliance; and in males but not females, aldosterone is also correlated with insulin resistance[17,18]. In the present study, overall, mean plasma aldosterone concentrations did not differ among the 3 insulin resistance tertiles; and the hemodynamic correlates of insulin resistance were not affected by statistical adjustment for aldosterone. This suggests that the association of insulin resistance with the hemodynamic variables is independent of aldosterone.

Table 4
Changes of hemodynamic responses to mental stress and graded infusions of norepinephrine

	Δ SBP (mm Hg)	Δ DBP (mm Hg)	Δ HR (beats/min)	Δ SVI ($mL/[min\ m^2]$)	Δ CI ($L/[min\ m^2]$)	Δ PVRI ($dyne.s.cm^{-5}/m^2$)	Δ VCI ($mL/[m^2$ mm Hg])
Computerized math testing	1.6 ± 0.5	1.0 ± 0.3	3.6 ± 0.3‡	−0.18 ± 0.38	0.12 ± 0.02‡	99 ± 119	−0.03 ± 0.01‡
NE infusion rate, μg/[kg min]							
0.01	5.2 ± 0.5‡	2.2 ± 0.4‡	−1.3 ± 0.3‡	−0.23 ± 0.4	−0.07 ± 0.02‡	329 ± 71‡	−0.03 ± 0.01‡
0.025	12.0 ± 0.6‡	4.5 ± 0.4‡	−2.2 ± 0.3‡	1.36 ± 0.53	0.01 ± 0.03	326 ± 60‡	−0.05 ± 0.01‡
0.05	21.4 ± 0.8‡	7.7 ± 0.4‡	−2.5 ± 0.4‡	4.4 ± 0.63‡ §	0.15 ± 0.03‡	412 ± 112‡	−0.07 ± 0.01‡

NE indicates norepinephrine; HR, heart rate; SVI, stroke volume index; CI, cardiac index; PVRI, peripheral vascular resistance index; VCI, vascular compliance index; Δ, change compared with baseline.
P value *≤ .05, †≤ .01, and ‡≤ .001 compared with baseline.
P value §≤ .01 statistically significant correlation with HOMA-IR (insulin resistance index).

Table 5
Stepwise (backward) multiple linear regression analyses

Independent variables ↓	Dependent variables											
	Stroke volume index			Cardiac index			Peripheral vascular resistance index[a]			Vascular compliance index[a]		
	$\beta \pm$ SE	CI	R^2	$\beta \pm$ SE	CI	R^2	$\beta \pm$ SE	CI	R^2	$\beta \pm$ SE	CI	R^2
Intercept	0.00 ± 0.18‡	3.80 to 4.51		0.0 ± 0.16‡	1.02 to 4.65		0.0 ± 0.18‡	6.80 to 7.50		0.0 ± 0.2†	0.15 to 0.94	
Age	−0.15 ± 0.004†	−0.02 to −0.003	2.5	−0.20 ± 0.004*	−0.02 to −0.01	4.2	0.27 ± 0.004‡	0.01 to 0.03	8.1	−0.21 ± 0.004‡	−0.03 to −0.008	4.9
Male sex	NA			NA			0.05 ± 0.05	−0.05 to 0.15	1.8	NA		
HOMA-IR	−0.31 ± 0.06‡	−0.43 to −0.21	9.8	−0.25 ± 0.05‡	−0.35 to −0.14	6.7	0.28 ± 0.006‡	0.18 to 0.41	8.3	−0.27 ± 0.06‡	−0.44 to −0.19	7.8
LDL cholesterol	−0.11 ± 0.00*	−0.003 to −0.000	1.4	NA			NA			−0.13 ± 0.00*	−0.004 to −0.000	1.8
HDL cholesterol	NA			NA			NA			NA		
Plasma aldosterone	NA			NA			NA			NA		
Systolic blood pressure	NA			NA			NA			NA		

CI indicates confidence interval; NA, not applicable.

[a] Systolic blood pressure was not included in the regression analyses because it was used in calculation of peripheral vascular resistance index and vascular compliance index.

* $P \leq .05$.

† $P \leq .01$.

‡ $P \leq .001$.

In insulin-resistant states, there is a shift in balance between the vasoconstrictor and the vasodilator actions of insulin that may impair endothelial-dependent vasodilation and accelerate the development of atherosclerosis [6,11,22,23]. All the major cells involved in atherosclerosis such as endothelial cells, vascular smooth muscle cells, monocytes/macrophages, and T-lymphocytes express insulin receptors [24-27]; and the relatively high insulin concentrations in insulin-resistant states enhance proliferation and migration of these proatherogenic cells. In addition, vascular compliance is reduced, resulting in increased arterial stiffness; and increased intima-medial thickness of the carotid artery has been reported in patients with the metabolic syndrome and in obese patients [28]. The current demonstration of an association of insulin resistance with increased peripheral vascular resistance and decreased vascular compliance is consistent with these observations.

Insulin resistance may also contribute directly to cardiac dysfunction, even in the absence of coronary artery disease [10]. In Sprague-Dawley rats, where the insulin resistance is induced by a high-cholesterol/-fructose diet, defects in myocardial insulin signaling are associated with reductions in cardiac output, ejection fraction, stroke volume, and end-diastolic volume [7]. Similarly, in mice fed a high-fat diet, insulin resistance results in increased left ventricular remodeling and dysfunction in a setting of chronic left ventricular overload [8]. Clinically, insulin resistance is also associated with left ventricular remodeling [7] and impaired systolic and diastolic function in the absence of structural heart disease and coronary artery disease [10]. Consistent with these observations, we observed that insulin resistance is associated with a reduced cardiac output and reduced stroke volume, independent of blood pressure.

Activation of sympathetic nervous system with increased vasoconstrictor tone opposes the vasodilator actions of insulin [29-31], and insulin resistance is also associated with increased sympathetic drive [32]. Compensatory

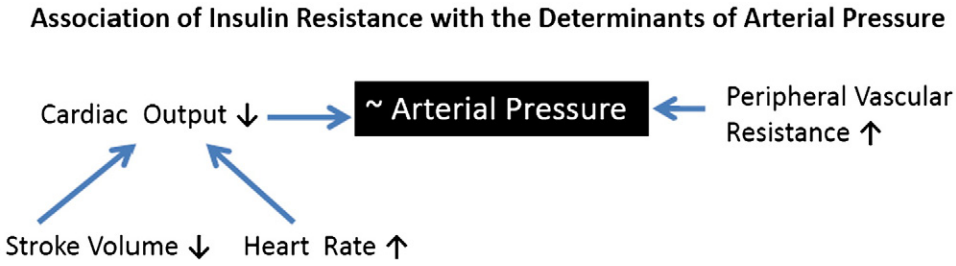

Fig. 2. Schematic diagram showing the relationship between insulin resistance and hemodynamic variables. Association of HOMA-IR with hemodynamic traits. The arrows adjacent to each trait depict the direction of the association. The association of HOMA-IR with blood pressure is equivocal.

hyperinsulinemia in insulin-resistant states may contribute to increased peripheral vascular resistance and to increased heart rate through sympathoexcitatory effects that are regulated by unimpaired mitogen-activated protein kinase–dependent insulin signaling pathways [33]. Adrenergic activity and heart rate are increased in patients with the metabolic syndrome [32]. In the present study, increased sympathetic drive may have contributed to the positive associations of insulin resistance with both peripheral resistance and heart rate. Although it is possible that some of the hemodynamic effects of insulin resistance are mediated by increased sympathetic drive and heart rate, stroke volume and vascular compliance are associated with HOMA-IR independent of heart rate. This strengthens the argument for an independent effect of insulin resistance on cardiovascular function. However, in contrast to ambient hemodynamic measures, hemodynamic responses to mental stress and norepinephrine infusion were not associated with insulin resistance. The only exception was an association of increasing insulin resistance with attenuation of the increment of stroke volume at the highest norepinephrine infusion rate. Conceivably, this stressor may unmask an adverse impact of insulin resistance on cardiac contractility.

There are some limitations to our study. This is a cross-sectional study, and an association of insulin resistance with hemodynamic variables does not necessarily indicate a cause and effect relationship. However, we have tried to eliminate the effect of some of the common risk factors for cardiovascular disease by statistically adjusting for total cholesterol, age, sex, and blood pressure. Although clinical use of impedance plethysmography to measure cardiac output has not been approved by the Food and Drug Administration, it remains a reliable noninvasive tool when a large number of subjects are being studied in a research setting [34]. Plethysmographic measurements of cardiac output have been shown to correlate with Fick and flow-probe measurements in both obese and nonobese subjects [35]. Care was taken to reassure that electrodes were placed correctly, and subjects did not have any known conditions that interfere with the measurements [36-38]. Repeat hemodynamic measurements in the same individuals on 2 separate days were highly correlated.

The observations in this study suggest that an exclusive focus of an effect of insulin resistance on its association with hypertension or type 2 diabetes mellitus may ignore independent pathophysiologic contributions of insulin resistance to cardiovascular disease. Compared with whites, African Americans have a higher prevalence of left ventricular hypertrophy, congestive heart failure, stroke, and chronic kidney disease [39,40]. Results of the present study raise the possibility that insulin resistance directly contributes to vascular disease and heart failure in African Americans. We speculate that therapeutic approaches for reversing insulin resistance, even among those without diabetes mellitus or hypertension, might result in less cardiovascular disease morbidity and mortality. These pathologic consequences of insulin resistance may not be unique to African Americans, and this possibility remains to be evaluated in subsequent studies in different populations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2010.07.036.

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