

## Original Research Article

## Associations Between Insulin and Heart Rate Variability in Police Officers

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**ABSTRACT: Objective:** Low heart rate variability (HRV) has been linked to cardiovascular disease. Our objective was to examine the cross-sectional association between insulin and HRV.

**Methods:** Insulin levels were measured in 355 nondiabetic officers from the BCOPS study, following a 12 h fast. HRV was performed according to methods published by the task force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology for measurement and analysis of HRV. Mean values of high (HF) and low frequency (LF) HRV were compared across tertiles of insulin using ANOVA and ANCOVA; *p*-values were obtained from linear regression models.

**Results:** Higher mean levels of insulin were significantly associated with lower (i.e., worse) mean levels of HRV before and after risk-factor adjustment. The results for HF HRV (ms<sup>2</sup>) were as follows: 1st insulin (μU/ml) tertile (156.3; 95% confidence interval (CI) = 128.6–189.9); 2nd tertile (154.3; 95% CI = 124.3–191.5); 3rd tertile (127.9; 95% CI = 105.0–155.8), *p* for trend = 0.017. Results with LF HRV were similar to HF HRV. Insulin was also inversely and significantly associated with HRV among officers with BMI ≥25 kg/m<sup>2</sup>, with ≥25.5% body fat, and among those who reported low (<median) physical activity scores.

**Conclusions:** In this cohort, insulin levels were inversely and significantly associated with both HF and LF HRV, especially among those with higher levels of obesity and lower levels of physical activity, suggesting associations with autonomic nervous system function. Prospective studies of this association in other populations are warranted. *Am. J. Hum. Biol.* 26:56–63, 2014. © 2013 Wiley Periodicals, Inc.

Cardiovascular disease (CVD) is the number one cause of morbidity and mortality in the United States (Kung et al., 2008) and studies show that police officers experience a greater burden of CVD than persons in the general population (Zimmerman, 2012). Heart rate variability (HRV), which reflects the beat-to-beat variability in heart rate, is considered a noninvasive marker of the cardiovascular control system, the renin-angiotensin-aldosterone system, and the autonomic nervous system (Stockhorst et al., 2011). Lower HRV has been associated with ongoing subclinical inflammation (Haensel et al., 2008), an increased risk of CVD morbidity and mortality (Chandra et al., 2012; Fukuta et al., 2003; Oikawa et al., 2009), and diabetes mellitus (Malpas and Maling, 1990).

CVD has been linked to metabolic dysfunction, and several markers of metabolic function, one of which is insulin, may be associated with HRV. There is little information on the relationship between insulin and HRV but Schroeder et al. (2005) assessed the progression of autonomic impairment among individuals with nondiabetic hyperinsulinemia (Schroeder et al., 2005). Their results showed that, among nondiabetic subjects at baseline, individuals with hyperinsulinemia had lower HRV than subjects without hyperinsulinemia. The relationship between insulin and HRV was present in a dose-response manner throughout the insulin distribution. Other researchers have studied the relationship with HRV when insulin is administered but those results between insulin and HRV have been inconsistent. Stockhorst et al. (2011) observed that administration of insulin resulted in an

acute increase in the high frequency (HF) band of HRV while other investigators (Bellavere et al., 1996; Van De Borne et al., 1999) reported a decrease in the HF band of HRV following insulin administrations. In addition, van de Borne et al. did not observe any effect on the low frequency (LF) band of HRV from insulin. The results of an experiment performed on 12 nonobese young men (18–36 years) showed that insulin infusion increased sympathetic nervous system activity in the absence of changes in blood glucose (Rowe et al., 1981).

Decreased HRV has been observed in individuals with increased psychological stress levels (Lee and Theus, 2012; Rieger et al., 2013; Suh et al., 2013) and has been proposed as a link between psychosocial risk and workplace stress in the development of metabolic and CVD (Thayer et al., 2010). Police officers may be at increased risk for decreased HRV due to their constant exposure to several occupational stressors (Covey et al., 2013; Fekedulegn et al., 2012; Miller, 2006; Violanti, 2011). In a recently published article on this cohort of police officers,

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both male and female officers reported experiencing psychologically threatening events on a regular basis (approximately three or more events per day in the past month) with events involving organizational and administrative pressure occurring more often than other events (Hartley et al., 2011). Female officers reported overall slightly higher mean stress ratings, which are likely to be chronic, than male officers. Stress affects the hypothalamic-pituitary-adrenal axis resulting in higher levels of cortisol and abdominal obesity, with consequences for impaired insulin sensitivity (Bjorntorp, 2001; Bjorntorp and Rosmond, 1999). To the best of our knowledge, there are no published studies investigating the association between insulin and HRV in police officers. The objective of this study was to investigate the association between insulin and HRV and determine if gender significantly modified this association. We hypothesized that there would be an inverse association between insulin and HRV.

## METHODS

### *Study design and participants*

Between June 2004 and October 2009, ~710 police officers employed at the Buffalo, New York Police Department were invited to participate in the Buffalo Cardio-metabolic Occupational Police Stress (BCOPS) study, a cross-sectional comprehensive examination of the health consequences of stress in law enforcement officers. Some of them had previously participated in the 1999–2000 ( $n = 115$ ) and 2001–2003 ( $n = 100$ ) examinations. Data were collected at The Center for Health Research, School of Public Health and Health Professions, University at Buffalo, State University of New York (Violanti et al., 2006). The State University of New York at Buffalo Internal Review Board approved the study and informed consent was obtained from all participants. The original sample size was 464 but only 447 officers underwent the ECG procedure. Of the 447 officers who completed the resting ECG measurements, those who reported having a history of irregular heart rate during their health history examination ( $n = 25$ ) or had significant evidence of irregular beats or abnormal QRS intervals during the BCOPS exam ( $n = 32$ ) were excluded from these analyses, resulting in 390 officers with satisfactory HRV measurements. In addition, 33 retired officers, 16 officers who were diagnosed with diabetes, and 18 officers who did not have complete information on insulin levels were also excluded (categories are not mutually exclusive). The final sample size for these cross-sectional analyses on insulin and HRV was 355 officers (91 women and 264 men).

### *Clinic examination*

Each officer in this study had all measurements obtained on the same day. The officers were instructed to abstain from eating or drinking anything but water, strenuous physical exercise, and use of tobacco after 10 p.m. on the night before the day of examination. All officers were given a standardized breakfast of 280 calories around 8:30 a.m. after blood specimens were collected and before other components of the examination were performed.

### *Assessment of heart rate variability*

Details of the assessment of HRV have been published elsewhere (Andrew et al., 2013). Measurement of HRV was

performed according to standard methods published by the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology for measurement and analysis of HRV (Camm et al., 1996).

The ultrasound technician placed sequence time markers on the measured time series to indicate the beginning and end of the carotid ultrasound examination. Resting ECG time series were extracted from the first 5 min of carotid ultrasound examination. Each time series was processed using an automated data adaptive QRS detection package that inserts a time marker at each proposed R wave peak (Bsanalyze advanced biosignal processing system with ECG toolbox from Guger Technologies, Graz, Austria, www.gtec.at).

Data editing included visual inspection of the ECG time series overlaid with QRS markers and hand editing of R wave markers where needed.

The RR time series resulting from this process was processed using cubic spline interpolation to provide a time series with equal sample increments at two samples per second. The interpolated time series was then detrended using a smoothness priors method (Tarvainen et al., 2002). Next, the data were processed using a parametric autoregressive spectral analysis of order 16 (Boardman et al., 2002). The HF component of HRV is defined as the area under the power spectral density from 0.15 to 0.4 Hz. The LF component is the area under the power spectral density between frequencies 0.04 to 0.15 Hz. These were obtained by calculating the area under the estimated power spectral density curve for the appropriate frequency intervals. All of these calculations are carried out using the R language. These methods are standard for short-term HRV measurements.

### *Assessment of insulin*

Insulin was measured in fasting serum specimens by a chemiluminescent microparticle immunoassay (CMIA) test using the ARCHITECT i1000SR System. The normal range is 2–20  $\mu\text{U/ml}$ .

### *Assessment of covariates*

Officers provided information on demographic characteristics, lifestyle behaviors, and medical history and medication using self- and interviewer-administered questionnaires. Officers were asked how often they consumed alcoholic beverages with one drink defined as a 12 oz. can or bottle of beer, one medium glass of wine, or one shot of liquor. The total number of drinks consumed per week was used. Officers reported their smoking status as current, former, or never. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Trained and certified technicians from the Osteoporosis Research Center at the University at Buffalo measured percent body fat using the dual-energy X-ray absorptiometry (DXA Hologic QDR 4500A machine; Hologic, Waltham, MA).

Blood pressure was determined using the average of the second and third of three separate measurements of resting systolic and diastolic blood pressure obtained with a standard sphygmomanometer. Blood specimens were collected by a certified phlebotomist after officers had fasted for a minimum of 12 h. Laboratory analyses of glucose and lipids were measured by standard laboratory techniques on the Beckman Coulter LX20 clinical chemistry analyzer.

TABLE 1. Demographics and other selected characteristics by gender

Characteristics	All (n = 355) Mean ± SD	Women (n = 91) Mean ± SD	Men (n = 264) Mean ± SD	P-value
Age (years)	40.6 ± 6.8	40.3 ± 5.9	40.7 ± 7.1	0.664
Years of service	14.3 ± 7.2	13.5 ± 6.9	14.5 ± 7.3	0.240
BMI (kg/m <sup>2</sup> )	29.1 ± 4.6	25.8 ± 4.4	30.3 ± 4.1	<0.0001
Body fat (%)	25.9 ± 6.2	26.2 ± 6.1	25.8 ± 6.2	0.675
Waist circumference (cm)	94.2 ± 14.1	79.7 ± 10.8	99.2 ± 11.3	<0.0001
Diastolic BP (mm Hg)	77.4 ± 10.0	74.1 ± 9.8	78.5 ± 9.9	0.0003
Systolic BP (mm Hg)	120.8 ± 11.8	116.5 ± 13.5	122.3 ± 10.7	0.0003
Physical activity score	21.4 ± 18.2	22.0 ± 17.3	21.1 ± 18.5	0.703
Alcohol (no. of drinks per week)	5.0 ± 7.9	3.5 ± 4.6	5.6 ± 8.7	0.005
Glucose (mg/dl)	91.6 ± 9.5	86.6 ± 8.3	93.3 ± 9.3	<0.0001
HDL cholesterol (mg/dl)	46.6 ± 14.7	58.4 ± 15.7	42.6 ± 11.9	<0.0001
Triglycerides (mg/dl)	136.9 ± 136.8	88.1 ± 139.2	153.5 ± 132.2	<0.0001
Insulin (uU/ml) <sup>a</sup>	6.30 (5.82–6.83)	4.35 (3.70–5.12)	7.16 (6.56–7.81)	<0.0001
HRV (HF) (ms <sup>2</sup> ) <sup>a</sup>	150.4 (133.4–169.5)	197.6 (155.6–250.6)	136.9 (119.3–157.0)	0.008
HRV (LF) (ms <sup>2</sup> ) <sup>a</sup>	213.4 (193.8–234.9)	189.0 (155.4–230.0)	222.5 (199.1–248.4)	0.146
	N (%)	N (%)	N (%)	
Hypertension status				0.415
Hypertensive	73 (20.6)	16 (17.6)	57 (21.6)	
Not hypertensive	282 (79.4)	75 (82.4)	207 (78.4)	
Race/ethnicity				0.047
White	270 (77.4)	65 (71.4)	205 (79.5)	
African American	73 (20.9)	26 (28.6)	47 (18.2)	
Hispanic	6 (1.7)	0 (0)	6 (2.3)	
Education				0.035
≤ 12 years/GED	34 (9.7)	3 (3.3)	31 (11.9)	
College < 4 yr	192 (54.6)	56 (61.5)	136 (52.1)	
College ≥ 4 yr	126 (35.8)	32 (35.2)	94 (36.0)	
Shift work status				<0.0001
Day	131 (38.6)	57 (65.5)	74 (29.4)	
Afternoon	120 (35.4)	17 (19.5)	103 (40.9)	
Night	88 (26.0)	13 (14.9)	75 (29.8)	
Smoking status				0.005
Current	54 (15.4)	21 (23.6)	33 (12.6)	
Former	79 (22.5)	25 (28.1)	54 (20.6)	
Never	218 (62.1)	43 (48.3)	175 (66.8)	
Body mass index (kg/m <sup>2</sup> )				<0.0001
<25	65 (18.3)	46 (50.6)	19 (7.2)	
≥25	290 (81.7)	45 (49.5)	245 (92.8)	
Metabolic Syndrome				<0.0001
Present (≥3 components)	82 (23.2)	6 (6.7)	76 (28.8)	
Absent	272 (76.8)	84 (93.3)	188 (71.2)	
Insulin (uU/ml) (tertiles)				<0.0001
Low (1–5)	133 (37.5)	57 (62.6)	76 (28.8)	
Medium (6–8)	91 (25.6)	18 (19.8)	73 (27.7)	
High (9–55)	131 (36.9)	16 (17.6)	115 (43.6)	

BP, blood pressure.

P-values were obtained from *t*-tests and chi-square tests.

Presence of metabolic syndrome is defined as ≥3 of the components.

<sup>a</sup>Results were first log-transformed then back-transformed.

Physical activity during the previous seven days was obtained with the Seven-Day Physical Activity Recall questionnaire used in the Stanford Five-City Project (Sallis et al., 1985). Participants reported the duration (hours per weekday and hours per weekend) and intensity (moderate, hard, and very hard) of three types of physical activity (occupational, household, and sports). A total physical activity score was then computed by summing the intensities of the three types of physical activity performed during the weekday and weekend, and multiplying that number by the reported duration.

#### Statistical analysis

Univariate analysis was used to describe characteristics of the study participants. Because of the skewed distributions, insulin and HRV were log-transformed prior to

analyses and then back-transformed for reporting as means and 95% confidence intervals (CIs). Mean values of HRV were obtained across tertiles of insulin using analysis of variance (ANOVA). *p*-values for trends were obtained from linear regression analysis. Variables were chosen as potential confounders and included in the multivariate models based on their roles as confounding variables in published studies or if they were significantly associated with both the independent and dependent variables in the current study. Analysis of covariance (ANCOVA) was used to examine the effect of adjustment for several covariates (age, gender, race/ethnicity, hypertension status, smoking status, alcohol intake, physical activity, HDL cholesterol, and triglycerides) on the relationship between insulin and HRV. Gender was assessed for effect modification. Given the strong associations between obesity and insulin and between physical activity

TABLE 2. Correlations and mean levels of HF and LF HRV with selected covariates

	HF HRV	LF HRV
Age (years)	-0.331, <0.0001	-0.260, <0.0001
BMI (kg/m <sup>2</sup> )	-0.151, 0.004	-0.134, 0.012
Body fat (%)	-0.003, 0.955	0.034, 0.535
Waist circumference (cm)	-0.236, <0.0001	-0.162, 0.002
Diastolic BP (mm Hg)	-0.245, <0.0001	-0.082, 0.122
Systolic BP (mm Hg)	-0.229, <0.0001	-0.163, 0.002
Physical activity score	0.179, 0.001	0.145, 0.006
Alcohol (no. of drinks per week)	-0.117, 0.09	-0.139, 0.010
Glucose (mg/dl)	-0.136, 0.011	-0.014, 0.794
HDL cholesterol (mg/dl)	0.052, 0.332	-0.039, 0.467
Triglycerides (mg/dl)	-0.139, 0.009	-0.069, 0.197
	Mean (95% CI)	Mean (95% CI)
Hypertension status		
Hypertensive	96.1 (74.1–124.5)	167.3 (135.6–206.4)
Not hypertensive	168.8 (148.0–192.6)	227.2 (204.2–252.9)
P-value <sup>a</sup>	<0.001	0.011
Race/ethnicity		
White/Hispanic	139.6 (121.9–159.8)	216.8 (194.3–241.9)
African American	187.8 (144.3–244.4)	198.7 (160.5–245.9)
P-value <sup>a</sup>	0.050	0.475
Smoking status		
Current	144.2 (106.1–195.9)	193.6 (151.2–247.8)
Former	133.2 (103.4–171.7)	197.2 (160.8–241.8)
Never	155.2 (133.2–180.8)	223.4 (197.6–252.6)
P-value <sup>a</sup>	0.586	0.425

BP, blood pressure.

<sup>a</sup>P-values are from ANOVA and are for any difference between the means.

and HRV, associations between insulin and HRV were assessed among officers with high and low levels of BMI, percent body fat and physical activity. SAS version 9.2 was used to analyze these data (SAS, 2008).

## RESULTS

Descriptive statistics of several characteristics are presented in Table 1. The mean age of all police officers was 40.6 ± 6.8 years (Table 1). The majority of the officers were white (77.4%) and 25.6% were women. All anthropometric and blood pressure measures were significantly higher in men as compared to women. Compared to women, men had significantly higher mean levels of insulin: 7.2 (95% CI: 6.6–7.8) vs. 4.4 μU/ml (95% CI: 3.7–5.1) and glucose [93.3 ± (standard deviation, SD) 9.3 vs. 86.6 ± 8.3 mg/dl], and significantly lower mean levels of HF HRV [136.9 (95% CI: 119.3–157.0) vs. 197.6 ms<sup>2</sup> (95% CI: 155.6–250.6)].

Table 2 shows the unadjusted associations between selected variables and HRV. HF HRV was inversely correlated with age, all anthropometric measures, blood pressure, glucose, and triglycerides, and positively correlated with physical activity score. Mean HF HRV was significantly lower among officers with hypertension [96.1 ms<sup>2</sup> (95% CI: 4.1–124.5) as compared to those without hypertension (168.8 ms<sup>2</sup> (95% CI: 148.0–192.6)], *p* < 0.001; and significantly higher among African American officers [187.8 ms<sup>2</sup> (95% CI: 144.3–244.4)] as compared to white/Hispanic officers [139.6 ms<sup>2</sup> (95% CI: 121.9–159.8)], *p* = 0.050.

The associations between selected variables and insulin were also analyzed (data not shown). Age, years of police service, and all anthropometric variables were strongly and positively correlated with insulin. Officers who were diagnosed as hypertensive had significantly higher mean

levels of insulin as compared to those who were not diagnosed as hypertensive, 9.4 (95% CI: 7.9–11.1) and 5.7 μU/ml (95% CI: 5.2–6.2), respectively; *p* < 0.001. Increasingly higher levels of education were associated with decreasing mean levels of insulin, *p* = 0.007.

In Table 3, unadjusted and adjusted mean values and 95% CIs of HF and LF HRV are presented across tertiles of insulin. As tertiles of insulin increased, mean values of both HF and LF HRV decreased monotonically. After adjustment for age, gender, race/ethnicity, hypertension status, smoking status, alcohol intake, physical activity, HDL cholesterol, and triglycerides, the associations between insulin and HRV were only slightly attenuated and remained strongly significant. We did not find significant effect modification by gender.

Mean values and 95% CIs of HRV are presented across tertiles of insulin (created specifically for each category of BMI), stratified by BMI, in Table 4. Insulin levels were not significantly associated with either HF HRV or LF HRV among officers with BMI < 25 kg/m<sup>2</sup>. However, among officers with BMI ≥ 25 kg/m<sup>2</sup>, insulin was inversely and significantly associated with HRV of both frequencies. After adjustment for confounding variables and CVD risk factors, the associations remained strongly significant. Among officers with BMI ≥ 25 kg/m<sup>2</sup>, the mean values and 95% CIs of HF HRV for each tertile of insulin were as follows: 1st insulin tertile, mean = 149.0 (95% CI: 117.6–188.6); 2nd tertile, mean = 139.1 (95% CI: 112.7–171.7); and 3rd tertile, mean = 124.7 ms<sup>2</sup> (95% CI: 99.5–156.4); adjusted *p*-value for trend = 0.034. The association between insulin and LF HRV was similar to that between insulin and HF HRV, but slightly stronger, *p*-value for trend = 0.002.

In Table 5, mean values and 95% CIs of HRV are presented across tertiles of insulin (created specifically for each category of percent body fat), stratified by percent body fat. Among officers who had < 25.5% body fat, the association between insulin and HRV was not statistically significant, whereas, among officers with ≥ 25.5% body fat, insulin was significantly and inversely associated with LF HRV (*p* for trend = 0.001) after adjustment for age, gender, race/ethnicity, hypertension status, smoking status, alcohol intake, physical activity, HDL cholesterol, and triglycerides. The inverse association with HF HRV did not quite reach statistical significance.

In Table 6, mean values and 95% CIs of HRV are presented across tertiles of insulin (created specifically for each category of physical activity), stratified by physical activity. As observed with BMI and percent body fat, stratification revealed different associations between the two groups. The association between insulin and HRV was not statistically significant among officers who reported high physical activity levels. In contrast, insulin was inversely and significantly associated with HF and LF HRV among officers who reported low physical activity, *p* for trend = 0.030 (for both), after adjustment for age, gender, race/ethnicity, hypertension status, smoking status, alcohol intake, HDL cholesterol, and triglycerides.

## DISCUSSION

Reduced HRV is a marker of cardiac autonomic dysfunction (Vinik et al., 2011; Ziegler, 1994) and is known to be associated with increased CVD morbidity and mortality (Chandra et al., 2012; Oikawa et al., 2009). In our study,

TABLE 3. Mean values and 95% confidence intervals (CIs) of HRV by tertiles of insulin

	Tertiles of insulin (uU/ml)			P-value
	1st tertile Range: 1–5; n = 133 Mean (95% CI)	2nd tertile Range: 6–8; n = 91 Mean (95% CI)	3rd tertile Range: 9–55; n = 131 Mean (95% CI)	
HF HRV				
Model 1	188.2 (155.2–228.3)	153.6 (121.7–194.0)	117.9 (97.1–143.2)	<0.0001
Model 2	170.8 (141.3–206.3)	155.8 (124.9–194.4)	128.9 (106.7–155.6)	0.003
Model 3	156.3 (128.6–189.9)	154.3 (124.3–191.5)	127.9 (105.0–155.8)	0.017
LF HRV				
Model 1	245.7 (210.4–287.0)	225.4 (186.8–272.0)	178.0 (152.2–208.1)	0.002
Model 2	249.5 (213.6–291.3)	221.7 (184.9–265.8)	177.3 (151.9–206.9)	0.001
Model 3	237.4 (201.9–279.2)	222.5 (185.9–266.2)	177.0 (150.3–208.5)	0.008

Results for HF and LF HRV were first log-transformed then back-transformed.

Range refers to the minimum and maximum levels for each tertile of insulin.

P-values were obtained from linear regression models.

Model 1: Unadjusted

Model 2: Adjusted for age and gender

Model 3: Adjusted for age, gender, race/ethnicity, hypertension, smoking status, alcohol intake, physical activity, HDL cholesterol, and triglycerides.

TABLE 4. Mean values and 95% confidence intervals (CIs) of HRV by BMI-specific tertiles of insulin, stratified by BMI

	Tertiles of insulin			P-value
	1st tertile Mean (95% CI)	2nd tertile Mean (95% CI)	3rd tertile Mean (95% CI)	
<b>BMI <math>\geq 25</math> kg/m<sup>2</sup></b>	<b>Range: 1–5; n = 90</b>	<b>Range: 6–9; n = 100</b>	<b>Range: 10–55; n = 100</b>	
HF HRV				
Model 1	180.5 (141.9–229.5)	145.2 (115.5–182.4)	112.1 (89.2–140.8)	<0.001
Model 2	149.0 (117.6–188.6)	139.1 (112.7–171.7)	124.7 (99.5–156.4)	0.034
LF HRV				
Model 1	267.0 (219.3–324.9)	224.5 (186.3–270.5)	168.7 (140.0–203.2)	<0.001
Model 2	253.4 (207.1–310.1)	212.6 (177.5–254.5)	175.5 (144.6–212.9)	0.002
<b>BMI <math>&lt; 25</math> kg/m<sup>2</sup></b>	<b>Range: 1–2; n = 19</b>	<b>Range: 3–5; n = 24</b>	<b>Range: 6–18; n = 22</b>	
HF HRV				
Model 1	234.1 (147.6–371.3)	185.6 (123.1–279.8)	172.4 (112.3–264.6)	0.255
Model 2	209.7 (125.3–350.7)	175.8 (113.1–273.4)	179.7 (111.5–289.7)	0.498
LF HRV				
Model 1	193.4 (139.5–268.1)	217.6 (162.7–291.0)	210.0 (155.0–284.5)	0.874
Model 2	181.9 (126.5–261.6)	219.7 (160.9–300.1)	220.6 (157.5–309.0)	0.494

Results for HF and LF HRV were first log-transformed then back-transformed.

Range refers to the minimum and maximum levels for each tertile of insulin.

P-values were obtained from linear regression models.

Model 1: Unadjusted.

Model 2: Adjusted for age, gender, race/ethnicity, hypertension, smoking status, alcohol intake, physical activity, HDL cholesterol, and triglycerides.

higher levels of insulin were associated with lower levels of HRV of both frequencies among this cohort of nondiabetic police officers. The inverse association between insulin and HRV was also observed in officers with BMI  $\geq 25$  kg/m<sup>2</sup>, in officers who had  $\geq 25.5\%$  body fat, and in those who reported low physical activity. In our study, the association appeared to be slightly stronger between insulin and LF HRV than between insulin and HF HRV. LF HRV is modulated by both sympathetic and parasympathetic nervous system activity while HF HRV is modulated by parasympathetic nervous system activity (Stein and Pu, 2012). Future research that incorporates a stimulus to elicit sympathetic activity is warranted to determine whether the association with insulin is differentially associated with parasympathetic versus sympathetic function.

Our results that suggest lower vagal control accompanies higher fasting levels of insulin are consistent with some of the results from previous studies. Berkelaar et al. (2013) examined the effects of serum insulin levels on

vagal control over the heart and the association between fasting insulin levels and vagal control. Their results showed that insulin levels were negatively correlated with vagal control, but these associations disappeared after adjustment for age, BMI, and insulin sensitivity. The authors suggested that BMI and insulin sensitivity may be the key factors that are influencing cardiac vagal control, and not insulin levels. Results from a study conducted on ARIC participants showed that, in those individuals without diabetes, fasting serum insulin was inversely associated with HF HRV (Liao et al., 1995). The authors observed the biggest decrease in HF HRV in those persons in the highest quartile of fasting insulin ( $\geq 14$   $\mu$ U/dl). After stratifying by BMI using a cut point of BMI  $\geq 27$  kg/m<sup>2</sup>, they found similar inverse associations between serum insulin and HF HRV in the higher and lower BMI groups. Galinier et al. (1999) found that patients with hyperinsulinemia or insulin resistance had a significant decrease in LF HRV, which reflected sympathetic modulation of HRV.

TABLE 5. Mean values and 95% confidence intervals (CIs) of HRV by body fat-specific tertiles of insulin, stratified by body fat

	Tertiles of insulin			P-value
	1st tertile Mean (95% CI)	2nd tertile Mean (95% CI)	3rd tertile Mean (95% CI)	
<b>Body fat <math>\geq 25.5\%</math></b>	<b>Range: 1–5; n = 59</b>	<b>Range: 6–9; n = 58</b>	<b>Range: 10–55; n = 56</b>	
HF HRV				
Model 1	230.0 (175.7–301.2)	149.5 (113.9–196.2)	117.7 (89.3–155.2)	0.001
Model 2	189.0 (142.7–250.3)	153.1 (117.9–198.7)	133.6 (100.1–178.1)	0.091
LF HRV				
Model 1	299.7 (241.8–371.6)	215.4 (173.4–267.5)	168.5 (135.1–210.1)	<0.001
Model 2	306.7 (243.3–386.7)	206.7 (166.6–256.3)	166.5 (131.3–211.2)	0.001
<b>Body fat &lt;25.5%</b>	<b>Range: 1–4; n = 54</b>	<b>Range: 5–8; n = 68</b>	<b>Range: 9–36; n = 60</b>	
HF HRV				
Model 1	162.5 (117.7–224.3)	157.8 (118.4–210.4)	110.4 (81.3–149.8)	0.007
Model 2	139.8 (102.2–191.0)	145.4 (112.1–188.6)	116.8 (85.8–159.0)	0.083
LF HRV				
Model 1	201.8 (155.6–261.7)	232.6 (184.5–293.3)	179.9 (140.5–230.2)	0.232
Model 2	191.4 (146.8–249.6)	219.9 (176.4–274.3)	187.5 (144.3–243.6)	0.634

Results for HF and LF HRV were first log-transformed then back-transformed.

P-values were obtained from linear regression models.

Model 1: Unadjusted.

Model 2: Adjusted for age, gender, race/ethnicity, hypertension, smoking status, alcohol intake, physical activity, HDL cholesterol, and triglycerides.

TABLE 6. Mean values and 95% confidence intervals (CIs) of HRV by physical activity-specific tertiles of insulin, stratified by physical activity

	Tertiles of insulin			P-value
	1st tertile Mean (95% CI)	2nd tertile Mean (95% CI)	3rd tertile Mean (95% CI)	
<b>High physical activity</b>	<b>Range: 1–4; n = 55</b>	<b>Range: 5–8; n = 60</b>	<b>Range: 9–55; n = 63</b>	
HF HRV				
Model 1	210.0 (155.6–283.3)	168.1 (126.2–223.9)	136.6 (103.3–180.7)	0.015
Model 2	172.2 (126.0–235.4)	141.1 (107.2–185.6)	166.0 (121.8–226.1)	0.556
LF HRV				
Model 1	246.4 (192.6–315.2)	236.3 (186.7–299.2)	203.1 (161.4–255.7)	0.236
Model 2	261.4 (202.1–338.2)	227.3 (181.3–284.8)	187.1 (145.0–241.3)	0.133
<b>Low Physical activity</b>	<b>Range: 1–5; n = 61</b>	<b>Range: 6–9; n = 63</b>	<b>Range: 10–36; n = 53</b>	
HF HRV				
Model 1	174.9 (131.5–232.5)	146.5 (110.6–193.9)	91.0 (67.0–123.6)	0.001
Model 2	156.3 (118.0–206.9)	142.2 (109.1–185.3)	97.5 (71.7–132.5)	0.030
LF HRV				
Model 1	249.7 (199.1–313.0)	206.3 (165.2–257.8)	150.7 (118.2–192.1)	0.001
Model 2	239.1 (189.1–302.3)	193.5 (155.0–241.4)	164.6 (127.4–212.7)	0.030

Results for HF and LF HRV were first log-transformed then back-transformed.

P-values were obtained from linear regression models.

Model 1: Unadjusted.

Model 2: Adjusted for age, gender, race/ethnicity, hypertension, smoking status, alcohol intake, HDL cholesterol, and triglycerides.

High physical activity:  $\geq 16.5$  (the median).

Chronically elevated levels of insulin may indicate insulin resistance. Stein et al. (2008) explored the relationship between insulin resistance (and inflammation factors) and lower HRV in normoglycemic older adults. Their results showed that greater insulin resistance was consistently correlated with lower HRV even after adjustment for inflammatory factors. In another study, the authors investigated whether young Indian men having low BMI had different autonomic nervous responses to acute hyperinsulinemia when compared to others who had a normal BMI (Sucharita et al., 2011). They observed that LF HRV significantly increased and HF HRV significantly decreased with hyperinsulinemia but that there were no differences in the magnitude of responses between the two BMI groups. Because there were no officers considered to have low BMI in our study, we compared normal to high BMI and we observed that inverse associations between insulin and HRV were only present among officers with BMI  $\geq 25$  kg/m<sup>2</sup>.

Some studies demonstrate that the relationship between insulin and HRV is dependent on the insulin-sensitive status of the individuals being studied. In one study, male subjects were divided into insulin sensitive and insulin resistant groups to study the effect of insulin on HRV (Bergholm et al., 2001). The results showed that, under normoglycemic conditions, insulin changed HRV toward sympathetic predominance in insulin sensitive subjects whereas, in the less insulin-sensitive subjects, insulin did not change any of the components of HRV. According to the authors, their data demonstrated it was the individual's insulin sensitivity status that modulated the response of HRV to insulin since both groups of individuals were similar with respect to BMI, waist-to-hip ratio, and age. Paolisso et al. (2000) also investigated the effects of insulin infusion on cardiac autonomic nervous system activity in healthy subjects and in patients with various types of insulin-resistance. They found that insulin stimulated ANS activity in healthy subjects but not in

insulin-resistant patients; and that those effects were different in the two groups.

Exercise training or physical activity positively affects cardiac autonomic function (Gouloupoulou et al., 2010) and various CVD risk factors (Tibana et al., 2013), and may influence the relationship between insulin (or glucose) and autonomic function. In one study, 464 postmenopausal women (45–75 years) were randomized to one of three exercise training groups or a nonexercise control for 6-months period (Earnest et al., 2010). After 6 months of exercise, measures of autonomic function improved and this improvement was associated with a reduction in insulin levels. We assessed the association between insulin and HRV while stratifying on physical activity and our results showed that there was an inverse association between insulin and HRV among officers who reported low physical activity.

Results which are inconsistent with our findings have also been reported. Stockhorst et al. (2011) showed that, in healthy humans, an acute increase in serum insulin, either due to insulin injection or to the subsequent increase in insulin after administration of glucose, was significantly correlated with an acute increase in the HF-band of HRV. However, the associations detected in the present study are likely due to long-term alterations in insulin levels rather than to acute changes.

There is evidence of plausible biological mechanisms in the relationship between the circulating levels of insulin and HRV. The pancreatic islets of Langerhans have an abundance of nerve fibers from the sympathetic and parasympathetic branches of the autonomic nervous system (Ahren, 2000; Caumo and Luzi, 2004; Woods and Porte, 1974). Insulin receptors located in several regions of the central nervous system such as the median hypothalamus may also play a role in the relationship between insulin and the autonomic nervous system (Sauter et al., 1983). Insulin, by binding to its receptors in the arcuate nucleus area of the hypothalamus, activates several pathways that culminate in increased sympathetic nervous system activity (Cassaglia et al., 2011; Chronwall, 1985; Dampney, 2011). Further support comes from the finding that stimulation of the arcuate nucleus leads to an increase in sympathetic activity and heart rate (Nakamura et al., 2009; Ruggeri et al., 2001). Therefore, elevations in blood insulin levels can stimulate sympathetic nervous system activity (Anderson et al., 1991; Young et al., 2010) and vagal activation also stimulates insulin secretion (Woods and Porte, 1974).

There are a few limitations that must be mentioned. Because of the cross-sectional design of this study, causal inference cannot be made nor can the chronological sequence of the main variables be determined. The results of our study could only be generalizable to police officers who are affiliated with departments of similar size and geographic location.

Our study also has several strengths. To the best of our knowledge, this is the first study to investigate the association between fasting insulin and HRV among police officers. HRV was measured and processed using tightly controlled standardized methods. Insulin values were determined using a standardized test by an accredited laboratory experienced in conducting analyses for various types of research studies. Data were collected on several variables allowing for assessment of effect modification and adjustment of confounders and CVD risk factors.

## CONCLUSIONS

In summary, higher levels of insulin were associated with lower levels of HRV of both frequencies among these police officers. Higher levels of HRV are desirable because they are associated with decreased risk of CVD and several CVD-related conditions (Bigger et al., 1995; Chandra et al., 2012; Fukuta et al., 2003). Our results are consistent with those of previous studies, which show an inverse relationship between insulin and HRV. Health programs for police officers could include surveillance of and interventions for obesity, which is strongly associated with elevated insulin levels, with an overall goal of maintaining optimal HRV levels. This is especially important for this occupational cohort that experiences high stress levels (Hartley et al., 2011), since individuals who experience increased job-related stress have been shown to have decreased HRV and reduced recovery of autonomic nervous system function (Rieger et al., 2013). Future studies, employing larger sample sizes and longitudinal study designs will be useful in determining whether elevated insulin levels predict subsequent decline in HRV.

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