Abnormalities in circadian blood pressure variability and endothelial function: pragmatic markers for adverse cardiometabolic profiles in asymptomatic obese adults

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Abstract

Background: Cardiovascular disease (CVD) risk, although perceived to be high, is often difficult to demonstrate in disease free (healthy) obese adults.

Hypothesis: Changes in circadian blood pressure variability (CBPV) and endothelial function (EF) may be early correlates of cardiometabolic disorders.

Methods: Asymptomatic men and women in 3 groups: normal weight (n = 10), overweight (n = 10) and obese (n = 15) were evaluated. Blood pressure and heart rate were recorded over 7 days: every 30 minutes during the day and every 60 minutes during the night, by automatic ambulatory monitoring. Resting EF was assessed in a fasting state between 8-10 AM by brachial ultrasound. Anthropometric and cardiometabolic indicators were measured and correlations with CBPV and EF were investigated.

Results: The 3 groups had (Mean(SD)) BMI: 22.6(1.6), 27(3) and 34(5) kg/m², respectively, weight: 64(16), 79(14), 95(16) kg and waist circumference: 79(9), 93(10), 107(13) cm. None in normal-weight or overweight groups had abnormal CBPV, while 8 of 15 obese adults had one or more CBPV abnormalities (p < 0.05). Obese adults with CBPV abnormalities had elevated hs-CRP (15.3(9.3) mg/L), fibrinogen (593(97) mg/dl), fasting serum glucose (102(16) mg/dL), and cardiac risk ratios (Total-C/HDL-C: 5.2(1.9), LDL-C/HDL-C: 3.1(1.4)). Adults in the 3 respective groups who did not have CBPV abnormalities had flow-mediated brachial artery dilatation (FMD) of 0.22(0.06); 0.20(0.04), 0.23(0.02) mm over resting diameter. Obese participants with CBPV abnormalities (Mesor-hypotension, circadian hyper amplitude tension, elevated pulse pressure), had attenuated FMD at 78, 52, and 56% of resting reference diameter (means 0.18(0.07), 0.12(0.08), and 0.13(0.05) mm; p < 0.05), respectively.

Conclusions: Asymptomatic obese adults with abnormal CBPV and EF exhibit unfavorable cardiometabolic profiles.

Introduction

Obesity with its increasing prevalence, and as a consequence of its associated co-morbidities, is rapidly becoming the leading global cause for cardiovascular morbidity and mortality [1,2]. Cardiovascular disease (CVD) remains the number one cause of death, not only in the United States [3], but also worldwide [4]. The conventional risk factors: age, gender, smoking status, diabetes mellitus (DM), hypertension (HTN), dyslipidemia (DysL), and metabolic syndrome (MetS), are all known to have strong positive associations with the risk for CVD-related adverse events [5,6]. The obesity epidemic has, however, altered the paradigm for assessing CVD risk with factors like DM, HTN, DysL, and the MetS.

Diabetes mellitus, the well-recognized CVD risk equivalent [7,8], where obtaining tight glycemic control is thought to reduce the enhanced CVD risk [9], is exacerbated by the overweight or obese status. Due to an increasing recognition that CVD risk remains high when serum glucose concentrations are greater than 100 mg/dL.
variation which includes generally higher day-time, and lower night-time pressures, a night-time descent and an assessment of either normality or abnormality which is measured at fixed intervals for 7 days (with devices for ambulatory use) provides ample data for an unequivocal determination caused by adverse cardiometabolic factors. The early recognition of an elevated risk for developing cardiovascular disease related adverse events.
the ages of 30-75 years, with no personal history of or ongoing treatment for any chronic medical conditions.

**Inclusion/exclusion criteria**

Apparently healthy men and women between the ages of 30-75 years, with no history of DM, HTN, DysL, MetS, and/or CVD were included. Adults with a personal history of or ongoing treatment for diabetes, hypertension or any other chronic cardiac, renal, gastro-intestinal, pulmonary or any other systemic disease process requiring chronic intake of prescription medications, were excluded.

**Seven-day automatic ambulatory blood pressure monitoring**

An automatic BP monitoring device (Spacelabs’ Medical) for ambulatory use was attached to a BP cuff to obtain BP and heart rate (HR) readings at 30-min intervals during the day (6:30 AM to 9:30 PM) and 60-min intervals at night (10 PM to 6 AM) while the participants went about their activities. Data were downloaded into the database about mid-way and at the end of the 7-day recording span.

**Endothelial function by brachial ultrasound**

Assessment of resting endothelial function was done in a fasting state, after having avoided stimulants for 12 hours, at the same fixed clock hour (range 8-10 AM), using a Toshiba’ brachial ultrasound device. This device uses 7.5 MHz multi-frequency linear array transducer and a MIA Vascular Tools Brachial Analyzer Version 5.8.1 to determine brachial artery diameter. This technique has been previously validated and is in use with our clinical core. After obtaining reference (resting) brachial artery diameter measures, a forearm BP cuff was used to occlude the brachial artery for 5 minutes. The increase in brachial artery diameter (over the reference measure) due to the flow-mediated dilatation of the brachial artery after the release of the occlusion, served as a measure of endothelial function. One subject from each group (normal-weight, overweight and obese) also had endothelial function assessment.

**Risks and discomforts**

These non-invasive devices used a BP cuff that is inflated and released to obtain BP readings and data on endothelial function. The automatic ambulatory BP device attached to a BP cuff under the clothes was placed on the belt or carried in a pouch. Repeated measurements of BP and HR at timed intervals over 7 days, while the participant was at work or at home, allowed for acclimatization to the minimal discomfort, which is similar to having BP measured. Endothelial function was also obtained by using a BP cuff, coupled with an ultrasound probe that measures brachial artery diameter at rest (reference), during occlusion and the post-occlusion increase after release.

**Demographic, anthropometric and laboratory measures**

Standard demographic and anthropometric measures were obtained for all the participants. Waist circumference (a surrogate marker for central adiposity), serum hs-CRP and fibrinogen (for the assessment of systemic inflammation), fasting serum glucose and HbA1C (for the assessment of glycemic status) and fasting complete lipid profile (for the assessment of serum lipid sub-fractions, and obtaining cardiac risk ratios) were obtained.

**Normal-weight, overweight, obese, normoglycemia, prediabetes, prehypertension and premetabolic syndrome**

Participants were placed into normal weight (BMI < 25 kg/m²) overweight (BMI between 25-29.9 kg/m²) and obese (BMI > 30 kg/m²) categories. Normoglycemia and prediabetes, for the purpose of CVD risk assessment, were defined as a fasting serum glucose less than 100 mg/dL and a fasting serum glucose of more then 100 mg/dL but less then 126 mg/dL, respectively (impaired fasting glucose or IFG: ADA diagnostic criteria [26]). The diagnosis of prehypertension was based on resting (after a 5-minute rest) mean of (two successive assessments 1 minute apart) clinic BP measures of systolic (S) BP > 120 but < 139 and/or diastolic (D) BP > 80 but < 89 mm Hg (JNC 7 criteria [27])). Premetabolic syndrome was defined using the diagnostic criteria for the metabolic syndrome (NCEP ATP III criteria), with the substitution of prediabetes and prehypertension criteria for glucose and BP measures.

**Data analysis and statistical methods**

ABPM data gathered at the PBRC were electronically sent to the Halberg Chronobiology Center, University of Minnesota for statistical analysis. Endothelial function data were analyzed at the PBRC and then merged with the ABPM data sent back from Dr. Halberg’s laboratory. A summary in time (sphygmochron) was prepared that reported, among other measures, the midline-estimating-statistic of rhythm (MESOR or M), the timing of high values (acrophase), and the extent of predictable change within a day (double circadian amplitude) for SBP, DBP and HR. Normal circadian BP variability for SBP and DBP over a 24-hour span is shown in Figure 1. Seven-day monitoring ensures the consistency of either normality or abnormality over each one of the seven days and reports the average over the seven-day span.
MESOR Hypotension (M-Hypotension) or MESOR Hypertension (M-Hypertension) in this system is defined as a BP MESOR below the lower 5% or above the upper 95% prediction limit of peers matched by age and gender. M-Hypertension for SBP and DBP is shown in Figure 2.

Excessive circadian BP excursion (circadian hyper amplitude tension or CHAT) is a circadian double amplitude for SBP and/or DBP above the upper 95% prediction limit for peers. BP ecphasia is defined as an acrophase (timing) for BP (but not HR) occurring outside of the anticipated 90% prediction limits. HR variability is deficient (DHRV) when the standard deviation (SD) of HR is < 7.5 bpm. Pulse pressure is elevated (EPP) when it exceeds 60 mmHg. DHRV and EPP are shown in Figure 3 and Figure 4, respectively.

Day-night ratios were also computed for the 7-day record as a whole and for each day separately, for a classification in terms of "dipping". Due to the normal daytime BP being more than the nighttime BP, a negative day-night ratio was classified as "reverse dipping". A positive day-night ratio between 10% and 20% was classified as "dipping", whereas a ratio of less than 10% or greater than 20% was classified as "non-dipping" or "excessive dipping", respectively.

The occurrence of any of the above abnormal circadian patterns of BP and/or HR, overall and for each day separately, in terms of circadian characteristics and in terms of the day-night ratio, was determined for each individual in the three groups (normal-weight, overweight and obese). Serial measurement over 7 days ensured the consistency of either normality or abnormality. The groups were compared using an Exact Test or Poisson regression for frequency of occurrence data and Analysis of Variance of quantitative measurements.

Results

Table 1 describes the clinical characteristics and details the circadian BP variability abnormalities and endothelial function in the normal-weight, overweight, and obese adults. The 3 groups, consisting of normal-weight (Mean ± SD; 52 ± 13 y, range 32-71 y), overweight (52 ± 7 y, range 40-62 y) and obese (56 ± 10 y, range 41-70 y) adults, were not different in age, but by design had an incremental increase in weight and BMI. All of the twenty normal-weight and overweight participants had normal circadian BP variability, while 8 out of 15 obese participants had at least one or more variety of abnormal circadian BP variability (four participants had one abnormality each, while the other four had two variability abnormalities each) (p <
Figure 2 MESOR-hypertension

Figure 3 Acceptable and decreased heart rate variability
Table 1: Clinical characteristics, circadian BP variability and endothelial function in disease free normal-weight, overweight and obese adults

|                  | Normal (n = 10) | Overweight (n = 10) | Obese (n = 15) | P                  |
|------------------|----------------|---------------------|----------------|--------------------|
| Age (Y)          | 52 ± 12        | 52 ± 7              | 56 ± 10        | NS *               |
| Gender (W/M)     | 4/6            | 3/7                 | 10/5           | NS                |
| Weight (kg)      | 64 ± 16        | 79 ± 14             | 95 ± 16        | NA *               |
| BMI (kg/m²)      | 22.6 ± 3       | 27.3 ± 3            | 33.9 ± 5       | NA *               |
| Waist Circ (cm)  | 79 ± 9         | 93 ± 10             | 117 ± 13       | < 0.05 *           |
| Abnormal CBPV    | 0/10           | 0/10                | 8/15           | < 0.05 **          |
| MESOR-Hypotension| 0/10           | 0/10                | 5/15           | < 0.05 **          |
| MESOR-Hypertension| 0/10          | 0/10                | 2/15           | NS                 |
| CHAT¹             | 0/10           | 0/10                | 1/15           | NS                 |
| EPP²              | 0/10           | 0/10                | 4/15           | < 0.05 **          |
| Total CBPV       | 0/10           | 0/10                | 12/15          | < 0.05 **          |
| abnormalities    |                |                     |                |                    |
| Endothelial      | 0/1            | 0/1                 | 3/4            | < 0.05 **          |
| Dysfunction      |                |                     |                |                    |

¹Circadian Hyper-Amplitude Tension
²Elevated Pulse Pressure
DATA: MEAN ± SD
* Analysis of Variance
**Exact test
0.05; Exact Test). The 8 obese participants had a total of twelve circadian BP variability abnormalities: systolic and/or diastolic MESOR-hypotension (M-Hypotension: 5/10; p < 0.05) or -hypertension (M-Hypertension: 2/10), excessive BP excursion (CHAT: 1/10) and/or elevated pulse pressure (EPP: 4/10; p < 0.05). Overall, of the total fifteen obese participants, 7 obese participants had normal circadian variability and 8 obese participants had twelve circadian BP variability abnormalities. No abnormalities were found with the day-night ratios.

Normal-weight and overweight participants had a flow-mediated brachial artery dilatation of 0.22 ± 0.06 and 0.20 ± 0.04 mm over resting (above reference) diameter, respectively. Obese participants without circadian BP abnormalities had a similar (to normal and overweight) flow-mediated brachial artery dilatation of 0.23 ± 0.02 mm over resting (above reference) diameter, compared to an attenuated dilatation of 0.18 ± 0.07, 0.12 ± 0.08, and 0.13 ± 0.05 mm in those obese participants who had circadian BP variability abnormalities (M-Hypotension, CHAT and EPP, at 78, 52 and 56% of the expected; p = 0.3, 0.05 and 0.006, respectively).

Table 2 summarizes the cardiovascular disease risk profile in the normal-weight (n = 10) and overweight (n = 10) with normal CBPV and EF and the obese (n = 8) adult participants with abnormal CBPV. The normal-weight and overweight participants had a significantly lower mean waist circumference than the obese participants with both the women and the men well below the entry threshold of 88 and 102 cm, respectively, for inclusion in the metabolic syndrome. The obese participants, on the other hand with a statistically significantly higher waist circumference met the criteria for inclusion into the metabolic syndrome. The normal-weight and overweight adults had a normal spot office SBP/DBP, pulse pressure of 41 ± 7, 43 ± 8 mm Hg and heart rate of 67 ± 9, 74 ± 12 bpm. The 8 obese participants with abnormalities, however, had prehypertension (INC 7 criteria: SBP 120-139 and/or DBP 80-80 mm Hg) with normal pulse pressure and heart rate. The normal-weight and overweight participants had normal fasting serum glucose, contrasted with the 8 obese participants with abnormalities who had prediabetes (ADA criteria: FSG 100-125 mg/dL). The normal-weight and overweight participants had normal lipid profiles with desirable total-C, triglycerides, HDL-C, and LDL-C along with desirable cardiac risk ratios. The 8 obese participants with abnormalities had greater than the desirable total-C, triglycerides, LDL-C and less than desirable HDL-C. Their cardiac risk ratios were also over the desirable range.

Table 3 compares the seven obese participants with normal circadian BP variability with the eight obese participants who had abnormalities. The seven obese participants (BMI 32 kg/m$^2$) who had normal circadian BP variability had normal glucose, hs-CRP, fibrinogen, triglycerides, HDL-C and cardiac risk ratios. In contrast the

|                  | Normal (n = 10) | Overweight (n = 10) | Obese (n = 8) | P**       |
|------------------|-----------------|---------------------|---------------|-----------|
| WC (Women < 88 cm)* | 71 ± 4          | 84 ± 6              | 109 ± 15      | < 0.05    |
| WC (Men < 102 cm)* | 84 ± 7          | 97 ± 9              | 114 ± 6       | < 0.05    |
| SBP (< 120 mm Hg)* | 113 ± 8         | 118 ± 10            | 129 ± 12      | NS        |
| DBP (< 80 mm Hg)* | 72 ± 5          | 75 ± 5              | 80 ± 6        | NS        |
| FSG (< 100 mg/dL)* | 89 ± 5          | 89 ± 8              | 102 ± 16      | < 0.05    |
| Total-C (< 200 mg/dL)* | 181 ± 23     | 180 ± 20            | 223 ± 38      | < 0.05    |
| LDL-C (< 130 mg/dL)* | 109 ± 25       | 96 ± 13             | 133 ± 34      | < 0.05    |
| HDL-C (> 50 mg/dL)* | 63 ± 4          | 54 ± 16             | 46 ± 13       | NS        |
| TG (< 150 mg/dL)* | 49 ± 12         | 112 ± 60            | 220 ± 111     | < 0.05    |
| Total-C/HDL-C ratio (< 5)* | 2.9 ± 0.6 | 3.6 ± 0.9            | 5.2 ± 1.9     | NS        |
| LDL-C/HDL-C ratio (< 3)* | 1.7 ± 0.5   | 1.9 ± 0.7            | 3.1 ± 1.4     | < 0.05    |

Numbers in Italic are outside the desirable range

DATA: MEAN ± SD
* (In parenthesis: Desirable values)
** Analysis of Variance
adults with no abnormalities (n = 7) had normal fibrinogen concentrations (Mean ± SEM) of 411 ± 18 mg/dL.

Participants with abnormal circadian BP variability disorders: M-Hypotension (n = 5) had fibrinogen concentration of 638 ± 38 mg/dL (p < 0.05), with M-Hypertension (n = 2) 477 ± 7 mg/dL, with CHAT (n = 1) 600 mg/dL and with EPP (n = 4) 581 ± 60 mg/dL.

Figure 5 details the pro-inflammatory milieu in the obese adults. Panel (6 A) depicts fasting serum glucose (FSG) concentrations in the obese adults with normal and abnormal

![Figure 5 Pro-inflammatory milieu in obese adults](image)

![Figure 6 Glycemic milieu in obese adults](image)
circadian BP variability. Obese adults with no abnormalities (n = 7) had normal FSG concentrations (Mean ± SEM) of 94 ± 6 mg/dL. Participants with abnormal circadian BP variability disorders: M-Hypotension (n = 5) had FSG of 102 ± 2 mg/dL (p < 0.05), with M-Hypertension (n = 2) 111 ± 24 mg/dL, with CHAT (n = 1) 85 mg/dL and with EPP (n = 4) 105 ± 11 mg/L. Panel (6 B) depicts percent glycosylated hemoglobin (HbA1C) in the obese adults with normal and abnormal circadian BP variability. Obese adults with no abnormalities (n = 7) had normal HbA1C (Mean ± SEM) of 5.5 ± 0.05%. Participants with abnormal circadian BP variability: M-Hypotension (n = 5) had HbA1C of 5.8 ± 0.3% (p < 0.05), with M-Hypertension (n = 2) 5.9 ± 0.6%, with CHAT (n = 1) 5.4% and with EPP (n = 4) 6.1 ± 0.3%.

Figure 7 illustrates the normal and abnormal flow-mediated brachial artery dilation curves in a representative obese adult with and without circadian BP variability abnormalities. Brachial artery dilation upon release of occlusion above the resting (reference) measure reported in millimeters is the measure of endothelial function. Panel (7 A) shows an increase in brachial artery diameter after release of brachial artery occlusion, representing normal endothelial function in an obese adult with no circadian BP variability abnormalities. Panel (7 B) shows a flatter brachial artery diameter after release of brachial artery occlusion, representing endothelial dysfunction in an obese adult with circadian BP variability abnormalities.

Discussion
The data from this study show that only those asymptomatic (disease free) obese adults (that had prediabetes, prehypertension, elevated systemic inflammation and cardiac risk ratios), when compared with disease-free normal-weight, overweight and obese adults (with normoglycemia, desirable blood pressure, systemic inflammation and cardiac ratios) have significant circadian BP variability abnormalities and endothelial dysfunction. Circadian variability of blood pressure and heart rate measured over 7 days provides a dynamic, functional assessment of the cardiovascular system. It also ensures the consistency of either normality, or abnormality of the circadian BP variability measures. Both the obese participants with M-Hypertension also had an elevated pulse pressure. Of the five obese participants with M-Hypotension, two also had an elevated pulse pressure. Thus four of the eight participants with abnormal BP variability had, not one, but two varieties of circadian BP variability abnormalities (8 obese participants had 12 variability abnormalities). Normal-weight, overweight and obese participants had a flow-mediated brachial artery dilation of 0.22 ± 0.06, 0.20 ± 0.04 and mm over resting (above reference) diameter, compared to an attenuated dilation of 0.18 ± 0.07, 0.12 ± 0.08, and 0.13 ± 0.05 mm in those obese participants who had circadian BP variability abnormalities.

Abnormal circadian BP variability, endothelial function and cardiovascular morbidity and mortality
The effect of abnormal circadian BP variability upon untoward cardiovascular events is both separate and additive. Having more than one abnormality increases this risk: In a reference population of 214 patients (some with M-Hypertension) presenting with none of the 3 abnormal variability measures (decreased heart rate variability (DHRV), EPP, or CHAT), morbidity within a 6-year follow-up was found in 8 cases (3.7%). The presence of one abnormality (DRHVC or EPP) alone raised the incidence of morbidity to 30.8%. When these two risk factors (DRHVC and EPP) were both present, morbidity was doubled (66.7%). The presence of CHAT increased morbidity from 3.7% to 23.5% in the absence of the other two risk
factors, from 30.8% to 50% when either DHRV or EPP was also present, or from 66.7% to 100% when all 3 risk factors are present [28]. Halberg et al. [29] have shown that even in the absence of conventional CVD risk factors (like DM, HTN, and DysL); abnormalities in circadian BP variability are risk factors for CVD and early death. Others have shown the superior predictive ability of ambulatory BP monitoring data vs. conventional office BP measures in adults with hypertension.

The endothelium is a highly active organ which regulates intravascular homeostasis by integrating numerous functions such as glycemia, blood pressure, pro-inflammatory/anti-inflammatory processes and coagulation. Endothelial dysfunction, the initial perturbation in the process of atherosclerosis, in asymptomatic individuals portends increased vascular disease risk [30]. Obese adults with abnormal circadian BP variability (M-Hypotension, CHAT, and EPP) also had endothelial dysfunction (flow mediated brachial diameter increase of 0.18(0.07), 0.12(0.08), and 0.13(0.05) mm over resting diameter or flow mediated dilation at only 78, 52, and 56% of the resting diameter, respectively, p <0.05). Abnormalities of both these measures: abnormal circadian BP variability (reflective of the functional aspects of the cardiovascular system), and endothelial dysfunction (reflective of a sum total of various effectors including glycemia, blood pressure, coagulation, pro-inflammatory and anti-inflammatory factors) in asymptomatic (disease free) obese adults are novel non-invasive methods for assessing the dynamic aspects of cardiovascular disease risk.

**Recognized CVD risk factors**

Gradual weight gain in clinically healthy overweight and obese adults is preferentially manifest as an enlarging waist circumference [31]. Abdominal obesity, clinically measured as an increased waist circumference and suggestive of an expanding visceral adipose tissue compartment, has an independent association with coronary heart disease [32]. Visceral adipose tissue, which strongly correlates with most metabolic risk factors [33], upon expansion, alters its usual and customary adipokine secretion menu [34]. There is an increased flux in the factors influencing the pro-inflammatory and renin-angiotensin-aldosterone system, in parallel with attenuation in the anti-inflammatory factors. The altered pro-inflammatory (increased) and anti-inflammatory (decreased) balance, among other reasons promotes insulin resistance [35]. Elevated HbA1c is related to new onset CVD over a relatively short follow-up period in both men and women without diabetes, who do not develop diabetes, even after adjustment for other major risk factors [36]. Dysregulated pro-inflammatory: anti-inflammatory balance, increased serum hs-CRP [37], total leukocyte count [38], serum uric acid [39], and decreased adiponectin [34] are associated with increased cardiovascular disease. Disease-free obese with an exacerbated proinflammatory milieu exhibit prediabetes and prehypertension [16]. Prediabetes is associated with abnormal circadian BP variability [15], prehypertension clusters with other CVD risk factors [40] and metabolic syndrome more strongly predicts CVD than its individual components [41]. An imbalance between the central and the peripheral clock mechanisms has recently been suggested as the cause for the endothelial function [42]. 24-hour ambulatory blood pressure measures have been used to predict target-organ disease and clinical outcome in patients with hypertension [43] and more recently, elevations in nocturnal BP have been shown to precede diabetic nephropathy in hypertensive patients with T2DM [44].

Overweight or obese adults with larger than normal waistline, along with subtle metabolic alterations, either with elevated FSG (prediabetes [26], elevated SBP and/or DBP (prehypertension [27]), and/or a combination of risk factors (premetabolic syndrome) are commonplace in routine clinical practice. These adults with unrecognized elevated CVD risk, more often than not, are lost to regular follow-up. This results in a lost opportunity for primary prevention of CVD. We believe that increased CVD in asymptomatic normal-weight, overweight and/or obese adults can readily recognized by the abnormal circadian BP variability, and endothelial dysfunction. Non-pharmacologic, as well as pharmacologic measures can be utilized to reverse these early abnormalities. Non-pharmacologic measures: a 7% weight loss from reference (improving glycemia), and increasing physical activity up to 150 minutes per week, (improving both glycemia and blood pressure) could be advocated. Pharmacologic measures: treatment with thiazolidinediones (reducing insulin resistance and pro-inflammatory milieu, along with remodeling of the adipose tissue), biguanides (reducing insulin resistance), angiotensin converting enzyme inhibitors or angiotensin receptor blockers (reducing blood pressure, improving glycemia and systemic inflammation) and HMG-CoA reductase inhibitors or statins (systemic inflammation, improving cardiac risk ratios and endothelial function) could be utilized.

The results from this study show that latent CVD risk in disease-free (healthy) obese adults assessed with no or low risk by conventional risk assessment methods, can be unmasked by simple non-invasive measures. The obese participants exhibiting normal circadian BP variability had normal endothelial function, normotension, normoglycemia and were within the desirable limits for systemic inflammation, triglycerides, HDL-C, and cardiac risk ratios. Asymptomatic obese participants with abnormal circadian BP variability and endothelial dysfunction also had: an increased visceral adipose tissue, a heightened pro-inflammatory profile, prediabetes, prehypertension
and abnormal cardiac risk ratios. Abnormal circadian BP variability and endothelial dysfunction, taken together with the altered adverse cardiometabolic profile, are indicative of an unrecognized CVD risk in disease free obese men and women.

**Study limitations**

The study has several limitations that warrant discussion. The study participants were adult asymptomatic volunteers who were screening for various clinical studies at the Pennington Center, and may not be representative of the general population. Further, it is a cross-sectional study in which the temporal sequence of emergence of dysregulated assessments is unknown. Finally, the small sample size may have compromised the power to detect population differences among the normal-weight, overweight, and obese groups. Despite these shortcomings, this investigation documents statistically significant novel findings of a clinical correlation between circadian BP variability and endothelial function abnormalities and systemic proinflammation, prediabetes, prehypertension, elevated cardiac risk ratios, and establishes a foundation for further investigation of the underlying mechanisms.

**Conclusion**

While studies with larger numbers of participants are clearly indicated, these findings taken in conjunction with the recognized subtle abnormal circadian BP variability in prediabetes [15] strengthen our overall hypothesis that progressive visceral adipose tissue expansion with the accompanying systemic pro-inflammatory and glycemic changes [16] and the overall vascular response to these metabolic perturbations, influence circadian BP variability and endothelial function. Taken together with other anthropometric and laboratory measures, these are indicative of an enhanced CVD risk. Circadian BP variability and endothelial function, along with subtle abnormalities of pro-inflammatory and glycemic milieu, can be novel measures for recognizing latent CVD risk in otherwise asymptomatic obese and possibly in other populations.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

AKG conceived of the study and drafted the manuscript. GC performed the chronobiological analyses for the circadian blood pressure data. WTJ performed the statistical analysis. AKG, WTJ, VD, FLG, and FH edited the manuscript. All authors have read and approved the final manuscript.

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