Mechanisms and Clinical Implications of Blood Pressure Variability

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INTRODUCTION

In the past thirty years, techniques that allow systolic and diastolic blood pressure values to be assessed in ambulant subjects have provided conclusive evidence that blood pressure undergoes profound and spontaneous fluctuations over the 24-hour period. Al least three are the reasons which explain the growing interest of investigators and clinicians on these fluctuations, which represent the so called blood pressure variability phenomenon. First, an accurate analysis of blood pressure variability during the 24 hours has an undisputed pathophysiological relevance, allowing information on the mechanisms involved in blood pressure homeostatic control to be collected both in physiological and in pathological conditions, such as essential and secondary hypertension, congestive heart failure and other cardiovascular or non-cardiovascular diseases, such as diabetes and renal insufficiency affecting autonomic control of circulation. Second, such analysis would improve the diagnosis of hypertension by allowing to achieve more conclusive information on the end-organ damage associated with high blood pressure values as well as on the organ damage progression over the years. Finally, it can represent a valuable tool for assessing the efficacy of antihypertensive drug treatment.

This paper will review the nature, magnitude and possible mechanisms of blood pressure variations occurring over the 24-hour period. It will then discuss the clinical relevance of blood pressure variability by providing evidence that this hemodynamic parameter may represent an independent determinant of the target-organ damage frequently detected in the hypertensive patient. Finally the therapeutic implications of the above mentioned findings will be briefly highlighted.

TWENTY FOUR HOUR BLOOD PRESSURE VARIABILITY

Intra-arterial blood pressure monitoring in ambulant subjects has shown that blood pressure values may vary by more than 50-60 mmHg over the 24 hours (1). These variations originate from short-lasting pressor and depressor episodes that give the blood pressure recording a typical unstable appearance even over short periods in immobilized patients. They also originate, however, from the regular occurrence of markedly higher day-time and lower night-time values, the day-night blood pressure difference being usually around 15-20 mmHg (1).

Blood pressure variability has been widely assessed by calculation of the standard deviation of 24 hour systolic, diastolic, and mean arterial pressure. This allowed investigators to determine that 1) variability of 24 hour mean arterial pressure is about 10% of the mean value, with large interindividual differences and 2) systolic blood pressure variability is usually greater than the diastolic one, although this difference is attenuated when percent (coefficient of variation) rather than absolute (standard deviation) values are employed in the calculation (1-3). Twenty four hour blood pressure standard deviation can be precisely estimated only from analysis of the beat-to-beat blood pressure tracing, its actual magnitude escaping the intermittent blood pressure readings typical of automatic blood pressure monitoring (4). However, data recently collected by our group indicate that not only intra-arterial blood pressure recordings but also beat-to-beat finger blood pressure values, non invasively obtained via the portable version of the Finapres device called Portapres, can be employed with little error to estimate 24 hour blood pressure variabilities if diastolic and mean pressures are used (5).

Several attempts have been made throughout the years to complement 24 hour blood pressure standard deviations with other indices of blood pressure variability. In our studies, for example, we distinguish an among-half-hour blood pressure standard deviation (variability among half-hours), which reflects day and night and other relatively sustained blood pressure differences, and a within-half-hour blood pressure standard deviation (variability within half-hours), which reflects the short-lasting blood pressure fluctuations occurring in subperiods of limited duration (1-3). Other more complex components of 24 hour blood pressure variability can be identified by sophisticated approaches, such as power spectrum analysis of the blood pressure signal (2-3).

Blood pressure may also vary between months and seasons. This has been recently documented by the results of a study from our group showing that in a large population sample of the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) Study clinic, home and 24 hour ambulatory systolic and diastolic blood pressures undergo marked interseasonal differences, the lowest values being detectable in the summer period, while the highest in the winter one (6). Such differences, which are less pronounced for 24 hour day-time and night-time average ambulatory pressures than for clinic and home blood pressures, can be detected not only in normotensive but also in untreated hypertensive subjects and in treated hypertensive individuals as well. The PAMELA Study also allowed to clarify that, in contrast to what it has been previously suggested, no difference exists in clinic, home and ambulatory blood pressure values during the different days of the working week (6).

Several other issues related to blood pressure variability deserve to be briefly mentioned. One, blood pressure fluctuations increase progressively with the subjects' age, particularly when short-term variability is considered (2,3). Two, nearly all studies that have examined blood pressure variability in essential hypertension agree that the standard deviations for 24 hour blood pressure rise progressively with increasing levels of blood pressure (1-3). This is unlikely a result of an increase in day-night blood pressure differences, since nocturnal hypotension appears to be similar for magnitude in both normotensive individuals and in patients with high blood pressure, but it rather appears to be related to an increase in the magnitude of short-lasting blood pressure oscillations.

MECHANISMS OF BLOOD PRESSURE VARIABILITY

Although the precise mechanisms responsible for 24 hour blood pressure variability have been not yet satisfactorily clarified, several evidences collected during the past few years have unequivocally shown that behavioral, neural, reflex and humoral factors participate in the phenomenon.

As far as behavioral factors are concerned, there is conclusive evidence that acute dynamic physical exercise and emotional stress may increase blood pressure values and blood pressure fluctuations, while other conditions, such as sleep and digestion may cause a clear cut reduction (3,7). An emotional condition which markedly affects blood pressure values is that triggered by the sphygmomanometric blood pressure measurements made by the physician. This phenomenon, known as the "white-coat effect", is characterized by a sudden and marked blood pressure rise which persists over the whole period of the doctor's visit and disappears at a variable inter-individual rate after the doctor's departure (8). Recent findings provided by our group (9) have shown that the pressor response to the alerting reaction accompanying sphygmomanometric blood pressure measurements is coupled with complex changes in sympathetic nerve activity (directly quantified by the microneurographic technique) to the skin circulation and skeletal muscle district by activating sympathetic outflow to the former and concomitantly inhibiting adrenergic drive to the latter. It is likely that this heterogeneous pattern of response may have a central origin, i.e. it may be inborn in diencephalic areas integrating cardiovascular adjustments to emotional behavior, whose stimulation has been shown in experimental animals to elicit adrenergic activation to the heart, skin and visceral areas with inhibition to skeletal muscle.

As above mentioned, blood pressure fluctuations are also largely related to changes in respiration as well as to rhythmic alterations in central autonomic drive mediated by baroreflex mechanisms (3,7,10,11). Indeed, reflex influences stemming from the arterial baroreceptors have been shown in experimental

animals to exert an important buffering action on spontaneous blood pressure variability (12), their inactivation by surgical section of the carotid sinus and aortic nerves favoring by a marked increase in the magnitude of blood pressure fluctuations (13). A similar phenomenon has been reported also in human subjects undergoing neck surgery for a variety of diseases (14). Two further sets of data strengthening the importance of baroreflex mechanisms in blood pressure variability deserve to be mentioned. The first one refers to the evidence that the sensitivity of the arterial baroreflex, assessed via the traditional laboratory technique based on intravenous infusion of phenylephrine and nitroprusside, and the blood pressure oscillations, assessed during the 24 hours, are linked by an inverse relationship, i.e. greater the blood pressure variability lower the ability of the arterial baroreceptors to modulate blood pressure and heart rate (15). The second one is represented by the finding that the magnitude of hourly standard deviations of systolic blood pressure is inversely related to the average of the slopes relating spontaneous progressive increases or reductions in systolic blood pressure with the progressive bradycardia or tachycardia (15). Taken together these findings strongly support the concept that central neural factors as well as baroreflex mechanisms are important determinants of the blood pressure variability phenomenon.

Finally humoral factors (angiotensin, endothelin, nitric oxide, bradykinines, insulin) may participate in the determination of blood pressure fluctuations, although the evidence so far provided in this regard cannot be considered as conclusive (3,10,11). In contrast, there is evidence, although indirect, that in man there is a relation between blood pressure variability and resting sympathetic activity (10,11). We have recently shown that not only blood pressure variability but also sympathetic activity, directly quantified in humans by the microneurographic technique in a peroneal nerve, becomes progressively greater from normotensive to mild and more severe essential hypertensive subjects (16-17). If the relationship between sympathetic factors and blood pressure fluctuations will be more stringently documented in future studies, this observation will provide evidence that an enhanced cardiovascular drive is involved in the increase in blood pressure variability characterizing the essential hypertensive state.

CLINICAL RELEVANCE OF BLOOD PRESSURE VARIABILITY

Although it has been shown that high clinic blood pressure values to some extent is predictive of increased cardiovascular morbidity and mortality (18), a number of patients with high clinic blood pressure will not experience morbid or fatal cardiovascular events. This finding may be explained, at least in part, by the fact that isolated blood pressure measurements made during clinic visits do not precisely reflect the prevailing blood pressures occurring during normal daily life conditions, suggesting a potential superiority of the 24 hour ambulatory blood pressure monitoring approach over the sphygmomanometric one. This superiority is supported by the well documented evidence that target organ damage associated with high blood pressure is more closely related to 24 hour ambulatory systolic or diastolic blood pressure than to the corresponding sphygmomanometric values (19). This has been shown for echocardiographic left ventricular hypertrophy, systolic and diastolic dysfunction, vascular hypertrophy, cerebral lacunae and infarction, renal damage and retinopathy (20-28). This has been recently further documented by the entry-data of the ELSA (European Lacidipine Study on Atherosclerosis) Study, in which carotid artery vessel wall abnormalities, assessed by ultrasonography, were found to be more strictly related to 24 hour average blood pressure values than to clinic blood pressures (29). Finally, in a recently published longitudinal study, the SAMPLE (Study on Ambulatory Pressure and Lisinopril Evaluation) Study, it has been unequivocally shown that in hypertensive subjects with left ventricular hypertrophy, regression of the abnormal thickness of left ventricular walls induced by antihypertensive drugs is much more closely predicted by treatment-induced changes in ambulatory rather than in clinic blood pressure values (30). It can thus be concluded that the clinical superiority of ambulatory versus clinic blood pressures has been clearly demonstrated both by cross-sectional and prospective studies.

Not only absolute blood pressure values but also blood pressure fluctuations during the 24 hour period have been documented to participate at determining end-organ damage. It has been for example shown that the extent of target organ damage correlates with the number of daily blood pressure peaks occurring during the daytime and associated with environmental, exercise or stressful stimuli (2,3,20). It has also been shown that, for a given 24-hour average blood pressure, the score of the target organ damage

associated with hypertension directly and closely correlates with 24 hour blood pressure standard deviations (19), and that a greater blood pressure variability also correlates with the increase in end-organ damage (in particular the degree of left ventricular hypertrophy) observed over the subsequent seven year period (31). These data suggest, although they do not prove conclusively, that the adverse effects of hypertension on the cardiovascular system are reflected and determined not only by the degree of the blood pressure elevation, but also by the magnitude of the blood pressure variability occurring over the 24 hour period.

THERAPEUTIC IMPLICATIONS

Given the relevance in the clinical setting not only of 24 hour absolute blood pressure but also of blood pressure variability, its reduction should be considered as one of the major goals of antihypertensive drug treatment. This goal cannot be considered at present as an easy one to be achieved (2,3,32). However, due to the importance of the adrenergic nervous system in determining and/or enhancing spontaneous blood pressure fluctuations, it should be expected that antihypertensive drugs with central sympatholitic properties would allow to improve the abnormal pattern of blood pressure variability seen in essential hypertension. In addition, a therapeutic sympathetic deactivation will allow to obtain further favorable effects, such as a regression of left ventricular hypertrophy, an improvement in the metabolic profile and, by reducing vascular hypertrophy, an improvement in tissue perfusion. All these effects would thus allow to achieve in treated hypertensive patients a cardiovascular protection greater for magnitude than that induced by the simple blood pressure reduction.

SUMMARY

Several studies have unequivocally shown that the end-organ damage associated with the hypertensive condition is more closely related to 24 hour average blood pressure values than to clinic blood pressure. Blood pressure, however, is highly variable over the day-time and night-time period and of major interest is whether average 24 hour blood pressure values, as well as 24 hour blood pressure variability, correlate with, and are possibly responsible for, the hypertension-related alterations of the end-organ structure and function. This paper will address this issue by discussing the main features of blood pressure variability in hypertension. It will also examine the mechanisms involved in this phenomenon, with particular emphasis on the pathogenetic role of sympathetic neural factors. The clinical relevance of blood pressure variability in promoting target organ damage, as well as its therapeutic implications, will be finally highlighted.

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