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Prediabetes and Blood Pressure Effects on Heart Rate Variability, QT-Interval Duration, and Left Ventricular Hypertrophy in Overweight-Obese Adolescents

Shirleatha Lee, PhD, RN, CNE^{a,*}, Patricia Ann Cowan, PhD, RN^b,
Glenn T. Wetzel, PhD, MD^b, Pedro Velasquez-Mieyer, MD^b

^aThe University of Memphis, Memphis, TN

^bThe University of Tennessee Health Science Center, Memphis, TN

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This ancillary, descriptive correlational study examined the effect of glucose regulation, blood pressure (BP), and their combined effects on cardiac autonomic function in 128 overweight-obese 11–18-year-olds. Measures included body mass index, resting BP, fasting glucose, glucose tolerance, and cardiac autonomic function (heart rate variability, QT, and Cornell voltage). After adjusting for age and gender, multivariate analysis of covariance revealed no differences in cardiac autonomic measures based on glucose regulation ($p = .319$), BP ($p = .286$), or the interaction between glucose regulation and BP ($p = .132$). The additive effect of prediabetes and elevated BP did not impact cardiac autonomic function in overweight-obese youth.

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THE AUTONOMIC NERVOUS system regulates cardiac muscle, smooth muscle, and glands of the body through sympathetic and parasympathetic stimulation. An imbalance in autonomic nervous system function is a marker for increased cardiovascular risk and is associated with metabolic abnormalities including obesity, prediabetes, and diabetes (Karason, Molgaard, Wikstrand, & Sjostrom, 1999). The 2007–2008 National Health and Nutrition Examination Survey estimates that 17% of children and adolescents are obese (Centers for Disease Control and Prevention, 2010). The increased prevalence of childhood obesity has, in turn, resulted in a myriad of chronic conditions affecting obese children (Goran, Ball, & Cruz, 2003; Khositseth, Suthutvoravut, Chongviriyaphan, & Ruangkanhasetr, 2006). Two conditions that have become increasingly more prevalent in obese youth include elevated blood pressure (EVBP) and prediabetes. Currently,

the American Diabetes Association (2008) estimates that two million overweight adolescents have prediabetes, and researchers report that obese children are three times more likely to have high blood pressure than are nonobese children (Sorof & Daniels, 2002). Prediabetes is a condition of impaired fasting glucose, impaired glucose tolerance, or both (American Diabetes Association, 2008), and obese children tend to progress from prediabetes to type 2 diabetes at a faster rate than adults do (Cruz et al., 2005). Evidence suggests that in the presence of obesity, sympathetic stimulation of the autonomic nervous system (Sekine, Izumi, Yamagami, & Kagamimori, 2001) inhibits insulin secretion from the β -cells (Carnethon et al., 2006). This sympathetic predominance seen in conjunction with obesity has been identified also in patients with EVBP (Frontoni, Bracaglia, & Gigli, 2005).

It is well documented that diabetes causes cardiac autonomic neuropathy (Carnethon et al., 2006; Pappachan et al., 2008; Perciaccante, Fiorentini, Paris, Serra, & Tubani, 2006; Scott & Kench, 2004; Valensi, Paries, & Attali, 2003) and affects insulin release. EVBP is also associated with

* Corresponding author: Shirleatha Lee, PhD, RN, CNE.

E-mail address: sntaylr1@memphis.edu (S. Lee).

autonomic imbalance (Pal, Pal, Nanda, Amudharaj, & Karthik, 2009). However, it is unknown whether overweight-obese adolescents with prediabetes exhibit impaired cardiac autonomic function and whether concomitant hypertension may further compound this effect (Wu et al., 2008). Cardiac autonomic imbalance may manifest as impaired heart rate variability (Bilchick & Berger, 2006), prolonged QT-interval duration (Viitasalo, Karjalainen, Makijarvi, & Toivonen, 1998), and development of left ventricular hypertrophy (Maule, Milan, Grosso, & Veglio, 2006). These measures are important in the assessment of cardiac autonomic function because decreased heart rate variability (Reed, Robertson, & Addison, 2005), prolonged QT interval (QT Syndrome, 2005), and left ventricular hypertrophy (Kahan & Bergfeldt, 2005) may lead to an increased risk of sudden cardiac death. Research findings that examine the effect of prediabetes and EVBP on cardiac autonomic function in overweight and obese youth have not been identified. The high prevalence of prediabetes (Rodbard, 2008), EVBP (McCarthy et al., 2008), and autonomic nervous system dysfunction (Sekine et al., 2001) in obese children supports further investigation into the effect of prediabetes and EVBP on measures of cardiac autonomic function.

Heart Rate Variability

Heart rate variability is modulated by both sympathetic and parasympathetic activity (Bilchick & Berger, 2006) of the autonomic nervous system. It is the normal beat-to-beat alterations of heart rate and reflects the autonomic nervous system's ability to respond to the environment (McMillan, 2002). Increased sympathetic activity and reduced parasympathetic activity increase ventricular workload and myocardial oxygen demand (Soares, Moreno, Cravo, & Nobrega, 2005). As a result, ischemia can occur and alter the ionic currents throughout the myocardial cellular membrane. This alteration may produce electrical instability, life-threatening arrhythmias, and sudden cardiac death (Soares et al., 2005). Although many uncertainties surround the effect of glucose metabolism and blood pressure on heart rate variability in obese adolescents, heart rate variability changes have been noted in patients with diabetes (McMillan, 2002) and EVBP (Alter, Grimm, Vollrath, Czerny, & Maisch, 2006).

The predominant method for analysis of heart rate variability is time and frequency domain analysis; these measurements provide information about autonomic nervous system function (Gang & Malik, 2003). Time domain analyses are calculated using mathematical equations and reflect parasympathetic modulation and circadian rhythmicity. The time domain measure of standard deviation of all R-R intervals (SDNN) reflects autonomic circadian rhythmicity (Cowan, 1995), and the high frequency (HF) analysis reflects parasympathetic modulation (Butera, Bonnet, Kachaner, Sidi, & Villain, 2003).

QT-Interval Duration

The QT interval represents ventricular depolarization and repolarization and is the measurement from the onset of the QRS complex to the end deflection of the T wave (Furukawa et al., 2006; Hunt, 2005). It is also modulated by autonomic function (Viitasalo et al., 1998) because in light of cardiac automaticity, heart rate is controlled largely by autonomic function (Alter et al., 2006). A delay in ventricular repolarization prolonging the QT interval predisposes the heart to arrhythmias (Lanjewar, Pathak, & Lokhandwala, 2004; QT Syndrome, 2005) and sudden cardiac death (Lanjewar et al., 2004; QT Syndrome, 2005).

QT prolongation has been identified in the presence of obesity (Takebayashi, Aso, Matsutomo, Wakabayashi, & Inukai, 2004) and diabetes (Brown, Giles, Greenlund, & Croft, 2001; Girola, Enrini, Garbetta, Tufano, & Caviezel, 2001) and in children with EVBP (Kocak et al., 1999). Researchers also indicate that 30% of obese individuals with impaired glucose regulation (prediabetes) have prolonged QT-interval duration (Poirier et al., 2006).

Left Ventricular Hypertrophy

Left ventricular hypertrophy is enlargement of the ventricles (American Heart Association, 2010) that is often related to an increased workload on the heart. The prevalence of left ventricular hypertrophy has been shown to increase with autonomic imbalance (Maule et al., 2006). Left ventricular hypertrophy makes the heart muscle progressively less effective in generating and conducting electrical impulses (Corrado, Bacharova, Antzvelitch, & Kanters, 2007). Defects in conduction can lead to arrhythmias, particularly torsades de pointes, that may result in sudden cardiac death (Kahan & Bergfeldt, 2005).

The most common cause of left ventricular hypertrophy is EVBP (Edhouse, Thakur, & Khalil, 2002) that is associated with sympathetic dominance and parasympathetic withdrawal (Passino et al., 2004). In 34%–38% of children with untreated hypertension or even mild hypertension, left ventricular hypertrophy occurs (Ippisch & Daniels, 2008). The presence of obesity and prediabetes presents an additional risk for left ventricular hypertrophy. Hyperglycemia produces advanced glycation end products that form stable and irreversible cross-links with collagen polymers in myocardial and arterial walls, decreasing myocardial compensation and leading to left ventricular hypertrophy (Fujita et al., 2007). Although these studies support the linkage between obesity, prediabetes, hypertension, and left ventricular hypertrophy, studies have not examined the relationship of prediabetes and EVBP to electrocardiogram voltage measures for left ventricular hypertrophy in overweight-obese children.

Purpose

Autonomic dysfunction is linked to childhood obesity, prediabetes, and EVBP, and substantial evidence suggests that autonomic imbalance leads to increased morbidity and mortality (Liatis, Tentolouris, & Katsilambros, 2004; Thayer, Yamamoto, & Brosschot, 2009). Alterations in autonomic function that are associated with decreased heart rate variability (Soares et al., 2005), QT prolongation (Lanjewar et al., 2004), and left ventricular hypertrophy may result in sudden cardiac death (Kahan & Bergfeldt, 2005). However, few studies in overweight and obese children have examined autonomic function (Kaufman, Kaiser, Steinberger, Kelly, & Dengel, 2007), cardiovascular function (Khositseth et al., 2006), or electrocardiographic changes.

Researchers suggest that the current screening recommendation for obese youth underestimates cardiovascular and metabolic risk (Velasquez-Mieyer, Neira, Nieto, & Cowan, 2007). The purpose of this study was to examine glucose regulation and blood pressure effects on cardiac autonomic measures of heart rate variability, QT duration, and electrical voltage measures of left ventricular hypertrophy in overweight and obese youth. The examination of these additional cardiac risk factors, which are modulated by autonomic function, may aid in identifying obese youth at increased risk for obesity-associated comorbidities and sudden cardiac death.

The following research questions will be examined.

1. What is the relationship between severity of obesity (body mass index [BMI]) and heart rate variability measures of SDNN and HF, QT, and electrical voltage measures for left ventricular hypertrophy in youth?
2. Is there a significant difference in the frequency of EVBP among glucose regulation groups (prediabetes vs. normal glucose)?
3. After controlling for age and gender, is there a significant difference among overweight-obese youth for cardiac autonomic measures of heart rate variability (SDNN and HF), QT, and electrical voltage measures for left ventricular hypertrophy based on
 - a. glucose regulation (prediabetes vs. normal glucose);
 - b. blood pressure (EVBP vs. normal blood pressure [NBP]); and
 - c. glucose and blood pressure groups combined (prediabetes with EVBP, prediabetes with NBP, normal glucose with EVBP, and normal glucose with NBP)?

Hypothesis 1: As severity of obesity (BMI) increases, heart rate variability measures of SDNN and HF will decrease, QT will become more prolonged, and electrical voltage measures for left ventricular hypertrophy will increase.

Hypothesis 2: Overweight-obese youth with prediabetes will have a significantly higher frequency of EVBP than will peers with normal glucose level.

Hypothesis 3: Lower heart rate variability, more prolonged QT, and higher measures of electrical voltage for left ventricular hypertrophy will be exhibited in overweight-obese youth with the following:

- a. prediabetes in comparison with peers with normal glucose level
- b. EVBP in comparison with peers with NBP
- c. prediabetes and EVBP combined in comparison with all other groups.

Methods

This ancillary study used a descriptive correlational design and included a convenience sample of overweight-obese youth ($n = 128$) who were aged 11–18 years. The original study examined enteroinsular axis activity, cardiorespiratory fitness, and autonomic nervous system modulation in a sample of Black and White overweight and obese adolescents to explore racial differences in glucose metabolism, incretins (glucagon-like peptide-1), autonomic function, and lifestyle behaviors. This study differs from the original study because we will examine autonomic function using electrocardiographic measures of heart rate variability, QT, and left ventricular hypertrophy for this population.

Sample

A total of 188 participant charts were reviewed from the original study sample recruited from a large metropolitan city in the mid-south region of the United States. Participants for the original study were recruited from the community and area pediatric, family practice, and pediatric obesity clinics. The original study included participants who were overweight or obese (BMI \geq 85th percentile for age and gender), weighed less than 350 lb, had no previous history of diabetes, and were not taking medications that affected body weight, autonomic nervous system function, blood pressure, glucose, or lipid metabolism. Pregnant adolescents were excluded from the study. From the chart reviews of these original 188 participants, 128 were selected for inclusion in this ancillary study. Individuals were included if their 24-hr Holter monitor had >18 hr of usable data, their electrocardiogram was analyzable, and their blood pressure and glucose tolerance testing results were available. The average age of this ancillary study sample was 14.32 ± 1.91 years, with 63.3% female and 60.2% Black.

Measures

Overweight and Obesity

BMI was used to classify youth as overweight or obese (in kg/m^2) according to age and gender percentiles. Overweight was defined in adolescents as a BMI (weight [kg] / height² [m^2]) \geq 85th percentile for age and gender based on Centers for Disease Control and Prevention growth charts, whereas obesity equated to a BMI \geq 95th percentile by age and gender percentile distributions (O'Brien et al., 2007).

Prediabetes

After a 10-hr overnight fast, fasting glucose levels were obtained, and either a 2-hr oral glucose tolerance test or a mixed meal tolerance test was performed. For the oral glucose tolerance test, participants consumed 1 g of dextrose/kg of body weight (up to 75 g), and blood samples were obtained at 0, 15, 30, 60, 90, and 120 min for glucose and insulin levels. For the mixed meal tolerance test, a standardized liquid meal was ingested (Sustacal/Boost; 6 kcal/kg of body weight, maximum of 360 kcal consumed), and blood samples for insulin and glucose were obtained at 0, 15, 30, 60, 90, and 120 min. The oral glucose tolerance test and the mixed meal tolerance test measures “insulin action, B-cell function, and the rate of meal glucose appearance” (Dalla Man et al., 2005, p. 3265). Findings have indicated a significant correlation between mixed meal tolerance test and oral glucose tolerance test results (Marena, Montegrosso, De Michieli, Pisu, & Pagano, 1992). Prediabetes was determined when fasting glucose levels were between 100 and 126 mg/dl or 2-hr plasma glucose levels were between 140 and 200 mg/dl (American Diabetes Association, 2009).

Blood Pressure

A resting blood pressure was obtained with a sphygmomanometer and appropriate-size cuff. Normative blood pressure tables developed by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents were utilized for single blood pressure readings. These guidelines have recently incorporated prehypertension (McNiece et al., 2007), as prehypertension is linked to increased cardiovascular risk (American Heart Association, 2009; Qureshi, Suri, Kirmani, Divani, & Mohammad, 2005). A systolic or diastolic blood pressure ≥ 95 th percentile (hypertension) and a systolic or diastolic blood pressure ≥ 90 th but less than the 95th percentile (prehypertension) were combined to form the EVBP group. NBP in youth was considered a systolic/diastolic blood pressure < 90 th percentile for age, height, and gender (McNiece et al., 2007).

Heart Rate Variability

The Marquette Electronics Version 5.8 Ambulatory Electrocardiogram Analysis and Editing System was utilized for editing and analysis of Holter recorded data for heart rate variability. Recordings were scanned into the Multi-parameter Arrhythmia Review Station PC Analysis and Editing system (GE Marquette Medical Systems, Milwaukee, WI) Version 5.8. The QRS complexes were digitally processed and assigned a template for manual validation and overreading. After validation, heart rate variability analysis was performed using the computerized system according to the manufacturer settings.

Time and frequency domain analysis provides information about autonomic nervous system activity. The time domain measure utilized within this study is the SDNN, and it reflects autonomic circadian rhythmicity (Cowan, 1995).

This method was used because SDNN is predictive of mortality (Lampert, Ickovics, Horwitz, & Lee, 2005), and an SDNN < 50 ms has been linked to sudden cardiac death (Faulkner, Quinn, Rimmer, & Rich, 2005). Power spectral analysis transforms variations in R-R intervals into frequency waveforms reflecting low (0.04–0.15 Hz), high (0.15–0.40 Hz), and total (0.1–1.0 Hz) frequencies that are components of sympathetic and parasympathetic modulation. HF reflects parasympathetic modulation exclusively (Butera et al., 2003), and the low frequency component is representative of sympathetic and parasympathetic function. Twenty-four-hour Holter measures of HF components and time domain measures of SDNN were utilized in the analysis of heart rate variability data, with each recording containing at least 18 hr of analyzable data.

QT Interval

A 12-lead electrocardiogram was conducted on all participants at a standard paper speed of 25 mm/s at rest. The 12-lead electrocardiogram reports from the original study were used to determine the QT interval. The QT interval was measured from the beginning of the QRS complex to the end deflection of the T wave in three consecutive waveforms in lead II. The corrected QT (QTc) was then calculated for each of the three QT-interval measures using Bazett's formula (QT / \sqrt{RR}) to correct for variations in heart rate. The three QTc measures were averaged, and average QTc intervals measuring > 0.440 s in males and > 0.460 s in females were considered prolonged (Crotti, Celano, Dagradi, & Schwartz, 2008).

Left Ventricular Hypertrophy

Electrical voltage measures for left ventricular hypertrophy were also obtained from the 12-lead electrocardiogram. Studies in children examining electrocardiographic detection of ventricular hypertrophy and correlations with echocardiograms are limited (Hancock et al., 2009). For this study, left ventricular hypertrophy was determined using the Cornell voltage criteria by measuring the S wave in lead $V_3 + R$ wave in lead aVL. The Cornell voltage index ($S_{V_3} + R_{aVL}$) is a more recently published criterion for measuring left ventricular hypertrophy by electrocardiogram (Hancock et al., 2009). Although this method of left ventricular hypertrophy detection has not been validated in children, it appears to be the best electrocardiogram criteria for detecting left ventricular hypertrophy in persons who are overweight and obese (Alpert, 2004; Eckel, 2003). In obese individuals, electrical forces within the heart become more posterior, and the S_{V_3} is the most representative voltage for evaluating posterior electrical forces (Eckel, 2003). When left ventricular hypertrophy is present in obese individuals, the heart is shifted more horizontally in the chest cavity, which explicates the importance of the R_{aVL} (Eckel, 2003). Like many other electrocardiographic criteria that have been shown to improve detection of left ventricular hypertrophy in adults, the Cornell voltage criterion has not been tested in

children (Rijnbeek et al., 2008). Therefore, when utilized in children, it is best used as a screening tool to be correlated with other measures of hypertrophy (Hancock et al., 2009).

To determine Cornell voltage, the R wave was measured as the first positive deflection in the QRS complex, following the Q wave and arising from ventricular activation. The S wave was measured as the negative deflection following the R wave in the QRS complex. The normal voltages for the S wave in lead V₃ and the R wave in aVL have yet to be determined for overweight-obese adolescents, but according to criteria in obese adults, left ventricular hypertrophy is considered to be present in males and females if S_{V3} + R_{aVL} is >2.8 and >2.0 mV, respectively. This criterion was also utilized to determine the presence of left ventricular hypertrophy in this sample of overweight-obese youth.

Procedures

Institutional review board approval was obtained. Written and verbal consent and assent were received from parents/legal guardians and participants, respectively, during the original study. The principle investigator maintained each participant's confidentiality and anonymity. Data measures were obtained for overweight-obese adolescents aged 11–18 years ($n = 128$) from the original study for analysis. With the exception of QT and Cornell voltage measures obtained from the 12-lead electrocardiogram reports, all study measures were collected during the original study and provided to the researcher for data analysis (Table 1).

Table 1 Variables and Measurements

Variable	Measurement
Overweight-Obese	BMI ≥ 85 th or ≥ 95 th percentile, respectively, for overweight and obese according to age and gender percentiles
Prediabetes	Impaired fasting glucose = fasting blood glucose between 100 and 126 mg/dl or impaired glucose tolerance = 2-hour postload between 140 and 200 mg/dl
EVBP	Systolic or diastolic BP measures ≥ 90 th percentile for age and gender
Heart rate variability	24-hr Holter measures of SDNN that reflects circadian fluctuation and HF that reflects parasympathetic function.
QTc interval	12-Lead electrocardiogram (QTc = QT / \sqrt{RR}); >0.440 s in males and >0.460 s in females = prolonged
Cornell voltage for left ventricular hypertrophy	12-Lead electrocardiogram (S wave in V ₃ + R wave in aVL); >2.8 mV in males or >2.0 mV in females = left ventricular hypertrophy

Note: BP = blood pressure.

Table 2 Demographics and Cardiac Autonomic Measures ($n = 128$)

Measures	Total Group
Gender (% female)	63.3
Race (% Black)	60.2
Age, mean \pm SD (years)	14.32 \pm 1.91
BMI, mean \pm SD (kg/m ²)	37.18 \pm 7.40
Systolic BP, mean \pm SD (mm Hg)	123.62 \pm 13.30
Diastolic BP, mean \pm SD (mm Hg)	69.47 \pm 8.36
EVBP (%)	51.5
Prediabetes (%)	28.1
SDNN, mean \pm SD (ms)	138.94 \pm 39.67
HF, mean \pm SD (ms ²)	6.23 \pm 1.86
Average QTc duration, mean \pm SD (s)	0.408 \pm 0.350
QTc prolonged (%)	10.1
Cornell voltage criteria, mean \pm SD (mV)	0.86 \pm 0.35
Left ventricular hypertrophy (%)	0.0

Note: BP = blood pressure.

Analysis

Data analysis was conducted using Statistical Software for the Social Sciences software Version 17.0. Pearson's correlation coefficients were estimated to examine the relationship between severity of obesity and heart rate variability, QT, and Cornell voltage measures for left ventricular hypertrophy. Chi-square analysis was then used to determine if overweight-obese youth with prediabetes had a significantly higher frequency of EVBP than did peers with normal glucose level.

We then adjusted for age and gender and used analysis of covariance to compare continuous variables of cardiac autonomic function (SDNN, HF, QTc, and Cornell voltage) among glucose regulation groups followed by blood pressure groups. Lastly, the participants were divided into four groups: prediabetes with EVBP, prediabetes with NBP, normal glucose with EVBP, and normal glucose with NBP. Thereafter, we applied multivariate and univariate analysis of covariance to determine if cardiac autonomic measures of heart rate variability (SDNN and HF), QT, or Cornell voltage for left ventricular hypertrophy differed significantly among all four groups. The significance level was set at .05 a priori for all research questions.

Results

According to age and gender percentiles for BMI, 6 (4.7%) youth in this study were overweight and 122 (95.3%) were obese. The mean BMI was 37.18 kg/m² (range, 23–57.7 kg/m²), which is equivalent to stage II obesity in adults. Findings indicated that severity of obesity (BMI) was not significantly correlated with HF ($r = -.077$, $p = .385$) or SDNN ($r = -.075$, $p = .400$) measures of heart rate variability, QTc duration ($r = 0.087$, $p = .331$), or Cornell voltage measures for left ventricular hypertrophy ($r = .004$, $p = .968$).

Table 3 Categorical Comparison of Glucose Regulation Groups Based on BP Status

Variable	EVBP (n = 66, 51.5%)	Normal BP (n = 62, 48.4%)	Total (n = 128, 100%)
Prediabetes	23 (17.9%)	13 (10.1%)	36 (28.1%)
Normal glucose	43 (33.5%)	49 (38.2%)	92 (71.8%)

Note: $\chi^2 = 3.047$, $p = .081$. BP = blood pressure.

Thirty-six participants (28%) were identified as having prediabetes (impaired fasting glucose = 16.4%; impaired glucose tolerance = 11.7%). Findings also revealed that 66 (51.5%) participants were considered to have EVBP (Table 2). Elevations in systolic blood pressure were more common than elevations in diastolic blood pressure (51.5% vs. 0.09%), with diastolic elevations occurring always in the presence of systolic elevations. The prediabetes and normal glucose groups had a similar frequency of EVBP, and chi-square analysis did not reveal a statistically significant difference between glucose groups for blood pressure categories (17% vs. 33%; $\chi^2 = 3.047$, $p = .081$; Table 3).

Table 4 displays the univariate analysis of covariance with an adjustment for the confounders of age and gender, for examination of cardiac autonomic measures (SDNN, HF, QTc, and Cornell voltage). Participants with EVBP displayed significantly higher measures of Cornell voltage for left ventricular hypertrophy than did peers with NBP (0.94 vs. 0.80 mV, respectively; $p = .058$) when controlling for age and gender; however, all other cardiac autonomic measures were not significantly different among blood pressure groups.

When controlling for age and gender, the multivariate analysis of covariance indicated that no significant difference existed across all dependent variables of cardiac autonomic function (SDNN, HF, QTc, and Cornell voltage) for glucose regulation ($p = .319$), for blood pressure ($p = .286$), or for the interaction effect between glucose regulation and blood pressure ($p = .132$) using Wilks' Lambda. Table 5 shows the univariate analysis of covariance among the four assigned subject groups: prediabetes with EVBP, prediabetes with NBP, normal glucose with EVBP, and normal glucose with

NBP, adjusting for age and gender. Cardiac autonomic measures of heart rate variability (SDNN and HF), QTc, and Cornell voltage were not significantly different among these four groups based on univariate analysis of covariance.

Discussion

Research Question 1: The Relationship Between the Severity of Obesity and Cardiac Autonomic Measures

Studies suggest that obesity is associated with cardiac autonomic dysfunction (Gutin et al., 2005). We hypothesized that as severity of obesity (BMI) increased, heart rate variability measures of SDNN and HF would be lower, QT would be more prolonged, and electrical voltage measures for left ventricular hypertrophy would increase. The results of our study indicated that severity of obesity did not correlate with heart rate variability (SDNN and HF), QTc interval, or Cornell voltage measures. Divergent findings have been reported for heart rate variability (SDNN and HF) and QT-interval duration when obesity is present. Our study findings, however, support research that indicates that overall heart rate variability measures are not decreased in obese youth (Martini et al., 2001), and no correlation exists between QT duration and BMI (Girola et al., 2001).

As for the severity of obesity and left ventricular hypertrophy, although it is well documented that a relationship exists (Chinali et al., 2006; Flynn & Alderman, 2005; Kuperstein, Hanly, Niroumand, & Sasson, 2001; Maggio et al., 2008), studies that examined Cornell voltage measures for left ventricular hypertrophy in overweight-obese youth have not been identified. Although no adolescents within our study were considered to have left ventricular hypertrophy according to the criterion utilized, this information would provide useful data for further discussion. The youth within our study were all markedly overweight or obese with very little variability in BMI, and this could have contributed to the general lack of correlation for the severity of obesity among all cardiac autonomic measures.

Table 4 Comparison of Adjusted Means of Cardiac Autonomic Measures for Glucose Regulation Followed by Blood Pressure Groups Based on Univariate Analysis of Covariance

Measures	Prediabetes (n = 36)	Normal Glucose (n = 92)	p	EVBP (n = 66)	NBP (n = 62)	p
Heart rate variability						
SDNN (ms)	128.85 ± 6.64	141.57 ± 3.99	.104	138.18 ± 4.96	132.23 ± 6.00	.449
HF (ms ²)	6.37 ± 0.38	6.09 ± 0.23	.529	6.55 ± 0.29	5.91 ± 0.35	.162
QTc (s)	0.409 ± 0.006	0.407 ± 0.004	.780	0.410 ± 0.005	0.406 ± 0.006	.563
Cornell voltage (mV)	0.901 ± 0.059	0.847 ± 0.036	.438	0.941 ± 0.044	0.807 ± 0.054	.058*

Note: The covariance included age and gender. Data are expressed as adjusted mean ± SE.

* $p \leq .05$.

Table 5 Comparison of Adjusted Means of Cardiac Autonomic Measures Among All Glucose and Blood Pressure Combined Groups Based on Univariate Analysis of Covariance

Measures	Prediabetes With EVBP (<i>n</i> = 23)	Prediabetes With NBP (<i>n</i> = 13)	Normal Glucose With EVBP (<i>n</i> = 43)	Normal Glucose With NBP (<i>n</i> = 49)	<i>p</i>
Heart rate variability					
SDNN (ms)	138.92 ± 7.99	116.31 ± 10.64	140.30 ± 5.88	143.76 ± 5.48	.083
HF (ms ²)	7.18 ± 0.46	5.57 ± 0.34	6.02 ± 0.34	6.13 ± 0.32	.091
QTc (s)	0.415 ± 0.070	0.403 ± 0.010	0.404 ± 0.005	0.410 ± 0.005	.178
Cornell voltage (mV)	0.952 ± 0.071	0.851 ± 0.095	0.931 ± 0.053	0.764 ± 0.049	.634

Note: The covariance included age and gender. Data are expressed as adjusted mean ± *SE*. *p* = nonsignificant for all measures.

Research Question 2: Frequency of EVBP Among Prediabetes and Normal Glucose Groups

It was important to explore the frequency of EVBP in overweight-obese youth with prediabetes because diabetes and EVBP frequently occur together and both impair cardiac autonomic function (Takahashi et al., 2001). A high prevalence of prediabetes in obese adolescents has been reported (Rodbard, 2008), and our study further supports this finding. Twenty-eight percent of overweight-obese youth within this study had prediabetes, which is higher than estimates of 17% in this population reported by the American Diabetes Association (2008). It is theorized that as blood glucose levels increase, blood viscosity increases as well, contributing to an overall increase in blood pressure (Cinar, Mete Senyol, & Duman, 2001). We hypothesized that overweight-obese youth with prediabetes would have a significantly higher frequency of EVBP than would peers with normal glucose level. Our findings indicate that the frequency of EVBP among youth with prediabetes is similar to those with normal glucose levels when obesity is present. This is contrary to study findings that suggest that children with even mild glucose impairment exhibit arterial stiffening (Khan, Kerr, Ross, Newton, & Belch, 2006) that can result in EVBP. The results of this study could suggest that during the prediabetes state in overweight-obese youth, blood glucose levels alone are not high enough to contribute to elevations in blood pressure.

Research Question 3: Glucose Regulation, Blood Pressure, and Combined Effects on Cardiac Autonomic Measures

Cardiac autonomic dysfunction is associated with both diabetes and EVBP that often occur simultaneously (Takahashi et al., 2001). These chronic diseases are becoming increasingly more prevalent in youth with obesity, contributing to increased cardiovascular risk. This is a major concern because obesity in adults is associated with autonomic imbalance (Karason et al., 1999) that affects heart rate variability (Bilchick & Berger, 2006) and QT-interval duration (Viitasalo et al., 1998) and increases the risk

for left ventricular hypertrophy (Maule et al., 2006) and sudden cardiac death. We hypothesized that lower heart rate variability, more prolonged QT, and higher measures of electrical voltage for left ventricular hypertrophy would be exhibited in overweight-obese youth with (a) prediabetes in comparison with peers with normal glucose levels, (b) EVBP in comparison with peers with NBP, and (c) prediabetes and EVBP combined in comparison with all other groups.

Twenty-eight percent of overweight-obese youth within this study had prediabetes and 51% had EVBP, far exceeding research reporting that 30% of overweight children have EVBP (McCarthy et al., 2008). We investigated if the link that exists between autonomic impairment and diabetes also exists for prediabetes in overweight-obese youth for these cardiac autonomic measures. In addition, we explored if blood pressure, alone or in combination with prediabetes, further augments autonomic impairment. Therefore, our study sought to determine if, after controlling for age and gender, there was a significant difference in cardiac autonomic measures of heart rate variability (SDNN and HF), QTc, and Cornell voltage measures for left ventricular hypertrophy among overweight-obese youth based on glucose regulation, blood pressure, or glucose regulation and blood pressure effects combined.

Glucose Regulation Effects on Cardiac Autonomic Measures

It has been noted that diabetes is linked to diminished heart rate variability (Perciaccante et al., 2006), prolonged QTc duration (Vinod Porwal, 2005), and the presence of left ventricular hypertrophy (Foppa et al., 2006). Within our study, overweight-obese youth with prediabetes had similar cardiac autonomic measures of heart rate variability (SDNN and HF), QTc, and Cornell voltage for left ventricular hypertrophy as those with normal glucose.

In regard to heart rate variability, an early complication of diabetes is cardiac autonomic neuropathy, and decreased heart rate variability is one of the earliest signs of cardiac autonomic neuropathy (Balcioğlu, Arslan, Türkoğlu, Özdemir, & Çengel, 2007). Balcioğlu et al. (2007) found a negative correlation between the duration of diabetes and measures of heart rate variability. However, during the prediabetes state in the overweight-obese youth within our

study, heart rate variability measures of SDNN and HF were not significantly different from values seen in those with normal glucose levels. Our findings are consistent with research in adults that suggests a weak relationship between prediabetes and heart rate variability measures (Schroeder et al., 2005). Age, gender, and physical activity differences are several factors that are known to influence heart rate variability. Massin and von Bernuth (1997) and Silveti, Drago, and Ragonese (2001) reported that heart rate variability measures of SDNN increased from infancy through early adolescence. Similarly, Galeev, Igisheva, and Kazin (2002) found that in children 6 to 16 years of age, SDNN values increased with age, as did HF values, reflecting increased parasympathetic function. Silveti et al. also reported greater SDNN values in males compared with females, and Buchheit, Platat, Oujaa, and Simon (2007) indicate that physical fitness levels may influence heart rate variability measures. Statistical adjustments for age and gender were made within this study; however, physical activity levels were not examined.

Second, in adolescents, a QTc interval >0.440 s in males and >0.460 s in females is considered prolonged (Crotti et al., 2008), and in this study, 3.1% of overweight-obese adolescents with prediabetes and 7.0% with normal glucose levels exhibited QTc-interval prolongation. As expected, the 10.1% overall prevalence of QTc prolongation in this sample of overweight-obese youth is lower than the 25% prevalence rate reported in individuals with type 2 diabetes (Vinod Porwal, 2005); however, the 10.1% prevalence of QTc prolongation in this population is still troubling.

Clinicians have always used precaution when prescribing medications that may adversely affect QT duration, especially to individuals with known QT prolongation. Prolongation of the QT interval can be acquired genetically, due to adverse drug reactions, and as hypothesized in accordance with obesity, diabetes, or EVBP. Our study findings suggest that in overweight-obese youth, glucose regulation does not significantly impact QTc duration and supports research that suggests that obesity alone may be one of the most common causes of QTc prolongation (El-Gamal et al., 1995). Therefore, overweight-obese adolescents with and without prediabetes should be considered at a low to moderate risk for QT prolongation when medications that may affect QT duration are prescribed, and these individuals should be monitored accordingly.

Lastly, studies in adults have shown that the development of left ventricular hypertrophy increased with increasing glucose intolerance (Lundblad & Eliasson, 2003) and higher BMI and fasting blood glucose levels (Ebinc, Ebinc, Ozkurt, Dogru, & Yilmaz, 2006). Few studies have examined the relationship of left ventricular hypertrophy with prediabetes in children. Obesity and prediabetes were identified in the study participants within this sample, although duration is unknown. Although none of the 128 participants in this study were considered to have left ventricular hypertrophy according to the Cornell criterion utilized, criteria for left

ventricular hypertrophy were based upon the adult standard. An adult standard was used because normative standards in overweight-obese adolescents using Cornell criteria have not yet been established. Despite this limitation, it has been suggested that the Cornell criteria appears to be the best electrocardiogram criteria for detecting left ventricular hypertrophy in persons who are overweight/obese (Alpert, 2004; Eckel, 2003). Further research is needed to validate this measure in overweight-obese youth. We agree that if ventricular hypertrophy is suspected, further diagnostic measures should be utilized to supplement the electrocardiogram screening measure (Hancock et al., 2009).

Blood Pressure Effects on Cardiac Autonomic Measures

The literature reports that when elevations in blood pressure are present, cardiac autonomic measures of heart rate variability are reduced (Alter et al., 2006), QT prolongation occurs (Kocak et al., 1999), and the prevalence of left ventricular hypertrophy increases (Ippisch & Daniels, 2008). Within our study, there was no significant difference for cardiac autonomic measures of heart rate variability (SDNN and HF) and QTc-interval duration for overweight-obese youth with EVBP in comparison with peers with NBP. However, overweight-obese youth with EVBP displayed significantly higher Cornell voltage measures for left ventricular hypertrophy than did those youth with NBP.

In regard to heart rate variability, the mean systolic and diastolic blood pressure measures were mildly elevated within our study. These findings are similar to the results reported by Franchi, Lazzeri, and LaVilla (1996), in which no differences were identified in heart rate variability when mild hypertension was present. In our study, individuals classified as having EVBP had prehypertension or stage 1 hypertension based on a single blood pressure reading. Although heart rate variability changes reflecting autonomic dysfunction have been noted in individuals with EVBP, the exact sequence of which develops first remains unclear (Alter et al., 2006). However, the results of our study suggest that mild elevations in blood pressure do not contribute further to significantly lower measures of heart rate variability when overweight-obesity is present.

In regard to QTc duration, Kocak et al. (1999) suggest that children with EVBP have an increased risk of developing QTc prolongation. In contrast, within our study, overweight-obese youth with EVBP had similar QTc duration to youth with NBP. Similarly, Franchi et al. (1996) reported that when mild hypertension was present, no differences were noted for QT duration, similar to heart rate variability measures. Thus, mild elevations in blood pressure may not significantly impact QTc duration.

Overweight-obese youth with EVBP had higher mean Cornell voltage measures for left ventricular hypertrophy than did peers with NBP. The statistically significant difference in Cornell voltage measures noted in overweight-obese youth with EVBP compared with those who had NBP suggests that the pathological sequence that takes

place in obese adults may be present also in overweight-obese adolescents. This supports findings that in obese (Wilborn et al., 2005) and nonobese (Liebson, 2002) participants, an association exists between elevation in blood pressure and left ventricular hypertrophy. Regardless of the pathological sequence, our findings support previous research that suggests that elevations in blood pressure in overweight-obese adolescents predicts the need for early intervention strategies to prevent the development of major health concerns (Torrance, McGuire, Lewanczuk, & McGavock, 2007). Left ventricular hypertrophy is present in a large percentage of individuals with EVBP and accounts for an increased risk of sudden cardiac death (Liebson, 2002). Although no participant in this sample was considered to have left ventricular hypertrophy based on electrocardiographic findings, mean Cornell voltage was higher in overweight-obese youth with EVBP and warrants further examination to identify adolescents at risk.

Combined Glucose and Blood Pressure Effects on Cardiac Autonomic Measures

Our study findings revealed that blood pressure and glucose regulation did not interact significantly with one another, and therefore, EVBP had no additive effect on glucose status (prediabetes or normal glucose) among cardiac autonomic measures. We then examined cardiac autonomic measures across four combined groups (prediabetes with EVBP, prediabetes with NBP, normal glucose with EVBP, and normal glucose with NBP). It was hypothesized that overweight-obese youth with prediabetes and EVBP combined would have lower heart rate variability, more prolonged QT, and higher Cornell voltage measures for left ventricular hypertrophy than would all other combined groups. The four groups did not differ significantly for heart rate variability (SDNN and HF), QT, or Cornell voltage. This finding is intriguing and leads to speculation that obesity alone may be the most influential factor that affects cardiac autonomic dysfunction. This would signify that prediabetes and EVBP combined do not further impact cardiac autonomic function when obesity is present in youth. However, further research would be necessary to support this theory.

Conclusion

In conclusion, autonomic dysfunction is a marker for increased cardiovascular risk, and this study sought to explore the independent and additive effects of prediabetes and blood pressure on cardiac autonomic measures of heart rate variability, QT, and Cornell voltage measures for left ventricular hypertrophy. Our findings suggest that cardiac autonomic alterations that occur in concert with obesity are not further compounded by prediabetes and EVBP in youth. It remains unknown whether alterations in autonomic nervous system function contribute to obesity or occur as a consequence of obesity (Tentolouris, Liatis, & Katsilambros,

2006), because the duration of obesity for the participants was not examined.

Findings also revealed that overweight-obese youth with EVBP were more likely to have increased Cornell voltage measures for left ventricular hypertrophy than were peers with NBP. Overall, cardiac autonomic measures were not significantly impacted by prediabetes or EVBP in overweight-obese youth. However, the increased prevalence of prediabetes within this study suggests that it is important to accurately assess BMI and perform follow-up testing for prediabetes in overweight-obese youth. Currently, the American Diabetes Association (2009) does not recommend screening for prediabetes in children because evidence does not support that early intervention would delay the onset of type 2 diabetes. However, early and accurate assessments are important because obesity in adolescents is significantly associated with abnormal glucose level (Plourde, 2006) and the transition from prediabetes to type 2 diabetes is shortened (Jolliffe & Janssen, 2006); therefore, early treatment is essential.

Autonomic measures of heart rate variability, QT-interval duration, and left ventricular hypertrophy have not been collectively explored in overweight-obese youth. One contributing factor is that the analysis of heart rate variability in the clinical setting is questionable because optimal limits have not been set for clinical use (Malik, 1996). In our study, heart rate variability measures of SDNN and HF mean values were similar to those identified in healthy nonobese youth (Faulkner, Hathaway, & Tolley, 2003). The critical threshold for QT prolongation is suggested to be 0.550 s (Suys et al., 2006), exceeding the mean QTc within our study of 0.408 s. Therefore, study findings suggest that in overweight-obese youth, decreased heart rate variability or QT prolongation meeting the critical threshold for sudden cardiac death is not expected. However, the prevalence of QT prolongation within this sample overall supports monitoring these youth for continued autonomic progression.

Lastly, the establishment of normative standards for electrocardiographic measures of left ventricular hypertrophy in overweight-obese youth is essential for continued research. Typically, the echocardiogram (Gertsch, 2004) or magnetic resonance imaging (MRI; Alfakih et al., 2004) are used as the preferred diagnostic methods for left ventricular hypertrophy. The 12-lead electrocardiogram has been validated as a measure of detecting left ventricular hypertrophy compared with the echocardiogram and MRI methods; however, it is not recommended that the electrocardiogram be used alone to diagnose left ventricular hypertrophy (Pewsnier et al., 2007). The electrocardiogram is a simple, noninvasive, cost-effective screening test that can be used to detect left ventricular hypertrophy (Rijnbeek et al., 2008). It is readily available in clinic settings and can be programmed to measure electrical voltage criteria for left ventricular hypertrophy in overweight-obese youth. In contrast, MRI and echocardiograms are not routinely performed in children and require referral to specialists.

Further research is necessary to more closely examine and compare Cornell voltage measures in normal-weight and overweight-obese adolescents with echocardiogram or MRI to develop normative standards appropriate for this population to provide more insights on the use of electrical voltage measures in overweight-obese youth. In addition, the examination of other electrocardiographic measures for determining left ventricular hypertrophy (Sokolow-Lyon, Romhilt-Estes, etc.) should be explored to determine if the Cornell voltage is the most predictive of left ventricular hypertrophy in overweight-obese youth.

Differences in our study results compared with findings reported in the literature may be due to variations in sample sizes, differences in measurement techniques, or characteristics of the participants. Physical activity levels, age, and gender have also been reported to affect autonomic measures. Although adjustments for age and gender were made in the analysis, potential effects of physical activity, pubertal status, duration of obesity, genetics, or race on autonomic measures were not examined and are a limitation of this study. Further research examining a more varied weight group with identification of the duration of obesity, prediabetes, and EVBP is also warranted to determine with more distinction the effect of prediabetes and EVBP on cardiac autonomic measures of heart rate variability, QTc-interval duration, and Cornell voltage measures for left ventricular hypertrophy in overweight-obese youth.

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