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Blood Pressure Variability: Evaluation, Prognosis and Clinical Significance

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ABSTRACT
One of the main risk factors for cardiovascular disease is blood pressure. The majority of research has employed mean blood pressure, which is assessed in "out of office" or clinic settings, as a risk indicator. On the other hand, both short- and long-term variations in blood pressure are discernible. In the past, blood pressure fluctuation has been seen as a problem that has to be addressed by better monitoring since it makes it difficult to estimate mean blood pressure accurately. This unpredictability has also been acknowledged as a possible risk factor in and of itself for at least 20 years. Long-term variations in blood pressure were found to be predictive of coronary events and stroke in high-risk individuals.
Keywords: Blood Pressure, Variability, Cardiovascular.

INTRODUCTION
A continuous variable, arterial pressure is physiologically characterized by noticeable oscillations that result from the intricate interplay of humoral, behavioral, reflex neuronal, hemodynamic, and environmental components [(1)]. These oscillations, a homoeostatic reaction, occur physiologically in normotensive people and are usually more pronounced in people with hypertension. Blood pressure (BP) variability is a complex phenomenon that falls into a number of categories (Table 1). The sympathetic nervous system, renin-angiotensin-aldosterone, baroceptive reflexes, and nitric oxide release, and behavioral alterations interact to produce the very short-term variability that is seen in beat-beat fluctuations. Circadian modulations are the primary characteristic of short-term variability, which is defined as pressure fluctuations over a 24-hour period [(2)].

Normal people experience the physiological nocturnal decrease in systolic and diastolic blood pressure (referred to as "dippers"), is one of the most significant. This decrease is less than 10% in certain patients with hypertensive phenotypic species, known as "non-dippers," and in "reverse dippers," the BP even rises at night [(3)]. A frequently sudden increase in arterial pressure in the early morning, referred to as the "morning surge" or "morning rise," is a second source of circadian variability; nonetheless, its exact characterization, particularly with regard to numerical threshold, remains highly contentious [(4)]. The patient's adherence to antihypertensive medication, as well as behavioral and environmental factors like temperature and altitude, impact medium-term variability, which encompasses daily and long-term variability, as exemplified by season-to-season and visit-to-visit fluctuation [(3)].

Table (1): The various forms of blood pressure variability and the factors that influence them [(3)].

Types of blood pressure variability	Determinants
Very short-term variability (beat-to-beat)	↑ Sympathetic activation ↓ Baro and chemoreceptive/ cardiopulmonary reflexes Humoral, rheological, environmental, behavioral, emotional factors Age, activity/sleep Ventilation
Short-term variability (in 24 h)	↑ Sympathetic activation ↓ Baro and chemoreceptive/ cardiopulmonary reflexes Humoral, rheological, environmental, behavioural, emotional factors Age, activity/sleep Improper dosage/titration of antihypertensive therapy ↑ Arterial stiffness
Medium-term variability (day-day)	Improper dosage/titration of antihypertensive therapy ↑ Arterial stiffness Age
Long-term variability (visit-visit < 5 years) and very long-term variability (visit-visit > 5 years)	Improper dosage/titration of antihypertensive therapy ↑ Arterial stiffness Age ↓ Adherence to therapy Blood pressure measurement errors Seasonal changes Ageing

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Differentiating between "long-term" (less than five years) and "very long-term" (more than five years) variability as suggested by **Hastie *et al.*** [5].

Evaluation of pressure variability:

Additionally, accurately assessing blood pressure fluctuation is difficult and even controversial [6]. Before the introduction of the "Penaz method," which uses finger sensors that take use of the photoplethysmography approach, the invasive Oxford intra-arterial technique was used to keep track of the beat-to-beat fluctuations for years [2]**.** The 24-hour Ambulatory Blood Pressure Monitoring (ABPM) technique, which is non-invasive, which takes readings every 15 to 30 minutes, was also used extensively to evaluate short-term variability. The coefficient of variation corrects for the standard deviation of mean arterial pressure, diastolic, and systolic readings as well as the direct relationship between typical and BP variability, can be used to determine 24-hour fluctuation from 24-hour pressure records [3].

However, stresses and day-night variations have an impact on the pressure values' coefficient of variation and standard deviation. When evaluating the short-term variability, alternative indices have been proposed. These consist of the residual variability (also called "residual BPV"), which is derived by employing spectral analysis to remove the slowest components of the actual average variability (also known as "average real variability," or ARV), the 24-hour blood pressure profile, and the average of the absolute changes between consecutive measurements [7]. It was also recommended to employ the weighted standard 24-hour blood pressure deviation (weighted 24-hour blood pressure SD). This carefully removes the impact of evening dipping by figuring out the day-night pressure average [3].

The rationale behind this final methodological change is that, as explained below, while a larger BP variability is a bad prognostic measure. The worse prognosis is associated with a smaller nocturnal pressure reduction, which lowers the 24-hour pressure variability. Consequently, an index that permits the removal of non-dipping or midnight dipping from the assessment of blood pressure variation over a 24-hour period may provide more accurate data from a therapeutic standpoint [3].

However, evaluation of medium- and long-term fluctuations is hampered by a number of issues, including the fact that it is frequently challenging to collect enough measurements to provide a reliable estimate; additionally, the measurement taken in the doctor's office (also known as "office BP") is influenced by the "white coat" effect and does not always represent the arterial pressure readings recorded during the patient's routine activities. Although the ABPM has organizational limitations, it is unquestionably a more dependable approach. Since home measurement (home blood pressure monitoring) enables repeated measurements every day under standardized settings, it appears to be the methodological technique most readily adaptable to large populations [1]**.**

Variability in blood pressure, microcirculation and macrocirculation:

The carotid-femoral pulse wave velocity, or cfPWV, is the gold standard for assessing the stiffness of major arteries without intrusive methods. It is known to be a highly accurate indicator of cardiovascular morbidity and mortality in both the general population and high-risk individuals. In patients with hypertension or the elderly, the proximal arteries are stiffer, therefore the central systolic and differential pressures rise when the reflected wave enters during the meso-systole and travels more quickly [8]**.**

Through a multivariate analysis, **Schillaci *et al.*** [7] demonstrated a strong relationship between the main arteries' stiffness and the 24-hour change in pressure. They also demonstrated how the definition of pressure variability affects the strength of this link, finding that cfPWV and ARV (or "average real variability") had stronger associations than the "weighted" 24-hour SD for blood pressure. But there wouldn't be a causal link between stiffness and pressure fluctuation; rather, it would be a vicious cycle whereby an increase in aortic stiffness would lead to a short-term increase in arterial pressure variability, which would then cause an increase in cfPWV. Through decreased baroreceptor sensitivity, a common feature of altered autonomic regulation in hypertensive patients, the aortic stiffness would grow also favor higher arterial pressure fluctuation [7].

The cfPWV, along with the indices of central hemodynamic estimation and pulse wave reflection, including central arterial pressure and the augmentation index (AIx), can independently predict cardiovascular events and death from all causes. According to **Omboni *et al.*** [9] there is a somewhat significant statistical correlation between 24-hour systolic blood pressure variability indices and arterial stiffness indices, as well as between pressure wave reflection markers like AIx and central systolic blood pressure and pressure variability. Similar to Schillaci's work, the association was stronger in this instance [9]**,** taking into account the weighted SD first, then the ARV [7]**.**

Additionally, a greater degree of pressure variability can be linked to changes in the microcirculation. The lowest vascular resistance of the forearm, an indicator of microvascular change, was discovered to correspond with the 24-hour arterial pressure standard deviation using ABPM as early as 1992 [10]. It has been suggested that microvascular and macrovascular alterations are reciprocal, which could impact pressure variability as well [8].

A reorganization of the microcirculation is indicated by an increase in the media/vessel lumen in essential hypertension [(11)]. These alterations not only intensify the effects of each hypertensive stimulus, but they also raise flow resistance and, as a result, arterial pressure levels [(12)]. This is because the increase in resistances is much more noticeable than in normotensives for the same vascular smooth muscle cell shortening. Thus, this effect of "vascular amplification" of the stimuli can be used to assess an increase in arterial pressure variability [(8)].

The pulsatory wave's reflection and, consequently, the central arterial pressure can be affected by changes in the microcirculation. Indeed, in addition to being the primary source of flow resistance, the microvascular structure is also most likely the source of the majority of wave reflections that raise central systolic pressure, particularly in the elderly [(8)].

There is a substantial correlation between the media/lumen ratio of retinal arterioles and tiny subcutaneous arteries and the systolic and central differential pressure as well as the 24-hour systolic and differential pressure [(13)].

As a result, vascular remodelling in the microcirculation is independently determined by the central differential pressure, which indicates that the big caliber arteries have undergone mechanical modifications. This association would imply that both macrovascular and changes in microvascular structure are linked to arterial hypertension. In actuality, two of the primary reasons for the rise in mean arterial pressure are rarefaction of small arteries and an increase in the media/lumen ratio, which might directly result in greater stiffness of the major arteries [(12)].

Additionally, the advancement of organ damage may be favored by the increased arterial stiffness, which may raise the differential pressure and harm the small arteries that supply the target organs (heart, brain, retina, and kidney). As a result, it is possible to hypothesize the existence of reciprocal interactions and a true vicious loop connecting the pressure variability and the microvascular and macrovascular changes (Fig. 1) [(12)].

Additionally, the significant rise in arterial pressure in the early morning hours may be explained by the structural changes in the microcirculation, which have been related to arterial stiffness and an increased risk of cardiovascular events [(11)]. Additionally, the detrimental effects of the early blood pressure surge may be mitigated by the larger degree of organ damage linked to arterial hypertension [(14)]. In the previously mentioned study [(11)], which supported previous research on the microcirculation of the forearm [(10)], the standard deviation of mean arterial pressure, as measured by the media/lumen ratio of small subcutaneous resistance arteries, and the morning rise in blood pressure were found to be statistically significant "ABPM". However, it is yet unknown if microcirculation alterations and morning blood pressure increase are causally related. The wall of small vessels may be directly harmed by morning pressure increases, even if a higher morning peak that exacerbates hypertensive stressors may result from a rise in the small arteries' media/lumen ratio.

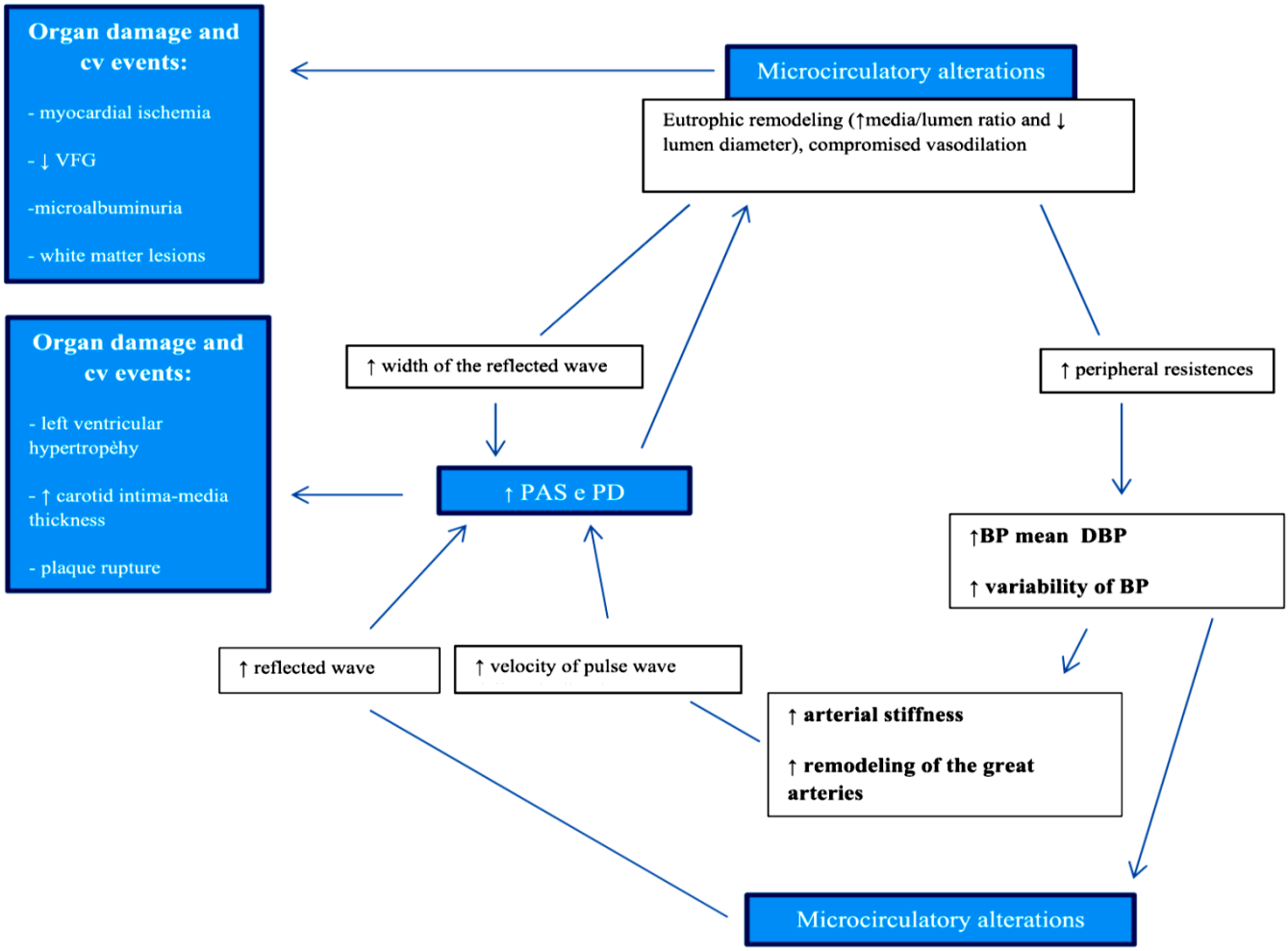

Figure (1): Microcirculation and macrocirculation relationships; possible effects on blood pressure swings in hypertensive people and accelerated aging. ↑ = increased; ↓ = decreased; PA = blood pressure; PAS = systolic blood pressure; PAD = diastolic blood pressure; PD = differential pressure; VFG = glomerular filtration rate; CV = cardiovascular [(11)].

The clinical and prognostic implications of blood pressure fluctuations:

As previously mentioned, high mean blood pressure is thought to be a predictor of unfavorable cardiovascular outcomes. However, because it indicates sympathetic activation and impaired baroceptive reflexes, 24-hour blood pressure variability has been demonstrated in numerous studies to be a predictor of cardiovascular problems and an indication of organ damage [(2)] (**Table 2**).

Table (2): Various forms of blood pressure variability and its significance for prognosis [11].

Types of blood pressure variability	Prognostic relevance
Very short-term variability (beat-to-beat)	↑ SOD ↑ CV events? ↑ Mortality? ↑ Renal damage?
Short-term variability (in 24 h)	↑ SOD (including appearance of micro-albuminuria, ↓ GFR and progression to end stage kidney disease) ↑ CV events (stroke, acute myocardial infarction) ↑ CV mortality ↑ Mortality from all causes
Medium-term variability (day-day)	↑ SOD (including appearance of micro-albuminuria and proteinuria, ↓ GFR) ↑ CV events (stroke, acute myocardial infarction) ↑ CV mortality ↑ Mortality from all causes
Long-term variability (visit-visit < 5 years) and very long-term variability (visit-visit > 5 years)	↑ SOD (including appearance of micro-albuminuria and ↓ GFR) ↑ CV events (stroke, acute myocardial infarction) ↑ CV mortality ↑ Mortality from ischemic heart disease ↑ Non-CV mortality ↑ Mortality from all causes ↑ Mortality from ischemic heart disease

Beat-to-beat fluctuation was not commonly measured in population studies. SOD stands for subclinical damage to the heart, arteries, and kidneys; CV is for cardiovascular; and GFR for glomerular filtration rate.

Cardiovascular disease risk was higher in subjects who did not dip and those who saw a greater increase in morning blood pressure. The predictive importance of the morning pressure rise remains uncertain due to the confounding effect of overnight pressure lowering. Although the two pressure behaviors have conflicting prognostic connotations, in actuality, the morning pressure surge may be lessened if there is no pressure drop during the night [2].

As mentioned earlier, even when mean blood pressure values were not considered, numerous studies connected higher 24-hour blood pressure variability to organ damage and an increased risk of cardiovascular disease. However, in other investigations, a slight increase in cardiovascular risk was associated with pressure fluctuation, indicating that mean blood pressure plays a significant role. Particularly in hypertensive individuals on treatment, visit-visit pressure variability outperformed short-term variability as a predictor of all-cause death, organ damage, and cardiovascular risk. Given that visit-to-visit fluctuation may be a reflection of the long-term efficacy of blood pressure management and treatment compliance, this number is not shocking. Increased visit-visit variability and maximal systolic blood pressure were significant predictors of cerebrovascular events in the ASCOT-BPLA study, regardless of mean systolic blood pressure [2].

However, in ELSA, visit-to-visit variability was not able to predict cardiovascular risk in people with mild to severe hypertension [2].

These contradictory findings suggest visit-to-visit variability may be a strong predictor of cardiovascular events and death in high-risk people, but it carries no additional risk in terms of mean arterial blood pressure values in low-risk subjects [2]. This implies that the underlying level of cardiovascular risk has a significant influence on the connection between cardiovascular risk and visit-to-visit variability. It has recently been shown that visit-to-visit variability and cardiovascular events have a very complex and potentially non-linear relationship, as the risk may increase for both higher and lower blood pressure changes [15].

Recently, **Olesen *et al.*** [16] looked into how aging might modulate the link between left ventricular hypertrophy, macrovascular changes, and blood pressure variability. Age would be a very minor factor, according to these authors.

The question of whether pressure variability is a therapeutic target or not is clinically significant because it

is still unclear if it is merely a risk factor associated with hypertension or if it is a risk factor in and of itself that antihypertensive medication can control. The most likely medications to lessen blood pressure fluctuations are those with a lengthy half-life and a consistent impact throughout a 24-hour period. The trough/peak ratio and the smoothness index are two indices that can be used in clinical practice to evaluate the overall impact of antihypertensive medications on blood pressure variability. The smoothness index requires additional data since it compares the arterial pressure as measured by the ABPM to the standard deviation of the change in blood pressure measurements before and after treatment. Both indices show how long the antihypertensive effect lasts and how it is distributed during the dosing period [(2)].

A small level of organ damage or a more noticeable reversal of the same during therapy appears to be linked to high smoothness index scores. However, there is still much uncertainty regarding the prognostic importance of pressure variability in general, particularly with regard to its capacity to offer extra information regarding average values [(2)].

One of the primary drawbacks is the absence of widely accepted, standardized techniques for identifying and quantifying pressure variability that are also applicable to a large scale. For instance, there is a lack of consensus regarding the most effective way to evaluate visit-to-visit variability or to lessen the influence of confounding variables, such as therapeutic adherence or non-adherence. Furthermore, the methods for defining and quantifying the variability in the 24-hour period are still in their infancy. As previously stated, variability in pressure increases proportionately to average values in addition to being a crucial part of our body's adaptation to our surroundings [(2)].

Future perspectives:

To sum up, more research is required to determine standardized techniques that may be used to examine pressure variations. Even while there are now no medications that only affect blood pressure fluctuation, this could help us better understand its true correlation with cardiovascular risk and, hence, potential treatment consequences. No pressure variability indices currently in use, such as the morning pressure rise, could significantly change the cardiovascular risk profile of the hypertensive patient beyond what blood pressure already suggests, according to a recent critical review of the role of blood pressure variability in cardiovascular risk stratification [(17)]. Therefore, the cardiovascular risk classification should focus on the absolute levels of arterial pressure, the most essential and modifiable risk factor from both non-pharmacological examinations and, most crucially, from drug therapy. Blood pressure variability measurement is useful, especially in research, but it can sometimes provide useful supplemental data, according to the European Society of Cardiology's and the European Society of Hypertension's Guidelines for the Clinical Management of Arterial Hypertension, which support this approach [(18)].

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