Analysis of the Arterial Stiffness Index obtained by ABPM (Ambulatory Blood Pressure Monitoring), to improve its prediction. Linear vs. exponential relationship.

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ABSTRACT

The Arterial Stiffness Index (AASI) is a calculation obtained through Ambulatory Blood Pressure Monitoring (ABPM), capable of indirectly simulating elasticity changes in the arterial wall; but there is heterogeneity in its scope as a predictor of vascular wall health. A comparison is made between linear regression vs. exponential regression, as well as an analysis of variance, according to the circadian patterns and the pulse pressure (PP) values. It is an analytical observational study in 106 individuals, most of them women (63%) and the average age was 53 ± 17.32 years. The coefficient of determination (r^2), for the linear relationship was 0.53 ± 0.17, similar to the exponential relationship with an r^2 of 0.52 ± 0.17 (p = 0.7032). Patients with PP < 52 mmHg presented AASI of 0.3839 ± 0.1428 and for PP > 53 mmHg an AASI of 0.5330 ± 0.1108 (p < 0.0001). When comparing the AASI between Dipper Vs Riser circadian patterns, there was homoscedasticity (p = 0.3717), on the contrary, in the intergroup evaluation with Non dippers, heteroscedasticity was observed (Dipper Vs Non dipper; p = 0.0316 and Non dipper Vs Riser; p = 0.01978). CONCLUSION: The best determination of AASI is by the linear regression line, correlating robustly with PP values > 53 mmHg and AASI > 0.5 (r = 0.9628). The behavior of the data in the non-dipper subgroup is heterogeneous, probably due to their own physiological characteristics. When determining blood pressure, through the sphygmomanometer, it is important to consider the influence of the pressure to deform the artery, in the calculation of the AASI. AASI could be an indirect measure of arterial stiffness and be more directly associated with arterial elasticity and its deformation capacity.

Keywords: Ambulatory Blood Pressure Monitoring, Arterial Stiffness, Arterial Deformation, Arterial Elasticity, Circadian Pattern, Pulse Pressure.

Análisis del Índice de Rigidez Arterial obtenido por MAPA (Monitoreo Ambulatorio de Presión Arterial), para mejorar su predicción. Relación lineal Vs exponencial.

RESUMEN

El Índice de Rigidez Arterial (AASI por sus siglas en inglés), es un cálculo obtenido a través del Monitoreo Ambulatorio de Presión Arterial (MAPA), capaz de simular indirectamente los cambios de elasticidad en la pared arterial; pero hay heterogeneidad, en el alcance como predictor de salud de la pared vascular. Se realiza una comparación entre la regresión lineal Vs regresión exponencial, así como un análisis de varianza, según los patrones circadianos y los valores de la presión del pulso (PP). Es un estudio observacional analítico en 106 individuos, la mayoría mujeres (63%) y la edad promedio fue $53 \pm 17,32$ años. El coeficiente de determinación (R^2), para la relación lineal fue $0,53 \pm 0,17$, similar a la relación exponencial con un R^2 de $0,52 \pm 0,17$ (p = 0,7032). Los pacientes con PP < 52 mmHg presentaron AASI de $0,3839 \pm 0,1428$ y para PP > 53 mmHg un AASI de $0,5330 \pm 0,1108$ (p < 0,0001). Al comparar el AASI entre patrones circadianos Dipper Vs Riser, hubo homocedasticidad (p = 0,3717), por el contrario, en la evaluación intergrupal con los Non dipper, se observó heterocedasticidad (Dipper Vs Non dipper; p = 0,0316 y Non dipper Vs Riser; p = 0,01978). CONCLUSION: La mejor determinación del AASI es por la recta de regresión lineal, correlacionándose de manera robusta con valores de la PP > 53 mmHg y AASI > 0,5 (r = 0,9628). El comportamiento de los datos, en el subgrupo Non dipper, es heterogéneo probablemente por sus propias características fisiológicas. En la determinación de la presión arterial, a través del esfingomanómetro, es importante considerar la influencia de la presión para deformar la arteria, en el cálculo del AASI. El AASI podría ser una medida indirecta de la rigidez arterial, y estar asociada más directamente con la elasticidad arterial y su capacidad de deformación.

Palabras claves: Monitoreo Ambulatorio de Presión Arterial, Rigidez Arterial, Deformación Arterial, Elasticidad Arterial, Patrón Circadiano, Presión del pulso.

PLAIN LANGUAGE SUMMARY

Arterial stiffness is a well-known cardiovascular risk marker. However, measuring it in daily practice is complex; therefore, calculating it through a method such as Ambulatory Blood Pressure Monitoring (ABPM) makes its evaluation attractive at the time of diagnosis and follow-up of cardiovascular disease. The Ambulatory Arterial Stiffness Index (AASI) is a simple mathematical calculation, obtaining the slope of all Diastolic Blood Pressure data with the corresponding Systolic Blood Pressure.

Pulse pressure and circadian pattern are variables obtained in the ABPM that, in different trials, have had different results when trying to correlate it with the AASI; perhaps due to the great dispersion of data that occurs when measuring blood pressure in patients with different phenotypes. It is proposed that the relationship of the data is not linear, but exponential (just like

the pressure-diameter curves). This would allow improving the operational performance of the AASI, for decision making.

However, our findings demonstrate that the best relationship is linear; and that an AASI > 0.5 is adequately associated with pulse pressure > 53 mmHg. The heterogeneous findings between the variables are due to the variance inherent to each of the population subgroups that deserve to be considered, as well as fluid dynamic variables that should be considered for future studies of arterial stiffness.

INTRODUCTION

High blood pressure is a pathology with a high impact on global public health, with great influence on morbidity and mortality rates. Worldwide, there were around 1390 million hypertensive patients in 2010, with a great disparity in prevalence depending on the income level of each region. [1]

High blood pressure is a highly prevalent condition in the global and national population. According to the Venezuelan Study of Cardiometabolic Health (EVESCAM), conducted by the Venezuelan Society of Internal Medicine, in 2017 it was estimated that more than a third of the Venezuelan population was hypertensive. [2]

With the evolution of the different cohorts of the Framingham study, additional parameters were evaluated that were previously considered physiological, and even essential in hemodynamic functioning. Among the first observations, the trend towards isolated systolic hypertension stood out, with a higher prevalence in older adults. [3]

Based on these findings, arterial stiffness is evaluated as a cardiovascular risk factor to be considered. However, the difficulties in obtaining reliable data on the arterial wall, with simple, reproducible clinical methods within the reach of physicians, have meant that progress has not been made in possible therapeutic approaches to this condition. [4,5]

Therefore, being able to use a simple methodology that allows us to emulate the physiological phenomena involved in arterial stiffness is, at least, a goal of great interest for the clinical physician. Ambulatory blood pressure monitoring (ABPM) is a simple, reproducible method that is readily available to clinicians and which in recent years has been included in various international guidelines for the diagnosis and treatment of arterial hypertension. [6]

The Ambulatory Arterial Stiffness Index (AASI) is a simple calculation obtained through ABPM, supported by evidence from the last decade, as capable of indirectly simulating changes in the elasticity of the arterial wall. In different trials, it has been reported that the Ambulatory Arterial Stiffness Index (AASI) predicts target organ damage, cardiovascular mortality and cerebrovascular events, even better than pulse pressure (PP). [3-5,7]

Palencia et al. (2017) conducted a study in which the different parameters of the ABPM were related to the AASI. In this study, the ambulatory arterial stiffness index (AASI) was positively correlated with PP, load, age and systolic blood pressure. However, it is noteworthy that the relationship obtained between these parameters was, at best, moderate. [8]

Considering that the arterial pressure-diameter (p-d) curve is non-linear, being exponential in form, and that therefore the greater the arterial stiffness, the more pronounced the p-d non-linearity should be (with a higher AASI value), likewise it can also be inferred that the relationship in the different ABPM parameters will be non-linear. [7]

Therefore, a comparison of the linear regression analysis and exponential regression analysis is carried out between diastolic blood pressure and systolic blood pressure, to evaluate which has the best goodness of fit for the calculation of the AASI. An analysis of the circadian pattern and pulse pressure obtained through the ABPM is also performed to evaluate their degree of influence in obtaining the AASI.

METHODS

Study population

This is an observational, analytical study, carried out on a population consisting of 1,042 patients, all over 18 years of age, who have been entered into the database of the Research Group of the Chair of Clinical Medicine and Therapeutics A of the Luis Razetti School - Central University of Venezuela, until June 1, 2023, who have undergone an Ambulatory Blood Pressure Monitoring study, whether hypertensive or not.

The sample was calculated taking into consideration a confidence level of 95% with a margin of error of up to 10%, obtaining a minimum necessary of 89 individuals. The selection was through simple random sampling.

The exclusion criterion was established as those ABPM that presented incomplete data.

As a study part of a line of research that uses a database, complying with the Declaration of Helsinki complemented by the Declaration of Taipei; the original study [8] was approved by the Bioethics Committee of the Military Hospital of Caracas. All participants gave their written informed consent.

Procedures

The database of the Research Group of the Chair of Clinical Medicine and Therapeutics A of the Luis Razetti School was obtained through the collection of data from patients who agreed to be included. The data were obtained through different Ambulatory Blood Pressure Monitoring equipment: BR-102 plus Schiller brand, Welch Allyn ABPM 6100S, SunTech Bravo model.

Simple random sampling was performed until obtaining at least the calculated sample. Data were extracted through an instrument designed for this purpose, to obtain basic demographic and clinical data necessary such as: gender, age, average systolic and diastolic blood pressure in 24 hours, diagnosis of hypertension, smoking habit, diagnosis of diabetes, pregnancy, type of antihypertensive treatment (monotherapy, combination therapy and groups of medications).

Additionally, circadian blood pressure patterns were extracted from the blood pressure monitoring data by calculating the changes in systolic blood pressure during waking hours compared to sleeping hours (Dipper between 10-20%, Over Dipper >20%, Non dipper <10%, Riser <0%). Average pulse pressure data for 24 hours were also obtained.

The Ambulatory Arterial Stiffness Index is obtained by calculating the slope of linear regression of all measurements of diastolic blood pressure on systolic blood pressure, in each registered individual, and is it subtracted from the unit. The results of the linear correlation are compared with the exponential correlation of the figures of diastolic blood pressure on systolic blood pressure, through the calculation of the coefficient of determination of each one, to estimate the difference in the relationship existing in each situation.

Statistical treatment

For nominal variables, they are expressed in frequencies and percentages. For discrete and continuous variables, estimates are made based on the central limit theorem to determine a distribution like the normal. Arithmetic means are calculated with standard deviation, ANOVA calculation for the study subgroups and determine difference of variance; as well as the Student T test to compare groups with similar variances. Pearson's correlation calculation is used to estimate the linear relationship, and the coefficient of determination is calculated to compare the linear correlation with the exponential correlation.

Box and whisker graphs are made to represent the behavior of the distribution and variability of the data.

RESULTS

Clinical and epidemiological characteristics

Data from 106 patients were obtained from the database, of which the majority were female (63%). The mean age was 53 ± 17.32 years. The mean 24-hour systolic blood pressure was 122 ± 12.88 mmHg and the mean 24-hour diastolic blood pressure was 73 ± 9.12 mmHg. Of this group of patients, at the time of performing the ABPM, 67% of the individuals were known to have a diagnosis of hypertension. Of the total of 106 patients, 62% were receiving antihypertensive pharmacological treatment, 5 patients (5%) were not complying with the therapeutic regimen at the time of ABPM. (Table 1)

Table 1. Epidemiological and clinical data of patients evaluated through Ambulatory Blood Pressure Monitoring.

Characteristics	Value
Total (n)	106
Gender	
Male n (%)	41 (37)
Female n (%)	65 (63)
Age (years) (X $\pm$ SD)	53 $\pm$ 17,32
Systolic blood pressure (mmHg $\pm$ SD)	122 $\pm$ 12,88
Diastolic blood pressure (mmHg $\pm$ SD)	73 $\pm$ 9,12
Hypertension diagnosis	
Hypertensive n (%)	71 (67)
Non hypertensive n (%)	35 (33)
Smoking habit	
Yes n (%)	11 (10)
No n (%)	95 (90)
Diabetes n (%)	14 (15)
Pregnant women n (%)	13 (12)
Without antihypertensive treatment n (%)	40 (38)
Antihypertensive treatment n (%)	66(62)
Monotherapy n (%)	37(56)
Combination therapy n (%)	29(44)
ACEI or ARB n (%)	49 (74)
Thiazides n (%)	15 (23)
Calcium channel blockers n (%)	23 (35)
β-blockers n (%)	20 (30)
α-agonists n (%)	4 (6)

ACEI: Angiotensin-converting enzyme inhibitors. ARB: Angiotensin receptor blockers

The AASI value is calculated according to gender, and it is observed that for the female group it is lower than for the male group. For the female group it was 0.3828 ± 0.1727 and for the males it was 0.4784 ± 0.1453 (p = 0.0043). In the case of the hypertensive group, higher AASI values were evident with 0.4381 ± 0.1631 as opposed to the non-hypertensive group with 0.3826 ± 0.1750, however, it can be considered a result due to chance due to the value of p = 0.1139. (Table 2)

Table 2. Ambulatory Arterial Stiffness Index by gender and hypertension diagnosis

Characteristics	AASI (X $\pm$ SD)	p
Gender		
Male	0,4784 $\pm$ 0,1453	0,0043
Female	0,3828 $\pm$ 0,1727	
Hypertension diagnosis		
Hypertensive	0,4381 $\pm$ 0,1631	0,1139
Non hypertensive	0,3826 $\pm$ 0,1750	

AASI: Ambulatory Arterial Stiffness Index

Level of significance p < 0,05.

Linear and exponential regression

The trend line is drawn up considering the dispersion graphs of each individual, for all diastolic pressure measurements (Y axis) on all systolic pressure measurements (X axis), applying linear and exponential trends in each case, and the determination index is calculated for each correlation, with the intention of comparing the difference in the variance of each case and evaluating which trend best explains the dispersion of the data. In Graph 1 it is observed that the linear relationship had an average determination coefficient of 0.53 ± 0.17, similar to the exponential relationship with an average determination coefficient of 0.52 ± 0.17 (p = 0.7032), which makes the behavior of both correlations similar with respect to the variance.

Taking these results into account, linear regression calculations are used to evaluate the rest of the data, since, being similar to the exponential relationship, it is the simplest statistical description to evaluate other ABPM parameters.

Graph 1. Comparison of the coefficient of determination (r^2) between the linear relationship vs. the exponential relationship of the Ambulatory Stiffness Index (AASI)
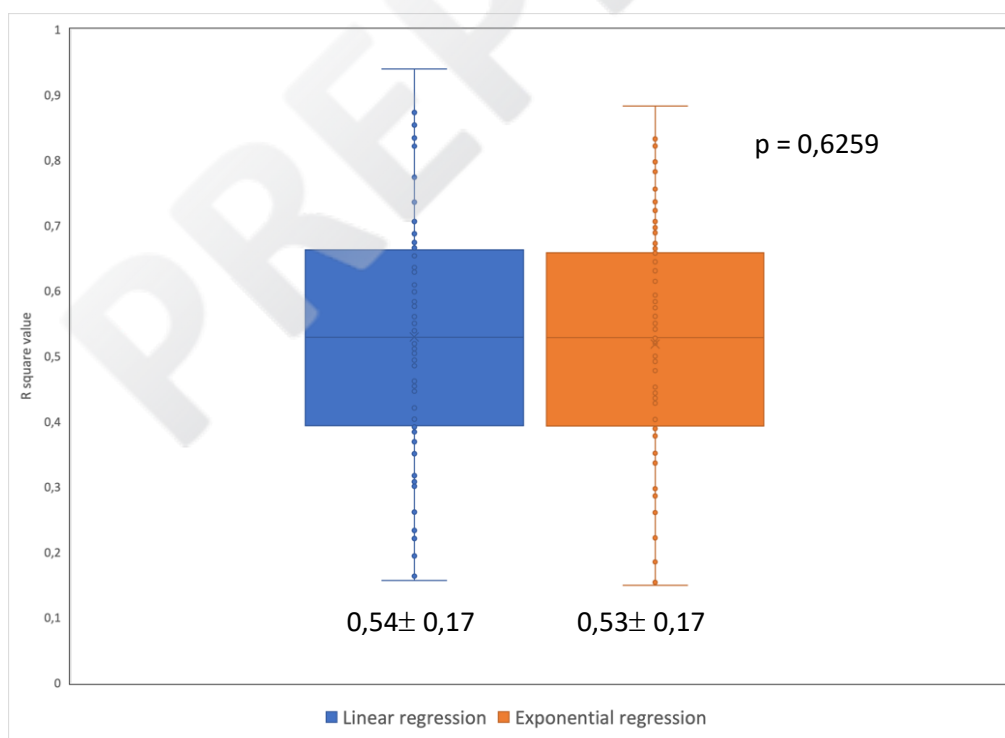
Pulse Pressure and AASI

When the AASI calculation was related to the average pulse pressure (PP) obtained in 24 hours, the results were grouped by quartiles: first quartile < 45 mmHg, second quartile from 46 to 52 mmHg, third quartile from 53 to 60 mmHg and fourth quartile > 61 mmHg. A progressive increase in the AASI value was evident, proportional to the increase in pulse pressure, for each recorded quartile.

An excellent linear correlation was evident, obtained by Pearson, with r = 0.9628. However, when evaluating the variance of the groups, it was evident that there was no difference between the first and second quartile (p = 0.1305), nor the third and fourth quartile (p = 0.2569); as well as the calculation of the T-test for equal variances (p = 0.5045 and p = 0.4034, respectively). (Table 3)

A subanalysis of the groups according to pulse pressure is performed, dividing it into two samples: < 52 mmHg and > 53 mmHg. For the < 52 mmHg group, an average AASI of 0.3839 ± 0.1428 is obtained, and for the > 53 mmHg group, an average AASI of 0.5330 ± 0.1108. For this case, the variance calculation (ANOVA) obtained p = 0.0836, but with a T-test analysis for equal variances of p < 0.0001. (Table 4)

Table 3. Ambulatory Arterial Stiffness Index according to the quartiles of the average pulse pressure in 24 hours

Pulse Pressure (mmHg)	AASI (X $\pm$ SD)	ANOVA P	T-test p	Pearson r
< 45	$0,3734 \pm 0,1503$	0,1305	0,5045	0,9628
46 – 52	$0,3952 \pm 0,1375$			
53 – 60	$0,5151 \pm 0,1234$	0,2569	0,4034	
> 61	$0,5523 \pm 0,1019$			

AASI: Ambulatory Arterial Stiffness Index
Level of significance p < 0,05.

Table 4. Ambulatory Arterial Stiffness Index according to average pulse pressure over 24 hours, in two groups.

Pulse Pressure (mmHg)	AASI (X $\pm$ SD)	ANOVA p	T-test p
< 52	$0,3839 \pm 0,1428$	0,0836	< 0,0001
> 53	$0,5330 \pm 0,1108$		

AASI: Ambulatory Arterial Stiffness Index
Level of significance p < 0,05.

Circadian patterns and AASI

In the sample, the different circadian patterns of systolic blood pressure were determined according to the change in the relationship between blood pressure values during wakefulness and the night-time sleep period, and 3 subgroups were obtained: Dipper (decrease 10-20%), Non-dipper (decrease

<10%) and Riser (nocturnal increase in systolic blood pressure). There was only one patient with an over-dipper pattern (decrease >20%).

When grouping the circadian pattern groups, an AASI of 0.3377 ± 0.1156 was obtained for the Dipper group, in the case of the Non dipper the AASI was 0.4324 ± 0.1611 and for the Riser subgroup an AASI of 0.5013 ± 0.1077 was observed, this showed an increase in stiffness arterial according to the severity of the circadian pattern change; even when applying analysis of variance, a significant difference is evident between the means of at least one of the groups evaluated ($p = 0.00015$). (Table 5).

Table 5. One-way analysis of variance (ANOVA) for the Ambulatory Arterial Stiffness Index means, according to the circadian patterns of systolic blood pressure during sleep compared to wakefulness.

Circadian patterns	AASI (X $\pm$ SD)	Variance	p
Dipper	0,3377 $\pm$ 0,1156	0,0138	
Non dipper	0,4324 $\pm$ 0,1611	0,0265	0,0001504
Riser	0,5013 $\pm$ 0,1077	0,0120	

AASI: Ambulatory Arterial Stiffness Index
Level of significance p < 0,05.

Given this, the results are compared intergroup, and the variance of the mean is compared by regrouping them as: Dipper / Non-Dipper, Dipper / Riser and Non-Dipper / Riser, to evaluate the consistency of the difference of the AASI in all circadian patterns. In this way, it is evident that only when comparing the Dipper and Riser subgroups there was no significant difference in the variances, so they can be considered as comparable groups ($p = 0.3717$), more so if there was a significant difference in the calculation of the T-Test ($p < 0.0001$). (Table 6)

Table 6. Analysis of variance (ANOVA) for two samples of the Ambulatory Arterial Stiffness Index, comparing the circadian patterns of systolic blood pressure during sleep versus wakefulness.

Circadian patterns	ANOVA p	T-test p
Dipper / Non dipper	0,0316	-
Dipper / Riser	0,3717	< 0,0001
Non Dipper / Riser	0,01978	-

Level of significance p < 0,05.

To better evaluate these results, a box and whisker graph was created, with the finding that the behavior of the Dipper and Riser groups are similar; unlike the Non-dipper group, where the dispersion of the data is greater. (Graph 2)

Graph 2. Ambulatory Arterial Stiffness Index according to the change in the circadian pattern of systolic blood pressure during sleep compared to wakefulness.
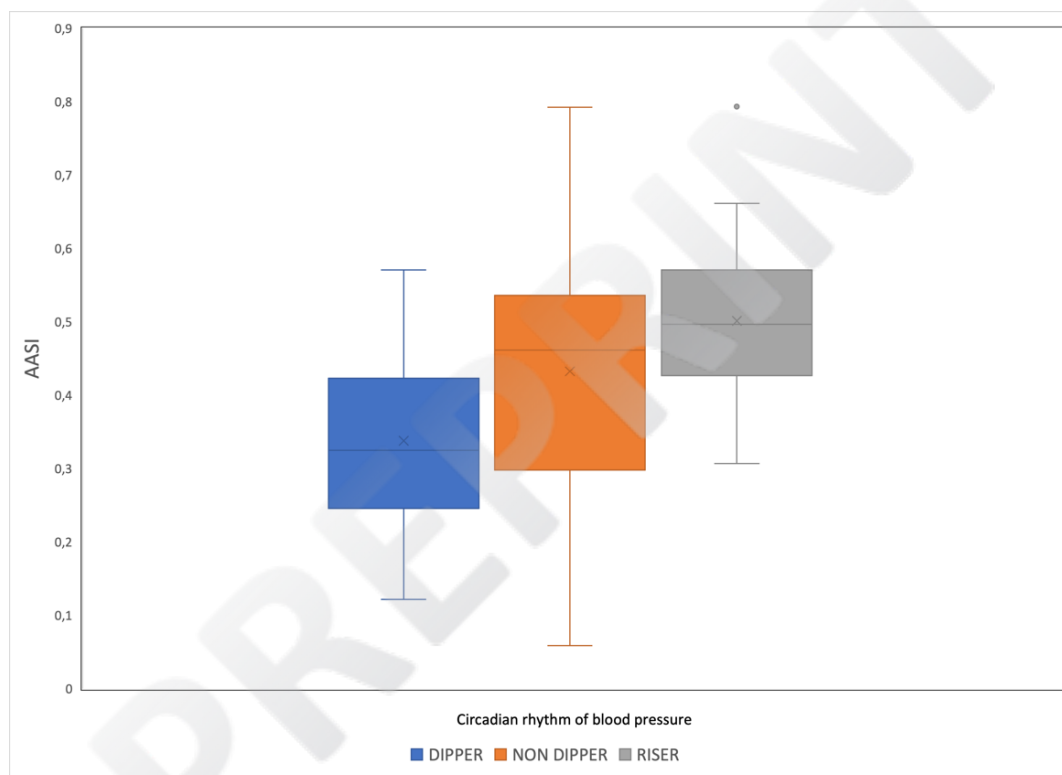
DISCUSSION

The AASI is an independent cardiovascular risk marker, capable of predicting cardiovascular mortality and the possibility of cerebrovascular events and even damage to target organs; with excellent reproducibility, which makes it an efficient and recommended calculation to be performed in all hypertensive patients. [9]

In the search to provide data that would allow improving the prediction of AASI, as a useful tool in addressing cardiovascular risk, this work obtained results that could contribute to clarifying the circumstances that may influence the arterial stiffness values obtained by ABPM.

In our results, the gender with the highest prevalence in performing ABPM was female, with a prevalence of 63%. In a large part of the studies about ABPM, the highest frequency in carrying out the monitoring study was the female sex. Examples of this were the studies by Raimondo et al. (2017), Bahrainwala et al (2015), Mortazavi et al. (2023), where women participated in more than 50% of the monitoring. [10-12]

According to our results, the lowest AASI value was found to be associated with female sex. This is consistent with most studies on arterial stiffness, Said et al (2018), Park et al (2022), Lu et al (2023),

and even Boss et al (2021). It is proposed that this situation is explained by the influence of the levels of estradiol and follicle-stimulating hormone on the compliance of the arterial tree, since this difference decreases until it equalizes in postmenopause. [13-16]

It is noteworthy that, in the results of the study, the difference between the AASI value of patients with or without a diagnosis of hypertension was not significant enough. Many of the trials that evaluate arterial stiffness by ABPM have not considered, in their analysis, a direct comparison of subgroups of hypertensive patients vs. non-hypertensive patients. It has only been mentioned that the dispersion in the data in obtaining the AASI increases as the patient presents more cardiovascular risk factors (e.g. age, circadian pattern). In fact, the study by Raimondo et al. (2017), based on this phenomenon, proposes that the AASI is more reliable in demonstrating vascular health than in accurately determining the degree of vascular wall compromise. [10] But Palencia et al. (2016) demonstrates how the AASI, as well as the level of brain natriuretic peptide (BNP), decreases with the use of hypertensive treatment. In our case, 62% of the patients were receiving some antihypertensive treatment (56% in monotherapy), which could influence the fact that there is no significant difference between the AASI of hypertensive and normotensive patients. [17]

Among the findings of the study by Valero et al (2009), it was observed that the AASI decreased as there was less dispersion of the data in the regression line. In other words, as the coefficient of determination (r^2) increased, the AASI tended to be lower; and vice versa. The lower the dispersion of the data (higher r^2), the AASI tended to be lower, that is, an artery with better compliance or less rigidity would provide blood pressure values with less dispersion. This observation could be related to the hypothesis of Raimondo et al (2017), when they suggested that the AASI is better for determining good vascular health. [10, 18]

Taking these observations into account, both the linear and exponential relationships were compared in each of the 106 patients included, to check which type of regression best fit the dispersion of the data. It was shown that, for both cases, the coefficient of determination was quite similar, which shows that linear regression is as good as exponential regression, and since the former is mathematically simpler for calculating AASI, it is the one that should continue to be used. It should be noted that the average of these coefficients of determination was not greater than 0.53. Although this demonstrates the dependence of diastolic pressure on systolic pressure, it is a moderate goodness of fit that could be associated with the variance between subgroups of patients.

Since the description of the AASI, it was assumed that there should be a direct correlation between the AASI and pulse pressure. Several studies have determined this association; for example, the study by Palencia et al (2017) demonstrated this association with a correlation coefficient of 0.49, which, although positive, is moderate. Kollias et al (2012) presented similar results after evaluating 51 trials with 29,186 patients; they obtained a correlation coefficient of 0.47 CI 95% (0.40 – 0.54), which can also be considered moderate, but the results among all the included trials were heterogeneous (I^2 93%, p < 0,001). [8, 19,20]

Kollias et al (2012), Raimondo et al (2017) and Said (2018) conclude that AASI and pulse pressure are independent variables as predictors of cardiovascular events. In our case, pulse pressure subgroups were established in quartiles: 1st quartile < 45 mmHg, 2nd quartile 46 – 52 mmHg, 3rd quartile 53 – 60 mmHg and 4th quartile > 61 mmHg; in this way, the correlation coefficient between AASI and pulse pressure rises to 0.9628, which would show a strong linear relationship between the

two parameters; however, these differences were not significant. This difference is confirmed by reorganizing into two groups, according to pulse pressure, and it is obtained that at values greater than 53 mmHg the AASI rises above 0.50; which clarifies the direct relationship that may exist between these variables, as long as it is with pathological values; which confirms the findings of Verdecchia et al (2018), as an adequate cut-off point for the abnormal pulse pressure value obtained by ABPM. [10, 13, 20-22]

Regarding the circadian pattern, Jerrad-Dume et al (2007) already warned, in an analysis adjusted for age and sex, that the smaller the drop in systolic blood pressure during sleep, the greater it would be the pulse wave velocity (or higher arterial stiffness). That is, if we classify nocturnal dipping on a severity scale, recognizing the dipper patient as normal, the non-dipper as abnormal (but moderately pathological) and the riser patient as extremely pathological, it could be assumed that the greatest arterial stiffness would be obtained in a patient with a more severe, directly proportional circadian pattern disorder. However, in that same trial, in a multivariate analysis, there was no difference between the dipper and non-dipper groups, while the riser group maintained high arterial stiffness. [23]

Similarly, Raimondo et al (2017) in their initial analysis, present that the AASI value could be proportionally elevated to the severity of the nocturnal dip alteration. But the latter changes when doing multivariate analysis (adjusted for age, gender, body mass index, and average systolic and diastolic blood pressure), showing that there was a significant relationship between the AASI value and dipper and extreme dipper patients, but that this relationship was lost in non-dipper and riser cases. Finally, the study by Boss et al (2021) also observed that the AASI value was elevated according to the alteration of nocturnal dip (AASI in dipper 0.39, AASI in non-dipper 0.48 and AASI in riser 0.56). [16, 20]

In our case, as in all the studies mentioned, an initial analysis shows that the AASI rises as the type of dip during sleep worsens (dipper with AASI of 0.3377 ± 0.1156, in the case of the non-dipper, the AASI was 0.4324 ± 0.1611 and for the riser subgroup an AASI of $0,5013 \pm 0,1077$ was observed), with significant results when doing analysis of variance. However, upon closer inspection, it is evident that the dipper and riser pattern subgroups have a similar data dispersion, with equal variances; unlike the non-dipper subgroup where the variance changes significantly, and the dispersion is much wider, which makes it a group with different behavior from the others. This could well explain the findings in the different works that have addressed the relationship between the circadian pattern and arterial stiffness, where there has been an emphasis on comparing subgroups with dissimilar nocturnal behavior, which merits an independent analysis, especially the non-dipper group.

Mortazavi et al (2023) make a similar observation, studying only the group of non-dipper patients, where they determined how the prevalence of this circadian phenomenon varied, just by using different methods to determine the effective sleep period (schedules set by the ABPM team, sleep schedules reported by the patient, or by actigraphy). The non-dipper subgroup should be evaluated independently, as it is a group of patients with different variance, and therefore merits multivariate analysis directed only at this group, rather than comparing it with the findings of dipper, extreme dipper, or riser patients. [12]

In conclusion, the AASI, although a valuable resource for determining cardiovascular risk, still presents findings that may generate discussion. These findings, as observed in our results, may be influenced by hemodynamic phenomena not considered that may modify the dispersion of data obtained in the different research works on the subject.

Histologically, it is known that the elastin/collagen ratio of the arterial wall is what determines the degree of stiffness that the vessel may present. Therefore, it may be surprising how antihypertensive treatment could modify this relationship in the short term, since there are trials where the AASI value decreases proportionally with the use of these medications (Palencia et al (2016) and Raimondo et al (2017)). This could raise further doubts as to whether the AASI only measures the degree of arterial stiffness. [8,10, 17, 24]

We usually assume that blood pressure measurement reflects the tension exerted by the arterial wall, through the pulse wave, either by the auscultatory method or the oscillometric method; and that depending on the amplitude of the wave, an equivalent value will be recorded in millimeters of mercury (mmHg), which corresponds to the period of systole or diastole. However, there are phenomena from the point of view of fluid dynamics and solid mechanics, which could influence the findings of this study, and of previous works, as well as could explain some inconsistencies, which deserve to be analyzed and formulate new hypotheses.

It is quite clear that the cuff of the sphygmomanometer must exert pressure on the artery, with the intention of decreasing the diameter, to reduce and prevent the flow that would subsequently be gradually released and thus obtain the corresponding blood pressure records. But, in order to achieve this phenomenon, it is necessary to overcome two forces or pressures antagonistic to the cuff: one of them is the pressure exerted by the blood flow on the vessel walls, which is a variable influenced by its diameter (p-d curves); the other is the pressure exerted by the vessel wall (according to the rigidity or elasticity of the material) to achieve the necessary deformation to occlude the lumen of the artery.

That is, it can be deduced that the pressure of the sphygmomanometer cuff (P_{cuff}) must be at least equivalent to the sum of the blood flow pressure ($P_{fluid/flow}$) plus the deformation pressure of the artery ($P_{deformation}$), and therefore this product, in mmHg, must be greater than each of its variables to achieve the phenomenon of arterial occlusion. [24,25] (Figure 2)

The usual concept assumes that the blood pressure reading should correspond proportionally to the blood flow pressure in both the systolic and diastolic periods, without including the influence of the pressure necessary for arterial deformation. This pressure has been taken into account to explain phenomena such as Osler's sign, isolated systolic hypertension, increased cardiovascular risk, and the like, but not to analyze its degree of relationship with the usual blood pressure values in the general population, as well as its impact.
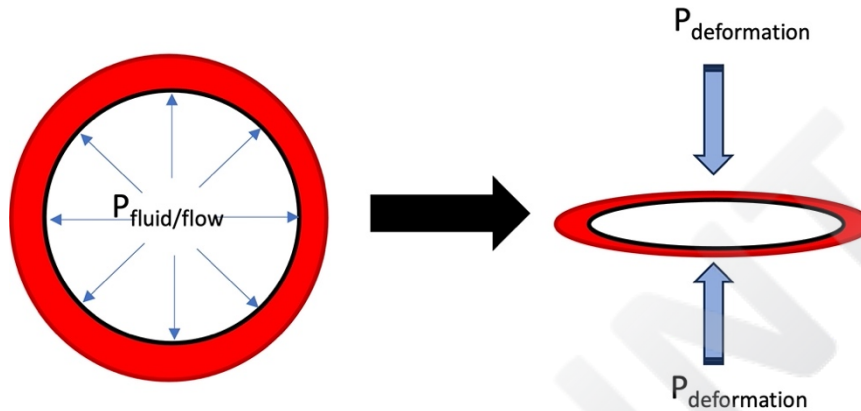
$$P_{cuff} \approx P_{fluid/flow} + P_{deformation}$$

Figure 2. Effect of the sphygmomanometer cuff on the arterial vessel. The pressure exerted by the cuff, when inflated, must be equivalent to the sum of the blood flow pressure ($P_{fluid/flow}$) and the arterial deformation pressure ($P_{deformation}$), for arterial occlusion.

It is possible that the pressure required for arterial deformation is an additional variable to consider. This is, of course, influenced by additional factors such as arterial stiffness and elasticity, which we usually use as synonyms, due to the proportional dependence they have on each other. But if we look at the mechanical and mathematical characteristics of these factors, we can analyze their subtle biomechanical differences. Mathematically, the stiffness of a pipe (similar to a blood vessel) depends on the product of the modulus of elasticity multiplied by the moment of inertia (this last term determined by geometric characteristics such as diameter and wall thickness), divided by the diameter of the arterial lumen; for this reason, the elasticity of the material directly influences the stiffness, but includes other variables that must be considered, in addition to elasticity. [25,26] (Equation 1).

$$\text{Stiffness} = \frac{E * I}{D_m^3}$$

Equation 1. Equation for the stiffness of a pipe. The stiffness of a blood vessel will depend, directly proportional, on the elasticity modulus of the material, but also on the moment of inertia, and indirectly proportional to the diameter of the lumen of the vessel. [26]

If we talk about the elastic behaviour of arteries in different situations and how this influences their deformation, it is ultimately part of measuring blood pressure. Young's modulus of elasticity implies that a given axial stress on a material corresponds to a deformation, which defines the elasticity of the element being studied. The elasticity regression analysis, before reaching its limit, is a straight line, with its own slope, depending on the material analyzed and its proportional stiffness. Contrary to the AASI calculation, the greater the slope, the greater the stiffness of the material since more tension is required to achieve the same deformation. In fact, this would explain why, in a rigid artery,

the systolic pressure increases much more than the diastolic pressure (since the distance that separates each of these deforming pressures is smaller in the case of diastolic blood pressure). [25] (Figure 3)
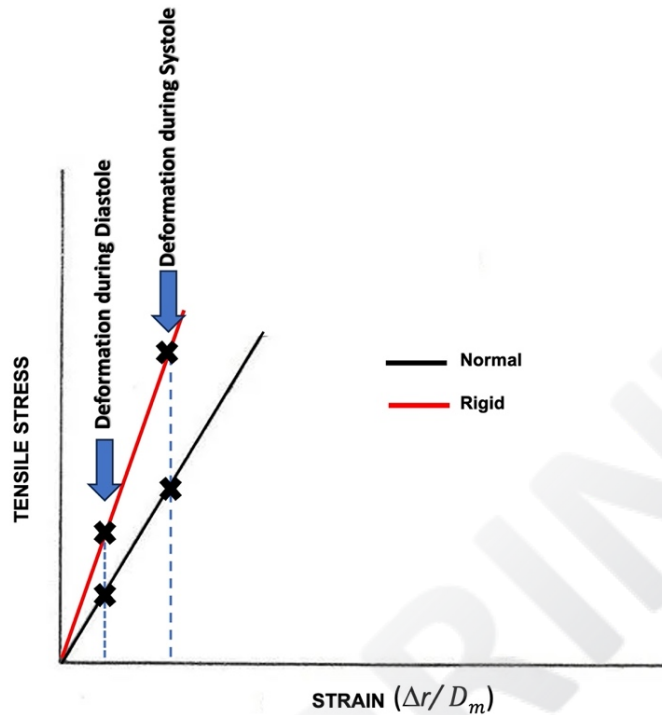

Figure 3. Young's Modulus of Elasticity. In a stiffer material, greater stress is required to cause the same deformation. Note that, when applying sufficient systolic and diastolic pressure, for the same deformation of the artery, the difference in diastolic pressure is much smaller than for the case of systolic pressure. [25]

Thus, the pressure required to achieve the deformation of the artery to measure the systolic and diastolic pressure must be equivalent to the modulus of elasticity multiplied by the deformation exerted. (Equation 2)

$$P_{\text{deformation}} \sim \left(\frac{E * I}{D_m^3}\right) \Delta r$$

Equation 2. The pressure obtained by the sphygmomanometer cuff is influenced by the pressure for the deformation of the artery. This must be equivalent to the product of the modulus of elasticity by the deformation of the material. [26]

If we assume this analysis and make the assumption that the blood flow is zero (there is no blood circulation), the cuff will still need to exert the deformation pressure, even if the recording is null due to the absence of a pulse wave. This statement can be supported by reanalyzing the equation of the regression line (y=mx+b) to obtain the AASI; there we will observe that the value of b (equivalent to the value of the diastolic pressure in the scenario of a systolic pressure equal to zero),

never cuts at zero, it will always have a value in mmHg (positive or negative) that may depend on the slope of the line. In other words, the artery, in theory, will always require a minimum diastolic pressure that guarantees a necessary lumen diameter and with minimal deformation. (Figure 4)
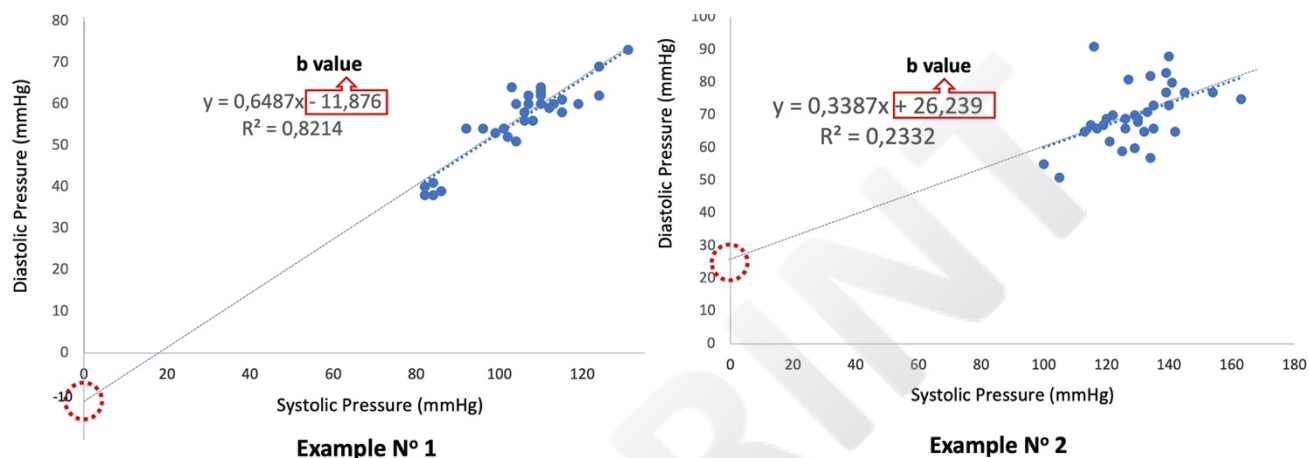

Figure 4. Regression line for the calculation of AASI. Note that the line on the "y" axis does not cut at zero; it will always have a positive or negative value that can be associated with the slope, and which is represented by the value of "b" in the equation. This value could have a direct influence on the deformation capacity of the artery. Source: Own data

Previous studies have already found that diastolic pressure could influence the results of arterial stiffness determination, without further analysis of the findings. One of these studies was that of Said et al (2018), where in a multivariate analysis it was observed that for the AASI values the diastolic pressure exerted an influence of at least 24% by calculating the β coefficient, unlike pulse pressure, which is more affected by the values of systolic pressure and mean arterial pressure. More recently, Kamboj et al (2021), in a meta-analysis that compared invasive Vs non-invasive blood pressure, determined that diastolic blood pressure was the one with the greatest discrepancy, and that it was not possible to predict; this could be presumed to be secondary to the fact that diastolic pressure is associated with the minimum necessary deformation pressure. [13,27]

Taking this analysis into account, future investigations should be carried out with variables not considered when calculating arterial stiffness by ABPM; considering that it is a useful measurement in clinical medicine. When determining the systolic and diastolic blood pressure values, through the sphygmomanometer cuff, it is important to consider the influence of the deformation pressure of the artery, which could influence the calculation of the AASI. The latter could be associated, in the equation of the regression line (y = mx+b), with the value of b; when calculating the AASI, which would be worthy of considering and evaluating.

The AASI could be an indirect measure of arterial stiffness and be more directly associated with arterial elasticity and its deformation capacity.

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Data availability statement. The data supporting the findings of this study are openly available on DSpace at http://hdl.handle.net/10872/23236.

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