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COMMENTARY

Blood pressure variability: a confounder and a cardiovascular risk factor

Dimitris E Papadogiannis and Athanase D Protogerou

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High blood pressure (BP) is a leading cause of cardiovascular (CV) disease. Although the diagnosis of high BP appears to be straightforward, in clinical practice, misdiagnosis is not rare, and even after many years of research there are still several unresolved issues regarding optimal BP classification.[1] For example, the phenomena of isolated office hypertension (that is, high BP when at the doctor's office despite a normal BP out of the office) and masked hypertension (that is, normal BP in the doctor's office and high BP out of the office) lead to frequent over- and under-diagnosis of BP-associated CV risk. One of the main causes of the misdiagnosis of hypertension is the variability of BP.

In this issue of the Journal, Cahan *et al.*[2] describe the role of 24-h BP variability (both daytime and 24-h variability, as assessed by ambulatory BP monitoring) in the misdiagnosis of hypertension when office BP recordings from a single visit were used as the basis for diagnosis. The results can be summarized as follows: in the presence of higher systolic BP variability, a higher difference (measured as absolute mm Hg) was observed between office BP and awake ambulatory BP monitoring readings. In other words, patients with isolated office hypertension ('white coat hypertension') and masked hypertension had higher BP variability than subjects with sustained normotension and sustained hypertension.

Before discussing these new data and the questions they raise, we briefly discuss several cardinal issues related to the physiology, quantification, and impact of BP variability on diagnosis and cardiovascular risk.

DE Papadogiannis and AD Protogerou are at the Hypertension Center, 1st Propaedeutic Department of Internal Medicine, National and Kapodistrian University of Athens, Laikon Hospital, 17 Agiou Thoma Street, Athens 11527, Greece.
E-mail: d_papadogiannis@yahoo.com

PHYSIOLOGY AND QUANTIFICATION OF BP VARIABILITY

Variability is broadly defined as the 'the state or characteristic of being variable' and describes how spread out a set of data is. With respect to BP, several (or rather most) aspects of variability are still unclear or even overlooked. First, BP varies over time (for example, beat to beat, minute to minute, hour to hour, day to day and visit to visit) but also in space (for example, along the upper limb, from the radial artery to the aorta).[3] The present study focused on time-dependent BP variability. Spatially dependent BP variability and the interaction between time and spatially dependent variability are still completely neglected by hypertension specialists. Second, although some level of time-dependent BP variability is an inherent characteristic of BP, there are several other causes of time-dependent BP variability. Briefly, the inherent time-dependent variability can be attributed to physiological (acute or circadian) fluctuations in the activity of the neuroendocrine system, which governs the function of the cardiovascular system. The observer, the device and the setting (office *vs.* out of office) are other possible sources of BP variability. Their contributions cannot be easily separated—or, to be more precise, can be only partly separated—from the inherent time-dependent BP variability, even in well-designed clinical experiments.[4] Third, there have been few studies on the effects on BP variability of stress (defined as any state of threatened homeostasis,[4,5] which is a cardinal modulator, both acutely and in the long term, of cardiovascular mechanics) and the response to stressors (real or imagined, mental or somatic). Finally, the underlying arterial mechanics associated with BP variability, such as variations in arteriolar tone, pressure wave reflections, total peripheral resistance and cardiac output, have not been adequately investigated.

In clinical studies, several markers of time-dependent BP variability have been used[6,7] (for example, s.d., coefficient of variation and even the maximum absolute differences). It is clear that these parameters are not independent of the mean BP value or the methodology that was used to collect the data; relevant factors include the setting, the time period (24 h or time from visit to visit) and the measurement device. Moreover, these markers incorporate not only the within-subject variability but also the variability observed in the study population. Thus, there are no data to date regarding the best marker of time-dependent BP variability.

IMPACT OF TIME-DEPENDENT BP VARIABILITY ON CLINICAL PRACTICE

In clinical practice, there are several different situations in which time-dependent BP variability is encountered. The most common situation is the often large minute-to-minute variation of BP in office recordings. The circadian, dipping/non-dipping and morning surge patterns represent other facets of the same issue that have important clinical implications for the diagnosis and treatment of hypertension (e.g., chronotherapy). Most importantly, although BP variability has been classically recognized as a confounding factor as far as the diagnosis of hypertension is concerned, new evidence[6,7] has revitalized interest in BP variability.[8] Visit-to-visit BP variability (but also 24-h BP variability) is now proposed to be an independent CV risk factor, beyond the mean level of BP.[6,7] This concept is potentially even more crucial for clinical practice because it has also been proposed that time-dependent BP variability

may be altered by specific classes of antihypertensive drugs.[9] In other words, time-dependent BP variability may represent a new CV risk factor, biomarker and target for treatment.

LIMITATIONS OF AND ISSUES RAISED BY THE PRESENT STUDY

The main finding of the study by Cahan *et al.*[2] is that high time-dependent 24-h BP variability is a predictor of white coat and masked hypertension. This effect was independent of drug treatment and was not associated with heart rate. These data have no direct clinical applications, given the fact that 24-h ambulatory BP monitoring is considered the gold standard for the clinical diagnosis of hypertension and always follows office BP readings. However, these data show very clearly the impact of time-dependent variability on the phenomena of white coat and masked hypertension as pathogenetic mechanism; they also show that this impact is independent of heart rate. Moreover, the present data raise the question of whether the excessive CV risk observed for subjects with masked hypertension (and to a lesser extent for subjects with white coat hypertension) in comparison with subjects with sustained normotension is related to the presence of excess BP variability. This issue merits future investigation with cross-sectional and prospective studies.

In the study by Cahan *et al.*, the classification of BP was based on a single office visit and a single 24-h ambulatory BP-monitoring period. However, the white coat effect and masked hypertension incorporate the variability of both office and out-of-office recordings. It is also known that the prevalences of white coat and masked hypertension are reduced when the frequency of office visits and 24-h recordings is increased.[1] Therefore, future studies should also address the association between the reduction in BP variability after consecutive office visits and 24-h BP recordings and the expected lower number of subjects with misdiagnosed hypertension. Finally, the results of this study should be further investigated in the setting of home BP recording to determine whether the expected similarities exist, as well as to identify the implied differences between men and women.

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