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COMMENTARY

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Should reduction of increased short-term blood pressure variability be a target of antihypertensive therapy?

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Abstract

It has long been known that blood pressure (BP) is characterized by marked short-term fluctuations occurring within a 24-h period and also by long-term oscillations occurring over more prolonged periods of time. An increased short-term blood pressure variability (BPV) appears to importantly contribute to target organ damage and to the enhanced cardiovascular risk of hypertensive patients, over and above the effect of an increase in mean BP levels. Reducing 24-h mean BP is the main aim of antihypertensive therapy, but initial data are available that additional cardiovascular protection can be achieved by reducing BPV. However, to definitively prove the prognostic role of short-term BPV and the need for its control by treatment, evidence is still needed from intervention trials aimed at demonstrating that by reducing BPV through administration of antihypertensive drugs, a reduction in organ damage and in the rate of cardiovascular events can be obtained.

1 | INTRODUCTION

An extensive and highly consistent body of evidence indicates that the average level of 24-h ambulatory blood pressure (BP) correlates more closely than casual BP with the cardiovascular (CV) and renal complications of arterial hypertension.[1,2] However, average pressures neglect the temporal variation in BP, which may be also prognostically relevant.[1,3-7] Since the pioneering observations of Stephen Hales, during the 18th century, BP has been recognized as a fluctuating parameter[2]; indeed, it has been shown to be characterized by marked spontaneous oscillations over short-term (minutes to hours) and long-term (days to months) periods. Important BP variations from summer to winter have also been consistently reported (seasonal BP variability). Although in physiological conditions these variations may represent an adaptive humoral and neural response to environmental, behavioral, and emotional stimuli occurring in daily life, they may also reflect alterations in CV regulatory mechanisms.[1] Historically, variability in BP has been viewed as a factor inhibiting accurate measurement of mean BP and as a phenomenon to be overcome by improved monitoring.[1,2] Far from being a "background noise" that hinders the assessment of "true BP,"[2] short-term BP variability (BPV) seems to be relevant to the pathophysiology of target organ damage and to the incidence of clinical events.[1,3-10]

2 | INDICES OF SHORT-TERM BLOOD PRESSURE VARIABILITY

Although the precise quantification of short-term BPV requires beat-to-beat BP recording, its assessment is also possible, even if less accurately, through the use of intermittent noninvasive 24-hour ambulatory BP monitoring (ABPM), at intervals from 15 to 20 minutes.[1] This allows the straightforward estimation of short-term BPV by calculating the 24-h BP standard deviation (SD) and the coefficient of variation (SD X 100/BP mean), which accounts for the dependence of the SD on mean BP levels.[1] Despite the

simplicity of their calculation, these indices are influenced not only by short-term BP variations but also by the degree of day–night BP reduction, and are sensitive to the instability of BP in response to specific stressors (posture, emotional stress, and pain). Accounting only for the dispersion of values around the mean, such indices are very rough indicator of BP dynamics, especially when obtained through a low-frequency discontinuous technique such as intermittent ABPM.[1] The methodological drawbacks of such an approach may partially explain the heterogeneous conclusions achieved by the available literature investigating the prognostic implications of short-term BPV, quantified as SD and assessed by noninvasive 24-h ABPM.[1] Alternative indices have been proposed for estimating faster BP changes: (A) The average real variability (ARV) of 24-h BP, inspired by the total variability concept of real analysis in mathematics, focuses on the sequence of BP readings, and reflects short-term, reading-to-reading, within-subject variability in BP levels. ARV is the average of the absolute differences of consecutive measurements; this statistical parameter is highly sensitive to individual BP measurement order and less sensitive to low sampling frequency of ABPM.[1,3] Some studies in hypertensive patients have shown that ARV is better associated with early renal damage,[9] and with CV risk[1,9] when compared with the traditional SD; (B) the Residual BPV, computed in the frequency domain through spectral analysis of 24-h BP fluctuations, assesses the spectral power of faster BP fluctuations remaining in the 24-h tracing after the exclusion of the slower circadian components of the 24-h BP profile[4]; (C) the "weighted" 24-h BP SD calculated removing the contribution provided by nighttime BP fall to the 24-h SD, by weighting the average of daytime and nighttime BP SD for the duration of the day and nighttime periods and by averaging the SD of these two time subperiods[1]; D) the variance independent of the mean (VIM) seeks to exclude the effect of mean BP from BPV by applying nonlinear regression analysis (ie, plotting SD against mean).[1] Since there is not sufficient evidence directly comparing all these estimates of BPV, it is not possible to indicate which index should be preferred.

3 | PROGNOSTIC VALUE OF SHORT-TERM BLOOD PRESSURE VARIABILITY

Some pioneering investigations performed in humans by using invasive continuous 24-h BP measurements' and early findings in sinoaortic-denervated rats have clearly shown that the adverse CV consequences of high BP not only depend on absolute BP values, but also on the magnitude of short-term BPV within a 24-h period.[1] Over recent decades, several clinical studies have supported the association of short-term BPV with a higher risk of CV events as well as of CV and all-cause mortality.[1,3-7]

In the "Pressioni Arteriose Monitorate e Loro Associazioni" (PAMELA) study, the adjusted risk of CV death showed a significant positive relationship with the residual diastolic BPV, as computed by the spectral powers of 24-h ABP recordings, after accounting for the contribution of day–night BP changes.[4] An analysis of the International Database on Ambulatory BP in relation to CV Outcomes (IDACO) showed a significant predictive value of short-term BPV for most of the outcomes assessed (ie, total and CV mortality as well as all types of fatal combined with nonfatal end points, with the exception of cardiac and coronary events), demonstrating that ARV of 24-h systolic/diastolic ambulatory BP is a better predictor compared to SD.[5] However, in the IDACO analysis, ARV contributed only 0.1% to the prediction of the risk of a composite CV event; such a low predictive value is probably related to the heterogeneity in the ABPM methodologies employed in the different countries from which the ABPM data were pooled.[5] In a further analysis of the ABP International database study, composed of a large population of untreated hypertensive subjects, the SD of nighttime systolic ambulatory BP was found to be an independent predictor of CV events, CV death, and all-cause mortality.[6]

More recently, a meta-analysis of observational cohorts and clinical trials by Stevens et al found that increasing values of short-term BPV (ie, as evaluated on the basis of ambulatory BP recordings) are associated with a significantly higher risk of CV events as well as with higher risk of CV and all-cause mortality.[7]

Regarding possible threshold values for short-term BPV, the analysis of the ABP international database showed that a SD of nighttime systolic ambulatory BP ≥ 12.2 mm Hg was associated with a greater risk of CV events (41%), CV death (55%), and all-cause mortality (59%). The corresponding values for the SD of diastolic BP ≥ 7.9 mm Hg were 48%, 132%, and 77%, respectively.[6] On the other hand, the IDACO analysis also presented the risk of total and CV mortality by quintiles of ARV, showing progressively increased risk among quintiles, with higher event rates observed for systolic/diastolic ARV values of 16.2/12.4 mm Hg, respectively.[5]

4 | SHORT-TERM BLOOD PRESSURE VARIABILITY AND SUBCLINICAL ORGAN DAMAGE

A number of studies assessed the cross-sectional relationships of short-term BPV with the indices of hypertension-mediated organ damage (HDMO), sometimes with discrepant conclusions.[1,8,9]

However, little is known about the associations between longitudinally assessed differences in BPV and the changes in HDMO. The paper of Triantafyllidi et al[10] published in the current issue of the Journal adds a new piece of evidence in this scenario, showing that the short-term BPV reduction (Delta BPV) obtained after 3 years of successful antihypertensive therapy was related to a decrease in left ventricular mass (Delta LVMI), independently of the baseline average BPs and other potential confounding factors. [10] This was true only in the subgroup (n = 119) of well-controlled hypertensive subjects belonging to an overall population of 180 newly diagnosed and never-treated hypertensive patients.[10]

Given that the changes in left ventricular mass are associated with the incidence of CV events, this finding may have prognostic implications.

Two conclusions may be derived from the results of this interesting study: The first and more obvious one is that the primary goal of antihypertensive treatment is the achievement of average BP control; the other one is that a reduction in BPV by treatment may translate potentially into a better outcome. Therefore, in order to optimize CV protection, antihypertensive treatment strategies should be targeted at reducing not only average BP levels but also the degree of BPV.

However, the study of Triantafyllidi et al[10] needs to be interpreted in the context of its limitations.

The association found between Delta BPV and Delta LVMI was adjusted in multivariate analyses for baseline average BP, but not for the reduction of average BPs, thus leaving unsettled the question on whether and how much the relationship between the changes in BPV and in LVM is independent from the reduction of the mean BP.

The study population is represented by a small selected group of Caucasian hypertensive patients without co-morbidities, such as diabetes and chronic kidney diseases. Therefore, the conclusions of this study cannot be extrapolated to non-white populations, and caution is needed when applying the results of this investigation to hypertensive patients with greater CV risk or to those with more advanced degree of kidney or CV damage.

5 | CONCLUSIONS

Interventional longitudinal outcome studies are needed to further clarify the questions regarding whether a reduction in BPV by treatment translates into a better outcome, and whether antihypertensive treatment strategies should be targeted at reducing not only average BP levels but also the degree of BPV.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHORS CONTRIBUTIONS

Giuseppe Mulè and Alessandra Sorce involved in drafting of manuscript. Giuseppe Mulè and Santina Cottone involved in critical final revision. Maria Giovanna Vario and Marta Giambrone involved in literature searching and critical revision. All the authors approved the final version of the paper.

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