Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Hypertension published online Mar 8, 2010;
DOI: 10.1161/HYPERTENSIONAHA.109.137273
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Abstract—Previous studies on the prognostic significance of the morning blood pressure surge (MS) produced inconsistent results. Using the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome, we analyzed 5645 subjects (mean age: 53.0 years; 54.0% women) randomly recruited in 8 countries. The sleep-through and the preawakening MS were the differences in the morning blood pressure with the lowest nighttime blood pressure and the preawakening blood pressure, respectively. We computed multivariable-adjusted hazard ratios comparing the risk in ethnic- and sex-specific deciles of the MS relative to the average risk in the whole study population. During follow-up (median: 11.4 years), 785 deaths and 611 fatal and nonfatal cardiovascular events occurred. While accounting for covariables and the night:day ratio of systolic pressure, the hazard ratio of all-cause mortality was 1.32 (95% CI: 1.09 to 1.59; $P=0.004$) in the top decile of the systolic sleep-through MS (≥37.0 mm Hg). For cardiovascular and noncardiovascular death, these hazard ratios were 1.18 (95% CI: 0.87 to 1.61; $P=0.30$) and 1.42 (95% CI: 1.11 to 1.80; $P=0.005$). For all cardiovascular, cardiac, coronary, and cerebrovascular events, the hazard ratios in the top decile of the systolic sleep-through MS were 1.30 (95% CI: 1.06 to 1.60; $P=0.01$), 1.52 (95% CI: 1.15 to 2.00; $P=0.004$), 1.45 (95% CI: 1.04 to 2.03; $P=0.03$), and 0.95 (95% CI: 0.68 to 1.32; $P=0.74$), respectively. Analysis of the preawakening systolic MS and the diastolic MS generated consistent results. In conclusion, a MS above the 90th percentile significantly and independently predicted cardiovascular outcome and might contribute to risk stratification by ambulatory blood pressure monitoring. **(*Hypertension*. 2010;55:1040-1048.)**

Key Words: ambulatory blood pressure ■ blood pressure measurement ■ morning surge ■ epidemiology ■ population science

Several studies showed that the incidence of cardiovascular complications peaks in the morning.[1,2] For instance, in the Multicenter Investigation of Limitation of Infarct Size Study[1] and in the Thrombolysis in Myocardial Infarction Phase II Trial,[2] the incidence of myocardial infarction was highest between 6:00 AM and 12:00 AM. Blood pressure also follows a circadian pattern, generally characterized by a fall during sleep and a sharp rise on awakening.[3] This observation gave rise to the hypothesis that an exaggerated morning surge of blood pressure might predict cardiovascular outcome. However, previous studies of populations[4] and hypertensive patients[5–7] produced contradictory results, possibly because of the small number of events and the lack of statistical power. A further issue complicating the interpretation of previous studies is the varying definitions of the morning surge in blood pressure.[8]

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Received June 29, 2009; first decision July 16, 2009; revision accepted January 14, 2010.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.109.137273**

With the goal to advance knowledge on the prognostic accuracy of the ambulatory blood pressure, a research consortium constructed the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome.[9–12] We used this resource to study whether the morning surge in blood pressure contributes to the stratification of cardiovascular risk.

Methods

Study Population

Previous publications (for details, see the Expanded Methods in the online Data Supplement, available at http://hyper.ahajournals.org) described the construction of the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome.[9–12] At the time of writing this report, the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome included prospective studies from 11 centers (11 786 subjects). All studies received ethical approval and have been reported in peer-reviewed publications. For the present analysis, we selected studies in which the participants completed a diary during ambulatory blood pressure monitoring, leaving 8 cohorts[13–19] and 9488 subjects for possible analysis. In line with previous reports,[9–12] we excluded 250 participants because they were <18 years of age and 2430 participants because they had <10 daytime or <5 nighttime blood pressure readings. For the analysis of the morning surge, we additionally disregarded 1163 subjects because they had <2 blood pressure readings during the 2 hours before (n=122) or after awakening (n=1041). Thus, the current analysis included 5645 participants: 1685 residents from Copenhagen, Denmark[13]; 532 subjects from Noorderkempen, Belgium[14]; 220 subjects from Novosibirsk, Russia[15,16]; 290 subjects from Padova, Italy[16]; 296 subjects from Kraków, Poland[16]; 1396 inhabitants from Ohasama, Japan[17]; 327 villagers from the JingNing county, China[18]; and 899 subjects from Montevideo, Uruguay.[19] All participants gave informed written consent.

Blood Pressure Measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[13–16,18] with validated auscultatory[17] (USM-700F, UEDA Electronic Works), or oscillometric[19] (OMRON HEM-705CP, Omron Corporation) devices, using the appropriate cuff size, with the participants in the sitting position.[13–19] Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home[14–16,18,19] or at an examination center.[13,17] Hypertension was a conventional blood pressure of ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or the use of antihypertensive drugs.

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day[17] or at intervals ranging from 15[13] to 20[14–16,18] minutes during daytime and from 30[17] to 60[13] minutes at night (for details, see the Expanded Methods available in the online Data Supplement). When accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10:00 AM to 8:00 PM in Europeans[13–16] and South Americans,[19] and from 8:00 AM to 6:00 PM in Asians.[17,18] The corresponding nighttime intervals ranged from 12:00 AM to 6:00 AM[13–16,19] and from 10:00 PM to 4:00 AM.[17,18] Within individual subjects, we weighted the means of the ambulatory blood pressure level by the interval between readings. To quantify the nocturnal fall in blood pressure, we computed the night:day blood pressure ratio from the nighttime and daytime blood pressures.

For analysis of the morning surge in blood pressure, we determined the awake and asleep periods from the subjects' diary cards. Subjects were asked to record the time when they got up in the morning and went to bed at night. The sleep-through morning surge was the difference between the morning pressure (the average blood pressure during the 2 hours after awakening) and the lowest nighttime blood pressure (the average of the lowest pressure and the 2 readings immediately preceding and after the lowest value).[5] The preawakening morning surge was the difference between the morning blood pressure (the average blood pressure during the 2 hours after awakening) and the preawakening blood pressure (the average blood pressure during the 2 hours before awakening).[4,5]

Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each subject's medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of ≥7.0 mmol/L,[13–19] a random blood glucose concentration of ≥11.1 mmol/L,[14,17,18] a self-reported diagnosis,[14,18,19] or diabetes mellitus documented in practice or hospital records.[19]

Ascertainment of Events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous publications (for details, see the Expanded Methods available in the online Data Supplement).[9,17,20–23] Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events consisted of coronary events and fatal and nonfatal heart failure. Cardiovascular events included all aforementioned events plus cardiovascular mortality. In all outcome analyses, we considered only the first event within each category.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute). We compared means and proportions by the large-sample z test and the χ^2 statistic, respectively. Statistical significance was a 2-sided P value of 0.05.

We used Kaplan-Meier survival function estimates and the log-rank test to compare the incidence rates of events in the top decile of the distributions of the sleep-through and preawakening morning surge with the rates in the rest of the study population. We used Cox regression to compute hazard ratios. We checked the proportional hazards assumption by the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS package. Because the relation between cardiovascular complications and the morning surge in blood pressure was not linear, we used the deviation from the population mean coding[24] to estimate the risk in the ethnic- and sex-specific deciles of the sleep-through and preawakening morning surge. This approach expresses the risk in each decile relative to the overall risk in the whole study population and allows computation of CIs for the hazard ratio in each decile without definition of an arbitrary reference group. In an attempt to refine the level of the morning surge that was associated with a significantly increased risk, we calculated for all cutoff points ranging from the fifth to the 95th percentile the hazard ratio expressing the risk in subjects whose morning surge exceeded the cutoff point versus the risk in the total study population. We plotted these hazard rates and their confidence limits versus the cutoff points and identified the cutoff point where the lower confidence limit crossed unity. We adjusted the hazard ratios for baseline characteristics, including cohort, sex, age, body mass index, the 24-hour blood pressure level, current smoking, use of alcohol, serum cholesterol, the presence of diabetes mellitus, a history of cardiovascular disease, and antihypertensive treatment. In fully adjusted models, the night:day blood pressure ratio was additionally included. In sensitivity analyses, we compared the hazard ratios according to baseline characteristics, using a normal approximation of the log-transformed point estimates and SEs.

Results

Characteristics of Participants

The 5465 participants included 3023 Europeans (53.6%), 1723 Asians (30.5%), and 899 South Americans (15.9%). Of

the 5645 participants, 3048 were women (54.0%), 1188 (21.1%) were taking blood pressure–lowering drugs, and 2305 (40.8%) had hypertension. Mean±SD age was 53.0±14.7 years. In the whole study population, the 24-hour blood pressure averaged 123.3±13.5 mm Hg systolic and 73.7±8.6 mm Hg diastolic. At enrollment, 1690 participants (29.9%) were current smokers, and 2667 (47.3%) reported intake of alcohol.

The median number of blood pressure readings (fifth to 95th percentile interval) used for the calculation of the within-subject preawakening blood pressure was 5 (2 to 9) and 4 (2 to 6) for the within-subject morning blood pressure. In all participants, the sleep-through and preawakening morning surge in systolic blood pressure averaged 20.7±12.9 and 13.1±11.9 mm Hg, respectively. However, there were significant ethnic and sex differences in the morning blood pressure surge. The mean values of the sleep-through systolic morning surge in the top decile were smaller in women than in men among Europeans (40.9 versus 43.2 mm Hg; $P=0.003$) and South Americans (38.8 versus 41.5 mm Hg; $P=0.041$), whereas the opposite was the case among Asians (52.4 versus 50.1 mm Hg; $P=0.064$). For the preawakening systolic morning surge, the differences between women and men showed similar trends: 26.8 versus 29.2 mm Hg ($P=0.062$), 22.5 versus 26.9 mm Hg ($P=0.059$), and 30.6 versus 27.4 mm Hg ($P=0.13$) in Europeans, South Americans, and Asians, respectively. These differences explain why we applied ethnicity- and sex-specific deciles to study the predictive value of the morning blood pressure surge. This also ensured an equal distribution of ethnicities and women and men across the deciles.

Table 1 shows the baseline characteristics of the participants categorized according to the 90th percentile of the sleep-through morning surge in systolic blood pressure. These 2 groups had significantly different characteristics ($P<0.05$), with the exception of the nighttime systolic pressure ($P=0.35$); the proportions of Europeans, Asians, and South Americans ($P>0.89$); and the percentages of women ($P=0.93$), smokers ($P=0.12$), and drinkers ($P=0.51$).

Table 1. Baseline Characteristics of the Participants Categorized According to the 90th Percentile of the Systolic Sleep-Through Morning Surge

	Sleep-Through Morning Surge		
Characteristics	<37.0 mm Hg*	≥37.0 mm Hg*	*P*
Total, n	5075	570	
European	2718 (53.6)	305 (53.5)	0.99
Asian	1550 (30.5)	173 (30.3)	0.92
South American	807 (15.9)	92 (16.1)	0.90
Women	2739 (54.0)	309 (54.2)	0.93
Antihypertensive treatment	992 (19.6)	196 (34.4)	<0.0001
Smokers	1503 (29.6)	187 (32.8)	0.12
Using alcohol	2390 (47.1)	277 (48.6)	0.51
Diabetes mellitus	334 (6.6)	51 (9.0)	0.04
Cardiovascular disorders	348 (6.9)	56 (9.8)	0.01
Age, y	52.5±14.6	57.7±14.5	<0.0001
Body mass index, kg/m^2	25.1±4.2	25.7±4.6	0.001
Conventional SBP, mm Hg	128.7±19.3	138.0±21.7	<0.0001
Ambulatory SBP, mm Hg			
24-hour	122.6±13.4	129.7±13.3	<0.0001
Daytime	128.9±14.3	137.6±14.2	<0.0001
Nighttime	111.8±14.4	112.4±15.0	0.35
Nighttime through	105.6±13.9	101.2±13.8	<0.0001
Preawakening	112.2±15.9	117.9±18.3	<0.0001
After awakening	123.7±15.4	145.8±15.2	<0.0001
Night:day ratio of SBP	0.87±0.08	0.82±0.08	<0.0001
Serum cholesterol, mmol/L	5.55±1.19	5.68±1.15	0.01

The 90th percentiles were determined after stratification for ethnicity and sex. Data are No. (%) or mean±SD. SBP indicates systolic blood pressure. *P* values are for the difference between the 2 groups.

*Mean value of the cutoff point across ethnicities and sex weighted for the No. of participants in each of the strata.

Incidence of Events

In the overall study population, median follow-up was 11.4 years (fifth to 95th percentile interval: 2.5 to 15.5 years). Across cohorts, median follow-up ranged from 2.5 years (fifth to 95th percentile interval: 2.3 to 2.6 years) in JingNing to 13.3 years (fifth to 95th percentile interval: 4.7 to 16.3 years) in Noorderkempen. During 57 412 person-years of follow-up, 785 participants died (13.7 per 1000 person-years), and 611 experienced a fatal or nonfatal cardiovascular complication (11.0 per 1000 person-years).

Mortality included 287 cardiovascular and 473 noncardiovascular deaths and 25 deaths from unknown cause. Considering cause-specific cardiovascular events, 281 patients experienced a fatal or nonfatal stroke. The first cerebrovascular event was fatal in 69 subjects. Of the 281 fatal and nonfatal cerebrovascular events, 140 were brain infarcts and 70 were hemorrhagic strokes, whereas the stroke subtype was unknown in 71 cases. Stroke occurred in 76 Europeans, 181 Asians, and 24 South Americans. Fatal or nonfatal cardiac events occurred in 317 subjects. The first cardiac event was fatal in 102 subjects. The 317 cardiac events included 47 fatal and 88 nonfatal cases of acute myocardial infarction, 20 sudden deaths, 10 deaths from ischemic heart diseases, 25 fatal and 84 nonfatal cases of heart failure, and 43 cases of surgical or percutaneous coronary revascularization. Of 317 fatal and nonfatal cardiac events, 222 occurred in Europeans, 43 in Asians, and 52 in South Americans.

Risk Associated With Sleep Trough and Preawakening Morning Surge

Figure 1 shows the Kaplan-Meier survival function estimates for total mortality and for all fatal combined with nonfatal cardiovascular events in subjects categorized according to the 90th percentile of the sleep-through and the preawakening morning surge in systolic blood pressure. The results for the morning surge in diastolic blood pressure were similar to that of systolic pressure. In this article, we, therefore, limit the presentation of the results to systolic blood pressure, whereas those for diastolic blood pressure appear in the online Data Supplement (Tables S1 through S3).

The morning surge in blood pressure varies with the difference between the daytime and nighttime blood pres-

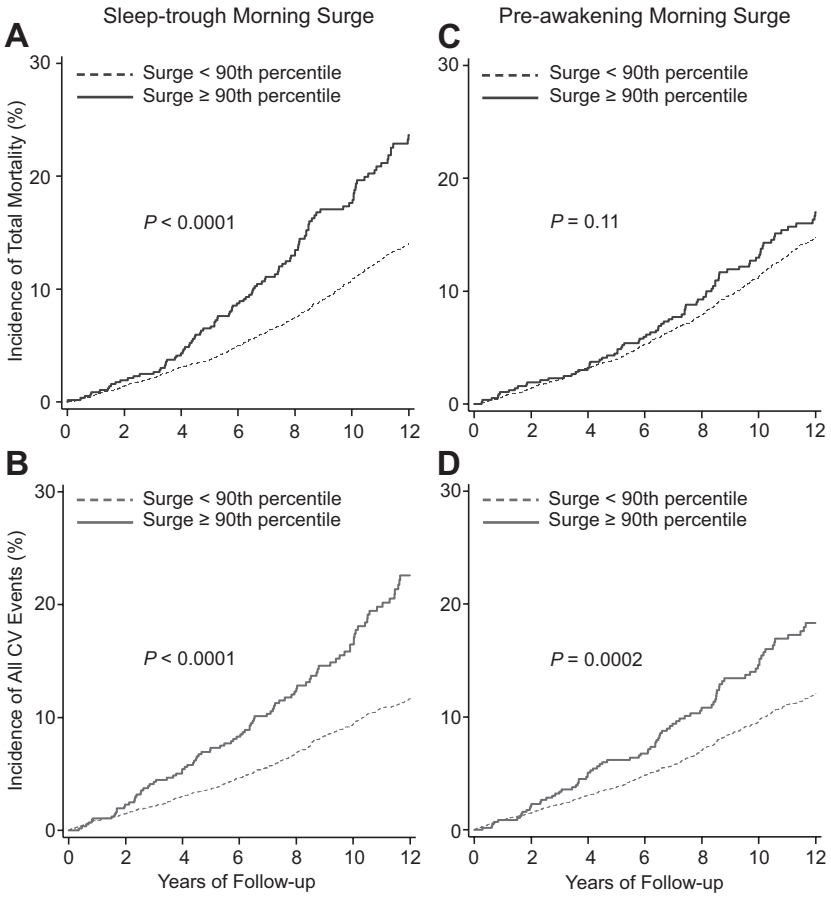

Figure 1. Cumulative incidence of total mortality (A and C) and all cardiovascular (CV) events (B and D) in subjects categorized according to the 90th percentile of the sleep-through (A and B) and the preawakening (C and D) morning surge in systolic blood pressure. *P* values are for the differences between the 2 groups by the log-rank test.

sures.[1–4] We, therefore, analyzed the prognostic significance of the morning surge in blood pressure with and without additional adjustment for the night:day blood pressure ratio (Table 2) while accounting for other risk factors. With adjustments applied for cohort, sex, age, body mass index, the 24-hour systolic blood pressure, current smoking, use of alcohol, serum cholesterol, the presence of diabetes mellitus, a history of cardiovascular disease, and antihypertensive drug

Table 2. Multivariable-Adjusted Hazard Ratios for the Sleep-Through and Preawakening Morning Surge in Systolic Blood Pressure

	Sleep-Through Surge (≥37.0 mm Hg)		Preawakening Surge (≥28.0 mm Hg)	
Outcomes (No. of Events)	Adjusted	Fully Adjusted	Adjusted	Fully Adjusted
Mortality				
All causes (785)	1.18 (0.99 to 1.42)	1.32 (1.09 to 1.59)†	1.11 (0.91 to 1.35)	1.23 (1.00 to 1.51)*
Cardiovascular (287)	1.06 (0.78 to 1.43)	1.18 (0.87 to 1.61)	1.08 (0.78 to 1.51)	1.22 (0.87 to 1.71)
Noncardiovascular (473)	1.28 (1.01 to 1.61)*	1.42 (1.11 to 1.80)†	1.13 (0.87 to 1.46)	1.23 (0.95 to 1.61)
Fatal and nonfatal events				
All cardiovascular (611)	1.18 (0.97 to 1.44)	1.30 (1.06 to 1.60)*	1.31 (1.06 to 1.61)†	1.45 (1.17 to 1.80)‡
Cardiac (317)	1.36 (1.04 to 1.78)*	1.52 (1.15 to 2.00)†	1.52 (1.14 to 2.01)†	1.69 (1.26 to 2.27)‡
Coronary (228)	1.35 (0.98 to 1.85)	1.45 (1.04 to 2.03)*	1.50 (1.08 to 2.09)*	1.64 (1.16 to 2.49)†
Cerebrovascular (281)	0.89 (0.65 to 1.23)	0.95 (0.68 to 1.32)	1.04 (0.75 to 1.44)	1.13 (0.81 to 1.58)
Infarction (140)	0.79 (0.49 to 1.27)	0.85 (0.52 to 1.39)	1.26 (0.82 to 1.92)	1.46 (0.93 to 2.30)
Hemorrhage (70)	1.57 (0.90 to 2.73)	1.46 (0.81 to 2.63)	1.18 (0.64 to 2.18)	1.11 (0.59 to 2.11)

Hazard ratios (95% CIs) express the risk in the top decile of the sleep-through or preawakening morning surge in systolic blood pressure compared with the overall risk in the whole study population. The Cox models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24-hour systolic blood pressure, and 9 design variables coding for the deciles. In fully adjusted models, the systolic night:day blood pressure ratio was additionally included in the Cox model. The cause of death was unknown in 25 cases.

*$P<0.05$ hazard ratio significance.

†$P<0.01$ hazard ratio significance.

‡$P<0.001$ hazard ratio significance.

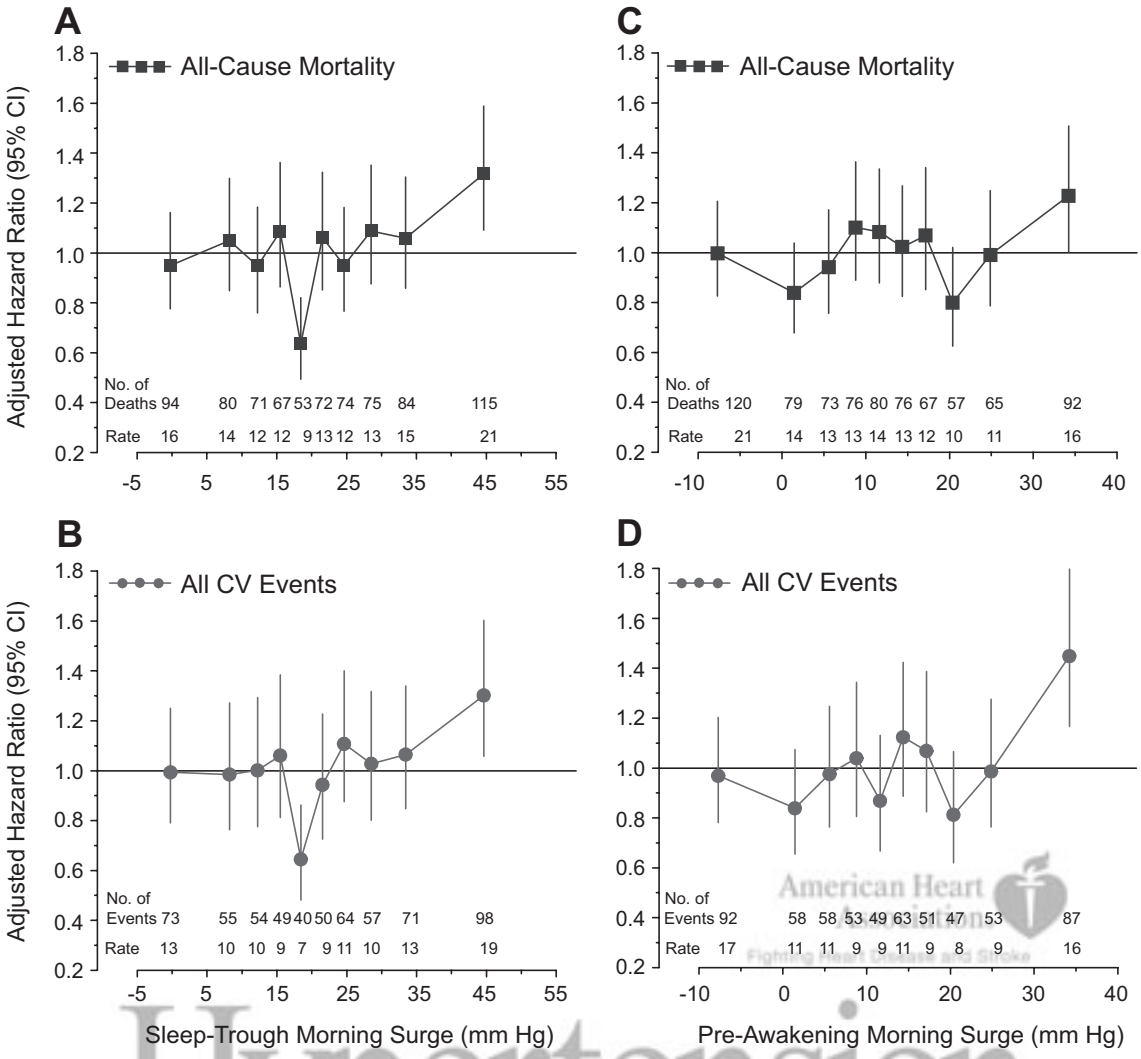

Figure 2. Multivariable-adjusted hazard ratios (95% CIs) for all-cause mortality (A and C) and for all fatal combined with nonfatal cardiovascular (CV) events (B and D) by ethnic- and sex-specific deciles of the sleep-through (A and B) and the preawakening (C and D) morning surge in systolic blood pressure in 5645 subjects. The hazard ratios express the risk in deciles compared with the average risk in the whole study population and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24-hour systolic blood pressure, and the systolic night:day blood pressure ratio. The number of events and incidence rates (events per 1000 person-years) are also given for each decile.

treatment, the risk of noncardiovascular mortality ($P=0.04$) and of all fatal combined with nonfatal cardiac events ($P=0.03$) was significantly higher in the top decile of the sleep-through morning surge compared with the average risk in the whole study population (Table 2). When further adjusted for the night:day ratio of systolic blood pressure, the risk of all-cause mortality was 32% ($P=0.004$) higher in the top decile of the sleep-through morning surge. For cardiovascular and noncardiovascular death, these estimates were 18% ($P=0.30$) and 42% ($P=0.005$) and for all cardiovascular, cardiac, coronary, and cerebrovascular events, 30% ($P=0.01$), 52% ($P=0.004$), 45% ($P=0.03$), and −5% ($P=0.74$), respectively (Table 2). Figure 2 shows the fully adjusted hazard ratios for all-cause mortality and for all fatal combined with nonfatal cardiovascular events by deciles of the morning blood pressure surge. Only in the top decile group was the risk significantly higher than the average risk in the whole population, whereas in the 50th percentile group, the risk was significantly lower by 35% ($P<0.01$) for all-cause mortality and for all cardiovascular events (Figure 2).

Compared with our findings for the systolic sleep-through morning surge, analysis of the systolic preawakening morning surge produced confirmatory results. While accounting for covariables and the night:day ratio of systolic pressure, subjects in the top decile group of the systolic preawakening morning surge had an increased risk of all-cause mortality (23%; $P=0.049$) and of all cardiovascular (45%; $P=0.0008$), cardiac (69%; $P=0.0004$), and coronary (64%; $P=0.01$) events compared with the average risk in the whole study population.

In an attempt to define in a more precise manner cutoff points for risk stratification in clinical practice, we explored the risk associated with all values of the sleep-through and preawakening morning surge in systolic blood pressure within the fifth to 95th percentile interval. The overall risk in the whole study population was used as a reference (Figure 3).

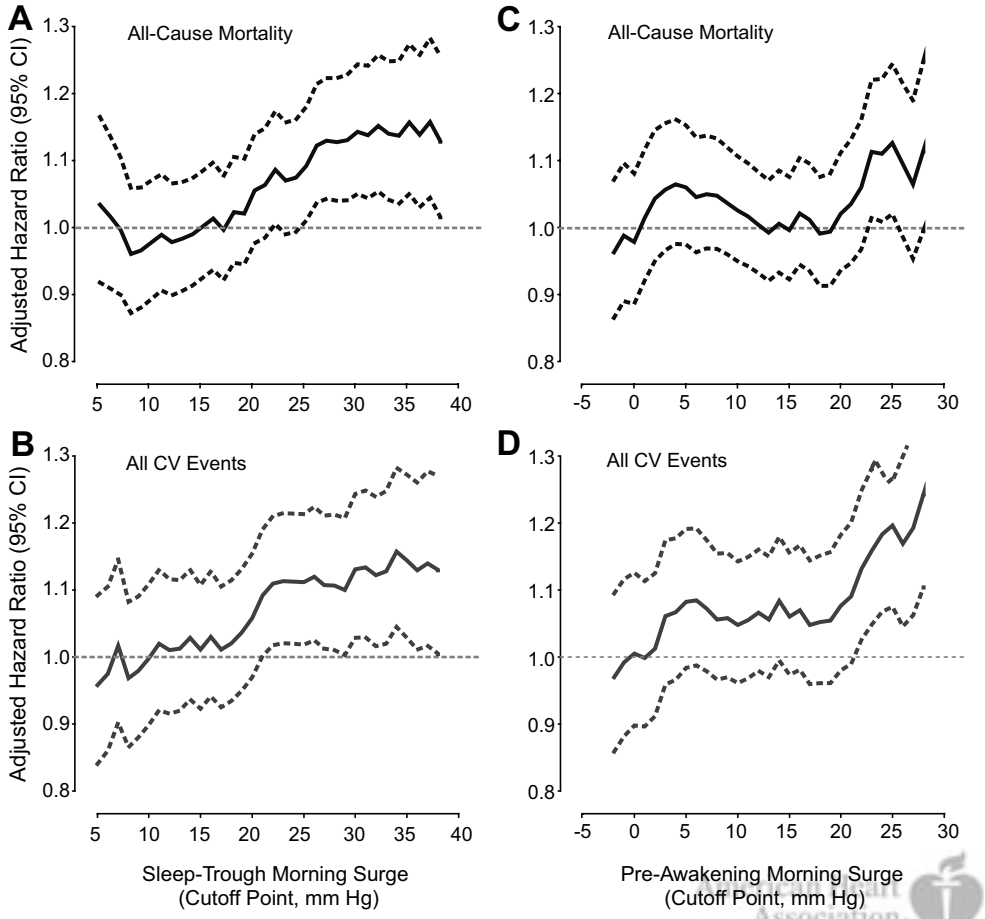

Figure 3. Multivariable-adjusted hazard ratios (solid lines) and their 95% CIs (dashed lines) for all-cause mortality (A and C) and for all fatal combined with nonfatal cardiovascular (CV) events (B and D) by cutoff points ranging from the fifth to 95th percentile for the sleep-through (A and B) and preawakening (C and D) morning surge in systolic blood pressure in 5645 subjects. The hazard ratios express the risk in subjects whose morning surge exceeds the cutoff point compared with the average risk in the whole study population. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24-hour systolic blood pressure, and the systolic night:day blood pressure ratio.

For the sleep-through morning surge in systolic blood pressure, the lower boundary of the 95% CI of the risk function crossed unity of the hazard ratio at 24.6 and 20.9 mm Hg for total mortality and all cardiovascular events, respectively. For the preawakening morning surge in systolic blood pressure, these crossings occurred at 22.7 mm Hg and 21.5 mm Hg, respectively. The results of these analyses suggest that, for both measures of the morning surge in systolic blood pressure, a value $<$20 mm Hg is probably not associated with increased risk (Figure 3).

Sensitivity Analyses

We checked the consistency of our results for total mortality and all cardiovascular events according to various baseline characteristics (Table 3). The hazard ratios expressing the risk in the top decile of the systolic morning surge were not statistically different across strata ($0.12<P<0.98$) with 2 exceptions. Irrespective of the definition of the morning surge in systolic blood pressure, in the top decile, smokers had a significantly higher risk for all-cause mortality than nonsmokers ($P\leq0.013$). The hazard ratios of all cardiovascular events for the sleep-through morning surge between drinkers and nondrinkers in the top decile were also different ($P=0.04$). However, the power to detect heterogeneity between strata was low. For example, considering a 2-sided α-level of 0.05, we had only 28% power to detect a 0.23 difference between women and men in the log-transformed hazard ratio of all-cause mortality for the sleep-through morning surge.

Discussion

Our current meta-analysis of individual data included $>$5000 people randomly recruited from 8 populations and covered on average 10 years of follow-up, during which 785 people died and 611 experienced a major cardiovascular complication. The key finding was that, while accounting for the night:day blood pressure ratio, the 24-hour blood pressure level, and other covariables, a morning surge in blood pressure exceeding the 90th percentile was a significant and independent predictor of mortality and cardiovascular events.

Ambulatory blood pressure monitoring enables testing of the hypothesis that the diurnal variation in the incidence of cardiovascular complications, such as stroke and myocardial infarction, tracks with changes in the blood pressure level.[25]

Table 3. Multivariable-Adjusted Hazard Ratios for the Sleep-Through and Preawakening Morning Surge in Systolic Blood Pressure According to Baseline Characteristics

	All-Cause Mortality				All Cardiovascular Events		
Stratification	At Risk, n	Deaths, n	Sleep-Through MS (≥37.0 mm Hg)	Preawakening MS (≥28.0 mm Hg)	Events, n	Sleep-Through MS (≥37.0 mm Hg)	Preawakening MS (≥28.0 mm Hg)
All participants	5645	785	1.32 (1.09 to 1.59)†	1.23 (1.00 to 1.51)*	611	1.30 (1.06 to 1.60)*	1.45 (1.17 to 1.80)‡
Women	3048	321	1.15 (0.86 to 1.54)	1.20 (0.88 to 1.64)	251	1.07 (0.78 to 1.49)	1.34 (0.96 to 1.87)
Men	2597	464	1.45 (1.14 to 1.86)†	1.28 (0.98 to 1.68)	360	1.49 (1.14 to 1.95)†	1.54 (1.15 to 2.05)†
<60 years	3558	134	1.27 (0.75 to 2.15)	1.22 (0.75 to 2.01)	151	1.35 (0.86 to 2.12)	1.36 (0.88 to 2.08)
≥60 years	2087	651	1.31 (1.07 to 1.61)†	1.22 (0.98 to 1.53)	460	1.28 (1.01 to 1.62)*	1.46 (1.14 to 1.88)†
No history of CVD	5241	660	1.28 (1.04 to 1.58)*	1.18 (0.94 to 1.47)	501	1.23 (0.98 to 1.56)	1.46 (1.16 to 1.85)†
History of CVD	404	125	1.74 (1.10 to 2.77)*	1.83 (1.10 to 3.04)*	110	1.64 (1.01 to 2.66)*	1.71 (0.99 to 2.94)
Untreated	4457	464	1.22 (0.93 to 1.58)	1.16 (0.89 to 1.51)	332	1.11 (0.82 to 1.51)	1.41 (1.06 to 1.87)*
Treated	1188	321	1.43 (1.09 to 1.89)*	1.35 (0.98 to 1.87)	279	1.46 (1.09 to 1.95)*	1.49 (1.07 to 2.08)*
Normotensive	3340	290	1.55 (1.11 to 2.16)*	1.27 (0.92 to 1.76)	178	1.54 (1.01 to 2.34)*	1.61 (1.11 to 2.34)*
Hypertensive	2305	495	1.28 (1.02 to 1.61)*	1.25 (0.96 to 1.63)	433	1.26 (0.99 to 1.60)	1.39 (1.07 to 1.82)*
Nonsmokers	3955	485	1.08 (0.84 to 1.39)§	0.91 (0.68 to 1.23)§	389	1.12 (0.86 to 1.47)	1.21 (0.90 to 1.62)
Smokers	1690	300	1.75 (1.31 to 2.33)‡§	1.79 (1.34 to 2.39)‡§	222	1.59 (1.14 to 2.22)†	1.84 (1.32 to 2.56)‡
Nondrinkers	2978	409	1.15 (0.87 to 1.51)	1.13 (0.84 to 1.51)	318	1.06 (0.78 to 1.43)§	1.32 (0.98 to 1.78)
Drinkers	2667	376	1.48 (1.14 to 1.91)†	1.36 (1.02 to 1.81)*	293	1.62 (1.22 to 2.14)‡§	1.64 (1.20 to 2.24)†
European	3023	408	1.38 (1.06 to 1.80)*	1.24 (0.93 to 1.65)	304	1.53 (1.15 to 2.05)†	1.83 (1.36 to 2.45)‡
Asian	1723	319	1.37 (1.03 to 1.84)*	1.24 (0.91 to 1.70)	234	1.17 (0.83 to 1.66)	1.26 (0.88 to 1.81)
South American	899	58	0.67 (0.28 to 1.60)	1.14 (0.51 to 2.59)	73	1.05 (0.56 to 1.96)	1.08 (0.54 to 2.13)

MS indicates the morning surge in systolic blood pressure. Hazard ratios (95% CIs) express the risk in the top decile compared with the average risk in the whole study population. The Cox models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24-hour systolic blood pressure, 9 design variables coding for the deciles, and the systolic night:day blood pressure ratio.

*$P<0.05$ hazard ratio significance.

†$P<0.01$ hazard ratio significance.

‡$P<0.001$ hazard ratio significance.

§Heterogeneity between corresponding subgroups ($P\leq0.04$).

The seminal article by Kario et al,[5] published in 2003, introduced the definitions of the sleep-through and preawakening morning surge in blood pressure as a way to study the risk associated with the rise in blood pressure on awakening. In 519 older hypertensive patients (mean age: 72 years) followed up for 41 months, Kario et al[5] compared the risk of silent and clinical cerebrovascular diseases in the top decile (≥55 mm Hg) of the systolic sleep-through morning surge with the risk in the other patients. After matching for age and the 24-hour blood pressure, the risk of multiple brain infarcts was ≈2-fold higher in patients belonging to the top decile of the systolic sleep-through morning surge. Moreover, with adjustment for the 24-hour blood pressure, nocturnal dipping status, and the prevalence of silent infarcts at enrollment, the morning surge remained a significant predictor of stroke.[5]

In 1430 subjects (mean age: 61 years; 64% women) randomly recruited from the Ohasama population, 128 cerebrovascular events occurred during a mean follow-up of 10.4 years.[4] The cerebrovascular complications included 86 ischemic strokes and 27 cases with intracerebral hemorrhage. With adjustments applied for the 24-hour systolic blood pressure and other cardiovascular risk factors, the preawakening morning surge in systolic pressure tended to be associated with an increased risk of cerebral hemorrhage (hazard ratio per 1 SD increase: 1.34; 95% CI: 0.95 to 1.89) but not with the risk of ischemic stroke (hazard ratio per 1 SD increase: 0.97; 95% CI: 0.79 to 1.19). The predictive value of the sleep-through morning surge was broadly similar to that of the preawakening morning surge.[4]

Gosse et al[6] studied 507 untreated hypertensive patients without complications at enrollment. The average follow-up of these patients was 92 months, during which 31 cardiovascular events including 6 deaths occurred. The morning surge was the difference between the first systolic measurement after standing up in the morning and the last systolic value within the 30 minutes before assuming a standing position in the morning. A 1-mm Hg increase in the morning surge, adjusted for the 24-hour systolic blood pressure and age, was associated with a 3.3% increase (95% CI: 0.8% to 5.8%) in the risk of cardiovascular events.[6]

An exaggerated morning surge in blood pressure potentially originates from a low nighttime-through blood pressure and/or a high blood pressure after awakening. We therefore presented the hazard ratios with and without additional adjustment for the night:day blood pressure ratio (Table 2). Including this ratio in the multivariable Cox models yielded higher hazard ratios for total mortality and for all cardiovascular, cardiac, and coronary events compared with those in Cox models not including the night:day blood pressure ratio.

Similarly as in previous reports,[4–6] subjects belonging to the top decile of the distribution of the morning surge in

blood pressure, in which all of "the results of interest" occurred, were older, more likely to be on antihypertensive drugs, had higher 24-hour and daytime blood pressures, and had a lower night:day blood pressure ratio. While adjusting for these risk factors in multivariable Cox models, the morning surge in blood pressure in the top decile remained a significant and independent predictor of total mortality and of all cardiovascular and cardiac events, over and beyond classic risk factors. Moreover, sensitivity analyses stratified for major risk factors were also confirmatory. By and large our current findings suggest that the morning surge in blood pressure independently contributes to the risk stratification on the basis of ambulatory blood pressure monitoring.

In contrast to previous studies,[4,5] the morning surge in blood pressure did not predict stroke. It is likely that the association between stroke and the morning surge depends on the stroke subtype.[4,5] In our current study, Asians belonging to the top decile were at a significantly higher risk of hemorrhagic stroke (51 cases; hazard ratio [95% CI]: 2.28 [1.09 to 4.26]; $P=0.03$) but not ischemic stroke (127 cases; hazard ratio: 1.41 [0.67 to 2.98]; $P=0.37$) compared with Asians with a lesser morning surge. These results were consistent with a previous report from the Ohasama Study[4] but was different from the study of Kario et al[5] in which the sleep-through morning surge significantly predicted cerebral infarcts. Different characteristics of the populations under study might explain this diversity. Indeed, the study by Kario et al[5] included older hypertensive patients (mean age: 72 years). The sleep-through morning surge in systolic blood pressure in the top decile (≥55 mm Hg) was greater in the study by Kario et al[5] than in our current report (≥35 mm Hg in Europeans and South Americans and ≥43 mm Hg in Asians).

Although the morning surge in both systolic pressure and diastolic pressure (see Data Supplement) predicted risk, we would suggest using only the rise in systolic blood pressure in the morning as a risk indicator, because in middle-aged and older subjects systolic rather than diastolic blood pressure is the predominant risk factor.[26] Using the morning surge in blood pressure as a risk indicator requires multiple blood pressure readings during sleep and during the preawakening and awakening periods. Subjects also have to complete a diary during ambulatory blood pressure monitoring to report the sleeping and awake periods. In our database, these 2 issues eliminated 4850 of 11 786 available subjects. Moreover, according to our recently published study in older patients with isolated systolic hypertension,[27] the morning surge in blood pressure, irrespective of its definition, was poorly reproducible. Nearly 30% of the subjects changed their surge status either in the short term (median: 33 days) or in the long term (median: 10 months).[27] These 3 factors might limit the clinical application of the morning surge in blood pressure as a cardiovascular risk factor.

The present study should be interpreted within the context of its possible limitations. Above all, none of the included studies was prospectively designed to evaluate the risk associated with the morning surge in blood pressure. On the other hand, our study was population based, prospective, large, and sufficiently powered with 785 deaths and 611 major cardiovascular events. Second, our study population consisted of more Europeans than Asians and South Americans. Although we did not detect any heterogeneity in the hazard ratios for all-cause mortality and all cardiovascular events, our findings may need replication in other populations. Third, our study did not address the mechanisms explaining why the morning surge behaves as an independent predictor of mortality and cardiovascular events. Several hypotheses have been put forward. A steep morning surge in blood pressure might cause structural damage to the large arteries if the pressure load during the morning period repeatedly exceeds the buffering capacity of the arteries. Indeed, an exaggerated pressure load leads to fracture of the elastin fibers, to disorganization and hypertrophy of the muscular layers of the arterial wall,[28] and to plaque rupture.[29] These mechanisms might be particularly active in atherosclerotic arteries,[28] in the presence of oxidative stress,[29,30] or in older subjects with impaired baroreflexes.[31]

Perspectives

Our study established the prognostic value of the morning surge in blood pressure in general populations. An exaggerated morning surge, exceeding the 90th percentile of the population, is an independent risk factor for mortality and cardiovascular and cardiac events, especially in smokers. Conversely, a sleep-through or preawakening morning surge in systolic blood pressure <20 mm Hg is probably not associated with an increased risk of death or cardiovascular events. Additional studies are necessary to refine the exact threshold to be used for risk stratification in clinical practice and to replicate our findings in other ethnicities, in particular blacks. Moreover, randomized clinical trials should investigate whether drug treatment specifically intervening with the morning surge in blood pressure might reverse the risk and improve prognosis.

Acknowledgments

We gratefully acknowledge the expert assistance of Sandra Covens and Ya Zhu (Studies Coordinating Centre, Leuven, Belgium). The International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes investigators are listed in the online Data Supplement.

Sources of Funding

The European Union (grants IC15-CT98-0329-EPOGH, LSHM-CT-2006-037093, and HEALTH-F4-2007-201550), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (Ministry of the Flemish Community, Brussels, Belgium) (grants G.0575.06 and G.0734.09), and the Katholieke Universiteit Leuven (grants OT/00/25 and OT/05/49) gave support to the Studies Coordinating Centre in Leuven. The European Union (grants LSHM-CT-2006-037093 and HEALTH-F4-2007-201550) also supported the research groups in Shanghai, Kraków, Padova, and Novosibirsk. The Bilateral Scientific and Technological Collaboration between China and Flanders, Ministry of the Flemish Community, Brussels (grant BIL02/10), supported the fellowship of Y.L. in Leuven. The Danish Heart Foundation (grant 01-2-9-9A-22914) and the Lundbeck Fonden (grant R32-A2740) supported the studies in Copenhagen. The Ministries of Education, Culture, Sports, Science, and Technology (grants 15790293, 17790381, 18390192, and 18590587) and of Health, Labor, and Welfare (Health Science Research grants and Medical Technology Evaluation Research grants), Grant-in-Aid from the Japanese Society for the Promotion of Science (16.54041

and 18.54042), the Japan Atherosclerosis Prevention Fund, the Uehara Memorial Foundation, and the Takeda Medical Research Foundation supported research in Japan. The National Natural Science Foundation of China (grants 30871360 and 30871081), Beijing, China, the Shanghai Commission of Science and Technology (grant 07JC14047 and the "Rising Star" program, grant 06QA14043), and the Shanghai Commission of Education (grant 07ZZ32 and the "Dawn" project, grant 08SG20) supported the JingNing study in China.

Disclosures

None.

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Data Supplement

Prognostic Value of the Morning Blood Pressure Surge in 5645 Subjects from 8 Populations

Short title: Prognosis of the Morning Blood Pressure Surge

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Expanded Methods

Study Population

As described in detail elsewhere,[1] we constructed the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO). Studies were eligible for inclusion, if they involved a random population sample, if baseline information on the ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included fatal and nonfatal outcomes. Of 13 studies,[2-13] we excluded 2, because at the time of writing of this manuscript follow-up had not yet been organized,[13] or because follow-up did not include nonfatal events.[12] All studies received ethical approval and have been reported in peer-reviewed publications. At the time of writing this report, the IDACO database included 11 786 subjects from 11 centers. For the present analysis, we selected studies in which the participants completed a diary during ambulatory blood pressure monitoring, leaving 8 cohorts[3-10] and 9488 subjects for possible analysis. In line with previous analyses,[14-17] we excluded 250 participants because they were younger than 18 years, and 2430 participants because they had fewer than 10 daytime or fewer than 5 nighttime blood pressure readings. For analysis of the morning surge, we additionally disregarded 1163 subjects, because they had less than 2 blood pressure readings during the 2 hours before (n=122) or after awakening (n=1041). Thus, the 5645 participants included in the current analysis consisted of 1685 residents from Copenhagen, Denmark;[8] 532 subjects from Noorderkempen, Belgium;[3] 220 subjects from Novosibirsk, Russia;[5,7] 290 subjects from Padova, Italy;[9] 296 subjects from Kraków, Poland;[7] 1396 inhabitants from Ohasama, Japan;[6] 327 villagers from the JingNing county, China;[10] and 899 subjects from Montevideo, Uruguay.[4] All participants gave informed written consent.

Blood Pressure Measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[3,5,7-10] with validated auscultatory[6] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[4] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting position.[3-10] Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home[3-5,7,9,10] or at an examination center.[6,8] Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs.

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day,[6] or at intervals ranging from 15[8] to 20[3,5,7,10] minutes during daytime and from 30[6] to 60[8] minutes at night. The devices implemented an oscillometric technique (SpaceLabs 90202 and 90207, SpaceLabs Inc, Redmond, USA[18]) in Noorderkempen,[3] Montevideo,[4] Novosibirsk,[5] Kraków,[7] Padova,[9] and JingNing.[10] The Takeda TM-2421 recorders (A&D, Tokyo, Japan[19]) used in Copenhagen[8] and the ABPM-630 devices (Nippon Colin, Komaki, Japan[20]) used in Ohasama[6] implemented both techniques, but only the oscillometric readings were analyzed.

The same SAS macro processed all ambulatory recordings, which generally remained unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[21] When accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10:00 AM to 8:00 PM in Europeans[3,5,7-9] and South Americans,[4] and from 8:00 AM to 6:00 PM in Asians.[6,10] The corresponding nighttime intervals ranged from midnight to 6:00 AM[3-5,7-9] and from 10:00 PM to 4:00 AM.[6,10] These fixed intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and nighttime blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.[10,22] Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings. To quantify the nocturnal fall in blood pressure, we computed the night:day blood pressure ratio from the nighttime and daytime blood pressures.

For analysis of the morning surge in blood pressure, we determined the awake and asleep periods from the subjects' diary cards. Subjects were asked to record the time when they got up in the morning and went to bed at night. The *sleep-trough morning surge* was the difference between the morning pressure (the average blood pressure during the 2 hours after awakening) and the lowest nighttime

blood pressure (the average of the lowest pressure and the 2 readings immediately preceding and following the lowest value).[23] The *preawaking morning surge* was the difference between the morning blood pressure (the average blood pressure during the 2 hours after awakening) and the preawaking blood pressure (the average blood pressure during the 2 hours before awakening).[23,24] The median (fifth to 95% percentiles) number of blood pressure readings for the calculation of the morning blood pressure and the preawaking blood pressure was 4 (2 to 6) and 5 (2 to 9), respectively.

Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each subject's medical history, and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L,[3-10] a random blood glucose concentration of at least 11.1 mmol/L,[3,6,10] a self-reported diagnosis,[3,4,10] or diabetes documented in practice or hospital records.[4]

Ascertainment of Events

In each cohort, outcomes were adjudicated against source documents described in previous publications.[1,6,8,11,25-27] The adjudication process was the same in the Belgian study[25] and all other studies contributing to the European Project on Genes in Hypertension (Novosibirsk, Pilsen, Padova, and Kraków).[26] Fatal and nonfatal stroke (ICD8/9 430–434 and 436, ICD10 I60–I64 and I67–I68) did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease (ICD8 411–412, ICD9 411 and 414, and ICD10 I20 and I24–I25), sudden death (CD8 427.2 and 795, and ICD9 427.5 and 798, and ICD10 I46 and R96), nonfatal myocardial infarction (ICD8/9 410, and ICD10 I21-I22), and coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure (ICD8 428 and 427.1–427.2 and 429, and ICD9 429, and ICD10 I50 and J81). Hospitalizations for unstable angina were coded as ischemic heart disease. In the Danish and Swedish cohorts, the diagnosis of heart failure required admission to hospital. In the other cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but in all cases it was validated against hospital files or the records held by family doctors. The composite cardiovascular endpoint included all aforementioned endpoints plus cardiovascular mortality (ICD8 390–448, and ICD9 390.0-459.9, and ICD10 I00-I79 and R96). In all outcome analyses, we only considered the first event within each category.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute). We compared means and proportions by the large sample z-test and the χ^2-statistic, respectively. Statistical significance was a 2-sided *P*-value of 0.05. After stratification for cohort and sex, we imputed missing values of body mass index (n=11) and serum cholesterol (n=88) from the regression slope on age. In subjects with unknown smoking status (n=7) or drinking habits (n= 286), we set the design variable to the cohort- and sex-specific mean of the codes (0,1).

We used Kaplan-Meier survival function estimates and the log-rank test to compare the incidence rates in the top decile group of the sleep-trough and preawakening morning surge with that of the rest of the study population. We used Cox regression to compute hazard ratios. We checked the proportional hazards assumption by the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS package. Because the relation between cardiovascular complications and the morning surge in blood pressure was not linear, we used the deviation from population mean coding[28] to define ethnic- and sex-specific deciles of the sleep-trough and preawakening morning surge. This approach expresses the risk in each decile relative to the overall risk in the whole study population and allows computation of confidence intervals for the hazard ratio in each decile without definition of an arbitrary reference group. We adjusted the hazard ratios for baseline characteristics, including cohort, sex, age, body mass index, the 24-h blood pressure level, current smoking, use of alcohol, serum cholesterol, the presence of diabetes mellitus, a history of cardiovascular disease, and antihypertensive treatment. In fully adjusted models, the night:day blood pressure ratio was additionally included as a covariable. In the sensitivity analyses, we compared the hazard ratios according to

baseline characteristics using a normal approximation of the log-transformed point estimates and standard errors.

Appendix

IDACO Centers and Investigators:
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Data Base Management and Coordination:
T. W. Hansen, M. Kikuya, Y.Li, T. Richart, J. A. Staessen (Project Coordinator), and L. Thijs (Supervisor Database Management) constructed the IDACO database at the Studies Coordinating Centre in Leuven, Belgium.

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Table S1. Baseline Characteristics of the Participants Categorized According to the 90th Percentile of the Diastolic Sleep-Trough Morning Surge

Characteristics	Sleep-Trough Morning Surge		*P*
	< 28.5 mm Hg*	≥ 28.5 mm Hg*	
Total, n	5072	573	
European	2717 (53.6)	306 (53.4)	0.99
Asian	1548 (30.5)	175 (30.5)	0.99
South American	807 (15.9)	92 (16.1)	0.90
Women	2740 (54.0)	308 (53.8)	0.90
Antihypertensive treatment	1010 (19.9)	178 (31.1)	<0.0001
Smokers	1499 (29.6)	191 (33.3)	0.06
Using alcohol	2424 (47.8)	243 (42.4)	0.01
Diabetes mellitus	342 (6.7)	43 (7.5)	0.49
Cardiovascular disorders	351 (6.9)	53 (9.3)	0.04
Age, y	52.9±14.5	54.1±16.0	0.08
Body mass index, kg/m^2	25.1±4.2	25.6±4.4	0.009
Conventional DBP, mm Hg	79.1±11.6	82.3±12.1	<0.0001
Ambulatory DBP, mm Hg			
24-hour	73.3±8.5	76.8±8.2	<0.0001
Daytime	78.2±9.2	83.1±9.3	<0.0001
Nighttime	64.6±9.2	63.6±9.1	0.01
Nighttime trough	60.0±9.2	55.5±8.2	<0.0001
Preawakening	65.4±10.3	67.9±11.5	<0.0001
After awakening	75.1±10.4	89.2±9.5	<0.0001
Night:day ratio of DBP	0.83±0.09	0.77±0.09	<0.0001
Serum cholesterol, mmol/L	5.56±1.19	5.57±1.16	0.91

The 90th percentiles were determined after stratification for ethnicity and sex. Data are number (%) or mean±SD. DBP indicates diastolic blood pressure. *P*-values are for the difference between the two groups.
* Mean values of the cut-off point across ethnicities and sex weighted for the number of participants in each of the strata.

Table S2. Multivariable-Adjusted Hazard Ratios for the Sleep-Trough and Pre-Awakening Morning Surge in Diastolic Blood Pressure

Outcomes (Nº of events)	Sleep-Trough Surge (≥28.5 mm Hg)		Pre-Awakening Surge (≥21.6 mm Hg)	
	Adjusted	Fully Adjusted	Adjusted	Fully Adjusted
Mortality				
All causes (785)	1.34 (1.11–1.62)†	1.44 (1.18–1.75)‡	1.17 (0.95–1.45)	1.26 (1.01–1.56)*
Cardiovascular (287)	1.48 (1.11–1.98)†	1.59 (1.17–2.15)†	1.13 (0.79–1.61)	1.24 (0.86–1.80)
Non-Cardiovascular (473)	1.28 (0.99–1.66)	1.37 (1.05–1.78)*	1.29 (0.99–1.69)	1.37 (1.04–1.81)*
Fatal and nonfatal events				
All cardiovascular (611)	1.10 (0.89–1.37)	1.18 (0.94–1.48)	1.12 (0.88–1.41)	1.21 (0.95–1.54)
Cardiac (317)	1.22 (0.90–1.66)	1.31 (0.96–1.78)	1.29 (0.93–1.78)	1.40 (1.00–1.96)*
Coronary (228)	1.14 (0.80–1.63)	1.19 (0.82–1.72)	1.15 (0.78–1.69)	1.22 (0.82–1.82)
Cerebrovascular (281)	0.98 (0.70–1.36)	1.03 (0.73–1.46)	0.91 (0.64–1.30)	0.97 (0.67–1.40)
Infarction (140)	0.81 (0.50–1.33)	0.85 (0.51–1.41)	0.83 (0.50–1.39)	0.89 (0.53–1.51)
Hemorrhage (70)	1.67 (0.96–2.91)	1.57 (0.87–2.83)	1.71 (0.96–3.04)	1.62 (0.88–2.98)

Hazard ratios (95% confidence intervals) express the risk in the top decile of the sleep-trough or preawakening morning surge in diastolic blood pressure compared with the overall risk in the whole study population. The Cox models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24-hour diastolic blood pressure and 9 design variables coding for the deciles. In fully adjusted models, the diastolic night:day blood pressure ratio was additionally included in the Cox model. The cause of death was unknown in 25 cases. Significance of the hazard ratios: * $P<0.05$, † $P<0.01$, ‡ $P<0.001$.

Table S3. Multivariable-Adjusted Hazard Ratios for the Sleep-Trough and Pre-Awakening Morning Surge in Diastolic Blood Pressure According to Baseline Characteristics

Strata			All-Cause Mortality			All Cardiovascular Events	
	At risk (n)	Deaths (n)	Sleep-Trough MS (≥28.5 mm Hg)	Pre-Awakening MS (≥ 21.6 mm Hg)	Events (n)	Sleep-Trough MS (≥ 28.5 mm Hg)	Pre-Awakening MS (≥ 21.6 mm Hg)
All participants	5645	785	1.44 (1.18–1.75)‡	1.26 (1.01–1.56)*	611	1.18 (0.94–1.48)	1.21 (0.95–1.54)
Women	3048	321	1.37 (1.02–1.84)*	1.38 (0.99–1.90)	251	0.99 (0.70–1.41)	1.30 (0.91–1.84)
Men	2597	464	1.47 (1.13–1.92)†	1.16 (0.86–1.58)	360	1.27 (0.94–1.71)	1.13 (0.81–1.59)
<60 years	3558	134	1.85 (1.14–3.00)*	1.84 (1.17–2.89)†	151	1.32 (0.83–2.10)	1.55 (1.02–2.36)*
≥60 years	2087	651	1.37 (1.11–1.71)†	1.13 (0.88–1.45)	460	1.14 (0.88–1.48)	1.07 (0.79–1.44)
No history of CVD	5241	660	1.41 (1.13–1.75)†	1.17 (0.92–1.49)	501	1.15 (0.90–1.49)	1.12 (0.86–1.45)†
History of CVD	404	125	1.70 (1.04–2.79)*	1.79 (0.99–3.21)	110	1.21 (0.71–2.06)	1.60 (0.84–3.03)
Untreated	4457	464	1.49 (1.13–1.98)†	1.25 (0.92–1.71)	332	1.24 (0.88–1.75)	1.44 (1.03–2.01)*
Treated	1188	321	1.41 (1.07–1.85)*	1.30 (0.95–1.78)	279	1.19 (0.88–1.60)	1.06 (0.75–1.51)
Normotensive	3340	290	1.75 (1.23–2.51)†	1.26 (0.83–1.92)	178	1.89 (1.22–2.92)†	1.72 (1.09–2.71)*
Hypertensive	2305	495	1.35 (1.06–1.70)*	1.27 (0.98–1.64)	433	1.02 (0.79–1.33)	1.07 (0.81–1.43)
Non-smokers	3955	485	1.34 (1.04–1.71)*	1.30 (0.97–1.74)	389	1.08 (0.82–1.44)	1.19 (0.86–1.64)
Smokers	1690	300	1.53 (1.11–2.12)†	1.19 (0.85–1.67)	222	1.24 (0.85–1.82)	1.22 (0.84–1.78)
Non-drinkers	2978	409	1.33 (1.02–1.74)*	1.26 (0.94–1.68)	318	1.17 (0.87–1.58)	1.15 (0.84–1.57)
Drinkers	2667	376	1.55 (1.15–2.07)†	1.25 (0.89–1.76)	293	1.13 (0.79–1.61)	1.30 (0.88–1.92)
European	3023	408	1.15 (0.84–1.56)	1.02 (0.73–1.43)	304	1.19 (0.85–1.69)	1.25 (0.87–1.81)
Asian	1723	319	1.58 (1.19–2.10)†	1.42 (1.03–1.97)*	234	1.25 (0.89–1.77)	1.03 (0.69–1.52)
South American	899	58	2.08 (1.09–3.96)*	2.47 (1.17–5.21)*	73	1.00 (0.52–1.91)	1.88 (1.03–3.42)*

MS indicates the morning surge in diastolic blood pressure. Hazard ratios (95% confidence intervals) express the risk in the top decile compared with the average risk in the whole study population. The Cox models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24-hour diastolic blood pressure, 9 design variables coding for the deciles and the diastolic night:day blood pressure ratio. Significance of the hazard ratios: * $P<0.05$; † $P<0.01$; and ‡ $P<0.001$.

The Risk of Waking-Up. Impact of the Morning Surge in Blood Pressure

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Hypertension published online Mar 8, 2010;
DOI: 10.1161/HYPERTENSIONAHA.109.148908
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

 Print ISSN: 0194-911X. Online ISSN: 1524-4563

The Risk of Waking-Up
Impact of the Morning Surge in Blood Pressure

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Through ambulatory blood pressure (BP) monitoring, we know that BP usually follows a distinct circadian rhythm, characterized by a nocturnal decline during sleep of 10% to 30%, followed by a moderate-to-marked increase coinciding with the time of awakening.[1] For >2 decades, there has been great interest in the early morning period by preventive cardiologists and hypertension specialists, because it became evident that the onset of acute events, including sudden death, myocardial infarction, and stroke peak in the first 4 to 6 hours postawakening.[2,3] Because BP, heart rate, and these cardiovascular events all follow the same temporal pattern, it has been suspected that a pathophysiological relationship exists between hemodynamic aberrations, such as the early morning BP surge and vascular damage.[3]

Previous researchers have characterized the morning BP surge associated with increased target organ injury.[3,4] Risk factors for a profile of excessive early morning hypertension include older age, excessive alcohol and/or smoking, longer sleep times and later awakening times, cold weather climates, and day of the week (primarily Monday!).[5,6] Several studies performed in the past decade have found significant relations among the early morning BP surge and vascular disease,[7] cardiac hypertrophy,[4] and white matter lesions of the brain.[6,8] Prospective studies in Japanese individuals[8,9] have demonstrated a clinical impact of the early morning BP surge in predicting cardiovascular events. In one such cohort with ≈3.5 years of follow-up, for each 10-mm Hg increase in the early morning systolic BP surge obtained at baseline, the risk of stroke increased by 22%.[8] Of note, this change of BP on arising predicted cardiovascular events independently of age, the average 24-hour systolic BP, and antihypertensive therapy. In a separate population in Ohasama, Japan, that had a 10-year median follow-up period,[9] a large early morning BP surge was associated with the development of hemorrhagic stroke. Furthermore, in a smaller cohort study in France,[10] a higher cardiovascular morbidity and mortality rate was observed in patients with the highest morning BP surge compared with those patients in the lowest morning BP surge group.

Thus, previous studies have suggested a parallel relationship between the early morning BP surge and cardiovascular outcomes but have been lacking in event numbers and enough statistical power to clarify at just what level of the morning BP surge the risk will appear to become excessive. In this issue of *Hypertension*, Yi et al[11] have used the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome to address these questions. It is clear that their analyses have more advantages than previous studies: first, the population is large and heterogenous (5645 people, and more than half are women from 8 countries on 3 continents); second, the follow-up period and event numbers are substantially greater than all of the previous studies with 11.4 years of median follow-up and >600 cardiovascular events. The investigators used 2 different definitions of the morning surge in BP; the first was called the "sleep-through morning surge" and was defined as the difference between the morning pressure during the first 2 hours after awakening and the average of the lowest nighttime BP. This was similar to the definition used by Kario et al[8] in their seminal description of the impact of the morning BP surge on stroke events in an older Japanese cohort. The second definition was the "preawakening morning surge" and was the calculated difference between the morning BP during the first 2 hours after awakening and the BP during the first 2 hours before awakening. The top decile for these 2 definitions of morning BP surge was 37 and 28 mm Hg, respectively. In addition, the absolute morning surge in BP was 145.8 versus 123.7 mm Hg in those subjects who were in the 90th percentile versus those below the 90th percentile using the systolic sleep-through morning surge definition. In general, the trends for the 2 methods were similar: the morning BP surge was associated with a 30% to 45% increase in hazard for cardiovascular events. Of note, both definitions were fairly robust and similar for cardiac events but not for stroke events. The reason for this is unclear, but the authors did note demographic differences, because subjects in Asian countries were at a significantly higher risk for hemorrhagic stroke in the top morning surge decile but not for ischemic strokes, a finding at odds with the study by Kario et al.[8]

Of interest from the clinical perspective is the analysis of Yi et al[11] to determine the "cutoff" point at which cardiovascular harm begins to occur. Using both definitions, the authors suggest that a systolic morning BP surge by either definition of <20 mm Hg is unlikely to be associated with increased risk. This is useful, and it would be important to know what absolute systolic BP correlates with the surge values used to plot against the adjusted hazard ratios. Lacking in this analysis, however, is characterization of the population as it relates to the morning BP surge. Might individuals with

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(*Hypertension*. 2010;55:835-837.)

Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.109.148908

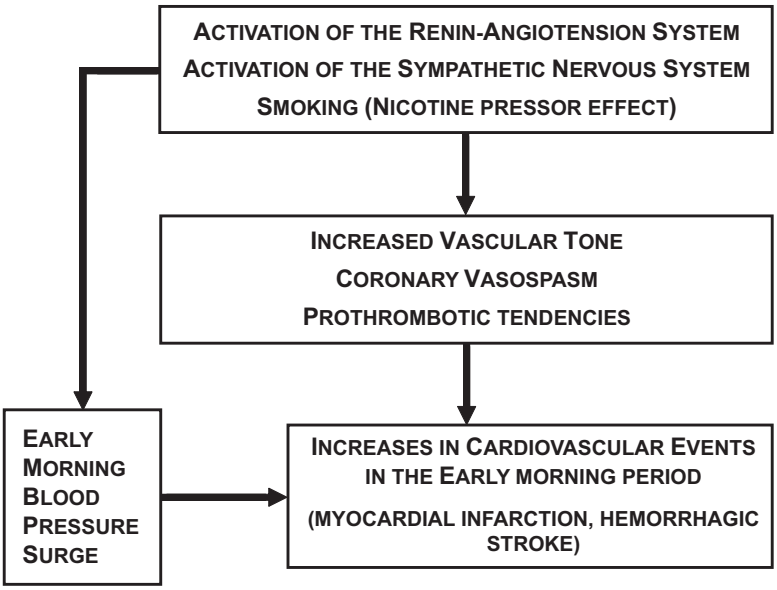

Figure. Sequence of events leading to early morning cardiovascular events.

a history of previous vascular events or major cardiovascular comorbidities (eg, diabetes mellitus or chronic kidney disease) show increased risk with lesser morning BP surge values compared with a healthier hypertensive patient group?

A substantial number of investigations have been conducted on the mechanism of the morning surge in BP and its potential relationship to cardiovascular harm.[3] Increased, sympathetic nervous system activity and activation of the renin-angiotensin system have both been determined to be possible contributors to increases in vascular resistance and the morning BP surge. Whether these mechanisms of morning BP elevation independently convey vascular harm is not clear but is of theoretical concern, because it is known that α-adrenergic stimulation and renin-angiotensin-aldosterone activation can increase vascular tone, coronary vasospasm, and prothrombotic tendencies in the early morning period (see Figure).[1,3]

Now that there is better characterization of the evidence linking an exaggerated morning BP surge of 28 to 37 mm Hg to cardiovascular morbidity and mortality, it seems reasonable to consider targeting this time of day with antihypertensive drug therapy. In fact, a substantial attempt to evaluate the benefit of a therapy that targeted BP and heart rate in the early morning period with controlled-onset extended-release verapamil versus conventional diuretic and/or β-blocker therapy on early morning cardiovascular events was initiated >12 years ago.[12] The Controlled Onset Verapamil Investigation for Cardiovascular Endpoints Trial was a 17 000-patient study that defined morning cardiovascular events as those occurring in the first 6 hours postawakening and originally should have had enough statistical power to evaluate this prespecified outcome on targeted versus nontargeted therapy. Unfortunately, because of premature discontinuation of the trial 3 years early by the study sponsor, there were not nearly enough events to make any assessment of the early morning event outcomes.

It seems unlikely that another large-scale trial will be conducted to evaluate whether reduction of the morning surge in BP will reduce cardiovascular morbidity and mortality because, that trial would have to have an enormous sample size and be carried out for many years at a substantial cost. There are, however, a number of studies that demonstrate that it may not be difficult to intervene in morning BP surge values with targeted antihypertensive therapies.[13,14] α-Adrenergic blockade at bedtime[13] may be an effective means to both lower the morning BP surge and reduce left ventricular mass index, as well as microalbuminuria, in patients with uncontrolled "morning hypertension." In addition, renin-angiotensin blocking agents that maintain pharmacodynamic effects into the early morning period have been shown to have a significant effect on the morning surge in BP.[14] Because the early morning period coincides with the end of the dosing period of once-daily medications, attenuation of antihypertensive efficacy is relatively common. On the basis of the results of this important new study by Yi et al,[11] more scrutiny should be given to control of the early morning BP, especially in patients at high risk for cardiovascular diseases and those who continue to smoke cigarettes.

Sources of Funding

This work was supported by National Institutes of Health grants RO1 AG022092 and 5R01 DA24667-2 and the Donaghue Medical Research Foundation (West Hartford, CT).

Disclosures

None.

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