Original Article

Morning Blood Pressure Surge: The Reliability of Different Definitions

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Preliminary evidence suggests that the morning surge (MS) in blood pressure (BP) is an independent predictor of cerebrovascular disease. However, the optimal definition of MS is uncertain. To compare the reproducibility of several MS definitions used in the literature, 132 untreated hypertensives were assessed with ambulatory BP monitoring twice, 2 weeks apart. Five MS definitions were compared. MS-1: the average BP of the first hour after rising minus the average BP of the first hour before rising; MS-2: BP 2 h after rising minus that of 2 h before rising; MS-3: BP 3 h after rising minus that of 3 h before rising; MS-4: BP 2 h after rising minus the average BP during sleep; MS-5: BP 2 h after rising minus the average BP of 3 consecutive readings, centered on the lowest reading during sleep. The reproducibility of each MS definition was assessed using the concordance correlation coefficient (CCC), the standard deviation of differences (SDD) and the coefficient of variation (CV) between repeated MS assessments, and the agreement in detecting "surgers," defined as subjects at the top quartile (Q4) of the MS distribution. CCCs were 0.20/0.30, 0.43/0.45, 0.53/0.51, 0.51/0.47, and 0.46/0.48 (systolic/diastolic) for MS-1 to MS-5 respectively; SDDs were 14.3/11.4, 12.1/9.9, 11.2/9.5, 10.3/8.2, and 11.9/9.8, respectively; CVs were 0.49/0.57, 0.44/0.39, 0.37/0.35, 0.36/0.31, and 0.27/0.24, respectively; and the agreement in detecting "surgers" was 69%/70%, 71%/76%, 75%/75%, 81%/83%, and 74%/75%, with κ of 0.18/0.20, 0.23/0.36, 0.33/0.33, 0.49/0.53 and 0.29/0.31, respectively. There are important differences in the reproducibility of MS calculated by different methods. MS4 appears to provide the most reproducible definition of MS. (*Hypertens Res* 2008; 31: 1589–1594)

Key Words: **morning surge, blood pressure, ambulatory monitoring, reproducibility**

Introduction

Long-term studies have shown that ambulatory blood pressure (BP) is superior to conventional office measurements in predicting cardiovascular morbidity and mortality (*1*). Interestingly, several aspects of the diurnal BP profile have been shown to provide additional prognostic information beyond that provided by the 24-h average value.

Studies have shown that nighttime ambulatory BP is a stronger predictor of cardiovascular mortality than daytime or 24-h average BP, even after adjustment for daytime BP (*2*, *3*). Furthermore, the non-dipping diurnal pattern, defined as a reduction of the normal nocturnal decline in BP during sleep, has also been associated with increased cardiovascular risk, independently of the 24-h average BP (*4*, *5*). Recently, attention has been focused on the morning surge (MS) in BP upon arising from bed, which appears to parallel the MS in the incidence of cardiovascular events (*6*). In subjects with nighttime as well as afternoon sleep (siesta), the respective morning and evening BP surges have been shown to strictly parallel the surge in physical activity (assessed by wrist actigraphy) and also the surge in stroke onset (*7*).

Ambulatory BP monitoring allows for quantification of the MS in BP by providing measurements in the hours before and after awaking. Studies have shown that an exaggerated MS is associated with left ventricular hypertrophy (*8–11*) and dysfunction (*10*), carotid atherosclerosis (*12*), arterial stiffness

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(*11*) and microalbuminuria (*11*). More importantly, an exaggerated MS has been associated with stroke risk independent of ambulatory BP level (*13*, *14*), cerebral hemorrhage (*15*) and cardiovascular events (*8*). Therefore, it has been suggested that MS might be an additional new target in the treatment of hypertension for the prevention of target organ damage and cardiovascular events (*13*, *16*).

Several definitions have been used to quantify the MS on the basis of ambulatory BP data. For the assessment of post-rising BP, some investigators have used a fixed post-rising time period (ranging from 1 to 4 h) (*13–15*, *17–19*), whereas the first single post-rising measurement (*8*), or the highest measurement of the first (*20*) or first 2 (*21*) or 4 h post-rising (*16*) have also been used. For the calculation of pre-rising BP, some studies averaged all nighttime measurements (*22*, *23*), others averaged the lowest reading in the 1st (*20*) or the 4 h pre-rising (*16*), or calculated the average of the lowest nighttime reading and the two closest readings (before and after the lowest one) (*9*, *13*, *14*, *24*).

The reliability of measurement of any aspect of BP is crucial for both research and clinical application. The objective of this study was to compare the reliability of the MS measurement calculated using different definitions in the same patients.

Methods

Inclusion Criteria

Untreated subjects referred to an outpatients' hypertension clinic for hypertension, with an average diastolic BP 90–115 mmHg at the initial clinic visit, were recruited. Subjects treated for hypertension whose diagnosis of hypertension was questionable were also considered for inclusion after a 2-week wash out period. Exclusion criteria were: age <18 years, electrocardiographic left ventricular hypertrophy, diabetes mellitus, known cardiovascular, renal or liver disease, clinic BP>200/115 mmHg (systolic/diastolic), evidence of secondary hypertension, and unwillingness to participate in the study. The protocol was approved by the hospital scientific committee. Data from this study involving office, home and ambulatory BP have been previously published (*25*, *26*). For the present analysis, the ambulatory BP data collected in this study were used.

Ambulatory BP Monitoring

Twenty-four hour ambulatory BP monitoring was performed twice on routine workdays 2 weeks apart using SpaceLabs 90207 oscillometric devices (SpaceLabs Inc., Redmond, USA; bladder size 23×12 cm, or 30×14 cm where appropriate) (*27*). Subjects were instructed to follow their usual daily activities but to remain still with the forearm extended during each reading. A brief diary was supplied to report the time when they went to bed and arose during ambulatory BP monitoring. Before each ambulatory BP monitoring session, the accuracy of the devices was tested against a standard mercury sphygmomanometer by manual activation (three successive readings; Y connector) in order to ensure that there was no consistent difference of >10 mmHg in the measured BP.

MS Definitions

The calculation of the MS in BP was based on five different definitions used in previous studies: MS-1: the average of BP readings of the first hour after rising minus the average of readings of the first hour before rising (*17*); MS-2: BP readings 2 h after rising minus those of 2 h before rising (*13–15*); MS-3: BP readings 3 h after rising minus those of 3 h before rising (*19*); MS-4: BP readings 2 h after rising minus the average of all readings during sleep (*22*, *23*); MS-5: BP readings 2 h after rising minus the average of 3 consecutive BP readings, centered on the lowest reading during sleep (*9*, *13*, *14*, *24*).

Criteria of MS Reliability

The reliability of MS based on each definition was assessed using the following criteria: 1) Stability of the average MS values based on their SD. 2) Reproducibility, quantified by concordance correlation coefficients (CCC), the SD of differences (SDD) and the coefficient of variation (CV) between the MS values of the two ambulatory BP recordings. 3) Agreement between the two ambulatory BP recordings in detecting "morning surgers" (defined as subjects with an MS in the top quartile [Q4] of the MS distribution), quantified by calculating the percentage of subjects with agreement in the diagnosis and the κ statistic.

Data Analysis

Ambulatory BP data and additional recorded information from the report files generated by the ambulatory BP monitors were batch imported and organized in a relational database (Microsoft-Access 2000) using a Visual Basic program. This program designed by L.G.R. (author) for statistical analysis of ambulatory BP–derived data reads the ASCII text files generated by the ambulatory BP monitor and performs multiple data procedures and analyses, including flagging erroneous readings, valid readings and duplicate readings (repeats), and calculates the average awake and asleep BP according to an individual's in-bed and out-of-bed periods. Measurements flagged by the software as being technically erroneous were excluded, as were measurements with a systolic BP<50 or >260 mmHg and those with a diastolic BP<30 or >150 mmHg. The different MS definitions were incorporated into the program as reading selections and calculations. Ambulatory BP recordings with fewer than 30 valid awake measurements or fewer than 12 nighttime measurements based on the individual's diary were excluded from analysis. The data

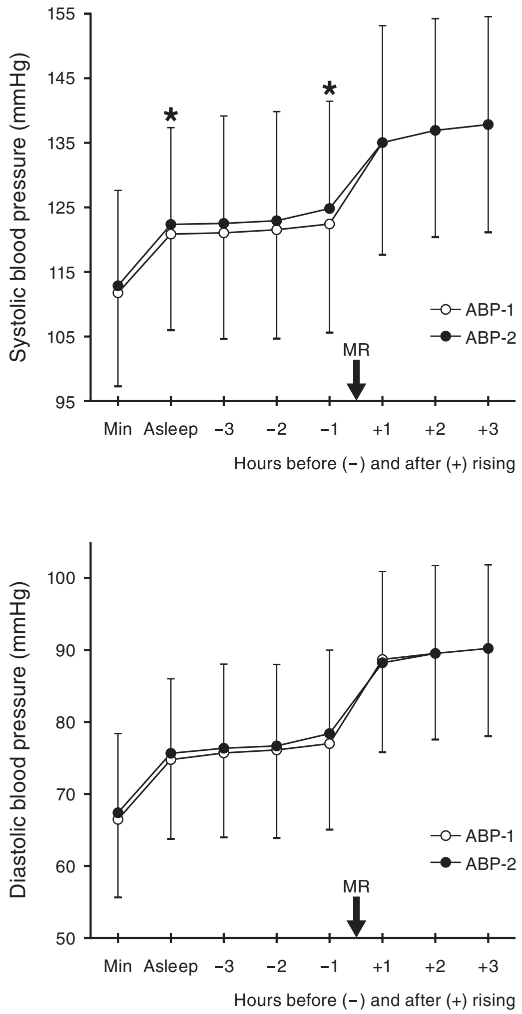

Fig. 1. *Ambulatory blood pressure before and after the morning rise. ABP-1, ABP-2, first and second ambulatory blood pressure recording, respectively; MR, morning rise; Min, average of the 3 consecutive readings centered on the lowest reading during sleep; Asleep, average blood pressure during sleep. *$p<0.04$ for comparison of systolic BP between first and second ambulatory recording (see Results).*

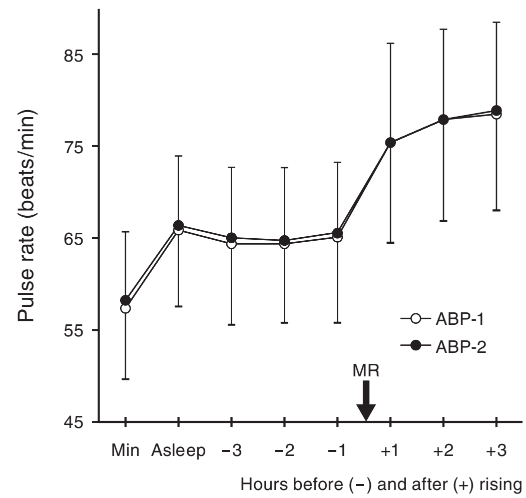

Fig. 2. *Ambulatory pulse rate before and after the morning rise (abbreviations as in Fig. 1).*

were transferred to the Minitab software for statistical analysis (Minitab, Inc., State College, USA; release 13.31). Student's paired *t*-tests were used for the comparison of BP measurements in the same subjects, with Bonferroni's correction for multiple comparisons applied where appropriate. CV (SD/μ, where SD is the average of the SD values of the two MS assessments for each individual and μ is the average of the mean MS values of the two MS assessments for each individual), CCC and the SD of the differences between the two ambulatory BP recordings were calculated for each MS definition together with the κ statistic, for agreement in the diagnosis of morning surgers. A probability value of $p<0.05$ was considered statistically significant.

Results

A total of 142 consecutive subjects were recruited and 10 were excluded because of incomplete BP data. In total, 132 subjects were included in the analysis (mean age 48.4±10.2 [SD] years, 71 [54%] men). The average body mass index was 28.2±4.3 kg/m^2 (25–30 kg/m^2 in 51% of subjects and >30 kg/m^2 in 26%). Current smokers constituted 32% of subjects (10% with <10 cigarettes/d, 10% 10–20 cigarettes/d and 12% >20 cigarettes/d) and 59% reported current alcohol consumption (38% with <80 g/week, 7% 80–140 g/weeek and 14% >140 g/week). Clinical BP at the initial visit was 149.9±16.4/98.8±9.1 mmHg, systolic/diastolic (average of the second and third reading taken after 5 min sitting at rest, standard mercury sphygmomanometer, Korotkoff phase V for diastolic BP). Nineteen subjects (14%) were on an antihypertensive drug treatment that was withdrawn at least 2 weeks before study entry. There was no significant difference in the average 24-h ambulatory BP between the first (132.8±13.5/85.3±9.9 mmHg, systolic/diastolic) and the second recording (133.3±13.3/85.5±9.7 mmHg). The mean difference was 0.5±8.5 mmHg for systolic BP (95% confidence intervals −1.0, 2.0, n.s.) and 0.2±5.9 mmHg for diastolic (−0.8, 1.2, n.s.).

The average hourly BP and pulse rate values in the time interval −3 to +3 h from the morning rise, as well as the average nocturnal asleep value and the minimum reading during nighttime sleep in the two ambulatory recordings are presented in Figs. 1 and 2. All pre-rising BP values tended to be higher in the second recording (there were significant differences in the systolic BP of the first hour before rising and in the average systolic asleep BP), whereas there was no difference in the 3 h post-rising (Fig. 1). There was no difference in

Table 1. Reproducibility of Five Definitions of the Morning Surge in Systolic Blood Pressure

Definition	ABP-1	ABP-2	CCC	SDD	CV	Agreement (%)*	κ**
MS-1	12.6±10.8	10.4±11.8	0.20	14.3	0.49	69	0.18
MS-2	15.3±11.3	14.1±11.4	0.43	12.1	0.44	71	0.23
MS-3	16.6±11.8	15.8±11.6	0.53	11.2	0.37	75	0.33
MS-4	16.3±10.3	15.0±11.3	0.51	10.3	0.36	81	0.49
MS-5	25.1±10.4	24.3±12.5	0.46	11.9	0.27	74	0.29

MS-1 to MS-5, morning surge assessed by 5 different definitions (see Methods); ABP-1 and ABP-2, morning surge in the first and the second ambulatory blood pressure recording; CCC, concordance correlation coefficients between the two morning surge assessments; SDD, standard deviation of differences; CV, coefficient of variation. *Agreement between ABP-1 and ABP-2 in the diagnosis of morning surgers; **κ statistic for agreement in the diagnosis.

Table 2. Reproducibility of Five Definitions of the Morning Surge in Diastolic Blood Pressure

Definition	ABP-1	ABP-2	CCC	SDD	CV	Agreement (%)*	κ**
MS-1	11.6±8.9	10.0±9.4	0.30	11.4	0.57	70	0.20
MS-2	13.6±8.8	12.9±8.9	0.45	9.9	0.39	76	0.36
MS-3	14.5±8.9	14.3±8.8	0.51	9.5	0.35	75	0.33
MS-4	15.0±8.1	15.0±8.8	0.47	8.2	0.31	83	0.53
MS-5	23.2±8.6	22.3±10.1	0.48	9.8	0.24	75	0.31

Abbreviations as in Table 1. *Agreement between ABP-1 and ABP-2 in the diagnosis of morning surgers; **κ statistic for agreement in the diagnosis.

the pre- and post-rising pulse rates between the two ambulatory recordings (Fig. 2).

The MS in systolic and diastolic BP calculated by the five different definitions for each of the two ambulatory recordings is presented on Table 1. There was a tendency for the magnitude of the MS assessed by all five definitions to be consistently lower in the second ambulatory recording (Table 1), which is attributed to the higher pre-rising and asleep BP in this recording (Fig. 1). All differences among MS values calculated by different definitions were statistically significant (after adjusting for multiple comparisons), apart from the MS-3 to MS-4 difference (no difference in systolic or diastolic MS in both ambulatory recordings) and the MS-2 to MS-3 difference (no difference in systolic BP in both recordings). The study findings regarding the criteria used for the assessment of the reliability of the different MS definitions are presented in Tables 1 and 2.

Criterion 1

There was no consistent trend showing any of the MS definitions to have a significantly lower SD in the two ambulatory recordings for systolic or diastolic BP (Tables 1, 2). However, MS-4 had the lowest SD in both ambulatory recordings for systolic and diastolic BP.

Criterion 2

All the reproducibility criteria showed MS-1 to be poorly reproducible, whereas MS-3 and MS-4 gave the highest CCC and the lowest SDD values between the two assessments (Tables 1, 2). MS-4 appeared to be slightly superior to MS-3 in terms of the SDD value (Fig. 3). However, MS-5 gave the lowest CV value for both systolic and diastolic MS.

Criterion 3

Regarding the agreement between the two ambulatory recordings in detecting the morning surgers, again MS-1 had the poorest agreement, whereas MS-2, MS-3 and MS-5 provided similar levels of agreement and κ statistic values. MS-4 was superior to the other definitions in terms of the agreement in the diagnosis (>80%) and the κ statistic value (>0.41), which suggested moderate agreement (Tables 1, 2).

When the MS was quantified as a proportional (%) rather than absolute (mmHg) BP change, the findings regarding the abovementioned criteria were similar, yielding a slight improvement in the reproducibility of systolic MS and deterioration of diastolic MS across all definitions (data not shown).

Discussion

This study provides a direct comparison of the reproducibility of five different definitions of MS used in the literature. The findings suggest that these definitions do not provide equally reproducible MS values. Overall MS-4 appears to be the most reliable approach to assessing the morning BP surge. The

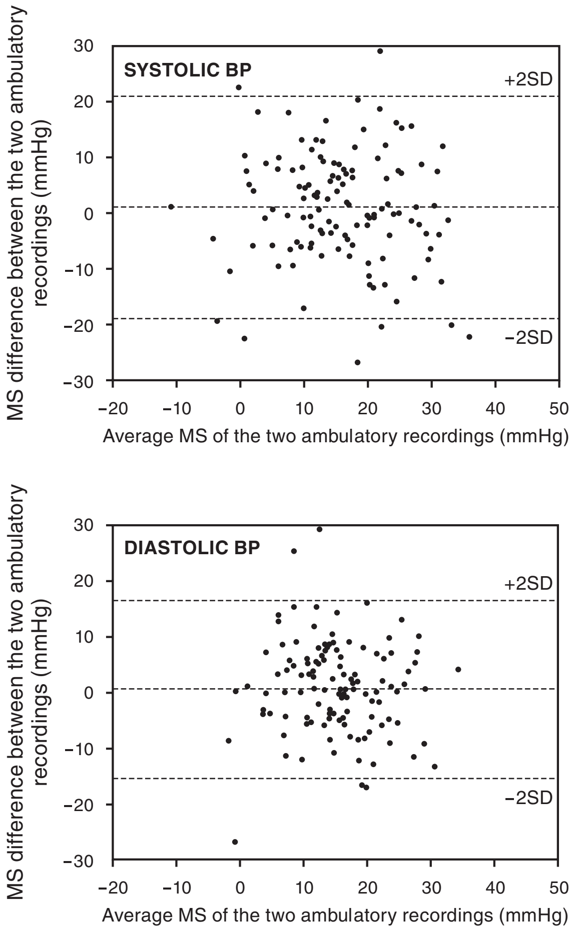

Fig. 3. *Bland-Altman plots showing the reproducibility of the morning blood pressure surge calculated as the average blood pressure readings taken 2 h after rising minus the average of all readings during sleep (MS-4).*

lower CV value of MS-5 is attributed to the higher MS values provided by this definition, which are used in the denominator of the CV formula.

There is one published study that assessed the reproducibility of MS using only one MS definition (MS-5) in 36 subjects (*24*). A reproducibility assessment using test-retest correlation and CV produced similar findings to those of the present study. However a direct comparison of the reproducibility of different MS definitions was not provided in that study (*24*).

The similarity in the pre- and post-rising BP curves and the MS in the two ambulatory BP profiles recorded 2 weeks apart in the total study group is striking (Fig. 1). The pulse pressure profiles, which reflect sympathetic system activity changes, suggest a strong similarity in physical activity levels in the two routine workdays when ambulatory BP was monitored (Fig. 2). However, the SD of differences between repeated MS values, which is a more appropriate criterion of reproducibility than CCC and CV, as well as the agreement in detecting morning surgers between the two assessments, which is the most clinically relevant criterion of reproducibility, clearly show that MS calculated by any definition used in previous studies is not particularly reproducible, and large differences in repeated ambulatory monitoring exceeding 10 mmHg are not uncommon for both systolic and diastolic MS (Fig. 3).

This is not surprising because it is known that although the average 24-h ambulatory is more reproducible than office measurements (*26*) the reproducibility is dependent on the number of BP readings averaged, with the average of a few readings having poor reproducibility (*28*). This probably explains why MS-4 appeared to be more reproducible (because of the larger number of readings used for the calculation of pre- and post-rising BP), whereas MS-1, which was based on the fewest number of BP readings, was the least reproducible definition.

Interestingly, the clinical detection of subjects with exaggerated MS, defined as those at the top quartile of each MS distribution, showed agreement in the classification between the two ambulatory recordings in more than 80% of subjects, for both systolic and diastolic BP (Tables 1, 2). This is particularly helpful if the MS is to be used for the assessment of individual patients in clinical practice. However, one out of five subjects in this study changed classification (surger or not) from the first to the second ambulatory BP recording. Thus, as is the case with other aspects of the ambulatory BP profile (*e.g.*, non-dipping pattern (*29*)), it seems that a single ambulatory BP recording is not adequate to characterize the MS profile of an individual.

Several of the MS parameters used in this analysis are affected by the BP level. However, all the MS definitions applied are equally affected by this confounder and therefore the study findings regarding their reproducibility are not affected by the BP level. Hence, adjustment for the BP level was not performed.

In conclusion, there are differences in the reproducibility of the MS as calculated using different definitions. The reproducibility of the MS appears to be dependent on the number of BP readings that are averaged to define the pre- and post-rising BP. Even using the most reproducible definition, repeated ambulatory BP monitoring is required to characterize the MS profile of an individual.

Ideally, the optimal definition of MS should be supported by data showing its ability to predict the risk of morbidity and mortality. Only one study provided a direct comparison of the prognostic ability of two different MS definitions, and showed MS-5 to be superior to MS-2 in predicting stroke in elderly hypertensives (*13*). Further research is needed to investigate the optimal MS definition in terms of reproducibility and prognostic ability, which might be appropriate for clinical application.

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