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# Effects of Antihypertensive Therapy on Matrix Metalloproteinase-9 Levels in Controlled Hypertensive Patients

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**Short Title:** Antihypertensive Drugs and MMP-9 Levels

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**Abstract**

Ambulatory blood pressure monitoring (ABPM), alongside peripheral blood pressure (BP) measurements, provides valuable insights into central hemodynamics, including pulse wave velocity (PWV), augmentation index (AI75%), and central pressure—factors closely linked to arterial stiffness. The progression of arterial stiffness is associated with matrix metalloproteinase-9 (MMP-9), an extracellular matrix enzyme. This study aims to assess the correlation between variables obtained through ABPM and MMP-9 levels across different BP categories. A total of 101 individuals were enrolled, divided into three groups: 21 normotensive (NT), 36 prehypertensive (PH), and 44 controlled hypertensive (CHT) participants. Peripheral and central BP parameters were evaluated using the Mobil-O-Graph® 24-hour PWA monitor, and plasma MMP-9 levels were measured in all participants. Participants' ages ranged from 30 to 71 years. MMP-9 concentrations were significantly higher in the PH group (4.74 ± 0.5 ng/mL) compared to the CHT group (4.41 ± 0.5 ng/mL; p = 0.002). MMP-9 levels showed a correlation with cardiac output and heart rate during all three ABPM evaluation periods (24 hours, wakefulness, and sleep). PWV values were higher in the CHT group than in the PH group (8.1 ± 1.2 vs. 6.9 ± 1; p = 0.0003), whereas AI75% did not differ significantly between the groups (22.6 ± 8.9 vs. 19.8 ± 7.4; p = NS). Prehypertensive individuals exhibit higher MMP-9 levels compared to controlled hypertensive patients, suggesting that antihypertensive therapy may contribute to reduced plasma MMP-9 levels.

**Keywords:** Hypertension, Prehypertension, Ambulatory blood pressure monitoring, Arterial stiffness, Matrix metalloproteinase.

## 1. Introduction

Ambulatory blood pressure monitoring (ABPM) represents a significant advancement in blood pressure (BP) measurement techniques, offering a high volume of readings over 24 hours and enabling the identification of various clinical scenarios related to arterial hypertension [1,2]. ABPM is particularly valuable for diagnosing conditions such as hypertension and borderline hypertension, white coat hypertension, resistant hypertension, nocturnal hypertension, gestational hypertension, and masked hypertension. Additionally, it aids in evaluating treatment efficacy, stratifying cardiovascular risk, and predicting cardiovascular outcomes [1,3,4].



Some indicators allow the assessment of the relationship between parameters measured during 24-hour ABPM and target organ damage (TOD) [4]. Studies suggest that systolic blood pressure (SBP) measured via ABPM shows a stronger association with TOD, such as left ventricular hypertrophy and stroke, compared to office-measured SBP [5]. Moreover, ABPM effectively detects individuals at high risk for cardiovascular disease (CVD) [6]. Importantly, ABPM identifies variations in BP during sleep, particularly in individuals with insufficient nocturnal BP reduction, referred to as "non-dippers" [4,6,7].

Beyond peripheral blood pressure values, ABPM also enables the estimation of central hemodynamic parameters, including central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), augmentation index (AI), and pulse wave velocity (PWV). These measures provide a more direct assessment of the pressure load on target organs such as the heart, brain, and large arteries, and are considered stronger predictors of cardiovascular risk than peripheral BP alone. Alterations in central hemodynamics are closely linked to arterial stiffness, a process influenced by extracellular matrix remodeling. Matrix metalloproteinase-9 (MMP-9), in particular, contributes to vascular changes by degrading structural components of the arterial wall, thereby promoting stiffness and cardiovascular disease progression.



The elastic properties of the arterial walls vary across the arterial tree, influenced by molecular, cellular, and histological characteristics [10]. Imbalances in the activation and inactivation of MMP-9 have been linked to vasomotor alterations. MMP-9 is involved in the degradation of extracellular matrix components, contributing to the development of CVD and the arterial stiffening process [11,12].

Therefore, this study aims to correlate peripheral and central hemodynamic variables obtained through ABPM with plasma MMP-9 levels in individuals with different BP classifications.

## 2. Methodology

### *2.1. Ethical Aspects*

This study was approved by the Research Ethics Committee of the Medical School of São José do Rio Preto (FAMERP) under protocol CAAE no. 07606212.5.0000.5415 and approval no. 94.248/2012. All participants were invited to take part voluntarily, having received complete information about the study objectives and procedures. They were assured that their choice to participate—or decline—would not affect their ongoing medical care. The research was conducted in strict accordance with the ethical principles established in the Declaration of Helsinki.



### *2.2. Study design*

The study was designed as a cross-sectional observational investigation with participants divided into three groups: normotensive (NT), prehypertensive (PH), and controlled hypertensive (CHT) patients under pharmacological treatment. All individuals underwent 24-hour ambulatory blood pressure monitoring (ABPM) to assess peripheral and central hemodynamic parameters, and blood samples were collected for biochemical analysis and plasma MMP-9 quantification.

### 2.3. *Inclusion and Exclusion Criteria*

Participants eligible for inclusion were men and women aged 30 to 71 years, an age range chosen to encompass adults in whom hypertension and vascular remodeling are most prevalent, while ensuring representation of both sexes to reflect real-world clinical practice. A total of 101 individuals was recruited and distributed into three groups. The control group consisted of 21 untreated NT, defined as having systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg. The PH included 36 individuals with SBP values between 120 and 139 mmHg and/or DBP between 80 and 89 mmHg. The third group comprised 44 CHT under regular follow-up at a specialized outpatient hypertension clinic, with SBP <140 mmHg and DBP <90 mmHg while receiving antihypertensive therapy.

Exclusion criteria encompassed pregnancy, low life expectancy, chronic conditions that could hinder study participation (e.g., malignancies), cognitive impairment, inability to obtain blood pressure measurements, or refusal to provide written informed consent. Additionally, NT participants were excluded if they had a prior diagnosis of hypertension or previous use of antihypertensive medication.

### *2.4. Sample size*

Since this study was conducted in a specialized outpatient clinic, reflecting real-world clinical conditions, a convenience sample was recruited. This approach enabled the inclusion of readily available, representative participants from routine medical practice. To ensure the statistical validity of the findings, a post-hoc power analysis was performed using G*Power 3.1 to assess the statistical power of the study based on the observed effect size. The comparison of plasma MMP-9 levels between PH and CHT groups revealed a significant difference (mean difference = 0.33 ng/mL, SD ≈ 0.5, $p = 0.002$). Using a two-tailed t-test for independent samples, the following parameters were applied: effect size (Cohen's d) = 0.66, $\alpha$ error probability = 0.05, and sample sizes of 36 (PH) and 44 (CHT). The resulting post-hoc power ($1 - \beta$) was approximately 0.91, indicating a 91% probability of detecting a true effect of the observed magnitude. This high statistical power reinforces the robustness of the results and demonstrates that, even with a convenience sample, the study had sufficient sample size to detect moderate to large differences in MMP-9 levels between the groups.



### *2.5. Pharmacological treatment*

In this study, the CHT group consisted exclusively of individuals undergoing pharmacological treatment with antihypertensive agents. The most commonly used medications included angiotensin II receptor blockers (ARBs; 21 individuals, 48.5%), ACE inhibitors (ACEi; 13 individuals, 30.4%), calcium channel blockers (CCBs; 15 individuals, 33.3%), thiazide diuretics (18 individuals, 40.9%), and beta-blockers (1 individual, 24.6%), often administered in combination. Additionally, 14 individuals (31.8%) in this group were receiving statins for lipid management. In contrast, participants in the NT and PH groups were not using any antihypertensive or lipid-lowering medications at the time of evaluation, in accordance with the study's inclusion criteria. This clear pharmacological distinction among groups enabled the investigation of MMP-9 levels and hemodynamic parameters in both treated and untreated individuals, providing insights into the potential impact of antihypertensive therapy on vascular remodeling and inflammatory biomarkers

### *2.6. Clinical and Biochemical Analysis*

Participant information was collected using a questionnaire covering medical history, associated conditions (e.g., diabetes mellitus), medications, smoking status, and family history. Anthropometric measurements (weight and height) were taken using standard scales. Peripheral blood was collected to analyze biochemical parameters, including fasting blood glucose, serum creatinine, uric acid, potassium, and lipid profiles. The lipid profile included total cholesterol, cholesterol fractions, and triglycerides, measured after 12 hours of fastin.



### *2.7. Metalloproteinase-9 Quantification*

Venous blood samples were obtained using vacutainer tubes containing EDTA (Becton-Dickinson, São Paulo, Brazil) and centrifuged at 3500 revolutions per minute for ten minutes. Plasma samples were immediately stored at -70°C for subsequent metalloproteinase-9 (MMP-9) quantification. MMP-9 levels were measured using a human MMP-9 ELISA kit (R&D Systems, Inc., Minneapolis, MN, USA). For statistical analysis, MMP-9 values were transformed into their negative logarithmic form to ensure normal distribution.

### *2.8. Ambulatory Blood Pressure Monitoring (ABPM): Peripheral and Central Parameters*

Ambulatory blood pressure monitoring (ABPM) was performed using a validated portable digital recorder (Dyna-Mapa AOP/Mobil-O-Graph-NG, Cardios, São Paulo, Brazil). An appropriately sized cuff was placed on the non-dominant arm, and measurements were obtained every 30 minutes over a 24-hour period during a standard activity day. Peripheral parameters recorded included systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), heart rate (HR), and pulse pressure (PP).

In addition to peripheral values, the Dyna-Mapa AOP system employs oscillometric pulse wave analysis to derive central hemodynamic parameters from brachial recordings. These included central systolic BP (cSBP), central diastolic BP (cDBP), central pulse pressure (cPP), cardiac output (CO), peripheral vascular resistance (PVR), augmentation index normalized to a heart rate of 75 bpm

(AIx75), and pulse wave velocity (PWV). Central parameters provide a more direct estimate of the pressure load on target organs and vascular stiffness than peripheral BP alone. PWV was used as a direct marker of large artery stiffness, while cSBP, cPP, and AIx75 served as indirect indicators of arterial stiffness and wave reflection. The augmentation index (AIx) was calculated from the aortic pressure waveform and normalized to 75 bpm following the method proposed by Wilkinson et al. [24].

All participants underwent ABPM during a standard activity day. Measurements of peripheral and central BP parameters were taken every 30 minutes, and mean values were calculated for three periods: 24-hour, wakefulness, and sleep. The nocturnal dip was defined as a reduction of at least 10% in SBP and DBP from wakefulness to sleep, whereas non-dipping was classified when this reduction was attenuated (<10%), absent, or reversed (BP increase), in accordance with the European Society of Hypertension guidelines [2].



### *2.9. Statistical Analysis*

Continuous variables were expressed as mean ± standard deviation (SD). Normality was assessed using appropriate statistical tests, and MMP-9 values were logarithmically transformed to achieve normal distribution prior to analysis, allowing their treatment as parametric data. Categorical variables were expressed as absolute frequencies and percentages. Group comparisons for quantitative variables were performed using one-way ANOVA, followed by Tukey's post hoc test.

Pearson's correlation coefficient was calculated to assess relationships between ABPM variables and MMP-9 levels. Qualitative variables were analyzed using the chi-square or Fisher's exact test.

A descriptive and inferential comparisons between groups (NT, PH, and CHT), a multivariate analysis was performed to assess the potential influence of confounding variables on MMP-9 levels. Variables with significant differences across groups—such as age, gender, BMI, diabetes status, statin use, fasting glucose, HDL-cholesterol, triglycerides, and uric acid-–were included in a multiple linear regression model with Ln MMP-9 as the dependent variable.

Statistical significance was defined as p-value <0.05 (alpha error of 5%). All analyses were conducted using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).



## 3. Results

Table 1 presents the demographic characteristics and biochemical variables of the study participants. Hypertensive individuals demonstrated a higher mean age compared to the NT group (n = 21) and the PH group (n = 36). Additionally, diabetes was more prevalent in the CHT group (n = 44; 25%) compared to the NT group (0%; p = 0.008) and the PH group (5.5%; p = 0.01). The sample sizes differed across groups because recruitment was based on convenience sampling and clinical availability. Consequently, more controlled hypertensive patients were enrolled from the outpatient clinic, while fewer normotensive individuals met the strict inclusion criteria.

Regarding biochemical parameters, serum glucose, HDL-c, and uric acid levels showed statistically significant differences between the CHT and NT groups. The PH group also differed significantly from the NT group in terms of HDL-c, triglycerides, and uric acid levels. Furthermore, MMP-9 concentrations were higher in the PH group compared to the CHT group (log 4.74 vs. log 4.41; $p < 0.05$), as illustrated in Figure 1.



Table 2 summarizes the results obtained from ABPM. Over the 24-hour period, SBP, cSBP, and PWV were significantly elevated in the CHT group compared to the PH group. During the wakefulness period, only PWV remained significantly higher in the CHT group. In the sleep period, both peripheral (SBP, PP) and central hemodynamic parameters (cSBP, PWV) were significantly higher in the CHT group compared to the PH group.

To analyze BP variations, the participants of the three groups were categorized as dippers or non-dippers, and the variables PWV, AI75%, and MMP-9 were compared between these subgroups. PWV values were notably higher in the non-dipper group, with significant differences observed during the 24-hour and sleep periods (Figure 2 and Table 3).

Table 4 displays the correlation analysis of ABPM parameters with MMP-9 levels, which was conducted across different periods for all three groups combined. The sample size for each group was considered in this analysis to ensure accurate representation.

## 4. Discussion

The present study identified differences in peripheral and central hemodynamic variables obtained by ABPM among the PH, NT, and CHT groups. The PH group exhibited higher values than the NT group for all ABPM variables except HR and AI75%, but lower values compared to the CHT group. Regarding MMP-9, a modest positive correlation was observed solely with HR and CO during the three periods assessed by ABPM. Biochemical levels, including glycemia, LDL-c, triglycerides, and total cholesterol, were higher in PH individuals compared to CHT, though without statistical significance.

The differences in BP across groups identified by ABPM corroborate prior research comparing office BP measurements with 24-hour monitoring. These studies demonstrated a stronger association between ABPM results and CVD development [4-6]. Emerging non-invasive methods for evaluating peripheral BP alongside central hemodynamic parameters provide a comprehensive view of the arterial system and TOD. In this study, central hemodynamic parameters (cSBP, cDBP, and PWV) progressively increased from NT to PH to CHT, underscoring the clinical importance of central hemodynamic measurements. This validates concerns about pre-hypertension, as PH individuals already exhibit alterations in both peripheral and central hemodynamic parameters [14].

Although the study groups were not age-matched, the older average age in the CHT group aligns with the natural increase in hypertension prevalence with aging [15]. Hypertension is not solely a condition of elevated BP but involves an inflammatory process within the arterial wall, mediated by metalloproteinases [16,17]. Despite the established role of MMP-9 in hypertension, arterial stiffness, and CVD [11,12,18], no significant correlation was found between MMP-9 and peripheral or central hemodynamic variables monitored by ABPM, except for HR and CO.



These findings may reflect the impact of mechanical and sodium overload associated with hypertension, which activate genes responsible for elevated levels of circulating and arterial MMP-2 and MMP-9. These enzymes play a central role in the pathogenesis of hypertension [19]. Increased mechanical stress and arterial wall blood flow may lead to substantial MMP-2 and MMP-9 activity [20]. Elevated metalloproteinase levels related to BP could result from the activation of pro-inflammatory transcription factors such as NF-κB [21]. Previous studies suggest activated MMP-2 contributes to BP elevation by disrupting arterial wall homeostasis, enhancing vasoconstrictors like big endothelin-1, and reducing vasodilators such as endothelial nitric oxide synthase [22]. MMP-9 has also been implicated in reducing β2-adrenergic receptor density in arterioles, thereby raising arteriolar tone and BP [17,23].

Interestingly, MMP-9 levels were higher in PH individuals compared to CHT patients. This finding likely reflects the absence of pharmacological modulation in the PH group, where vascular remodeling and inflammatory activity remain unopposed, leading to increased extracellular matrix degradation. In contrast, antihypertensive therapy in CHT patients—particularly with agents such as candesartan, lisinopril, and lercanidipine—has been shown to attenuate MMP-9 expression by inhibiting angiotensin II–mediated pathways, reducing oxidative stress, and limiting vascular inflammation [24–28]. Thus, the lower MMP-9 levels observed in treated hypertensive patients may represent not only effective blood pressure control but also a protective effect of these drugs on vascular integrity. Supporting this interpretation, Valente et al. (2020) reported elevated MMP-9 concentrations in individuals experiencing hypertensive crises compared to those without, underscoring the enzyme's role as a marker of vascular injury and its potential clinical significance in cardiovascular conditions [29].

Although this study did not assess diet and physical activity, the biochemical findings align with evidence suggesting that lifestyle factors influence metabolic parameters (glycemia and lipids), which are linked to elevated BP [31]. PH subjects displayed higher total cholesterol, LDL-c, and triglyceride levels, as well as lower HDL-c levels compared to CHT patients. This disparity is likely attributable to the use of statins as part of the CHT group's treatment [32].

### *4.1. Limitations and Future Perspectives*

This study has several limitations. The relatively small sample size reduces statistical power and generalizability, while the cross-sectional design restricts causal inference, highlighting the need for longitudinal studies to clarify the temporal dynamics of MMP-9 and vascular remodeling [32-34]. The comparison between untreated PH and treated CHT individuals, both within the normotensive range, makes it difficult to separate the effects of disease severity, treatment, or baseline variability. A more robust design would include hypertensive patients before and after treatment or matched treated and untreated groups.



The absence of TIMP-1 evaluation, a key inhibitor of MMP-9, limits interpretation of enzymatic activity, and the lack of correlations with central hemodynamic parameters weakens its proposed role as a marker of arterial stiffness. Associations were restricted to heart rate and cardiac output, which are indirect measures. Some "controlled" hypertensive participants may not have been truly normotensive, as several central parameters remained elevated. The absence of a group with uncontrolled or newly diagnosed hypertension further restricts comparative insights.

Finally, interpretation of antihypertensive therapy as a modulator of MMP-9 remains speculative, since data on medication type, duration, and adherence were not collected. Prior studies have shown drug-specific effects on MMP-9, which were not accounted for here. Lifestyle factors such as diet, physical activity, and adherence were also not assessed, despite their known influence on vascular and metabolic outcomes. Future research should address these gaps with larger, longitudinal designs, incorporating TIMP-1 measurement, detailed pharmacological data, and lifestyle variables to better elucidate the role of MMP-9 in vascular remodeling.

## 5. Conclusion



In conclusion, this study demonstrated that serum MMP-9 levels were elevated in PH individuals compared to CHT patients, likely due to the reduction in MMP-9 associated with the use of antihypertensive drugs in the CHT group. Additionally, statins were used exclusively by CHT participants, which may have further contributed to lower MMP-9 levels through their anti-inflammatory effects and modulation of metalloproteinase expression. Furthermore, the findings reinforce differences in hemodynamic and biochemical markers among PH, NT, and CHT groups, underscoring the progressive increase in central hemodynamic parameters. Monitoring central hemodynamic variables—such as cSBP and PWV—is essential, particularly in PH individuals, as these measures provide valuable insights into early vascular changes and cardiovascular risk.

**List of Abbreviations**

- **ABPM** – Ambulatory Blood Pressure Monitoring
- **AIx75%** – Augmentation Index corrected to 75 bpm
- **BMI** – Body Mass Index
- **BP** – Blood Pressure
- **CHT** – Controlled Hypertensive
- **CO** – Cardiac Output
- **cSBP** – Central Systolic Blood Pressure
- **cDBP** – Central Diastolic Blood Pressure
- **CVD** – Cardiovascular Disease
- **DBP** – Diastolic Blood Pressure
- **EDTA** – Ethylenediaminetetraacetic Acid
- **ELISA** – Enzyme-Linked Immunosorbent Assay
- **HDL-c** – High-Density Lipoprotein Cholesterol
- **HR** – Heart Rate
- **LDL-c** – Low-Density Lipoprotein Cholesterol
- **MAP** – Mean Arterial Pressure
- **MMP-9** – Matrix Metalloproteinase-9
- **NT** – Normotensive
- **PH** – Prehypertensive
- **PP** – Pulse Pressure
- **PVR** – Peripheral Vascular Resistance
- **PWV** – Pulse Wave Velocity

- **SBP** – Systolic Blood Pressure
- **SD** – Standard Deviation
- **TIMP-1** – Tissue Inhibitor of Metalloproteinases-1
- **TOD** – Target Organ Damage

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**Conflict of Interest**

The authors declared no conflict of interest.

**Contributions of Authors statement**

José Vilela-Martin and Luciana N Cosenso-Martin participated in the study design, coordination, and data analysis and helped to draft the manuscript. Juan C Yugar-Toledo and Tatiana Palotta Minari participated in the study design, manuscript review, and performed the statistical analysis. Valquíria da Silva Lopes, Marco Antônio Vieira Silva, Kléber Aparecido de Oliveira, and Marco Aurélio de Almeida performed research. Riccardo Lacchini, José E Tanus-Santos, and Heitor Moreno participated in the review of the manuscript. All authors read and approved the final version of the manuscript.

**Data Availability Statement**

Data for this study were collected and managed using the REDCap 14.0.9 platform hosted by FUNFARME/FAMERP (Medical School of São José do Rio Preto; https://redcap.hospitaldebase.com.br). Requests for access to the data can be directed to the corresponding author, subject to privacy and ethical guidelines. To ensure confidentiality, public access to the data is not available.

**Informed Consent Statement**

All participants provided written informed consent prior to their inclusion in the study. Additionally, participants consented specifically to the publication of this research. Confidentiality and anonymity were rigorously maintained throughout the study process.

**Institutional Review Board Statement**

This study complied with the ethical principles outlined in the Declaration of Helsinki and received approval from the Human Research Ethics Committee of the Medical School of São José do Rio Preto (FAMERP) under protocol CAAE no. 07606212.5.0000.5415, nº 94.248/2012

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**Figures and Legends**

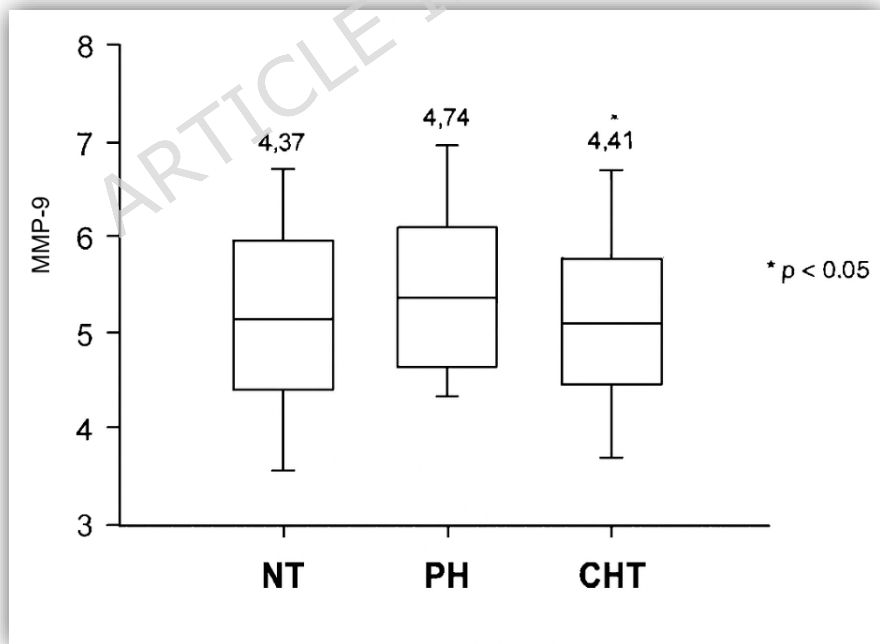
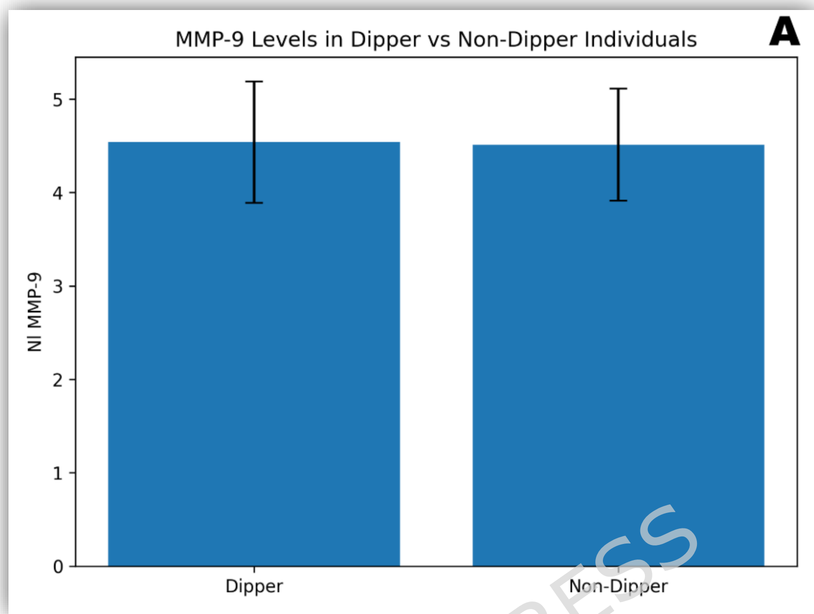
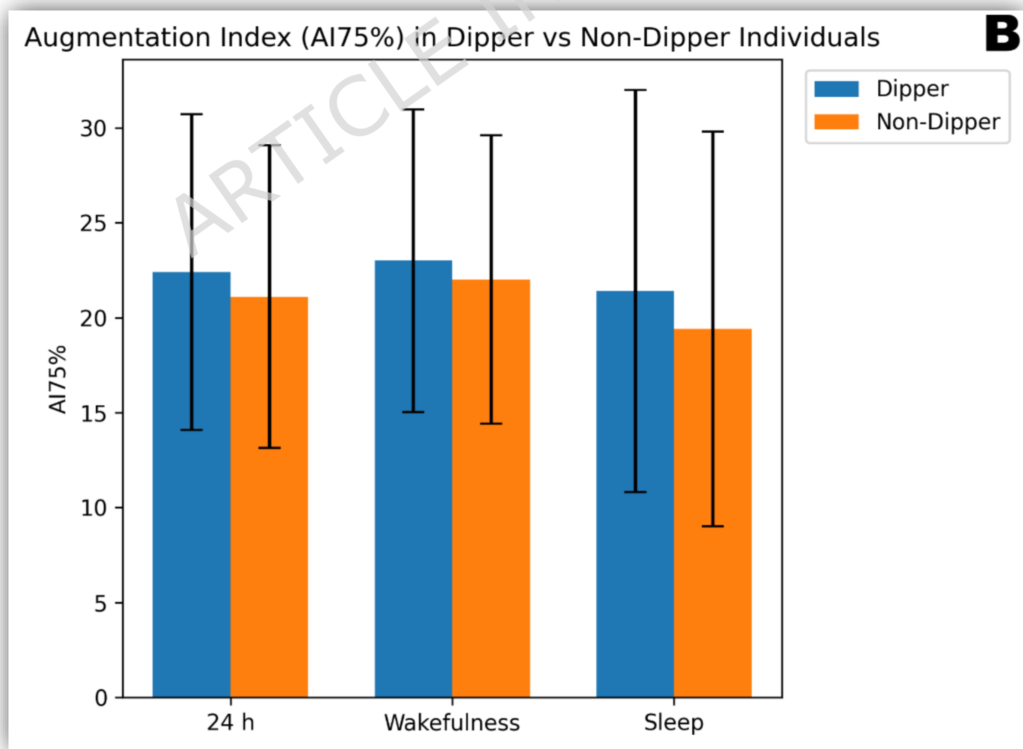



**Figure 1.** MMP-9 levels stratified by normotensive, pre-hypertensive, and controlled hypertensive groups. Nl: Negative Logarithm. NT:

normotensive group; PH: prehypertensive group; CHT: controlled hypertensive group.



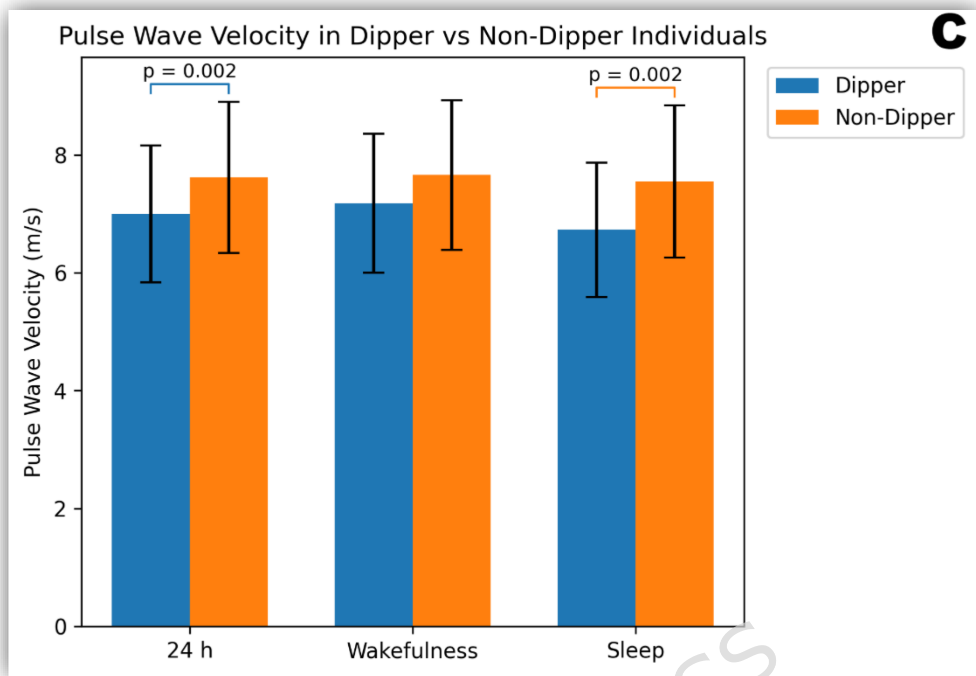



**Figure 2.** Comparison of vascular and inflammatory parameters between dipper and non-dipper individuals. Bar graphs display mean values ± standard deviation for each group. No significant difference was observed in serum levels of metalloproteinase-9 (MMP-9; mg/dL) **(A)**, augmentation index (AI75; %) during 24 hours, wakefulness, or sleep **(B).** Pulse wave velocity (PWV; m/s) was significantly higher in non-dippers during 24-hour monitoring ($p = 0.002$) and sleep ($p = 0.002$), indicating increased arterial stiffness in this group **(C).**

## Tables and Legends

**Table 1**. Clinical characteristics and biochemical variables of normotensive, pre-hypertensive, and controlled hypertensive individuals.

| **Characteristic** | **NT** | **PH** | **CHT** | ***p*-value** | | | | **Multiva Impact MMP** |
|---|---|---|---|---|---|---|---|---|
| | **(*n*=21)[a]** | **(*n*=36)[b]** | **(*n*=44)[c]** | ***(axbxc)*** | a x b | a x c | b x c | |
| Age (years) | 47.76±10.3 | 49.69±9.5 | 56.61±9.1 | 0.0008 | NS | < 0.01 | < 0.01 | NS |
| Gender (male; %) | 5; 23.8% | 24; 66.6% | 25; 56.8% | - | 0.002 | 0.01 | NS | NS |
| BMI (kg/m$^2$) | 25±5.4 | 27.8±4.5 | 29.5±4.3 | 0.001 | NS | 0.0004 | NS | NS |
| Smoker (%) | 3 (14.2%) | 7 (19.4%) | 7 (15.9%) | - | NS | NS | NS | NS |
| History of diabetes (%) | - | 2 (5.5%) | 11 (25%) | - | NS | 0.008 | 0.01 | NS |
| Skin color (White; %) | 16 (76.1%) | 32 (88.8%) | 38 (86.3%) | - | NS | NS | NS | NS |
| | | | | | | | | |
| Statins (n, %) | - | - | 14 (31.8%) | - | NS | 0.001 | 0.0001 | NS |
| | | | | | | | | |
| ***Biochemical parameters*** | | | | | | | | |
| Fasting glucose (mg/dL) | 84.9 ± 14.7 | 92.5 ± 11.5 | 103.6 ± 35 | 0.04 | NS | < 0.05 | NS | NS |
| HDL-cholesterol (mg/dL) | 60.3±16.7 | 46.1±8.9 | 48.3±11.6 | 0.001 | 0.001 | 0.001 | NS | NS |
| LDL-cholesterol (mg/dL) | 113.3±34.2 | 129.4±33.8 | 121.6±37.6 | NS | - | - | - | NS |
| Total cholesterol (mg/dL) | 198.6±28.5 | 206.8±31.1 | 201.1±41.9 | NS | - | - | - | NS |
| Triglycerides (mg/dL) | 98.7±33.1 | 163.8±85.2 | 146.7±90 | 0.02 | 0.007 | NS | NS | NS |
| Serum creatinine (mg/dL) | 0.84 ± 0.2 | 0.92 ± 0.1 | 0.94 ± 0.3 | NS | - | - | - | NS |
| Uric acid (mg/dL) | 3.9±1.1 | 6.3±1.8 | 6.3±2 | <0.0001 | 0.0001 | <0.001 | NS | NS |
| Potassium (mEq/L) | 4.2±0.4 | 4.4±0.3 | 4.3±0.5 | NS | - | - | - | NS |



NT: normotensive group; PH: prehypertensive group; CHT: controlled hypertensive group; BMI: body mass index. NS - non-significant. Values are means ± standard deviation. A multivariate analysis was performed including age, gender, BMI, diabetes status, statin use, and key laboratory parameters (e.g., fasting glucose, HDL-cholesterol, triglycerides, uric acid). None of these variables showed a significant independent effect on MMP-9 levels, indicating that the observed differences between groups were not influenced by these potential confounders.

**Table 2.** Peripheral and central hemodynamic parameters from ambulatory blood pressure monitoring (24-hour, wakefulness, and sleep) in normotensive, pre-hypertensive, and controlled hypertensive individuals

| **Period** | **NT** | **PH** | **CHT** | ***p*-value** | | | |
|---|---|---|---|---|---|---|---|
| | **(*n*=21)[a]** | **(*n*=36)[b]** | **(*n*=44)[c]** | ***(axbxc)*** | a x b | a x c | b x c |
| **24-h** | | | | | | | |
| SBP | 111.6±9.5 | 118±7.3 | 124.8±12.9 | 0.0002 | 0.02 | < 0.0001 | 0.03 |
| DBP | 69.6±10.4 | 75.3±6.4 | 78.7±10.3 | 0.003 | 0.02 | 0.0008 | NS |
| MAP | 87.9±10.4 | 94.8±6.2 | 99.8±11 | 0.0002 | 0.01 | < 0.0001 | NS |
| HR | 74.4±5.9 | 73.5±9.1 | 74.2±10.9 | NS | - | - | - |
| PP | 42.1±6.2 | 42.6±6 | 46±7.5 | 0.04 | NS | 0.02 | NS |
| cSBP | 104.9±9.5 | 109.6±7.1 | 115.9±11.6 | 0.0006 | NS | 0.0002 | 0.02 |
| cDBP | 70.6±10.8 | 76±7.3 | 80.1±10.6 | 0.003 | NS | 0.0008 | NS |
| AI75% | 22.3±7 | 19.8±7.4 | 22.6±8.9 | NS | - | - | - |
| CO | 4.0±0.3 | 4.08±0.4 | 4.2±0.5 | NS | - | - | - |
| PVR | 1.25±0.1 | 1.29±0.1 | 1.33±0.1 | NS | - | - | - |
| PWV | 6.6±1.1 | 6.9±1 | 8.1±1.2 | 0.0000 | NS | < 0.0001 | 0.0003 |
| Non-Dipper | 14 (66.6%) | 20 (55.5%) | 32 (72.7%) | | NS | NS | NS |
| | | | | | | | |
| **WAKEFULNESS** | | | | | | | |
| SBP | 115.1±8.7 | 122±7.9 | 127.5±12.4 | 0.0001 | 0.01 | < 0.0001 | NS |
| DBP | 73.2±10 | 79.5±6.9 | 81.8±9.9 | 0.005 | 0.01 | 0.001 | NS |
| MAP | 92±9.1 | 99±6.6 | 102.9±10.2 | 0.0002 | 0.004 | < 0.0001 | NS |
| HR | 78.1±6.4 | 78.1±9.4 | 78.2±11.4 | NS | - | - | - |
| PP | 41.8±6.2 | 42.5±6.3 | 45.6±8.1 | NS | - | - | - |
| cSBP | 107.4±8.7 | 112.9±7.8 | 117.8±11.2 | 0.0006 | 0.02 | 0.0001 | 0.0001 |
| cDBP | 74.9±10.5 | 81±7.4 | 84±9.9 | 0.003 | 0.02 | < 0.05 | 0.0001 |
| AI75% | 23.5±7.7 | 21±7 | 22.9±8.2 | NS | - | - | - |
| CO | 4.09±0.3 | 4.24±0.3 | 4.3±0.4 | NS | - | - | - |
| PVR | 1.28±0.1 | 1.31±0.1 | 1.33±0.1 | NS | - | - | - |
| PWV | 6.7±1.1 | 7.1±1 | 8.1±1.1 | < 0.0001 | NS | < 0.05 | < 0.05 |
| | | | | | | | |
| **SLEEP** | | | | | | | |
| SBP | 106±10.8 | 111.1±8.3 | 120.3±14.9 | 0.0002 | NS | < 0.01 | < 0.01 |
| DBP | 63.5±11.6 | 68.4±7.2 | 73.2±12.3 | 0.003 | NS | < 0.05 | NS |
| MAP | 83±10.5 | 87.9±7 | 94.8±13 | 0.005 | NS | < 0.01 | < 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HR | 68±7 | 65.9±9.8 | 67.3±10.5 | NS | - | - | - |
| PP | 42.4±7.1 | 42.7±6.5 | 47±7.4 | 0.01 | NS | 0.02 | < 0.05 |
| cSBP | 101.7±11.3 | 104.5±8.2 | 113.3±13.9 | 0.001 | NS | < 0.01 | < 0.05 |
| cDBP | 64.7±11.9 | 69.1±7.2 | 74.1±12.6 | 0.006 | NS | < 0.01 | 0.0001 |
| AI75% | 20.6±9 | 17.9±9.6 | 21.6±11.6 | NS | - | - | - |
| CO | 3.84±0.6 | 3.82±0.5 | 4.0±0.6 | NS | - | - | - |
| PVR | 1.22±0.1 | 1.27±0.1 | 1.31±0.2 | NS | - | - | - |
| PWV | 6.5±1.1 | 6.8±1 | 7.9±1.1 | < 0.0001 | 0.0001 | < 0.01 | < 0.01 |

NT: normotensive group; PH: prehypertensive group; CHT: controlled hypertensive group; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean artery pressure; HR: Heart rate; PP: Pulse pressure; cSBP: Central systolic blood pressure; cDBP: Central diastolic blood pressure; AI75%: Augmentation index; CO: Cardiac output; PVR: Peripheral vascular resistance; PWV: Pulse wave velocity. NS - non-significant. Values are means ± standard deviation

**Table 3**. MMP-9 levels, pulse wave velocity, and augmentation index in dipper and non-dipper individuals.

| | **Dipper (n = 35)** | **Non-Dipper (n = 66)** | ***p*-value** |
|---|---|---|---|
| **Nl MMP-9** | 4.54 ± 0.65 | 4.51 ± 0.6 | NS |
| **PWV 24 h** | 7 ± 1.16 | 7.62 ± 1.28 | 0.002 |
| **PWV wakefulness** | 7.18 ± 1.18 | 7.66 ± 1.27 | NS |
| **PWV sleep** | 6.73 ± 1.14 | 7.55 ± 1.29 | 0.002 |
| **AI75% 24 h** | 22.4 ± 8.32 | 21.1 ± 7.97 | NS |
| **AI75% wakefulness** | 23 ± 7.97 | 22 ± 7.6 | NS |
| **AI75% sleep** | 21.4 ± 10.6 | 19.4 ± 10.4 | NS |

Nl: Negative Logarithm; MMP-9: metalloproteinase-9; PWV: Pulse wave velocity; AI75%: augmentation index corrected for a heart rate at 75 bpm

**Table 4.** Correlation of MMP-9 levels with variables from ambulatory blood pressure monitoring (24-hour, wakefulness, and sleep) in normotensive, pre-hypertensive, and controlled hypertensive groups.

| Period | Variable | r | p-value |
|---|---|---|---|
| 24h | SBP | 0.099 | NS |
| | DBP | 0.088 | NS |
| | MAP | 0.096 | NS |
| | HR | 0.222 | 0.015 |
| | PP | 0.046 | NS |
| | cSBP | 0.102 | NS |
| | cDBP | 0.094 | NS |
| | AI75% | -0.024 | NS |
| | CO | 0.199 | 0.030 |
| | PVR | -0.100 | NS |
| | PWV | -0.109 | NS |
| Wakefulness | SBP | 0.087 | NS |
| | DBP | 0.063 | NS |
| | MAP | 0.082 | NS |
| | HR | 0.220 | 0.016 |
| | PP | 0.057 | NS |
| | cSBP | 0.080 | NS |
| | cDBP | 0.059 | NS |
| | AI75% | -0.004 | NS |
| | CO | 0.247 | 0.007 |
| | PVR | -0.142 | NS |
| | PWV | -0.110 | NS |
| Sleep | SBP | 0.106 | NS |
| | DBP | 0.110 | NS |
| | MAP | 0.113 | NS |
| | HR | 0.217 | 0.018 |
| | PP | 0.033 | NS |
| | cSBP | 0.112 | NS |
| | cDBP | 0.112 | NS |
| | AI75% | -0.025 | NS |
| | CO | 0.204 | 0.026 |
| | PVR | -0.069 | NS |
| | PWV | -0.001 | NS |

ABPM: Ambulatory blood pressure monitoring; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean artery pressure; HR: Heart rate; PP: Pulse pressure; cSBP: Central systolic blood pressure; cDBP: Central diastolic blood pressure; AI75%: augmentation index corrected for a heart rate at 75 bpm; CO: Cardiac output; PVR: Peripheral vascular resistance;

PWV: Pulse wave velocity; NS - non-significant