

The Residual Hemodynamic Gap in Clinical Practice: A Comparative Study Using Ambulatory Blood Pressure Monitoring

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Abstract

Hypertension management relies heavily on mean blood pressure (BP) targets. However, a "residual hemodynamic gap"—persistent advanced vascular and chronobiological abnormalities despite controlled average BP—remains a clinical challenge. An observational study characterized this gap in 540 subjects (169 normotensives; 371 hypertensives across monotherapy, dual, and triple regimens) using 24-hour Ambulatory Blood Pressure Monitoring (ABPM). Evaluated parameters included pulse pressure (PP), systolic load, variability, and circadian patterns. A Multivariate Analysis of Covariance (MANCOVA) within the hypertensive cohort assessed the impact of sex, diabetes, and smoking, adjusting for age. Hypertensive patients exhibited a profound residual hemodynamic gap compared to controls. Pathological circadian patterns predominated, with non-dipper (32–42%) and riser (19–29%) profiles being highly prevalent ($p = 0.011$). Multiple linear regression identified age as an independent predictor of elevated PP ($\beta = 0.20$; $p < 0.001$) and arterial stiffness ($\beta = 0.002$; $p = 0.015$). In the MANCOVA model, age emerged as the dominant independent covariate driving the global hemodynamic profile (Pillai's Trace = 0.107; $p < 0.001$). After controlling for age, no significant multivariate main effects were observed for sex (Pillai's Trace = 0.008; $p = 0.600$), diabetes (Pillai's Trace = 0.003; $p = 0.891$), or smoking status (Pillai's Trace = 0.017; $p = 0.196$). This study concludes that a substantial residual hemodynamic gap persists in treated hypertensive patients. Hypertension success metrics must shift from simple average BP control toward assessing and targeting these advanced, residual hemodynamic abnormalities via ABPM, to achieve true cardiovascular protection.

Introduction

Hypertension remains the most critical global public health challenge and the leading modifiable risk factor for cardiovascular morbidity and mortality. While recent European Society of Hypertension (ESH) guidelines advocate for more ambitious therapeutic targets, traditional evaluation methods often fall short. Relying solely on static office blood pressure (BP) measurements fails to capture the full complexity of a patient's real-world hemodynamic profile, often leading to a false sense of clinical security [1, 2]. Consequently, 24-hour Ambulatory Blood Pressure Monitoring (ABPM) has established itself as an indispensable precision tool for clinical follow-up, offering dynamic, real-world insights into BP variability and circadian patterns while demonstrating a vastly superior sensitivity to predict cardiovascular events compared to office metrics [2–5].

Beyond absolute 24-hour averages, target organ damage is profoundly driven by advanced hemodynamic parameters. Systolic blood pressure load and systolic variability are strong independent predictors of cardiovascular and cerebrovascular events, while markers like pulse pressure (PP) and the Ambulatory Arterial Stiffness Index (AASI) offer robust indirect measures of vascular remodeling and loss of arterial compliance [1, 6–7]. Although current clinical guidelines strongly endorse the early implementation of fixed-dose combination therapies to achieve rapid, multi-pathway control and stabilize inter-individual variability [2, 8–9], a critical clinical paradox persists: current treatments frequently fail to restore comprehensive hemodynamic and vascular normality. Advanced parameters like arterial

stiffness, systolic variability, and pathological circadian profiles (e.g., non-dipper and riser patterns) often remain significantly altered regardless of whether a patient receives monotherapy or complex combination regimens [3, 10].

This discrepancy defines the "residual hemodynamic gap"—a state where, despite achieving averaged numerical BP targets, persistent subclinical abnormalities maintain an elevated cardiovascular risk, potentially conditioned by underlying endothelial damage [11]. To analyze this gap, at least a detailed assessment of chronic barometric stress through systolic load and subclinical arterial damage using AASI is required [7, 12]. Furthermore, recent real-world evidence indicates that a significant proportion of stable patients on long-term monotherapy can achieve ABPM control rates comparable to those under dual or triple combination therapies [10]. These findings highlight the necessity of individualizing therapy and using ABPM to expose hidden tensional deficits that are completely invisible to conventional clinical practice [10].

To address these challenges, this study aims to evaluate the control rates of average BP alongside advanced hemodynamic parameters via ABPM, directly comparing normotensive controls against a hypertensive cohort stratified by their specific therapeutic regimens. By exploring these dynamics, we seek to determine the true impact of different antihypertensive schemes on comprehensive vascular health beyond mere arithmetic averages, providing data to establish more realistic, individualized hemodynamic targets in daily clinical practice.

METHODS

An analytical observational study was conducted, including a sample of normotensive and hypertensive patients evaluated by Ambulatory Blood Pressure Monitoring (ABPM) at a tertiary care center. The study period spanned from 2008 to 2026. Data were extracted from the database of the Research Group of the Chair of Medical Clinic and Therapeutics A.

To ensure analytical reliability, the study only included ABPM records with at least 48 successful measurements over 24 hours or 70% valid readings [4]. Patients with documented cardiac arrhythmias, especially atrial fibrillation, as well as pregnant patients, were excluded. Only patients who maintained their pharmacological regimen, without changes, for at least four weeks before the study were included. This ensured the evaluation of antihypertensive agents during their stable phase and avoided biases from initial dosage adjustments. The sample size reflected the available cases meeting these criteria.

The sample size represents a strictly refined consecutive cohort accrued over 18 years, rigorously selected to ensure high-quality ABPM recordings.

Blood pressure control by ABPM was defined as a 24-hour average below 130/80 mmHg, in accordance with the 2024 European Society of Hypertension (ESH) ABPM guidelines [13].

Evaluation of Vascular Health Parameters. Hemodynamic and vascular health parameters derived from ABPM were defined and categorized as follows:

- **Systolic Load:** Quantified as the percentage of systolic blood pressure readings exceeding normal daytime (≥ 135 mmHg) and nighttime (≥ 120 mmHg) thresholds, categorized into normal ($< 20\%$), intermediate ($20\text{--}40\%$), and high load tiers ($> 40\%$).
- **Systolic Variability:** Evaluated using the standard deviation (SD) of 24-hour systolic blood pressure values, establishing a maximum cutoff threshold of 15 mmHg for optimal control.
- **Ambulatory Arterial Stiffness Index (AASI):** Calculated from the regression slope of diastolic on systolic blood pressure readings during the 24-hour ambulatory monitoring period, reflecting arterial compliance and large-artery stiffness.
- **Circadian Pattern:** Determined by the nocturnal blood pressure drop relative to daytime values, classifying patients into dipper (reduction between 10% and 20%), non-dipper (blunted reduction between 0% and 10%), and riser (paradoxical nocturnal blood pressure elevation exceeding daytime values) phenotypes.

All procedures were performed in compliance with the ethical guidelines of the Declaration of Helsinki and the principles of the Declaration of Taipei. The original study protocol was reviewed and approved by the Research Coordination of the Faculty of Medicine at the Central University of Venezuela, protocol number C.I. 076/2024. Written informed consent was obtained from all participants before their inclusion in the database [10].

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation ($X \pm SD$), and categorical variables as absolute frequencies and percentages. The normal distribution of the dependent variables was assessed using the Shapiro-Wilk test. Data processing and statistical analyses were performed using Real Statistics Resource software V 9.7.6 and IBM SPSS Statistics software V 27.0.1.0.

An independent-samples t-test was used to compare the overall means of systolic and diastolic blood pressure, as well as the evaluated advanced hemodynamic parameters, between the treated hypertensive cohort and the normotensive control group. To compare the advanced hemodynamic parameters (systolic load, variability, pulse pressure, and AASI) across the different antihypertensive regimens (monotherapy, dual therapy, and triple therapy), a one-way analysis of variance (ANOVA) was executed. Differences in the frequencies of circadian patterns and the prevalence of normal parameters between groups were evaluated using Pearson's chi-squared (χ^2) test.

To identify the independent predictors for each specific hemodynamic parameter, multiple linear regression models were constructed, adjusting for age, sex, presence of diabetes, and smoking status. Unstandardized β coefficients with their respective 95% confidence intervals (95% CI) were calculated. Model goodness-of-fit was evaluated using the adjusted R^2 and the global F-test of significance. Model

diagnostics included multicollinearity assessment via the Variance Inflation Factor (VIF), accepting values close to 1.0 as indicative of the complete absence of collinearity.

Additionally, a multivariate analysis of covariance (MANCOVA) was executed to determine the global effect of fixed factors (sex, diabetes, and smoking status) and their interaction terms on the collective set of dependent hemodynamic variables, while simultaneously controlling for the influence of age as a continuous covariate. The global significance of the multivariate model was determined using Pillai's Trace statistic, given its established methodological robustness against heteroscedasticity in large samples.

For all statistical tests, a p-value < 0.05 was considered statistically significant.

RESULTS

The study included 540 patients, with a mean age of 54.6 ± 15.8 years. There was a marked predominance of females (65%). Regarding clinical profile, 69% (n = 371) had a diagnosis of hypertension, while 31% (n = 169) were normotensive. The prevalence of diabetes was 16%, and 20% reported current smoking habits. Among hypertensive patients, the most common therapeutic regimen was monotherapy (28%), followed by dual therapy (23%) and triple therapy (11%). The most frequently used class of drugs was angiotensin receptor blockers (ARBs, 64%), followed by calcium channel blockers (33%). (Table 1).

Table 1
Epidemiological characteristics of patients who
underwent 24-hour ABPM

Characteristics	Value
Total (n)	540
Gender	
Male n (%)	188 (35)
Female n (%)	352 (65)
Age (years, X ± SD)	54.6 ± 15.8
Systolic blood pressure (mmHg, X ± SD)	124 ± 15.3
Diastolic blood pressure (mmHg, X ± SD)	74 ± 10.8
Diagnosis of hypertension	
Hypertension n (%)	371 (69)
Normotensive n (%)	169 (31)
Smoking habit	
Yes n (%)	106 (20)
No n (%)	417 (77)
Diabetes	87 (16)
Therapeutic regimen	
Monotherapy n (%)	151 (28)
Dual therapy n (%)	123 (23)
Triple therapy n (%)	58 (11)
Use of antihypertensive class	
ACEI n (%)	35 (9)
ARBs n (%)	237 (64)
Thiazides n (%)	79 (21)
Calcium channel blockers n (%)	124 (33)
β-blockers n (%)	84 (23)
α-agonist n (%)	10 (3)

Angiotensin-converting enzyme inhibitors.

BRA: Angiotensin receptor blockers

Table 2 demonstrates the clinical distinction between these groups using Student’s t-test: normotensive patients exhibited significantly lower systolic (118 ± 14.34 mmHg) and diastolic blood pressure values (71 ± 10.94 mmHg) compared to the means of treated hypertensive patients (127 ± 14.99 mmHg and 75 ± 10.58 mmHg, respectively; $p < 0.001$). This finding confirms the validity of the clinical stratification, demonstrating that the treatment groups are effectively composed of patients with a true and established hypertensive phenotype, clearly differentiating them from the normotensive control cohort and providing pathophysiological soundness to subsequent comparisons.

Table 2
Mean blood pressure via ABPM between hypertensive and normotensive.

Blood pressure (mmHg)	Hypertensive (X ± SD)	Normotensive (X ± SD)	p-value*
Systolic BP in 24 hours	127 ± 14.99	118 ± 14.34	< 0.001
Diastolic BP in 24 hours	75 ± 10.58	71 ± 10.94	< 0.001

BP: Blood pressure.

* Student's t-test, two-tailed, unpaired.

Table 3
Multivariate analysis — Average systolic blood pressure over 24 hours (multiple linear regression).

Variable	Adjusted β Coefficient (mmHg) (95% CI)			p
	Monotherapy	Dual therapy	Triple therapy	
Gender	-3.33 (-8.15 to 1.55)	4.81 (-1.19 to 10.81)	-0.44 (-9.57 to 8.69)	0.095
Age (years)	0.02 (-0.13 to 0.17)	0.06 (-0.16 to 0.29)	0.03 (-0.25 to 0.30)	0.090
Diabetes	5.55 (-0.17 to 11.27)	4.41 (-3.02 to 11.84)	4.27 (-6.58 to 15.12)	0.236
Smoking status	0.68 (-4.94 to 6.29)	1.64 (-5.31 to 8.59)	5.86 (-4.42 to 16.14)	0.088

Multivariable linear regression of 24-hour systolic blood pressure (mmHg). Coefficients were adjusted for the 24-hour systolic blood pressure means. Models were stratified by treatment subgroups (monotherapy, n = 151; dual therapy, n = 123; triple therapy, n = 58). Predictors included age (years), sex (male vs. female), diabetes (yes/no), and smoking status (yes/no). The p-values correspond to the joint tests for each predictor (F-test, comparing the full model with the adjusted model). Adjusted R² (overall) = 0.074; adjusted R² (monotherapy) = 0.004; adjusted R² (dual therapy) = 0.006; adjusted R² (triple therapy) = -0.042.

When analyzing the mean systolic blood pressure (Table 3), it was observed that after adjusting for age, sex, diabetes, and smoking status, none of these factors acted as a statistically significant independent predictor ($p > 0.05$). This suggests that the control of average blood pressure values in this sample did not depend on isolated biological characteristics, but rather possibly on treatment adherence or individual response to therapy. However, the low goodness-of-fit (R^2) demonstrates that these predictors alone are insufficient to explain the model.

Table 4
Average blood pressure obtained by ABPM according to antihypertensive treatment.

Blood pressure	Monotherapy	Dual therapy	Triple therapy	ANOVA*
(mmHg)	(X ± SD)	(X ± SD)	(X ± SD)	p-value
Systolic BP in 24 hours	126 ± 14.22	126 ± 15.57	128 ± 15.22	0.551
Diastolic BP in 24 hours	74 ± 9.58	75 ± 11.35	75 ± 10.11	0.628

BP: Blood pressure.

* ANOVA with one-way analysis of variance.

Table 5
Circadian pattern by ABPM according to the use of antihypertensive treatment.

Circadian pattern	Normotensive	Monotherapy	Dual therapy	Triple therapy	χ^2 *
	n(%)	n (%)	n (%)	n (%)	p-value
Dipper	73(43)	47 (31)	38 (31)	20 (36)	0.011
Non dipper	67(40)	54 (42)	50 (41)	18 (32)	
Riser	15(9)	28 (19)	29 (24)	16 (29)	
Over dipper	14(8)	12 (8)	6 (5)	2 (4)	

* The intergroup χ^2 calculation compares the normotensive control group against the different hypertensive subgroups stratified by their specific antihypertensive regimens (monotherapy, dual therapy, and triple therapy). The intragroup χ^2 analysis within the hypertensive cohort yielded a value of $p = 0.518$.

The different treatment intensity levels (monotherapy, dual therapy, and triple therapy) were compared. Results from Tables 4 and 5 demonstrate that no significant differences existed in systolic ($p = 0.551$) or diastolic ($p = 0.628$) blood pressure levels across the regimens, suggesting that any therapeutic escalation was equally effective in reaching standard blood pressure targets. Table 5 and Fig. 1 show that, regarding circadian patterns, no intragroup differences were observed among the hypertensive subgroups. However, comparison with normotensive controls reveals that the dipper pattern clearly

predominated in the healthy cohort alongside a low frequency of riser profiles. Conversely, the non-dipper pattern predominated, and a higher prevalence of the riser profile was observed within the treated hypertensive groups ($p = 0.011$), underscoring a substantial gap in the comprehensive control of hypertensive patients when referenced against individuals with normal blood pressure.

Table 6
Behavior of hemodynamic parameters, obtained by ABPM, according to the antihypertensive treatment group.

Parameter	Monotherapy	Dual therapy	Triple therapy	ANOVA*
	(X ± SD)	(X ± SD)	(X ± SD)	p-value
Systolic load (%)	28 ± 26.39	32 ± 28.01	35 ± 28.13	0.434
Systolic variability (mmHg)	14.6 ± 4.16	15.0 ± 4.38	15.1 ± 3.68	0.608
Pulse pressure (mmHg)	53 ± 11.21	52 ± 10.55	54 ± 11,81	0.650
AASI	0.44 ± 0.19	0.44 ± 0.21	0.42 ± 0,22	0.902

* ANOVA with one-way analysis of variance.

The intragroup homogeneity among hypertensive patients, regardless of the therapeutic regimen received, extended to advanced hemodynamic parameters. This included pulse pressure, which showed no significant variations between groups ($p = 0.650$), as well as arterial stiffness and variability, as the AASI ($p = 0.902$) and systolic variability ($p = 0.608$) remained stable irrespective of the number of drugs. Regarding systolic load, an upward trend was observed (28% in monotherapy vs. 35% in triple therapy), though it did not reach statistical significance ($p = 0.434$) (Table 6). Furthermore, the logistic regression analysis (Fig. 2) revealed no significant differences in the odds ratio values when comparing monotherapy against combination strategies (dual and triple therapy).

Table 7
Hemodynamic parameters below the threshold, obtained by ABPM according to the use of antihypertensive treatment.

Parameter	Normotensive	Monotherapy	Dual therapy	Triple therapy	χ^2*
	n(%)	n (%)	n (%)	n (%)	p-value
Low systolic load	107(67)	75 (47)	61 (50)	23 (41)	< 0.001
Systolic variability	94(59)	87 (58)	72 (59)	30 (54)	< 0.001
Pulse pressure	134(84)	95 (63)	74 (60)	32 (57)	< 0.001
AASI low	122(77)	97 (68)	76 (65)	39 (74)	0.026

*The intergroup χ^2 calculation compares the normotensive control group against the different hypertensive subgroups stratified by their specific antihypertensive regimens (monotherapy, dual

therapy, and triple therapy). Low/normal parameter thresholds were defined as a systolic load $\leq 20\%$, systolic variability ≤ 15 mmHg, pulse pressure ≤ 53 mmHg, and a low AASI < 0.5 .

Table 8
Average values of hemodynamic parameters, obtained by ABPM between normotensive and hypertensive patients.

Parameter	Normotensive	Hipertensive	p-value*
	(X $\pm$ DE)	(X $\pm$ DE)	
Systolic load (%)	17 $\pm$ 19.84	30 $\pm$ 26.44	< 0.001
Systolic variability (mmHg)	15 $\pm$ 5.13	15 $\pm$ 3.87	0.383
Pulse pressure (mmHg)	48 $\pm$ 7.76	53 $\pm$ 11.04	< 0.001
AASI	0.37 $\pm$ 0.17	0,44 $\pm$ 0.20	< 0.001

* Intergroup independent-samples t-test comparing normotensive controls vs. hypertensive patients, regardless of the antihypertensive regimen received. When performing independent-samples t-tests comparing normotensive controls against specific antihypertensive treatment regimens, similar results were obtained: Normotensive vs. Monotherapy ($p < 0.001$), Normotensive vs. Dual therapy ($p < 0.001$), and Normotensive vs. Triple therapy ($p < 0.001$) for systolic load, pulse pressure, and AASI. Conversely, systolic variability analysis yielded: Normotensive vs. Monotherapy ($p = 0.233$), Normotensive vs. Dual therapy ($p = 0.604$), and Normotensive vs. Triple therapy ($p = 0.215$).

Additionally, data from Tables 7 and 8 and Fig. 3 demonstrate that while no intragroup differences exist among the hypertensive subgroups (monotherapy, dual therapy, and triple therapy) across the remaining hemodynamic patterns, a clear distinction emerges when compared to normotensive controls. The normotensive group more frequently exhibited lower or normal values for systolic load ($\leq 20\%$), systolic variability (≤ 15 mmHg), pulse pressure (≤ 53 mmHg), and AASI (< 0.5). Furthermore, when analyzed as continuous variables, the means for systolic load, pulse pressure, and AASI showed highly significant differences between hypertensive patients—regardless of their specific antihypertensive regimen subgroup—and normotensive controls ($p < 0.001$). Conversely, no such difference was observed for systolic variability, where mean values remained remarkably similar in both intergroup and intragroup analyses (15 $\pm$ 5.13 mmHg for normotensives vs. 15 $\pm$ 3.87 mmHg for hypertensives; $p = 0.383$). This demonstrates that target normal values are rarely achieved for the majority of advanced ABPM parameters, illustrating another critical dimension of the residual hemodynamic gap.

Table 9

Multivariate analysis – Hemodynamic parameters obtained by ABPM among patients with hypertension (multiple linear regression).

Dependent variable	Adjusted β Coefficient (mmHg) (95% CI)				
	Age	Gender	Diabetes	Smoking status	p-value
Systolic load	0.17 (-0.02 to 0.35)	-1.14 (-4.68 to 6.96)	6.01 (-1.01 to 13.04)	6.66 (0.02 to 13.31)	0.030
Systolic variability	0.03 (0.005 to 0.06)	0.06 (-0.84 to 0.95)	0.28 (-0.79 to 1.37)	-0.27 (-1.29 to 0.74)	0.174
Pulse pressure	0.20 (0.13 to 0.27)	-1.22 (-3.45 to 1.01)	2.68 (-0.004 to 5.40)	1.91 (-0.63 to 4.46)	< 0.001
AASI	0.002 (0.0003 to 0.003)	0.02 (-0.02 to 0.07)	0.04 (-0.01 to 0.09)	0.004 (-0.05 to 0.05)	0.044
Circadian Pattern	-0.004 (-0.007 to -0.0002)	0.07 (-0.04 to 0.17)	-0.02 (-0.14 to 0.11)	0.04 (-0.08 to 0.16)	0.122

Multivariable linear regression of hemodynamic parameters obtained via ABPM. Coefficients were adjusted for each specific parameter: overall systolic load, overall systolic variability, overall pulse pressure, and Ambulatory Arterial Stiffness Index (AASI), as well as by circadian pattern (Dipper+Overdipper vs. Riser + Non-dipper). Models were simultaneously adjusted for age (years), sex (male vs. female), diabetes (yes/no), and smoking status (yes/no). The p-values in the right column represent the global significance of the model (F-test). Hypertensive patients on both monotherapy and combination therapy were included in the models. Adjusted R^2 (circadian pattern) = 0.009; adjusted R^2 (pulse pressure) = 0.09; adjusted R^2 (systolic variability) = 0.006; adjusted R^2 (systolic load) = 0.018; adjusted R^2 (AASI) = 0.017. VIF values for all models were < 1.05, ruling out multicollinearity.

The multivariable analysis identified age as the most relevant determinant for hemodynamic impairment. It was observed that for each one-year increase in age, pulse pressure increased by 0.20 mmHg ($p < 0.001$), the ambulatory arterial stiffness index (AASI) increased by 0.002 units ($p = 0.015$), and systolic variability increased by 0.03 mmHg ($p = 0.019$) after adjusting for the remaining covariates.

Preliminary multivariate analysis was conducted to evaluate the influence of clinical factors on the hemodynamic profile. To account for the potential confounding effect of age, a Multivariate Analysis of Covariance (MANCOVA) was performed, using age as a covariate. The assumption of homogeneity of covariance matrices was evaluated using Box's M test ($p = 0.042$), and consequently, Pillai's Trace was selected as the robust multivariate test statistic.

The MANCOVA revealed that age was a significant independent covariate influencing the global hemodynamic profile (Pillai's Trace = 0.107; $F(4, 359) = 10.785$; $p < 0.001$; $\eta_p^2 = 0.107$). Conversely, after adjusting for age, no significant differences were observed among treatment subgroups regarding the

measured hemodynamic parameters, including Sex (Pillai's Trace = 0.008; $F(4, 359) = 0.689$; $p = 0.600$), Diabetes (Pillai's Trace = 0.003; $F(4, 359) = 0.280$; $p = 0.891$), and Smoking status (Pillai's Trace = 0.017; $F(4, 359) = 1.521$; $p = 0.196$). These results indicate that the observed hemodynamic impairment is a consistent phenomenon across treatment subgroups, independent of their clinical characteristics, with age being the primary modulating factor of the advanced hemodynamic parameters.

The intergroup χ^2 calculation corresponds to a p -value = 0.011; however, for the intragroup χ^2 calculation among hypertensive patients, the p -value is 0.518. No significant overall differences were found between the antihypertensive treatment groups in the multivariate analysis (MANOVA), Wilks L = 0.978; $p = 0.088$.

Odds ratio (OR) with 95% confidence interval (CI) for evaluating the control of hemodynamic parameters (AASI, pulse pressure, systolic variability, and systolic load), comparing monotherapy (reference) with combination therapy (dual and triple therapy). Vertical line OR = 1.0.

No significant overall differences were found between the antihypertensive treatment groups in the multivariate analysis (MANOVA), Wilks L = 0.978; $p = 0.088$.

DISCUSSION

The cornerstone of modern antihypertensive therapeutics must move beyond algorithmic normalization of blood pressure to embrace a personalized medicine approach, moving away from the "one size fits all" paradigm [9]. Although evidence from current international guidelines and consensus demonstrates clear benefits for patients initiating early combination antihypertensive therapy, recent findings from our research group suggest that in certain subsets, such as stable patients on prolonged monotherapy, this strategy is not mandatory without a rational evaluation via Ambulatory Blood Pressure Monitoring (ABPM). However, this analysis requires evaluating other variables that may account for the unequal impact observed across phenotypes and vascular health parameters [10, 14]. In clinical practice, a significant percentage of patients maintain effective ambulatory control on monotherapy regimens, compelling us to exercise analytical caution to avoid therapeutic inertia guided purely by office-based averages [2]. Clinical judgment must focus on treating the patient and their vascular biography rather than simply a mean value, making it necessary to integrate ABPM as a tool for pathophysiological diagnosis rather than a mere event counter and average calculator. The analysis and integration of these data allow for the estimation of additional damage and prognosis to achieve blood pressure goals. This is also reflected in current clinical evidence in hypertension, as shown in the most recent therapeutic guidelines, which suggest evaluating vascular health through Pulse Wave Velocity (PWV), Ankle-Brachial Index (ABI), and Intima-Media Thickness (IMT), among others. Nevertheless, through ABPM we obtain markers (Load, Variability, AASI, Circadian Pattern) that allow us to evaluate this condition, providing abundant information regarding their specific cutoff points and normality values, even though the therapeutic target in patients presenting with these altered parameters at the time of hypertension diagnosis remains unknown [9, 14–17].

Taking these considerations into account and observing our findings, we could well be facing an effect that demonstrates a gap, considering current criteria for control or therapeutic targets based solely on ABPM averages or office readings and the behavior of the remaining parameters in the study. Therefore, to close this gap between numerical control and real target-organ protection, we propose an interpretation based on the "residual hemodynamic gap" and considering the probable phenotypes of the hypertensive patient. A nocturnal diastolic blood pressure (DBP) greater than 70 mmHg may reveal a systemic vascular resistance gap that requires adjustments in the blockade of the renin-angiotensin-aldosterone system. On the other hand, a 24-hour average heart rate (HR) greater than 75 bpm may well indicate a cardiac output gap mediated by sympathetic hyperactivity, whereas a pulse pressure (PP) greater than 53 mmHg or an ambulatory arterial stiffness index (AASI) greater than 0.50 would define the stiffness gap. This distinction is vital, as it allows for individualized therapy: while elevated HR suggests the use of beta-blockers, marked stiffness demands optimizing the combination of ACE inhibitors or ARBs with calcium channel blockers [9–10, 14].

It is essential to recognize that arterial stiffness and pulse pressure are high-prognostic-value parameters that may reflect marked inertia against conventional pharmacological treatment. In our study, no significant differences were observed in AASI ($p = 0.902$) or PP ($p = 0.650$) when comparing the effect of monotherapy against various combination therapies. It is critical to emphasize that, given the cross-sectional design of this study, this homogeneity does not imply clinical inefficacy of multiple drug regimens but rather reflects a confounding by indication bias. Patients requiring dual or triple therapy inherently present with more severe hypertension phenotypes, longer disease duration, and previously established structural and endothelial vascular remodeling that is difficult to reverse solely through numerical escalation of pharmacological load. In the study by Nolde et al. (2023), which evaluated the impact of Irbesartan monotherapy versus low-dose quadruple therapy in treatment-naïve hypertensive patients, a more pronounced and stable decrease over time was evidenced with multi-drug therapy, along with a greater reduction in parameters such as systolic load, systolic variability, and circadian pattern; however, the values obtained remained higher than expected in a normotensive patient. Regarding systolic load, even under quadruple therapy, the average systolic load was 27.7% (intermediate load), systolic variability was 15.1 mmHg for patients on irbesartan and 14.6 mmHg for those on quadruple therapy, and regarding the circadian pattern, both groups showed an average systolic blood pressure decrease of 11 mmHg (corresponding to a dipper pattern); these results are similar to those obtained in our work [10, 11].

In our case, regarding global systolic variability, although the average absolute value in each of the compared groups relative to normotensive patients showed no significant difference between arithmetic means, differences were observed in relative frequency when achieving values below the maximum cutoff (15 mmHg). This apparent disparity is associated with the fact that patients on triple therapy constituted the subgroup with the lowest frequency of control for this parameter. The latter could be associated with the fact that this group frequently correlates with hard-to-control hypertension or resistant hypertension.

Furthermore, it is important to consider that these vascular health parameters may be influenced by other confounding variables, which can specifically affect endothelial impairment within each subgroup. The multivariate analysis conducted reflects this evaluation, showing that arterial stiffness, pulse pressure, and systolic variability are independently influenced by age (likely attributable to vascular aging itself). Although these data align with previous findings, such as those by Cerquoni et al. (2026), they must be interpreted with a clinical perspective: the goodness-of-fit calculation for the multivariate model remains modest (e.g., adjusted R^2 of 9% for pulse pressure). This conclusively demonstrates that while age intervenes significantly in the outcome, more than 90% of the variance in the residual hemodynamic gap depends on other unmeasured covariates (such as genetic factors, disease duration, or underlying neurohumoral alterations), underscoring the multifactorial nature of advanced vascular damage [10].

The findings of this study should be interpreted in the light of several methodological limitations. First, the observational and cross-sectional design precludes establishing direct causality or evaluating the longitudinal trajectory and temporal reversibility of hemodynamic parameters following the initiation of various therapeutic regimens. Second, although strict inclusion criteria were applied to ensure high-quality ABPM recordings, the extended data collection period (2008–2026) encompasses multiple updates in international clinical practice guidelines, which may have introduced subtle heterogeneity in historical dose-escalation decisions or drug choices. Finally, detailed information was unavailable regarding the exact duration of hypertension since initial diagnosis, long-term medication adherence (beyond the required 4-week pre-enrollment period), dietary sodium intake, or direct imaging and biomarker indicators of target organ damage (such as echocardiography or pulse wave velocity). These unmeasured variables could represent relevant confounding factors; therefore, future prospective studies should incorporate them to fully elucidate the complete biological determinants of the residual hemodynamic gap.

However, given these results, we reinforce the importance of evaluating the true impact of long-term combination therapy or monotherapy, both on average values and on achieving control of other hemodynamic parameters, through ABPM as the gold standard for the hypertensive patient (both for diagnosis and follow-up). The latter must be contextualized with findings from studies such as the ESPRIT trial (2025), which confirm that intensive blood pressure lowering has modest effects on quality of life, especially in the frail older adult group, reminding us that excessive medication can also erode the patient's functionality and autonomy. Additionally, it is plausible to consider the probable impact of different antihypertensive drugs on outcomes, both in blood pressure control and in other hemodynamic parameters, which would force therapeutics to shift toward targeting the probable phenotypes of the hypertensive patient [14, 18].

It is also important to consider that perhaps this residual hemodynamic gap, much like the average value targets for the hypertensive patient compared to the normotensive patient, should prompt future clinical trials to evaluate the real therapeutic efficacy on the hemodynamic parameters studied here, and perhaps propose new cutoff points in hypertensive patients that demonstrate a real reduction in cardiovascular risk, beyond the control of traditional cardiovascular risk factors.

The magnitude of residual risk linked to vascular and endothelial impairment must not be minimized, as it is well-demonstrated that these parameters are associated with target-organ damage, independent of the average blood pressure value, and may constitute the actual foundation of the dreaded therapeutic inertia. Ultimately, we must remember that the health of our arteries determines our true longevity, as Sir William Osler aptly stated: "A man is as old as his arteries" [4, 6–7, 9, 13, 15, 17].

CONCLUSIONS

Conventional long-term treatment regimens (monotherapy, dual, or triple therapy) show no statistically significant differences in their ability to modify markers of vascular health (AASI, pulse pressure, systolic load, and circadian pattern), indicating a persistent residual risk gap despite the apparent control of average blood pressure values. Rather than implying inefficacy of combination therapies, these findings likely reflect that patients requiring multidrug regimens have more advanced, established structural vascular damage that numerical therapeutic escalation alone cannot fully reverse.

While age emerged in the multivariate model as the strongest independent clinical covariate modulating the advanced hemodynamic profile, its overall explanatory power remains modest. This suggests that arterial stiffness and the residual hemodynamic gap are complex biological processes driven by multiple unmeasured factors, requiring earlier and more specific diagnostic and therapeutic interventions that go beyond simple dose adjustments according to algorithmic guidelines.

Hypertension management must evolve beyond ABPM blood pressure averages (and even further beyond isolated office readings), focusing instead on the ability to identify and reduce the "Residual Hemodynamic Gap." This can be achieved either by considering the phenotypes of the hypertensive patient or by evaluating the potential for new cutoff points, serving as therapeutic targets, within the hemodynamic parameters obtained via ABPM that are associated with a real reduction in cardiovascular risk.

Declarations

Author Contributions

Lilianny Pineda: Investigation, data curation, patient recruitment, and writing – original draft. José Ayala-Hernández: Conceptualization, methodology, formal analysis, software, writing – original draft, writing – review and editing, and project administration. Jorge Domínguez: Investigation, resources, data curation, and writing – review and editing. Cristina López-Sánchez: Conceptualization, methodology, resources, data curation, writing – review, editing, and supervision. Joliette Alvarado: Investigation, data curation, validation – review and editing. Paola Brigli: Investigation, data curation, validation – review and editing.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that there are no financial, personal, or professional conflicts of interest that could inappropriately influence or bias the work presented in this manuscript.

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Declaration of Taipei. The original study protocol was reviewed and approved by the Research Coordination of the Faculty of Medicine at the Central University of Venezuela, protocol number C.I. 076/2024.

Patient Consent

Informed consent was obtained from all individual participants included in the study before data collection and ambulatory blood pressure monitoring (ABPM) placement.

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Clinical Trial Registration

Not applicable. This was an observational, non-interventional study; therefore, clinical trial registration was not required.

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Figures

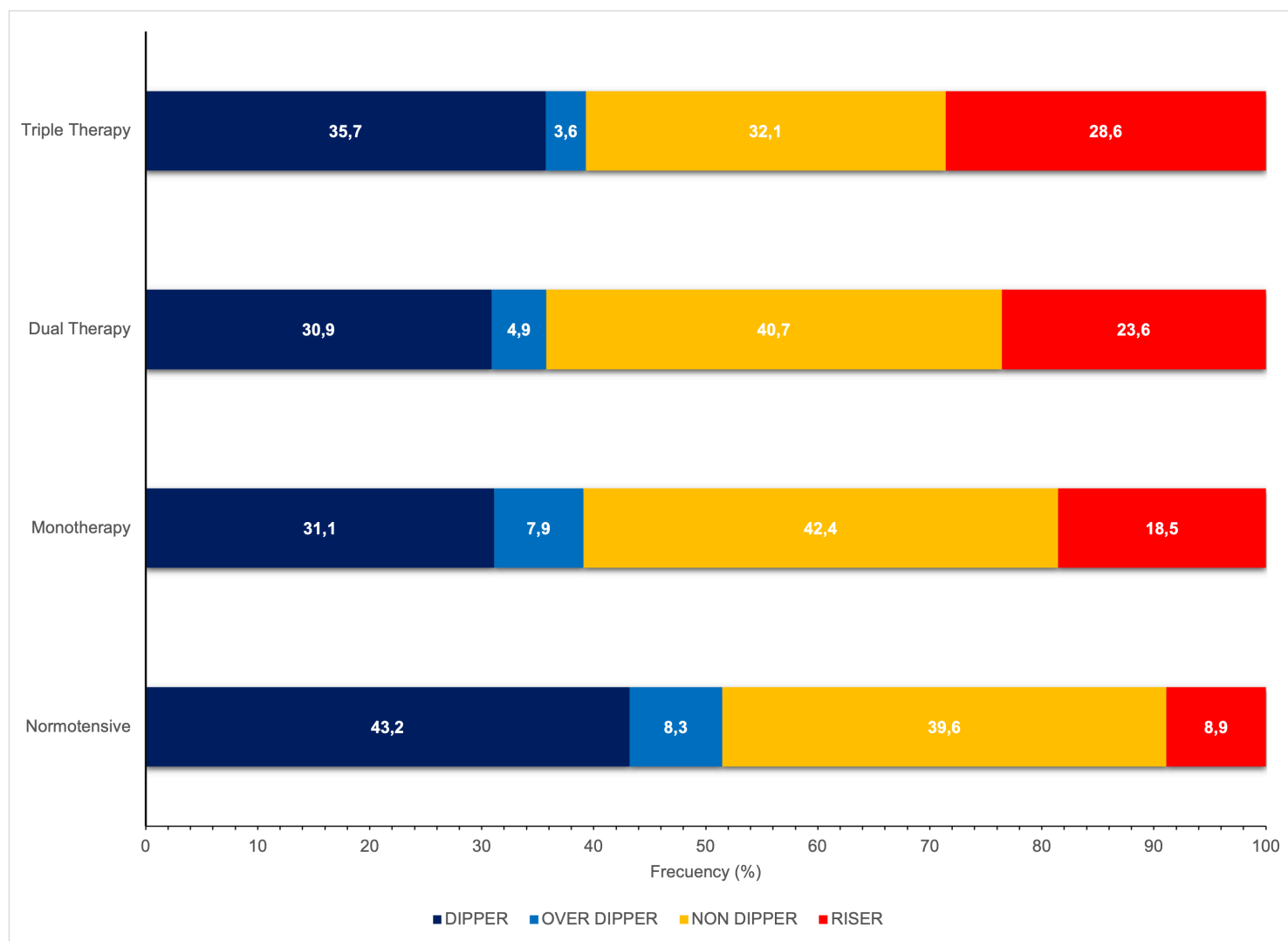


Figure 1

Frequency of circadian patterns obtained by ABPM compared between normotensive and hypertensive patients according to the antihypertensive regimen.

The intergroup χ^2 calculation corresponds to a p-value = 0.011; however, for the intragroup χ^2 calculation among hypertensive patients, the p-value is 0.518. No significant overall differences were found between the antihypertensive treatment groups in the multivariate analysis (MANOVA), Wilks L = 0.978; p = 0.088.

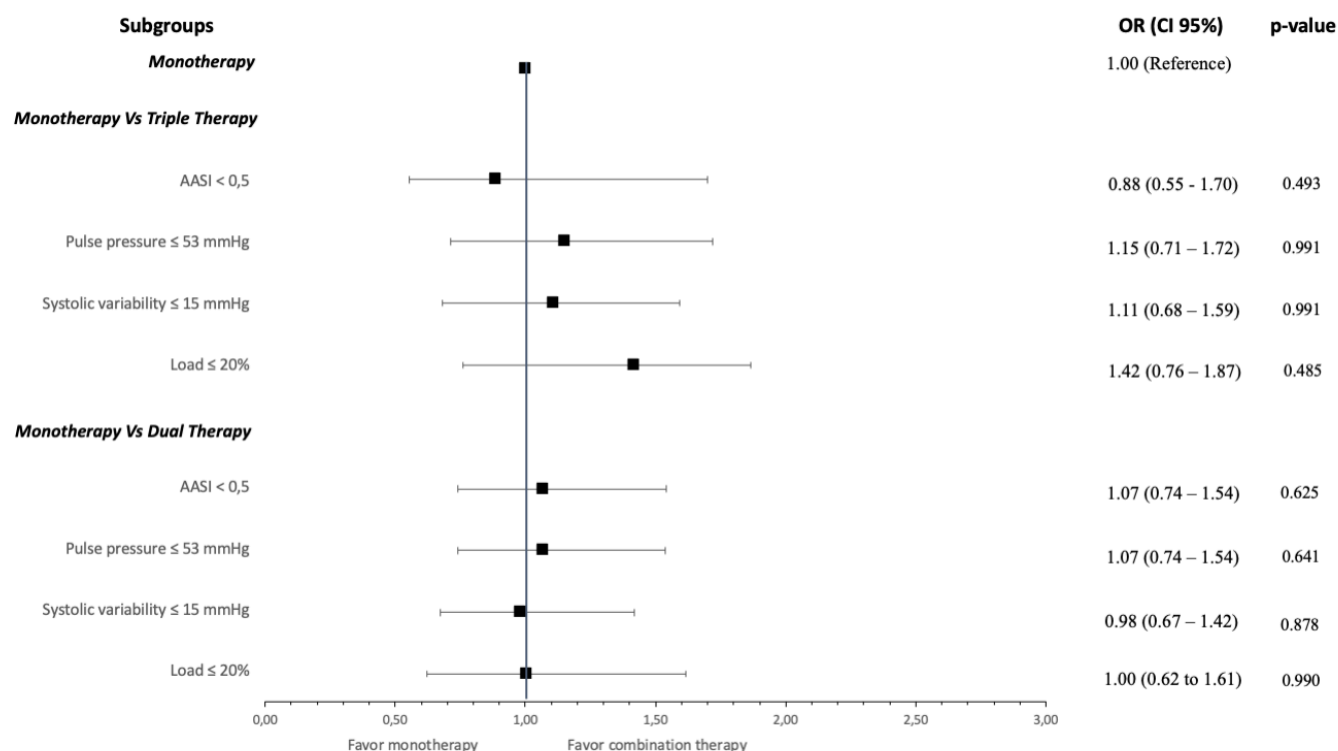


Figure 2

Forest Plot. Logistic regression to evaluate the control of hemodynamic parameters obtained by ABPM: monotherapy vs. combination therapy.

Odds ratio (OR) with 95% confidence interval (CI) for evaluating the control of hemodynamic parameters (AASI, pulse pressure, systolic variability, and systolic load), comparing monotherapy (reference) with combination therapy (dual and triple therapy). Vertical line OR = 1.0.

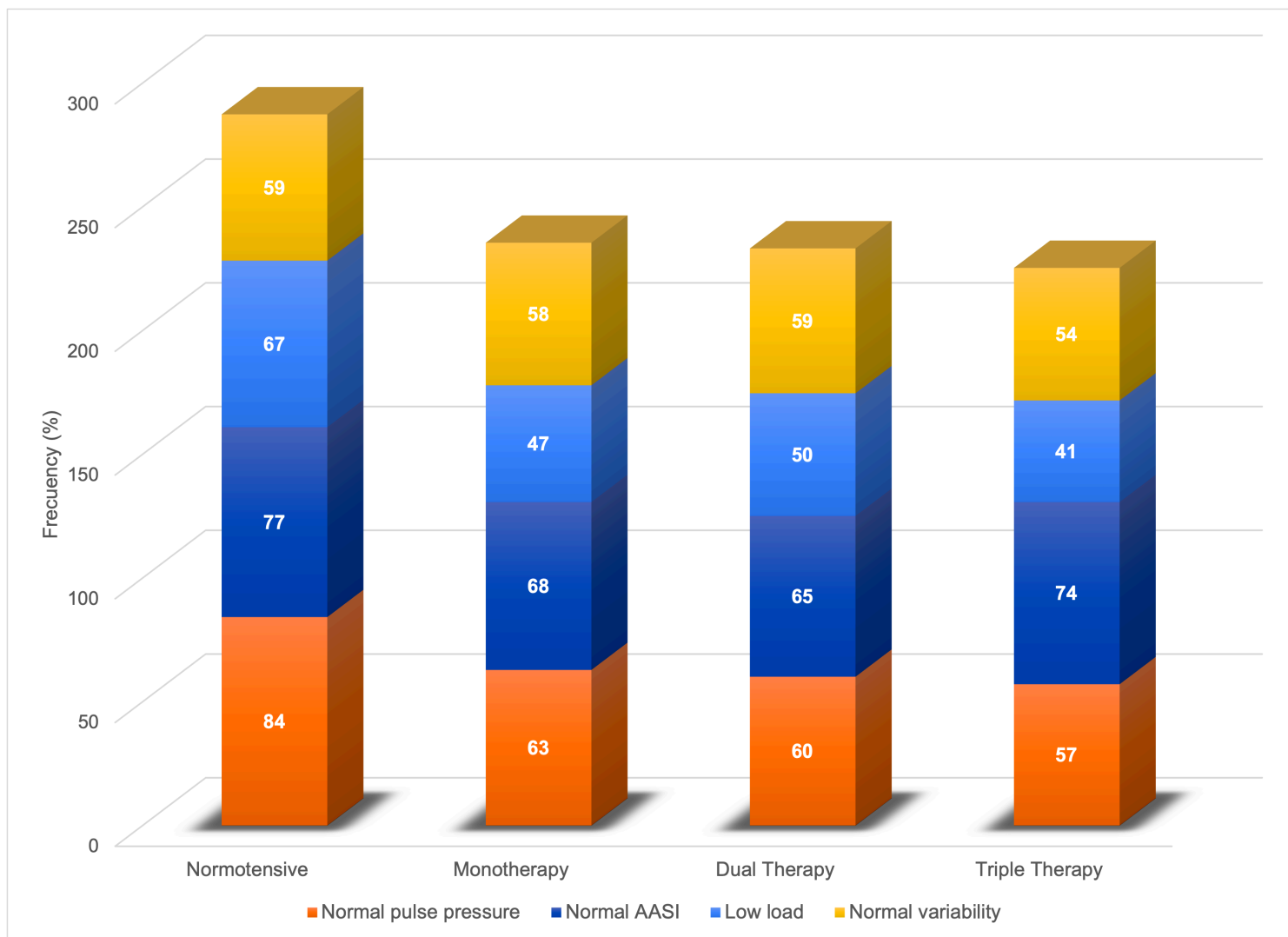


Figure 3

Frequency of normal values in hemodynamic parameters obtained by ABPM compared between normotensive and hypertensive patients according to the antihypertensive regimen.

No significant overall differences were found between the antihypertensive treatment groups in the multivariate analysis (MANOVA), Wilks L= 0.978; p = 0.088