Blood Pressure Variability
An Additional Target for Antihypertensive Treatment?
Giuseppe Schillaci, Giacomo Pucci, Gianfranco Parati

According to a widely held view, the adverse cardiovascular consequences of hypertension depend primarily on absolute blood pressure (BP) values, and reduction in average BP by treatment is considered to be the main target to be reached for preventing cardiovascular morbidity and mortality in hypertensive subjects. However, availability of ambulatory BP monitoring techniques has led to an increasing awareness of the continuous variability which characterizes BP,1 with often pronounced fluctuations occurring over both short- and long-lasting observation periods in response to environmental challenges and as a result of the activity of cardiovascular control mechanisms. In spite of such evidence, the clinical value of the BP fluctuations around the mean level has received limited attention so far. Indeed, “random” spontaneous fluctuations of BP have been usually disregarded as a trivial or erratic factor, potentially acting as a confounder of the association of an individual’s short- or long-term “true” average BP with the cardiovascular complications of hypertension. Within-subject BP variability had been mostly dismissed as a “background noise” that might dilute the solid prognostic effect of average BP values (the so-called “regression dilution bias”) and which must thus be neutralized by appropriate statistical techniques to appreciate the “true” prognostic value of the usual BP (ie, of the individual’s BP level averaged over a given recording period).2

The axiom that average BP is the most important (or even the only) factor to be considered in the clinical management of hypertensive patients has been called into question by a number of studies, performed over the last 30 years,3–8 which have suggested that also short-term BP fluctuations might have a prognostic relevance, predicting organ damage3–4 and cardiovascular events5–8 over and above the contribution provided by average BP values in patients with hypertension.

At the same time, other studies have investigated the possible determinants of 24-hour BP variability and have provided evidence that BP variability increases with increasing average BP levels and age,1,9 and its increase may accompany high-risk conditions, such as diabetes mellitus.10 Thus, the question is still open whether BP variability has a pathogenetic role in cardiovascular disease (direct causality) or whether it is a secondary phenomenon of subclinical vascular changes (reverse causality).11

Because of these uncertainties, the possible role of BP variability as a target for antihypertensive treatment has also been largely disregarded. In particular, given the close relationship found to occur between BP variability and average BP levels,1 it is still matter of debate whether antihypertensive drug treatment may reduce BP variability independent of the concomitant reduction in mean BP levels. An additional reason for the inadequate attention paid so far to the possible effects of treatment on BP variability is the limited evidence available in humans that a reduction in the degree of BP fluctuations might result in a parallel reduction in organ damage12 and, even more importantly, in the rate of cardiovascular events.

In a post hoc analysis of a subgroup of 1905 participants to the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial who underwent 24-hour ambulatory BP monitoring yearly, daytime BP variability (expressed either as SD or coefficient of variation of daytime systolic BP) was lower in theamlodipine group than in the atenolol group.13 In that study, however, ambulatory BP monitoring had not been performed at baseline in untreated subjects. In the main Anglo-Scandinavian Cardiac Outcomes Trial database, anamlodipine-based regimen was associated with a lower in-treatment visit-to-visit systolic BP variability than an atenolol-based regimen, and treatment-induced changes in visit-to-visit BP variability predicted the risk of future cardiovascular complications.13 However, visit-to-visit BP variability has only a weak relation (r=0.29 to 0.38) with an established measure of BP variability, that is, the SD of daytime BP on ambulatory monitoring,13 and might reflect poor patient compliance with treatment or errors and biases in clinic BP measurements more than alterations in cardiovascular control mechanisms or in vascular properties, an issue that deserves to be further addressed with a proper methodological approach. In a meta-analysis of 398 intervention BP-lowering trials,14 calcium antagonists reduced between-subject BP variability, expressed as the ratio between in-treatment BP variance and baseline BP variance (“variance ratio”), whereas β-blockers, angiotensin-converting-enzyme inhibitors, and angiotensin II receptor blockers increased variance ratio. An obvious limitation in interpreting these data, however, is that between-subject BP variability is only a rough surrogate measure of visit-to-visit
within-subject BP variability, being able to explain only 41% of the latter.15

In large-scale clinical trials, BP-lowering drugs have usually been shown to decrease short-term BP variability, although no significant changes were observed when BP variability was normalized for absolute BP level by using coefficients of variation.8,16 A demonstration of the possibility to reduce BP variability in diabetic patients with hypertension by treatment with the calcium-channel blocker lacidipine was provided only thanks to the implementation of a demanding and expensive technique for noninvasive, beat-by-beat, ambulatory BP monitoring over 24 hours (Portapres, Finapres Medical Systems BV, Amsterdam, the Netherlands).17 Thus, the evidence suggesting the existence of drug-specific effects on BP variability should still be regarded at most as an indirect one.

In the present issue of Hypertension, Zhang et al18 produce new data on the effects of different antihypertensive agents on BP variability. They analyzed ambulatory BP monitoring data of 577 patients before and after 3-month antihypertensive treatment in the setting of the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, a multicenter, international, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (placebo, amlodipine, candesartan, and indapamide sustained release). Within-subject mean and SD of 24-hour BP, weighted by time interval between consecutive readings according to an approach described previously by Bilo et al,19 were calculated in 3 time frames (daytime, nighttime, and 24 hours) to evaluate BP and BP variability. BP variability was also quantified according to the approach described by Mena et al,20 that is, by computing the average of the measurement by measurement BP changes, defined as “average real variability.” The mean 24-hour heart rate and heart rate variability were calculated with the same algorithms.

Zhang et al18 found that all 3 active treatments had a similar BP-lowering effect, whereas amlodipine and indapamide sustained release, but not candesartan, significantly reduced weighted BP variability after 3-month treatment. Only amlodipine, however, reduced average real variability. The main determinants of BP variability at baseline were age, mean BP, and the corresponding heart rate variability. However, the reduction in BP variability by amlodipine was significantly associated with the reduction in BP and the reduction in heart rate variability, whereas the corresponding reduction by indapamide sustained release was only associated with the reduction in heart rate variability at night. Moreover, with the exception of the reduction in 24-hour BP variability (improperly defined as “daily” BP variability by the authors) with indapamide, all of the other reductions in BP variability by amlodipine or indapamide remained significant after adjustment for average BP reduction.

Several mechanisms can be hypothesized by which antihypertensive treatment may lead to a reduction in BP variability. First, BP variability over a given period is strongly dependent on average BP levels,1,9 and BP variability reduction could be simply because of the effect of treatment on average BP. Indeed, in the present study, average BP reduction was a major determinant of BP variability reduction, although the latter remained significant after adjustment for average BP reduction at least in some conditions. Secondly, in the study by Zhang et al,18 the effects of amlodipine and indapamide sustained release on BP variability were explained in part by a reduction in heart rate variability, thus suggesting that a modulation of the autonomic nervous system regulation may play a role in the treatment-induced reduction in BP variability. Increased short-term BP variability may result from a depressed baroreflex function.1,21 A blunted baroreflex function may lead to excessive BP fluctuations in either direction in response to physical and mental stimuli, and changes in respiration and rhythmic alterations in central autonomic drive mediated by baroreflex mechanisms are important determinants of short-term BP variability.22 The sensitivity of the arterial baroreflex and 24-hour BP variability are linked by an inverse relationship, that is, the greater the BP variability, the lower the ability of the arterial baroreceptors to modulate BP and heart rate.23 However, it should be emphasized that proper assessment of the integrated modulation of BP and heart rate variability by the autonomic nervous system would require beat-by-beat assessment of BP and heart rate changes. Finally, it should be considered that a reduction in BP variability could also be related to an improvement in arterial distensibility,24,25 although this hypothesis deserves to be investigated further.

The findings of the study by Zhang et al18 should be interpreted within the context of its limitations. BP variability was assessed through noninvasive monitoring, with 1 BP reading every 15 minutes over the entire 24-hour period. Although this procedure is accurate in estimating average BP under resting and ambulatory conditions, and may provide an acceptable estimate also of the 24-hour BP SD,26 it may miss information on important BP changes occurring within seconds or minutes. In fact, a sampling interval of 15 minutes provides information on BP fluctuations occurring in the “very low” frequency range (1 beat of 1000), whereas the higher-frequency components of short-term BP variability go undetected and can only be assessed with a beat-to-beat measurement technique. Moreover, SD only gives information on the overall variability around the average period level, without insight into rapid BP changes. However, the reduction in BP variability with amlodipine treatment was also confirmed when BP variation was measured as average real variability, a parameter that is based on the average of the absolute differences of consecutive measurements and is less affected by BP trends.20 The relatively small number of study subjects and the short duration of treatment (3 months) make it impossible to draw conclusions about the long-term effects of antihypertensive treatment on BP variability.

The method used to quantify the reduction in BP variability in comparison with the placebo group and the multivariate approach followed to account for confounders when assessing the reduction in BP variability should have been better described. Moreover, the relation between changes in BP and in heart rate variability is not explored in depth, on the background of the well-known differences in the mechanisms responsible for heart rate variations on a beat-to-beat basis or over time periods of minutes and hours. Finally the discussion...
includes some unsupported extrapolations, such as the hypothesis that indapamide might reduce BP variability probably because of a reduction in arterial stiffness, a possibility not suggested by the present study data.

Given the results of the present study,\textsuperscript{19} and on the background of the current literature, should we consider BP variability reduction as an additional goal for antihypertensive treatment, along with the reduction in average BP values, in our current practice? Providing a definitive answer to this question is a difficult task, and probably the available evidence is not solid enough to support such a conclusion. This position is based not only on the limitations in the design and methodology of the study by Zhang et al\textsuperscript{18} but also on the fact that treatment-induced modifications in BP variability are difficult to measure in daily clinical practice, where patients are usually treated with different drug regimens, which change frequently according to clinical needs. Moreover, despite the fact that BP variability reduction, resulting from antihypertensive treatment, was shown to contribute independently to organ protection in experimental animals,\textsuperscript{27} there is currently no proof that BP variability reduction improves cardiovascular risk in human subjects. In spite of these considerations, however, the new findings, including those by Zhang et al,\textsuperscript{18} appear provocative enough to stimulate a reanalysis of the many available databases from large-scale observational studies and randomized clinical trials, as well as to suggest that BP variability reduction should be considered as a possible new target to explore by future intervention trials in hypertension.

Disclosures

None.

References

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