24-HR CENTRAL AMBULATORY BLOOD PRESSURE, ARTERIAL STIFFNESS, AND
NOCTURNAL FLUCTUATIONS
A THESIS
SUBMITTED TO THE GRADUATE SCHOOL
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE
MASTER OF SCIENCE
BY
OLIVIA E. JONES
DR. BRADLEY FLEENOR – ADVISOR

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the US and risk can be independently predicted by both arterial stiffness and increased blood pressure. Combating the epidemic of CVD relies heavily on accurate and reliable measures of both variables. Arterial stiffness is measured using the gold standard of carotid femoral pulse wave velocity (cfPWV). Blood pressure is predominantly measured in the primary care setting at the brachial site, however new measures of 24-hour brachial ambulatory blood pressure and central brachial pressure have shown superior to brachial office blood pressure in predicting CVD outcome (36). Furthermore, 24-hour brachial ambulatory blood pressure (bAMBP) has shown superior to clinic blood pressure in predicting CVD mortality and providing valuable nighttime measures (9, 10). Nighttime blood pressure allows for the identification of individuals who are non-dippers, or do not experience a diminished systolic blood pressure (SBP) while sleeping. Non-dipping is associated with CVD events and all-cause mortality, independent of daytime blood pressure (4, 5, 10, 20, 27).

Combining these two techniques, a novel, non-invasive measure of 24-hour central ambulatory blood pressure (cAMBP) has emerged. A recent study found cAMBP to be superior to bAMBP in its association with left ventricular hypertrophy and hypertension (41). In contrast, researchers found central pressure, even when monitored for 24 hours, was not a better predictor of target organ damage than peripheral office blood pressure (7). Due to conflicting data and the scarcity of research provided for this technique, further study is prompted to both validate and determine the prognostic value of using cAMBP as a means of predicting CVD.
It has been thoroughly explored that both arterial stiffness and blood pressure increase with aging, however the relationship is not well understood. There is a lack of research examining the relationship between cfPWV and cAMBP during both the day and nighttime hours in an apparently healthy population. Research supports the relationship between hypertension and arterial stiffness, yet the primary source of disease remains unclear (3, 24, 25). Researchers agree that arterial stiffening is a manifestation of vascular aging, specifically around the 5th decade of life when deterioration of the artery’s elasticity begins (8, 19, 39). cfPWV is related to the intrinsic elasticity of the artery and progressively increases 6-8% with each decade (8, 25). Furthermore, increased cfPWV is shown to be an independent predictor of non-dipping (3, 17). Although research supports the relationship between increased bBP, increased bAMBP, and non-dipping to arterial stiffness, insufficient studies have examined cAMBP and arterial stiffness. Therefore, the aim of this study is to examine the relationship between central 24-hour ambulatory blood pressure and arterial stiffness in both apparently healthy dippers and non-dippers. We hypothesize a positive relationship between aortic stiffness (cfPWV) and 24-hour central pressure (cAMBP) in apparently healthy individuals, with non-dippers presenting higher day/night cAMBP and cfPWV than dippers.

METHODOLOGY
Study Population

48 apparently healthy participants were included in the study. Participants included 20 men and 28 women, with a mean age of 63.7 ± 9.1 years. Eligibility included men and women 50 years of age or older, and free of known CVD, metabolic or related diseases. Additionally, participants were free of tobacco use, Beta-blocker therapy, active cancer treatments, or a body mass index (BMI) greater than 35 kg/m² (3, 8, 13, 25, 29, 41). The study was approved by the Institutional Review Board at Ball State University and all participants gave informed consent before entering the study.

Prescreening

The informed consent was signed by the participant followed by a Health History Questionnaire review to ensure eligibility. Height and weight were measured upon arrival to determine BMI (1). Participants were instructed to fast from food, alcohol, and caffeine intake 12 hours prior to testing, and avoid exercise for 36 hours prior (18).

1st Lab Visit – Standard Resting Measures

Dual-energy X-ray absorptiometry (DXA) values were attained to analyze bone mineral density, fat mass, and lean mass (15). Body fat percentage was obtained using skinfold measures. These measures were then applied to an equation to calculate physical fitness ($\text{VO}_{2\text{max}}$ (ml/kg/min)) = 61.66 - 0.328(yrs) + 5.45(F=0, M=1) + 1.832(PA [0-6]) - 0.436(%fat) - 0.143(HR) - 0.446(smoking [1-8]) (42). Waist circumference was measured to determine waist-to-hip ratio. Resting bBP and heart rate were measured using a brachial cuff/sphygmomanometer and pulse oximeter, respectively. Handgrip
assessment was performed to gauge muscular strength. A blood draw was performed to collect cholesterol, triglycerides, HDL/LDL, glucose and HbA1c.

Resting Central Hemodynamics/Arterial Stiffness Measures

PWA was performed to determine resting central hemodynamics, using a brachial cuff to collect supine bBP and brachial arterial waveforms (14, 38). A generalized transfer function was then applied to generate the aortic waveform (40). Additionally, surrogates to aortic wave reflection were collected including augmentation pressures and augmentation index, both independent predictors of CVD risk (30). Two measurements of PWA were taken with a third measurement necessary if the two-original had an aortic augmentation@75 >5%, bBP >5 mmHg, or did not obtain quality assurance. Following PWA analysis measurements, arterial stiffness was assessed by cfPWV using the SphygmoCor XCEL tonometer device. A cuff was placed on the upper leg and tonometry was performed on the carotid artery. A measuring tape was used to determine the distance between the carotid to the suprasternal notch, the suprasternal notch to the femoral pulse, and the femoral pulse to the top of the femoral cuff. The speed of the pulse was recorded and cfPWV was determined as the distance between the carotid and femoral sites divided by the transit time of the pulse wave. Two measurements within 0.5 m/s were obtained and averaged for data analysis.

Central Ambulatory Blood Pressure

Ambulatory blood pressure monitoring was assessed using the Oscar 2 AMBP system with SphygmoCor (SunTech Medical, Morrisville, NC and AtCor Medical, Sydney,
Australia) to measure cAMBP (2, 29). After the ambulatory cuff was fitted, daytime recording began at 0800 hours and continued until 2130; nighttime hours began at 2200 hours until the following day at 0800 hours. During daytime hours, inflation occurred every 30 minutes with nighttime measures occurring every hour. The cuff captured bBP and utilized a generalized transfer function to calculate cBP at each time point. 24-hour data was considered valid with a ≥80% rate of successful readings for both day and nighttime measures (29). Participants were given a log to record sleeping time, food intake, and body position while wearing the cuff. The self-report log to manually adjust daytime & nighttime measures following 24-hour data collection. Day and nighttime hours were manually adjusted to match the self-reported time participants went to bed and woke up. Participants were instructed to avoid caffeine, alcohol, and exercise during data collection.

Data Analysis

Data are presented as mean ± standard deviation (SD). Descriptive statistics were used to categorize participants into nocturnal groups (dippers or non-dippers) based on the decrease in mean SBP from day to nighttime (Non-dippers were classified as prehypertensive or hypertensive individuals who did not have a 10% drop in mean nighttime bSBP from mean daytime bSBP). Blood pressure mean for 24hr, daytime, and night-time hours was calculated using data from 08:00am-08:00am. Outliers greater than 2 SD away from the mean were excluded, as well as brachial or central pressures >200/100mmHg. Pearson’s correlation coefficient was used to determine the relationship between cfPWV and brachial and central mean AMBP, PP, MAP and cAP, cAIx,
cAlx@75. Unpaired t-tests were used to examine relationships between cfPWV in dippers and non-dippers. A p-value of <0.05 was considered statistically significant. Statistics were generated using Microsoft Excel and GraphPad Prism 8.0.

RESULTS

56 participants were screened for this study. Of those, eight were excluded due to not meeting study criteria. Two participants had a BMI >35 kg/m², one reported undiagnosed signs and symptoms of disease, two had known vascular and metabolic disease, and one chose not to participate after being screened. Two participants’ data were excluded due to insufficient ambulatory blood pressure recordings (data capture < 80%). Therefore, data from 48 participants was used in data analysis. Mean age was 63.7 ± 9.1 years. Additional participant characteristics can be found in Table 1.

Ambulatory Blood Pressure

Brachial and central blood pressure and wave reflection properties were averaged over 24 hours and split into 24-hr, daytime, and night-time. Univariate t-tests demonstrated a significant difference between day and nighttime pressures. Data are shown in Table 2.

Ambulatory Brachial Blood Pressure vs cfPWV

There was a significant positive relationship between 24-hr, daytime and nighttime bSBP, and bPP with cfPWV (P<0.05). Pearson’s correlation demonstrated no differences
when cfPWV was compared to 24 hr., daytime, or nighttime bDBP and bMAP (P>0.05). Results are shown in Table 3.

*Ambulatory Central Hemodynamics, Blood Pressure, and Augmentation Index vs cfPWV*

Hemodynamic variables, blood pressure, and augmentation indexes were split into 24-hour, daytime, and nighttime hours. There was a positive relationship between 24-hr, daytime and nighttime cSBP and cfPWV (Figure 1, P<0.05). Additionally, cMAP during nighttime hours was significantly associated with cfPWV (Figure 2, P<0.05). No relationships were found when cfPWV was compared to 24 hr., daytime, or nighttime cDBP, cPP, cAP, cAIx, cAIx@75, and 24-hour or daytime cMAP (Figure 3, P<0.05). Results are shown in Table 4.

*Resting Brachial and Central Pressures vs cfPWV*

A significant positive relationship was seen between resting and supine bSBP and cfPWV (P<0.05). However, no significance was seen between cfPWV and resting or supine bDBP, cSBP or cDBP (Table 5).

*Dippers and Non-Dippers*

Non-dippers were characterized as prehypertensive and hypertensive individuals (24-hr bAMBp >120/80mmHg) who did not experience a mean decrease in bSBP from day to nighttime of >10%. Of the 48 participants, 9 met the criteria for non-dipping.
Differences were found between cfPWV in dippers and non-dippers (P<0.05). However, there were no differences in brachial and central ambulatory measurements, or other subject characteristics between groups (Table 6).
Table 1. Participant Characteristics (N=48)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.7 ± 9.1</td>
</tr>
<tr>
<td>Gender (Male/Female %)</td>
<td>42/58</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.9 ± 9.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 14.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 3.8</td>
</tr>
<tr>
<td>cfPWV (m/s)</td>
<td>8.54 ± 1.37</td>
</tr>
<tr>
<td>Resting cSBP (mmHg)</td>
<td>121.4 ± 11.6</td>
</tr>
<tr>
<td>Resting cDBP (mmHg)</td>
<td>79.5 ± 7.6</td>
</tr>
<tr>
<td>Estimated VO₂ (ml/kg/min)</td>
<td>28.4 ± 7.6</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>182.3 ± 37.7</td>
</tr>
<tr>
<td>HTN medications (% medicated, N=9)</td>
<td>18.8</td>
</tr>
<tr>
<td>Thyroid medications (% medicated, N=10)</td>
<td>20.8</td>
</tr>
<tr>
<td>Non-Dippers (% non-dippers, N=9)</td>
<td>18.8</td>
</tr>
<tr>
<td>Healthy Vascular Aging (% with HVA, N=9)</td>
<td>18.8</td>
</tr>
</tbody>
</table>

**Abbreviations**: cm = centimeters, kg = kilograms, BMI = body mass index, kg/m² = kilograms per meters squared, mmHg = millimeters of mercury, ml/kg/min = milliliters per kilogram per minute, cfPWV = carotid-femoral pulse wave velocity, HVA = healthy vascular aging, HTN = hypertension
Table 2. - Ambulatory Brachial and Central Hemodynamic Means over 24 hrs., Daytime, and Nighttime

<table>
<thead>
<tr>
<th></th>
<th>24 hrs.</th>
<th>Daytime</th>
<th>Night-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>bSBP (mmHg)</td>
<td>121.7 ± 10.4</td>
<td>125.6 ± 11.6</td>
<td>111.2 ± 9.6*</td>
</tr>
<tr>
<td>bDBP (mmHg)</td>
<td>68.4 ± 6.2</td>
<td>71.4 ± 7.1</td>
<td>60.2 ± 6.2*</td>
</tr>
<tr>
<td>cSBP (mmHg)</td>
<td>113.3 ± 9.0</td>
<td>116.3 ± 10.1</td>
<td>105.3 ± 8.6*</td>
</tr>
<tr>
<td>cDBP (mmHg)</td>
<td>70.2 ± 6.1</td>
<td>73.4 ± 7.2</td>
<td>61.7 ± 6.0*</td>
</tr>
<tr>
<td>bPP (mmHg)</td>
<td>53.1 ± 10.1</td>
<td>54.2 ± 10.5</td>
<td>51.0 ± 9.5*</td>
</tr>
<tr>
<td>cPP (mmHg)</td>
<td>43.1 ± 8.2</td>
<td>42.9 ± 8.7</td>
<td>43.7 ± 8.7</td>
</tr>
<tr>
<td>cAIx (%)</td>
<td>37.7 ± 6.4</td>
<td>35.8 ± 7.0</td>
<td>42.8 ± 6.7*</td>
</tr>
<tr>
<td>cAIx @ 75 (%)</td>
<td>35.3 ± 6.4</td>
<td>34.5 ± 6.6</td>
<td>37.8 ± 7.9*</td>
</tr>
<tr>
<td>cAP (mmHg)</td>
<td>16.8 ± 4.6</td>
<td>16.0 ± 4.9</td>
<td>19.1 ± 5.1</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>70.4 ± 7.9</td>
<td>72.8 ± 6.9</td>
<td>64.7 ± 6.3*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD
* (P<0.05) denotes significance in daytime vs nighttime
Table 3. Ambulatory Brachial Blood Pressure vs cfPWV

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>R²</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>bSBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr. *</td>
<td>0.369</td>
<td>0.137</td>
<td>0.009</td>
</tr>
<tr>
<td>Daytime *</td>
<td>0.337</td>
<td>0.114</td>
<td>0.019</td>
</tr>
<tr>
<td>Nighttime *</td>
<td>0.425</td>
<td>0.180</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>bDBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.032</td>
<td>0.000</td>
<td>0.831</td>
</tr>
<tr>
<td>Daytime</td>
<td>-0.005</td>
<td>0.000</td>
<td>0.971</td>
</tr>
<tr>
<td>Nighttime</td>
<td>0.063</td>
<td>0.004</td>
<td>0.672</td>
</tr>
<tr>
<td><strong>bPP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr. *</td>
<td>0.372</td>
<td>0.138</td>
<td>0.009</td>
</tr>
<tr>
<td>Daytime *</td>
<td>0.399</td>
<td>0.159</td>
<td>0.005</td>
</tr>
<tr>
<td>Nighttime *</td>
<td>0.388</td>
<td>0.151</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>bMAP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.183</td>
<td>0.033</td>
<td>0.212</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.155</td>
<td>0.024</td>
<td>0.290</td>
</tr>
<tr>
<td>Nighttime</td>
<td>0.276</td>
<td>0.076</td>
<td>0.057</td>
</tr>
</tbody>
</table>

*denotes significance (P<0.05). bSBP – brachial systolic blood pressure (mmHg), bDBP – brachial diastolic blood pressure (mmHg), bPP – brachial pulse pressure (mmHg), bMAP – brachial mean arterial pressure (mmHg), cfPWV – carotid-femoral pulse wave velocity (m/s).
<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cSBP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.*</td>
<td>0.356</td>
<td>0.127</td>
<td>0.013</td>
</tr>
<tr>
<td>Daytime*</td>
<td>0.317</td>
<td>0.100</td>
<td>0.028</td>
</tr>
<tr>
<td>Nighttime*</td>
<td>0.419</td>
<td>0.176</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>cDBP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.046</td>
<td>0.002</td>
<td>0.755</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.033</td>
<td>0.001</td>
<td>0.819</td>
</tr>
<tr>
<td>Night-time</td>
<td>0.136</td>
<td>0.018</td>
<td>0.357</td>
</tr>
<tr>
<td><strong>cPP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.238</td>
<td>0.057</td>
<td>0.102</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.226</td>
<td>0.051</td>
<td>0.122</td>
</tr>
<tr>
<td>Night-time</td>
<td>0.242</td>
<td>0.059</td>
<td>0.098</td>
</tr>
<tr>
<td><strong>cAP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.091</td>
<td>0.008</td>
<td>0.537</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.079</td>
<td>0.006</td>
<td>0.593</td>
</tr>
<tr>
<td>Night-time</td>
<td>0.085</td>
<td>0.007</td>
<td>0.565</td>
</tr>
<tr>
<td><strong>cAlx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>-0.007</td>
<td>0.000</td>
<td>0.959</td>
</tr>
<tr>
<td>Daytime</td>
<td>-0.026</td>
<td>0.000</td>
<td>0.861</td>
</tr>
<tr>
<td>Night-time</td>
<td>-0.010</td>
<td>0.000</td>
<td>0.944</td>
</tr>
<tr>
<td><strong>cAlx @ 75</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>-0.120</td>
<td>0.014</td>
<td>0.416</td>
</tr>
<tr>
<td>Daytime</td>
<td>-0.145</td>
<td>0.021</td>
<td>0.324</td>
</tr>
<tr>
<td>Night-time</td>
<td>-0.078</td>
<td>0.006</td>
<td>0.598</td>
</tr>
<tr>
<td><strong>cMAP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.185</td>
<td>0.034</td>
<td>0.208</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.155</td>
<td>0.024</td>
<td>0.292</td>
</tr>
<tr>
<td>Nighttime*</td>
<td>0.286</td>
<td>0.081</td>
<td>0.049</td>
</tr>
</tbody>
</table>

*denotes significance (p<0.05). cSBP - central systolic blood pressure (mmHg), cDBP - central diastolic blood pressure (mmHg), cPP - central pulse pressure (mmHg), cAP - central augmentation pressure (mmHg), Alx - Augmentation index (%), Alx @ 75-Augmentation index @ 75 (%), cfPWV- carotid-femoral pulse wave velocity (m/s), cMAP – central mean arterial pressure (mmHg). “Table 4. Ambulatory Central Blood Pressure, Hemodynamics and Augmentation Index vs cfPWV”
Figure 1 - 24 hr., Daytime, and Night-time cSBP and cfPWV *(P < 0.05)
Figure 2 - 24 hr., Daytime, and Night-time cPP and cfPWV
*(P < 0.05)
Figure 3 - 24 hr., Daytime, and Night-time cMAP and cfPWV
*(P < 0.05)
Table 5. - Resting Brachial and Central Blood Pressures vs cfPWV

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>bSBP (seated)*</td>
<td>0.321</td>
<td>0.103</td>
<td>0.026</td>
</tr>
<tr>
<td>bDBP (seated)</td>
<td>-0.010</td>
<td>0.000</td>
<td>0.941</td>
</tr>
<tr>
<td>bPP (seated)*</td>
<td>0.412</td>
<td>0.170</td>
<td>0.004</td>
</tr>
<tr>
<td>bSBP (supine)*</td>
<td>0.361</td>
<td>0.130</td>
<td>0.012</td>
</tr>
<tr>
<td>bDBP (supine)</td>
<td>0.149</td>
<td>0.022</td>
<td>0.311</td>
</tr>
<tr>
<td>cSBP (supine)</td>
<td>0.317</td>
<td>0.101</td>
<td>0.278</td>
</tr>
<tr>
<td>cDBP (supine)</td>
<td>0.158</td>
<td>0.025</td>
<td>0.282</td>
</tr>
<tr>
<td>cPP (supine)*</td>
<td>0.291</td>
<td>0.084</td>
<td>0.044</td>
</tr>
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</table>

*denotes significance (P<0.05). bSBP – brachial systolic blood pressure (mmHg), bDBP – brachial diastolic blood pressure (mmHg), cSBP – central systolic blood pressure (mmHg), cDBP – central diastolic blood pressure (mmHg).
<table>
<thead>
<tr>
<th></th>
<th>Dippers (N=39)</th>
<th>Non-Dippers (N=9)</th>
</tr>
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<tbody>
<tr>
<td>cSBP (mmHg)</td>
<td>114.9 ± 11.4</td>
<td>116.3 ± 4.5</td>
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<tr>
<td>24-hr bSBP (mmHg)</td>
<td>123.1 ± 12.8</td>
<td>125.1 ± 4.9</td>
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<tr>
<td>cfPWV (m/s)</td>
<td>8.35 ± 1.3*</td>
<td>9.36 ± 1.2</td>
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<tr>
<td>Age (years)</td>
<td>63.2 ± 8.9</td>
<td>65.8 ± 10.2</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 3.6</td>
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<td>Est. VO₂ (ml/kg/min)</td>
<td>28.9 ± 7.6</td>
<td>26.4 ± 7.9</td>
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<td>Healthy Vascular Aging (% of group)</td>
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<td>HTN medication (% of group)</td>
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<tr>
<td>Thyroid medication (% of group)</td>
<td>15.4</td>
<td>44</td>
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</table>

*denotes a significance difference from non-dippers (P<0.05). cSBP – central systolic blood pressure, 24-hr bSBP – 24-hour brachial systolic blood pressure, cfPWV – carotid-femoral pulse wave velocity, BMI – body mass index, Est. VO₂ – estimated VO₂max based on Whaley et al. prediction equation (42), HTN – hypertension.
DISCUSSION

Emerging measurements of 24-hr central blood pressure help provide greater insight to circadian pressure fluctuations at the level of the heart. Measures of 24-hr cAMBP monitoring (cSBP and cPP) have shown superior to bAMBP measures in its association with left ventricular hypertrophy and predicting CVD damage and events (6, 28, 37, 41). However, considering the well-established relationship between aortic stiffening and brachial blood pressure, both independent predictors of CVD risk, research determining the relationship between measures of cAMBP (cSBP, cMAP, cPP) and aortic stiffness is warranted (9, 10, 25, 36). This study is the first to demonstrate in an apparently healthy, older population that 24-hr cAMBP monitoring, regardless of time of day, is positively associated with aortic stiffness (cfPWV). This relationship was also observed between nighttime cMAP and aortic stiffness, however, no association was found between aortic stiffness and 24-hr cPP. Regarding the global impact aortic stiffness and augmented central blood pressure have on increased cardiovascular disease risk, these findings demonstrate clinically relevant for disease prevention, treatment, and analysis in apparently healthy individuals.

24-cAMBP, Nighttime cMAP, and Aortic Stiffness

A primary finding from this study was that, in apparently healthy hypertensive and normotensive older individuals, 24-hr cAMBP is positively related to aortic stiffness. This is of value for clinicians as cfPWV has been linked to the presence of target organ damage, a precursor to various cardiovascular and renal diseases (34). 24-hr cAMBP
could provide an additional tool to allow preemptive screening on those at risk for various chronic diseases.

Due to the novelty of the techniques used, a limited amount of research exists examining cAMBP and cfPWV. de la Sierra tested 208 hypertensive individuals using various central and peripheral blood pressure methods (Mobil-O-Graph) for the prediction of target organ damage. They concluded that cBP, even when measured over 24-hrs, was not a better indicator of target organ damage than peripheral measures (7). Additionally, 24-hr cAMBP measures, when compared to bAMBP, are not shown to have a closer association with renal organ damage (11). Nonetheless, the current study supports previous conclusions that 24-hr cPP may not be a better predictor of target organ damage, specifically with an aortic stiffness-mediated effect. However, results from previous studies found cAMBP was superior to peripheral measures in improving prediction of cardiovascular events, left ventricular hypertrophy, and BP-associated heart damage in hypertensive adults (6, 37, 41). Due to the variable conclusions on central ambulatory pressure, we determine that 24-hr cAMBP monitoring, but not necessarily 24-hr cPP, holds clinical value due to its positive link to aortic stiffness.

A positive correlation was also found between nighttime cSBP and cMAP to aortic stiffness, thus suggesting an abnormal cBP circadian pattern in those with greater stiffness. Previous research supports the link between nighttime bMAP and bSBP to aortic stiffness, however this relationship has not yet been examined with 24-hr central measures (3). These circadian patterns in blood pressure are partly regulated by the sensitivity of the baroreceptor reflex and, in the presence of endothelial dysfunction, vascular structural changes can occur centrally that may reduce baroreceptor reflex
sensitivity (3, 4). This could help explain the pattern of higher nighttime cMAP in those with greater aortic stiffening.

24-hr cPP, Resting cPP, and Aortic Stiffness

Previous studies view cPP as a superior measurement to bPP for its link to target organ damage and cardiovascular events in both normotensive and hypertensive individuals (6, 13, 26, 28, 32, 35, 48). A previous study concluded that the greatest risk of CVD was seen in those with elevated cPP and cfPWV (26). The present study observed this association between supine resting cPP and aortic stiffness, however this was not seen with ambulatory cPP measurements. Our results suggest that CVD-related outcomes associated with increased cPP may be mediated by aortic stiffness, but only when measured in a clinical setting. This could be the result of thoracic fluid shifts that occur during measurements in the supine position which may cause an increase in central load. White Coat Syndrome, shown to have a 21% prevalence in untreated prehypertensive individuals, may affect clinic central pressure measurements and not 24-cPP measurements to help explain these nuances in cPP (9, 10, 31).

The current study also indicates that 24-hr pulsatile components of central blood pressure (cPP, cAlx, cAP) may not affect aortic stiffness more than central 24-hr static components (i.e. central systolic pressure). These results contradict a previous study by Jankowski et al. who concluded the pulsatile component of cBP and cPP are the primary factors related to cardiovascular risk and are superior to static components of central and brachial blood pressure (16). However, the study by Jankowski et al. performed invasive measures of cBP on coronary angiography recipients. Discrepancies with the current
study’s findings could be the result of the dissimilar populations studied as well as techniques applied.

**Resting bSBP, cSBP, and Aortic Stiffness**

The current study supports previous literature on the relationship between office bSBP and aortic stiffness (3, 20, 36). Our results support the notion that office bBP, when measured in the supine position, is linked to aortic stiffening. However, this relationship was not maintained with cSBP. In this context, a previous study examined body position on cSBP and concluded that central oscillometric measures were most reliable and present the most repeatability when participants were evaluated during supine rest (47). Considering this seemingly reliable method, yet a lack of correlation to our data, it is noteworthy to consider nighttime cSBP measures where participants are resting continuously in a supine position. Our data suggest that supine, sleeping cSBP is positively associated with aortic stiffness, while supine, resting cSBP is not. This could be explained by heightened parasympathetic activation reducing nighttime heart rate, leading to an increase in stroke volume due to greater preload and filling time. These mechanisms may cause increases in cSBP at night that would not be observed during supine rest. White Coat Syndrome may also be detected in some participants during the resting supine measures, while not throughout nighttime measures (9, 10, 31). Heightened sympathetic activity with White Coat Syndrome in a clinical setting may cause greater changes to heart rate than during nighttime measures. Furthermore, a possible medication effect could exist if participants generally take antihypertension medication in the morning, thus influencing the supine resting values obtained during morning testing.
24-hr bAMBP

Numerous researchers support the use of bAMBP over resting bBP as a stronger predictor of clinical outcomes (3, 20, 36) The current study agrees with the use of bAMBP for arterial stiffness-mediated outcomes. It is important to note the significance of nighttime brachial blood pressure values and its prognostic value for cardiovascular events and mortality in individuals over the age of 60 (9, 10, 44, 45). A study by Dolan et al examined 5292 untreated hypertensive patients for incidence rate of cardiovascular mortality outcome after brachial clinic and ambulatory monitoring. Researchers concluded bAMBP, specifically nighttime values, are the most potent predictor of mortality outcome (9). The current data agrees with previous literature and suggests ambulatory monitoring for brachial measures may be related to cardiovascular events due to a stiffness-mediated effect. Therefore, 24-hr brachial ambulatory monitoring may present valuable for determining aortic stiffening in individuals over the age of 50 and may offer prognostic value for CVD outcome.

Non-Dippers and Aortic Stiffness

It is well established that non-dipping is associated with aortic stiffening, cardiac remodeling, and end organ damage (4, 12, 20, 23). The current study was consistent with previous literature in demonstrating a positive relationship between those presenting a non-dipping status and greater aortic stiffening. Aortic stiffness, specifically when measured using cfPWV, has shown to be an independent predictor of dipping status with non-dippers presenting greater stiffness than dippers (3, 17). Although the current study
agrees with the vascular differences between nocturnal groups, it is important to note the similarities in blood pressure amid the two groups. There were no differences found in cAMBP or 24-hr bSBP among dippers and non-dippers. This could be the result of a medication effect as 15% of dippers were on hypertension medication versus 33% of non-dippers. Hypertension medications work to significantly decrease bSBP and reduce cSBP to a lesser degree, yet have no effect on aortic stiffness (21, 22, 46). Furthermore, previous literature suggests that aortic stiffness measures may independently predict bSBP response to anti-hypertensive medications (33). Therefore, our results support the value of measuring aortic stiffness in those with non-dipping patterns, specifically those on anti-hypertension medications who may have a masked CVD risk.

**bAMBP versus cAMBP**

The current study did not find any differences in diurnal patterns between cAMBP and bAMBP. We found no variances in circadian pattern changes from day-night or from night-day while simultaneously recording brachial and central pressure. This disagrees with previous research that described disproportionally higher nighttime cSBP and cPP than corresponding brachial pressures, even with treatment-induced BP reduction medications (43). However, this study examined simultaneous central and brachial pressures in treated and untreated hypertensive adults. A medication effect could help explain the incongruities among the studies as some classes of antihypertensive drugs result in lesser reductions in cSBP despite achieving target bSBP (21). The fact we did not see differences in brachial and central AMBP could be due to the apparently healthy
population studied and minimal medication treatment for hypertension (19% on hypertension medications).

**Conclusion**

In conclusion, the current study was the first to examine the relationship between 24 hr. central ambulatory blood pressure and aortic stiffness in an apparently healthy, older population. While no relationship was found between 24 hr. cPP and aortic stiffness, a positive relationship was found between 24 hr., daytime, and nighttime cSBP and aortic stiffness. Our results support previous findings regarding the value of nighttime brachial and central measures and nocturnal fluctuations, specifically in regard to aortic stiffness. Our results also indicate no differences in diurnal patterns between 24-hour central and brachial blood pressure. As a result of these findings, additional research is warranted for the clinical use of 24-hr cAMBP measurements using an Oscar 2 AMBP system with SphygmoCor, specifically to examine the influence of medications. Nonetheless, awareness of the emerging importance of central blood pressure techniques and ambulatory monitoring on disease outcome is essential. Our findings suggest that cAMBP monitoring may provide valuable implications on disease prevalence in older, apparently healthy adults in regard to aortic stiffening. These findings are clinically relevant as 24-hr cAMBP may provide additional preemptive screening on those at risk for various chronic diseases. Due to the conflicting nature of the current study’s results and previous literature, further studies are warranted.
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    Brachial Blood Pressures Obtained Through ABPM are Similarly Associated with 
    Renal Organ Damage in Arterial Hypertension. **Kidney Blood Press Res.** 

    blood pressure decrease and cardiovascular target organ damage in strictly selected 


APPENDIX

GRANT PROPOSAL

SPECIFIC AIMS

Cardiovascular disease (CVD) is the leading cause of death in the US and risk can be independently predicted by both arterial stiffness and increased blood pressure. Combating the epidemic of CVD relies heavily on accurate and reliable measures of both variables. Arterial stiffness is measured using the gold standard of carotid femoral pulse wave velocity (cfPWV). Blood pressure is primarily measured in the primary care setting at the brachial site, however new measures of 24-hour brachial ambulatory blood pressure and central brachial pressure have shown superior to brachial office blood pressure in predicting CVD outcome. Furthermore, 24-hour brachial ambulatory blood pressure provides valuable nighttime measures that determine one’s dipping status. Non-dippers, or a decrease in day-to-nighttime mean blood pressure >10%, have increased CVD risk independent of daytime blood pressure. Combining these two techniques, a novel measure of 24-hour central ambulatory blood pressure (cAMBP) has emerged allowing clinicians to examine the central load at the aorta throughout both the day and nighttime hours.

It has been thoroughly explored that both arterial stiffness and blood pressure increase with aging, however the relationship is not well understood. There is a lack of research examining the relationship between cfPWV and cAMBP during both the day and nighttime hours in an apparently healthy population.

- Thus, the aim of this study is to examine the relationship between 24-hour ambulatory blood pressure and arterial stiffness in both apparently healthy dippers and non-dippers.
- We hypothesize a positive relationship between arterial stiffness (cfPWV) and 24-hour central pressure (cAMBP) in apparently healthy individuals, with non-dippers presenting higher day/night cAMBP and cfPWV than dippers.

Based on pilot data and previous literature, we expect the following outcomes:

1. cAMBP is positively associated with cfPWV
2. cAMBP has a more positive association to cfPWV than standard office brachial blood pressure
3. Nighttime cAMBP is more positively associated with stiffness than daytime cAMBP
4. Non-Dippers have greater cAMBP and cfPWV values throughout both the day and night when compared to dippers

As independent risk factors of CVD, valid measures of arterial stiffness and blood pressure are crucial to the progression of disease management and prevention. With the
help of research validating current technology, AMBP and stiffness techniques can be used in the clinical setting to provide a more complete health profile when treating and preventing disease. cAMBP is a novel technique that could shift clinicians’ focus to disease prevention rather than disease management.

RESEARCH STRATEGY

BACKGROUND

CVD is the most common underlying cause of death in the US (4). Of the risk factors associated with CVD, hypertension remains a primary diagnosis affecting more than 33% of US adults (4, 26). Hypertension, or a sustained elevation in brachial blood pressure (bBP), is associated with increased risk of all-cause and CVD mortality (27, 29). Hypertension prevalence increases with age as the vessel wall is exposed to continual inflammation causing the elastic properties of the artery to deteriorate. This results in decreased compliance and increased mean pressure leading to microvascular damage, target organ damage and CVD events (17, 33). As a major modifiable risk factor, hypertension screening is vital to identify those at risk and prevent future outcomes (26).

Blood pressure is commonly measured at the brachial site in a primary care setting. However, new techniques have allowed for 24-hour monitoring in which daytime and nighttime brachial ambulatory blood pressure (bAMBP) can be measured. bAMBP has shown superior to clinic blood pressure in predicting CVD mortality, removing White Coat Syndrome, and providing valuable nighttime measures (10, 11). Nighttime blood pressure allows for the identification of individuals who are non-dippers, or do not experience a diminished systolic blood pressure (SBP) while sleeping. Non-dipping is associated with CVD events and all-cause mortality, independent of daytime blood pressure (5, 6, 11, 18, 23).

In addition, central blood pressure (cBP) has shown superior to bBP in predicting all-cause and CVD mortality (12, 33). cBP can be measured non-invasively using pulse wave analysis (PWA) to more accurately reflect loading at the aorta. Previous studies show central pressures to be superior to bBP in relation to vascular hypertrophy, degree of atherosclerosis, and CVD events (28, 29). In contrast, researchers have found bBP, but not cBP, to be sufficient in predicting CVD outcome (7). With higher pressures occurring in peripheral than central arteries, the value in replacing bBP with cBP may help clinicians predict preclinical outcomes, however this relationship requires further exploration. Therefore, with the evidence supporting both AMBP and cBP, the next logical step would be to combine these measures to examine central ambulatory blood pressure (cAMBP).

cAMBP is a novel, non-invasive technique for measuring daytime/nighttime SBP and central pressures, thus cAMBP may be superior to bAMBP in predicting target organ damage (30). A recent study found cAMBP to be superior to bAMBP in its association with left ventricular hypertrophy and hypertension (35). In contrast, researchers found central pressure, even when monitored for 24 hours, was not a better predictor of target organ damage than peripheral office blood pressure (8). Due to conflicting data and the scarcity of research provided for this technique, further study is prompted to both validate and determine the prognostic value of using cAMBP as a means of predicting CVD.
Research also supports the relationship between hypertension and arterial stiffness, yet the primary source of disease remains unclear (3, 20, 21). Researchers agree that arterial stiffening is a manifestation of vascular aging, specifically around the 5th decade of life when deterioration of the artery’s elasticity begins (9, 17, 32). Carotid femoral pulse wave velocity (cfPWV), the gold standard measurement of arterial stiffness, is related to the intrinsic elasticity of the artery and progressively increases 6-8% with each decade (9, 21). Furthermore, increased cfPWV is shown to be an independent predictor of non-dipping (3, 14). Although research supports the relationship between increased bBP, increased AMBP, and non-dipping to arterial stiffness, insufficient studies have examined cAMBP and arterial stiffness. Therefore, the aim of this study is to examine the relationship between central 24-hour ambulatory blood pressure and arterial stiffness in both apparently healthy dippers and non-dippers.

PRELIMINARY DATA
An unpublished pilot study was previously executed by the Clinical Exercise Physiology Lab showing a positive relationship between night-time bAMBP and cAMBP to cfPWV, while no relationships were found with resting bBP measures and cfPWV (Figure 1 presents cSBP and cfPWV; bSBP data follows similar trends). Additionally, a positive relationship between 24-hour central pulse pressure (cPP= central SBP-central DBP) and cfPWV (Figure 2; n=24, 17 dippers, 7 non-dippers). Considering nighttime values, pilot data showed a trend towards differences in resting cfPWV between dippers (7.925 m/s) and non-dippers (8.807 m/s; p = 0.07). These data support the value of nighttime measures and should be expanded to determine possible cfPWV differences between dippers and non-dippers (19).

![Figure 1](image1.png)

![Figure 2](image2.png)

APPROACH
Participants will be recruited from Ball State and the local Muncie, Indiana area via flyers and email. Due to the aging effects on stiffness, we plan to study men and women 50 years of age or older (9). Those considered for participation must also be free of known CVD, metabolic or related diseases and symptoms including chest pain, shortness of breath, and skipped heart beats. Ineligibility includes those using tobacco, on Beta-blocker therapy, receiving cancer treatment, or presenting a body mass index (BMI) greater than 35 kg/m². These standards are in place according to the operating...
procedures stated by Suntech for the Oscar 2 ABP monitoring system and previous literature examining the effects of stiffness, ambulatory and central pressures (3, 12, 21, 24, 35). Participants will interact with a researcher as outlined in the figure below.

**Prescreening**

The informed consent will be signed by the participant followed by an HHQ review to ensure the participant is free of known disease and symptoms. Height and weight will be measured upon arrival to determine BMI (1). If eligible, the participant will be instructed to fast from food, alcohol and caffeine intake 12 hours prior to testing, and avoid exercise for 36 hours prior (15).

**1st Lab Visit – Standard Resting Measures**

DXA values will be attained to analyze bone mineral density, fat mass, and lean mass (13). Skinfold measures to obtain body fat percentage will be used in the Whaley equation to calculate physical fitness (36). Waist circumference will be measured to determine waist-to-hip ratio. Resting bBP and heart rate will be measured using a brachial cuff/sphygmomanometer and pulse oximeter, respectively. Handgrip assessment will be performed on both hands to assess muscular strength. A blood draw will be performed to collect cholesterol, triglycerides, HDL/LDL, glucose and HbA1c. DXA and blood draw present mild hazard to participants as slight radiation exposure and possible vasovagal response may occur. However, procedures will be performed by trained staff in accordance with the policies and procedures outlined by the Clinical Exercise Physiology Program to ensure safe data collection (1).

**Central Pressure/Arterial Stiffness Measures**

PWA will be measured to determine resting central pressures. A brachial cuff is used to first collect supine bBP followed by measures of brachial arterial waveforms. A generalized transfer function is applied to generate an aortic waveform (34). Additionally, surrogates to aortic wave reflection will be collected, including augmentation pressures and augmentation index, which are independent predictors of CVD risk (25). Two measurements of PWA are taken with a third necessary if the two original measures have an aortic augmentation@75 >5%, bBP >5 mmHg, or do not obtain quality assurance. The SphygmoCor XCEL device is validated against invasive methods (2, 31). Immediately following, arterial stiffness will be assessed during the first lab visit using cfPWV (15). The SphygmoCor XCEL device will be used to determine the pulse transit time sensed by the tonometer at the carotid to the cuff at the femoral artery (m/s²). Greater pulse wave velocity values denote arterial stiffness, while the indicator for healthy arterial aging is a cfPWV at or below 7.6 m/s (22). Participants will be instructed to lie supine for 10 minutes prior to data collection while the technician measures distances between various
anatomical landmarks (38). Two measures of cfPWV will be taken with a third required if measurements are not within 0.5 m/s.

**Central Ambulatory Blood Pressure**

Ambulatory blood pressure monitoring will be assessed using the Oscar 2 AMBP system with SphygmoCor (SunTech Medical and AtCor Medical) to measure cAMBP. The Oscar 2 and SphygmoCor systems have been recommended for clinical use after validation with international protocol and presenting strong correlation to invasive measures (2, 16, 25, 31, 34). The ambulatory cuff will be fitted as the first data point is collected in the lab. Daytime recording will begin at 0800 hours and continue until 2130; nighttime hours begin at 2200 hours until the following day at 0800 hours. During daytime hours, inflation will occur every 30 minutes with nighttime measures occurring every hour. The cuff will capture bBP and utilize a generalized transfer function to calculate cBP at each time point. 24-hour data will be considered valid with an ≥80% rate of successful readings (24). Participants will be given a log to record food intake and body position while they are wearing the cuff and will be asked to avoid caffeine intake and exercise throughout data collection.

**Data Analysis**

Data will be presented as mean ± standard error. Descriptive statistics will be used to categorize participants into nocturnal groups (dippers or non-dippers) based on the decrease in mean SBP from day to nighttime. Pearson’s correlation will be used to determine the relationship between mean cAMBP and cfPWV. We will use unpaired t-tests to examine relationships between cfPWV in dippers and non-dippers. We will recruit a sample size of 26 participants to add to an existing pilot data set of 24. With a large effect size (0.5), we estimate 80% power will require a sample size of 29 individuals. Considering this, we will obtain a sample size of 50 subjects to detect a significant difference in cAMBP and cfPWV means, and differences in cfPWV between dipping/non-dipping groups at a significance level of 0.05.

**INNOVATION**

This study is a follow up to a previously conducted pilot study utilizing cAMBP as a novel measurement in relation to cfPWV. The current research could shift clinical practice from standard bBP measures to potentially superior cAMBP. The combination of cBP and AMBP will provide an understanding of central pressure behavior from day to night, identify individuals at risk for CVD, and provide enhanced therapeutic treatment techniques to prevent future outcomes. In conjunction, studying the relationship between cAMBP and arterial stiffness will allow insight to the interactive effects of blood pressure and central hemodynamics on arterial stiffening. This novel technique has the potential to change the way current clinical practices define, prevent and treat CVD while working to remove the burden arterial stiffness poses to our aging world population.

**SIGNIFICANCE**

cBP and AMBP are superior to clinic blood pressure in monitoring and evaluating risk of CVD. The combination of these techniques, cAMBP, may provide the most effective method for monitoring CVD risk. Additionally, cfPWV provides a non-invasive
method to assess blood pressure’s response on central hemodynamics. Due to the novelty of cAMBP, limited research has been done examining the relationship between cAMBP and cfPWV, specifically in relation to nighttime cAMBP. This research aims to influence the field of clinical exercise physiology as new measures of CVD risk could impact the way health professionals treat various symptoms of disease.

**EXPECTED FINDINGS**

In the event our data does not support our hypothesis, there are specific nuances that could have occurred. Due to the availability, the majority of data will be from adult fitness program participants who are largely physically active, Caucasian, middle-upper class individuals, therefore decreasing generalizability. We plan to recruit from the greater Muncie community in efforts to expand the ethnic and socioeconomic population sample. As the assessment of cAMBP is feasible, important questions regarding medication influence and reference values still need to be addressed. We do not plan to examine medications in the present study, yet medication data will be collected (37). Furthermore, although instructed to avoid exercise and caffeine, we are unable to control the participant’s habits during 24-hour data collection which may influence the data. Lastly, since we are unable to determine nocturnal fluctuations in the recruiting process, data skew could occur as nighttime dipping is more common than non-dipping. Considering these limitations, future research could focus on the influence of medications and socioeconomic status on nocturnal fluctuations in cAMBP and cfPWV, as well as recruit from a more clinical population. Currently, we aim to broaden the understanding of daytime/nighttime cAMBP and arterial stiffness to further the progression towards utilizing cAMBP as a tool in clinical practice.

**PERSONAL NARRATIVE**

Olivia Jones will be responsible for managing the project on arterial stiffness and ambulatory blood pressure. Ms. Jones is a second year Clinical Exercise Physiology Master of Science candidate at Ball State University with a Bachelor’s of Science degree in Exercise Physiology from Taylor University. She is experienced in project and team management, individual training with various populations, as well as the knowledge and structure of research. She has valuable research experience gained by directed research exposure during her undergraduate and graduate work. She has experience formulating questions based on existing literature, organizing an approach to respond, recruiting participants, collecting and analyzing data, and presenting summarized findings. In 2017, Olivia presented her research in poster format at Midwest ACSM on the differences in acute endothelial function in response to two distinct dietary patterns. She has also presented a colleague’s thesis project, *Relationships Among Muscle Function, Skeletal Muscle Mass, and Arterial Stiffness*, in poster format at Midwest and National ACSM conferences.

Throughout her graduate work, Olivia has gained valuable clinical experience in both a lab and hospital setting. She is adept at measures of body composition, blood draw, arterial stiffness, central pressure assessment and maximal exercise testing due to her time spent with participants in the Human Performance Lab. She previously was a part of the data collection team that generated the pilot data utilized for this study. This
gave her the prior experience with ambulatory blood pressure measures, participant recruiting and problem solving necessary to excel as she continues data collection. Furthermore, as an exercise technician in cardiopulmonary rehabilitation, Olivia possesses valuable interpersonal skills related to clinical data collection. She is proficient in ECG recordings and blood pressure monitoring given the technical aspect of her position, but also has the ability to adapt quickly to adverse outcomes while maintaining a clear ability to communicate.

She plans to manage the project while reporting directly to the director of the Clinical Exercise Physiology Lab. She also has a team of skilled graduate assistants as well as advisors to help navigate the logistics of the project. Olivia is a valuable member who presents strong organizational and communication skills and strives to be diligent in her area of clinical research.

REFERENCES


### Ambulatory Blood Pressure and Arterial Stiffness

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<th>Study</th>
<th>Sex/Age</th>
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<th>Vascular Response</th>
<th>BP Response</th>
<th>Take Home Message</th>
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</table>
| Asar (1996)| 106 M&F/20-72    | Apparently healthy, no meds| 24-hr monitoring | bAMBp, cfPWV              | Arterial stiffening = ↑bAMBp, ↑HR   | -           | 1) ↑PWV = ↑bAMBp and HR, especially during nighttime values  
2) those with ↑PWV had less dipp at night than those with lower PWV  
3) PWV = indepen. predictor of nighttime fall in SBP |  |
| Boggia (2007)| 7458 M&F/56±14 | England & Asia (general population) | 9 yr follow up | bBP, questionnaire, bAMBp | -                                   | -           | 1) Night bBP predicts all mortality, day bBP predicts CVD-related mortality  
2) non-dipp may mark pre-existing or concurrent disease  
3) both day and night AMBP are beneficial |  |
| Coleman (2011)| 95 M&F/<75 yrs | HTN                       | 24-hour trial   | cBP (applanation tonometry), bBP, echo | No difference in aortic stiffness | Supine: cBP, LVM & bBP ↑ in dippers vs non-dippers | 1) Seated bBP was the same for both groups  
2) Non-dipp had altered central hemod. compared to dippers  
3) This study exp the hemodynamics w/ non-dippers |
<table>
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<td>HTN, low CVD risk</td>
<td>24-hr monitoring, 10-yr follow-up</td>
<td>Resting cBP, 24-hr cAMBP</td>
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<td><strong>de la Sierra (2017)</strong></td>
<td>208 M &amp; F/57±12</td>
<td>HTN</td>
<td>1 day assessment – target organ damage: LVH, renal abnorm. or art. Stiffness (&gt;10 m/s)</td>
<td>b &amp; cAMBP, GFR, echo, aPWV</td>
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<tr>
<td><strong>Dolan (2005)</strong></td>
<td>5296 M&amp;F/51±14</td>
<td>Untreated HTN</td>
<td>8 yr follow up for mortality</td>
<td>Clinic BP &amp; 24-bAMBP</td>
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<tr>
<td><strong>Fagard (2005)</strong></td>
<td>391 M&amp;F/71±9</td>
<td>60+ yrs, apparently healthy, treated and untreated HTN</td>
<td>11 yr follow up for CVD event</td>
<td>Clinic bBP, at home BP, AMBP</td>
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<tr>
<td><strong>Fernandez-Llama (2017)</strong></td>
<td>208 M&amp;F/57±12</td>
<td>25% had renal organ damage</td>
<td>Lab visit</td>
<td>Office bBP &amp; cBP, aPWV, bAMBP, cAMBP</td>
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</tbody>
</table>
organ damage in HTN pts.
2) those w/ renal damage had blunted nocturnal decline both centrally % peripherally, as well as higher stiffness.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Description</th>
<th>Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang (2011)</td>
<td>1014 M&amp;F/52±13</td>
<td>Apparently healthy, normotensive, untreated HTN</td>
<td>Carotid tonometry (bBP &amp; PP), AMBP</td>
<td>Central measures &amp; AMBP are better predictors than bBP</td>
</tr>
<tr>
<td>Jankowski (2008)</td>
<td>1109 M &amp; F</td>
<td>Coronary angiography patients</td>
<td>Invasive cBP</td>
<td>Pulsatile &gt; static</td>
</tr>
<tr>
<td>Jerrard-Dunne (2007)</td>
<td>314 M&amp;F 48±8</td>
<td>Untreated HTN</td>
<td>bAMBP, cfPWV, radial tonometry</td>
<td>Night:day ratio can be used for dip/non-dip class. Instead of &lt;10% drop at night</td>
</tr>
</tbody>
</table>

1) cBP over bBP in predicting all-cause and CVD mortality
2) AMBP over cBP for predicting CVD mortality
3) cPP over all the best predictor of all-cause mortality

1) central pulsatility was most important for outcome
2) cPP was also related
3) cBP & bBP were not related

1) A J-shaped relationship between PWV and dipper status
2) non-dipp & reverse dipp had sig ↑ PWV than dipp, once multivariate was
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample</th>
<th>Methodology</th>
<th>Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lakatta (2003)</td>
<td>M &amp; F</td>
<td>Meta-analysis</td>
<td>Aging population</td>
<td>cfPWV, IMT, bBP, cBP</td>
<td>3) reverse dipp remained significant when used, only reverse dipp (using a night:day ratio) presents the highest disease risk.</td>
</tr>
<tr>
<td>Lekakis (2005)</td>
<td>72 M&amp;F/53±12</td>
<td>Untreated HTN</td>
<td>24-hr monitoring</td>
<td>bAMBp, radial tonometry &amp; PWA to estimate PWV</td>
<td>1) vascular aging + vascular disease are individual components of “vascular disease” 2) endothelial dysfunction can be seen in normotensive, non-symptomatic adults 3) vig exercise, low sodium diet, and ACE inhibitors may improve endothelial function.</td>
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<tr>
<td>Manisty (2012)</td>
<td>M &amp; F</td>
<td>Meta-analysis</td>
<td>B-blocker and diuretic meds</td>
<td>Radial tonometry, cfPWV, bBP, cBP</td>
<td>1) lesser ↓ in cBP compared to bBP 2) target bBP can be achieved, yet cBP will not ↓ to a desired value.</td>
</tr>
<tr>
<td>Study</td>
<td>Number of Participants</td>
<td>Demographics</td>
<td>Follow-Up</td>
<td>Methodology</td>
<td>Findings</td>
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<tr>
<td>McGaughey (2016)</td>
<td>58 studies</td>
<td>Meta-analysis</td>
<td>8 various anti-HTN meds, no change to stiffness</td>
<td>bSBP ↓ more than cSBP</td>
<td>anti-HTN meds ↓ bSBP more than cSBP</td>
</tr>
<tr>
<td>Najjar (2008)</td>
<td>449 M&amp;F/53±17</td>
<td>Normotensive and untreated HTN</td>
<td>cPWV at baseline, repeated BP measures</td>
<td>↑ aortic stiffness led to ↑ risk of future HTN</td>
<td>1) PWV is an independent predictor of ↑ SBP/HTN in hyper-and normotensives 2) PWV predictor of ↑ PP in those 60+ yrs</td>
</tr>
<tr>
<td>Niiranen (2019)</td>
<td>2119 M&amp;F/60</td>
<td>Framingham Heart study</td>
<td>12-year follow-up for CVD events</td>
<td>Greater cPWV &amp; cPP = ↑ CVD risk</td>
<td>1) cPWV and cPWV mismatch is common in this population 2) cPWV may modify the assoc. of cPP with CVD risk, with the greatest risk being observed in those with elevated cPWV and cPWV</td>
</tr>
<tr>
<td>Ohkubo (2002)</td>
<td>1542 M&amp;F/40+</td>
<td>Japanese (general population)</td>
<td>9 yr follow up for mortality</td>
<td>bAMPB</td>
<td>1) linear relation b/w nocturnal decline &amp; CVD morality, independent of bBP range</td>
</tr>
<tr>
<td>Omboni (2019)</td>
<td>646 M&amp;F/52 years</td>
<td>HTN (half treated)</td>
<td>24-hour monitoring</td>
<td>b&amp;cAMPB &amp; PWV with a cuff, LVM and IMT</td>
<td>24-hr SBP and PP = cardiac damage, mainly for cAMPB 1) b&amp;cAMPB were associated with cardiac damage 2) 24-hour cSBP &amp; cPP had a greater predictive</td>
</tr>
</tbody>
</table>
### Protogerou (2009)

- **Participants:** 375 M & F
- **Diagnosis:** HTN
- **Interventions:** ACE inhibitor, β-blocker therapy
- **Outcome Measures:** PWV, bSBP
- **Findings:**
  - SBP control is influenced by stiffness
  - Baseline PWV is a significant predictor of BP response to anti-HTN treatment, independent from age & CV risk factors
  - Achievement of SBP control appears to be influenced by aortic stiffness

### Roman (2007)

- **Participants:** 3520 M&F/58±14
- **Diagnosis:** 2500 free of CVD, 70% on HTN meds
- **Follow-up:** 3 yr follow up
- **Outcome Measures:** Radial tonometry, carotid ultrasound
- **Findings:**
  - Arterial stiffness: strongly related to carotid hyper. & atherosclerosis
  - cBP more accurately reflects loading than bBP
  - cPP is more strongly related to vascular hyper, atheros, and CV events than bBP

### Rouxinol-Diaz (2018)

- **Participants:** 2,800 M&F
- **Diagnosis:** HTN and normotensive
- **Follow-up:** -
- **Outcome Measures:** cBP, bAMBP, TOD measured through PWV
- **Findings:**
  - Abnormal bAMBP and cBP = risk of TOD
  - Central HTN poses the greatest threat of TOD

### Schutte (2017)

- **Participants:** -
- **Diagnosis:** Multicenter studies in Europe
- **Outcome Measures:** Meta-analysis of existing literature on cAMBP, cAMBP (Mobil-O-Graph)
- **Findings:**
  - cAMBP shows an ↑ trend towards sig w/LVH than bAMBP
  - cAMBP should be considered over bAMBP in the clinical setting
  - cAMBP is superior to clinical
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Characteristics</th>
<th>Measurements/Methods</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Wang</strong></td>
<td>1272 M&amp;F/60 yrs</td>
<td>Normo and untreated HTN, apparently healthy</td>
<td>10 yr follow up for all-cause and CVD mortality, bBP, arterial tonometry, ultrasound, echo</td>
<td>CVP predicted CVD mortality independent of arterial stiffness. cSBP most strongly correlates with LVM; cSBP &amp; cPP most strongly correlate with IMT and GFR.</td>
</tr>
<tr>
<td><strong>Weber</strong></td>
<td>289 M&amp;F/50 yrs</td>
<td>HTN, no medications</td>
<td>One visit, bBP, cABPM (bSBP &amp; cSBP), ECG</td>
<td>1) 24-hr cAMBP is superior to bAMBP in predicting LVH. 2) Closer relation b/w cBP to SBP &amp; PP than strictly bBP.</td>
</tr>
<tr>
<td><strong>Williams</strong></td>
<td>171 M&amp;F</td>
<td>HTN</td>
<td>Two visits: BP tonometer mounted into the strap of a wristwatch-like device</td>
<td>cAMBP &amp; bAMBP ↓ at night, but bAMBP ↓ more. 1) Higher night-time cAMBP for any given bAMBP at night — even with BP lowering therapy. 2) Night-time cAMBP could have prognostic import. 3) Brachial &amp; central have diff. diurnal patterns — not.</td>
</tr>
<tr>
<td><strong>Young (2015)</strong></td>
<td>20 M &amp; F</td>
<td>Healthy</td>
<td>Comparing oscillometric cBP measures values w/ fasting and body position</td>
<td>PWA</td>
</tr>
</tbody>
</table>

cfPWV – carotid femoral pulse wave velocity, aPWV – aortic pulse wave velocity, bAMBP – brachial ambulatory blood pressure, cAMBP – central ambulatory blood pressure, cBP – central blood pressure, bBP – brachial blood pressure, LVH – left ventricular hypertrophy, cPP – central pulse pressure, bPP – brachial pulse pressure