

## FOCUS ISSUE: ASPIRIN

# Aspirin Administered at Bedtime, But Not on Awakening, Has an Effect on Ambulatory Blood Pressure in Hypertensive Patients

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<b>OBJECTIVES</b>	The purpose of this research was to investigate in untreated hypertensive patients the effects on ambulatory blood pressure (BP) of aspirin (ASA) administered at different times of the day.
<b>BACKGROUND</b>	Previous studies have shown that ASA produces an administration time-dependent inhibition of angiotensin II. Low-dose ASA has also been shown to reduce BP when administered before bedtime, as opposed to upon awakening, in normotensive and hypertensive volunteers, and in pregnant women at high risk for preeclampsia.
<b>METHODS</b>	We studied 328 untreated patients with grade 1 hypertension, $44.0 \pm 12.6$ years of age, randomly divided into three groups: nonpharmacological hygienic-dietary recommendations, the same recommendations and ASA (100 mg/day) on awakening, or the same recommendations and ASA before bedtime. Blood pressure was measured every 20 min during the day and every 30 min at night for 48 consecutive h before and after 3 months of intervention.
<b>RESULTS</b>	After three months of nonpharmacological intervention, there was a small and nonsignificant reduction of BP ( $<0.2$ mm Hg; $p = 0.648$ ). Blood pressure was slightly elevated after aspirin on awakening (2.6/1.6 mm Hg in the 24-h mean of systolic/diastolic BP; $p = 0.002$ ). A significant BP reduction, however, was observed in the patients who received aspirin before bedtime (6.8/4.6 mm Hg in systolic/diastolic BP; $p < 0.001$ ).
<b>CONCLUSIONS</b>	This prospective trial documents a significant administration time-dependent effect of low-dose ASA on BP in untreated hypertensive patients. The timed administration of low-dose ASA could provide a valuable approach, beyond the secondary prevention of cardiovascular disease, in the added BP control of patients with mild essential hypertension. (J Am Coll Cardiol 2005;46:975–83) © 2005 by the American College of Cardiology Foundation

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Acetylsalicylic acid (aspirin [ASA]) is a non-steroidal anti-inflammatory drug (NSAID) with demonstrated inhibitory effects on cyclooxygenases (COX), responsible for arachidonic acid metabolism and prostaglandin production (1).

See page 984

Aspirin has been shown to provide marked benefits in the prevention of cardiovascular events (2–5), although the potential direct effects of ASA on cardiovascular function remain uncertain. Previous studies have demonstrated that ASA is a potent antioxidative agent that markedly reduces vascular production of superoxide in normotensive and hypertensive rats (6). In addition, ASA was found to prevent angiotensin-II-induced hypertension and cardiovascular hypertrophy, mainly through its antioxidative properties in preventing the generation of superoxide, although

ASA apparently did not appear to reduce hypertensive levels of blood pressure (BP) (7). No attention has been paid so far in these studies to potential administration time-dependencies in effects. However, a significant circadian variation has been demonstrated in several oxidative stress markers, including 8-hydroxydeoxyguanosine, malondialdehyde, and 8-isoprostane (8). The peak concentrations of the three markers occurred early in the evening, with trough values obtained during nocturnal sleep. These peak and trough times are highly correlated with those of serum nitric oxide (8–10).

Moreover, among many other variables related to the regulation of BP, previous results have demonstrated a predictable circadian variation in plasma renin activity, angiotensin II, catecholamines, atrial natriuretic peptides, aldosterone, and angiotensin-converting enzyme (11–13). Because the main steps in the mechanisms regulating BP are circadian stage-dependent (14), it is not surprising that medications that affect BP may display a circadian time-dependency in their pharmacokinetics and effects (15).

Previous laboratory animal and clinical trial research convincingly demonstrates administration time-dependent (with reference to circadian rhythms) effects of ASA. Thus, the effects of ASA on lipoperoxides, beta-adrenergic recep-

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#### Abbreviations and Acronyms

ABPM	= ambulatory blood pressure monitoring
ASA	= aspirin
BMI	= body mass index
BP	= blood pressure
COX	= cyclooxygenase
DBP	= diastolic blood pressure
HDR	= hygienic-dietary recommendations
HR	= heart rate
NSAID	= non-steroidal anti-inflammatory drug
PROBE	= prospective, randomized, open-label, blinded end point
SBP	= systolic blood pressure

tors, and BP in clinically healthy subjects depend on the circadian timing of ASA administration (16). On the other hand, ASA has also been shown not only to restore vascular refractoriness to angiotensin II (17), but also to produce an administration time-dependent >30% inhibition of angiotensin II (18). Most important, the administration time-dependent influence of ASA on BP was previously demonstrated in a randomized trial on healthy women (16) and other independent double-blind, randomized, placebo-controlled clinical trials conducted, first, on clinically healthy subjects (19), a second one on normotensive and hypertensive subjects (20), and a third one on pregnant women at high risk for preeclampsia (21). The findings of these BP studies, all of which used ambulatory BP monitoring (ABPM) to derive primary outcome variables, are consistent; the BP-lowering effect of low-dose ASA is achieved when administered at bedtime but not upon awakening. In fact, recent results from a pilot study in hypertensive patients indicated a small increase, but not decrease, of BP when ASA was ingested on awakening (22). In keeping with these chronopharmacological effects and the previous findings suggesting that ASA at low dose may have a potential beneficial effect on BP, the present independent, prospective study investigated the influence of ASA on BP in previously untreated hypertensive patients who received low-dose ASA at different times of the day according to their rest-activity cycle and who were evaluated by 48-h ABPM before and after three months of pharmacologic treatment.

## METHODS

**Subjects.** We randomized 336 untreated volunteers for this trial. Among those, 328 (113 men and 215 women),  $44.0 \pm 12.6$  years of age (range 23 to 79 years), completed the study and provided all required information. Participants were diagnosed with grade 1 (mild) essential hypertension, according to criteria of the recent European Society of Hypertension-European Society of Cardiology guidelines (23), based on conventional BP measurements (systolic blood pressure [SBP] between 140 and 159 mm Hg or diastolic blood pressure [DBP] between 90 and 99 mm Hg)

and corroboration by ABPM at the time of recruitment. A positive diagnosis of hypertension based on ABPM required that either the 24-h mean SBP/DBP be above 130/80 mm Hg, the diurnal mean be above 135/85 mm Hg, or the nocturnal mean be above 120/70 mm Hg (24,25).

All subjects received their routine medical care at the Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago de Compostela, Spain. Shift workers, heavy drinkers (alcohol intake >80 g/day), smokers (>20 cigarette/day), and heavy exercisers were excluded, as were individuals with contraindications to the use of ASA and those with either moderate or severe arterial hypertension (grade 2 or 3, that is BP  $\geq 160/100$  mm Hg) or secondary arterial hypertension and cardiovascular disorders, including angina, heart failure, stroke, nephropathy, and retinopathy or prior myocardial infarction or coronary revascularization as revealed by thorough clinical evaluation according to the standardized protocol at the Unit. The use of antihypertensive and any other medication was forbidden during the trial. The demographic characteristics of the participants are included in Table 1.

After providing informed consent to participate in this prospective, randomized, open-label, blinded end point (PROBE), parallel-group trial, subjects were randomly assigned to one of three possible groups, keeping a priori a proportion of 2-1-1 among groups to increase power for comparisons between treated and untreated patients: group 1, nonpharmacological hygienic-dietary recommendations (HDR) according to the recent guidelines for the management of mild hypertension (23); group 2, the same HDR and ASA (100 mg/day) on awakening; group 3, the same HDR and ASA (100 mg/day) before bedtime. The dose of 100 mg used in this trial corresponds with the actual lower dose commercially available in Spain within the accepted range of low-dose (75 to 150 mg [5]). Compliance was measured on the basis of tablet count and a personal interview with each volunteer; HDR included sodium restriction, information on the Dietary Approach to Stop Hypertension diet, limit alcohol intake, and regular aerobic exercise. Benefits of the PROBE design and its validity as compared to double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been previously documented (26). The Review Board on Human Studies at our institution approved the protocol.

Blood samples were obtained in the clinic from the antecubital vein after nocturnal fasting between 8 AM and 9 AM on the same days when 48-h ABPM was initiated, both immediately before and after three months of timed treatment. The patients collected their urine during the first 24 h of ABPM. Clinic BP measurements (six per study visit after being seated for at least 5 min, on the same day just before starting ABPM) were always obtained by the same investigator with a validated automatic oscillometric device (HEM-737, Omron Health Care Inc., Vernon Hills, Illinois) (27). Assignment of participants to treatment groups

**Table 1.** Demographic and Analytical Characteristics of Subjects Investigated

Variables	Hygienic-Dietary Recommendations	Aspirin (100 mg/day) Upon Awakening	Aspirin (100 mg/day) Before Bedtime	p for Group Comparison
Patients, n	169	77	82	
Gender, % men	35.5	35.1	32.0	0.920
Age, yrs	43.9 ± 13.7	43.8 ± 12.1	45.2 ± 12.5	0.712
Height, cm	163.9 ± 9.3	162.1 ± 9.4	161.7 ± 9.9	0.154
<b>Before intervention</b>				
Weight, kg	75.4 ± 13.1	76.9 ± 15.6	75.7 ± 12.5	0.703
BMI, kg/m <sup>2</sup>	28.1 ± 4.5	29.2 ± 5.2	28.9 ± 4.3	0.133
Waist, cm	90.0 ± 11.4	93.0 ± 13.0	91.4 ± 10.6	0.153
Hip, cm	105.1 ± 8.7	107.3 ± 8.8	106.2 ± 9.2	0.182
SBP, mm Hg*	146.8 ± 16.7	146.2 ± 13.8	147.2 ± 11.3	0.906
DBP, mm Hg*	85.1 ± 9.8	84.4 ± 7.9	85.9 ± 6.9	0.555
Hemoglobin, g/dl	14.3 ± 1.2	14.1 ± 1.3	14.1 ± 1.2	0.222
Glucose, mg/dl	93.1 ± 12.3	96.1 ± 11.8	95.8 ± 12.2	0.212
Creatinine, mg/dl	0.90 ± 0.18	0.86 ± 0.13	0.86 ± 0.14	0.083
Uric acid, mg/dl	5.3 ± 1.5	5.3 ± 1.3	5.1 ± 1.2	0.508
Cholesterol, mg/dl	209.8 ± 39.5	212.9 ± 38.6	213.2 ± 39.5	0.790
Triglycerides, mg/dl	106.9 ± 66.9	115.2 ± 73.8	100.3 ± 46.7	0.593
Fibrinogen, mg/dl	317.5 ± 80.4	294.4 ± 57.2	308.2 ± 61.7	0.166
Sodium (serum), mM/l	138.9 ± 1.9	139.1 ± 1.9	139.6 ± 2.1	0.096
Potassium (serum), mM/l	4.42 ± 0.35	4.34 ± 0.30	4.40 ± 0.37	0.280
Sodium (urine), mEq/24 h	115.1 ± 54.8	121.7 ± 52.4	113.4 ± 45.6	0.516
Potassium (urine), mEq/24 h	75.3 ± 24.1	81.2 ± 29.9	71.7 ± 23.5	0.245
<b>After intervention</b>				
Weight, kg	74.8 ± 13.1 (0.671)	76.5 ± 15.6 (0.875)	75.3 ± 12.5 (0.872)	0.644
BMI, kg/m <sup>2</sup>	27.9 ± 4.5 (0.645)	29.1 ± 5.1 (0.847)	28.8 ± 4.6 (0.888)	0.097
Waist, cm	89.8 ± 11.4 (0.464)	92.7 ± 13.1 (0.863)	91.6 ± 10.5 (0.900)	0.153
Hip, cm	104.6 ± 8.6 (0.122)	106.6 ± 9.1 (0.634)	106.6 ± 9.0 (0.804)	0.131
SBP, mm Hg*	144.0 ± 15.5 (0.096)	145.1 ± 13.0 (0.592)	143.1 ± 13.0 (<0.001)	0.715
DBP, mm Hg*	83.2 ± 10.0 (0.086)	83.4 ± 7.5 (0.424)	82.8 ± 8.4 (<0.001)	0.940
Hemoglobin, g/dl	14.3 ± 1.3 (0.752)	14.2 ± 1.5 (0.936)	13.9 ± 1.4 (0.484)	0.139
Glucose, mg/dl	93.9 ± 11.0 (0.533)	95.5 ± 18.0 (0.841)	95.5 ± 12.7 (0.861)	0.236
Creatinine, mg/dl	0.91 ± 0.18 (0.610)	0.87 ± 0.14 (0.640)	0.90 ± 0.17 (0.097)	0.292
Uric acid, mg/dl	5.5 ± 1.6 (0.474)	5.3 ± 1.3 (0.810)	5.2 ± 1.2 (0.651)	0.358
Cholesterol, mg/dl	206.3 ± 43.7 (0.494)	202.1 ± 31.2 (0.073)	203.8 ± 30.0 (0.131)	0.736
Triglycerides, mg/dl	107.3 ± 71.2 (0.962)	107.7 ± 80.0 (0.691)	109.3 ± 68.5 (0.382)	0.984
Fibrinogen, mg/dl	307.2 ± 67.5 (0.353)	286.5 ± 74.4 (0.562)	312.2 ± 79.2 (0.794)	0.192
Sodium (serum), mM/l	139.4 ± 2.0 (0.106)	139.8 ± 1.9 (0.046)	139.6 ± 1.7 (0.809)	0.323
Potassium (serum), mM/l	4.43 ± 0.34 (0.762)	4.43 ± 0.34 (0.105)	4.40 ± 0.29 (0.937)	0.139
Sodium (urine), mEq/24 h	128.8 ± 64.2 (0.333)	123.8 ± 49.4 (0.898)	125.5 ± 43.9 (0.311)	0.789
Potassium (urine), mEq/24 h	76.5 ± 30.1 (0.857)	77.2 ± 20.1 (0.623)	82.7 ± 30.1 (0.152)	0.697

All values given in mean ± SD. \*Values provided correspond to the average of six conventional blood pressure measurements obtained for each patient at the clinic before starting ambulatory blood pressure monitoring. Values in parentheses are p value from comparison with values before intervention.

BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

was done by one member of the research team, according to the order of recruitment, following an allocation table constructed by a computerized random-number generator. The assignment of subjects to each intervention group was blinded from the research team member conducting the clinic BP measurements and from those performing the statistical analysis of the data. The minimum sample size for this trial (75 patients for each treatment group) was calculated to show as significant at the 95% level with a power of 95% changes in the 24-h mean of BP above 3 mm Hg, according to the estimation of interindividual variability provided by previous studies (20).

**ABPM assessment.** The SBP, DBP, and heart rate (HR) of each participant were automatically measured every 20 min from 7 AM to 11 PM and every 30 min during the night for 48 consecutive hours with a validated SpaceLabs 90207

device (SpaceLabs Inc., Issaquah, Washington). Subjects were studied by ABPM under baseline conditions when subjects were free of medication, and again after three months of timed intervention with either ASA or HDR alone. They were assessed while adhering to their usual diurnal activity (8 AM to 11 PM for most) and nocturnal sleep routine. Participants were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the two days of ABPM. No one was hospitalized during monitoring; ABPM always began between 10 AM and noon. Blood pressure series were not considered valid for analysis if more than 30% of the measurements were lacking or if they had missing data for >2 h spans, or if they were collected from subjects while experiencing an irregular rest-activity schedule or a nighttime sleep span <6 h or >12 h during monitoring.

Protocol-correct data series were collected from 328 subjects. Baseline BP profiles of eight additional subjects (three originally assigned to HDR, three assigned to morning treatment with ASA, and two to bedtime treatment) were not used for analysis because the patients either discontinued timed treatment or because they failed to return for the second ABPM at the end of intervention.

**Actigraphy.** During 48-h ABPM each participant wore a Mini-Motion-Logger actigraph (Ambulatory Monitoring Inc., Ardsley, New York) on the dominant wrist to monitor physical activity every minute. This compact (about half the size of a wristwatch) device functions as an accelerometer. The internal clocks of the actigraph and the ABPM devices were synchronized through their respective interfaces by the same computer. The actigraphy data were used to determine the onset and offset times of diurnal activity and nocturnal sleep so as to accurately determine the diurnal and nocturnal BP means of each subject. The mean activity for the 5 min before each BP reading was then calculated for further statistical analysis on circadian variability of activity, according to previous studies on this area (28,29).

**Statistical methods.** Each individual's clock hour BP and HR values were first rereferenced from clock time to hours after awakening from nocturnal sleep, according to the information obtained from wrist actigraphy. This transformation avoided the introduction of bias due to differences among subjects in their sleep/activity routine (29); BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers (30). Thus, readings with SBP >250 or <70 mm Hg, DBP >150 or <40 mm Hg, and pulse pressure >150 or <20 mm Hg were automatically discarded. Hourly BP means obtained before and after treatment were compared by *t* test corrected for multiple testing. In so doing, the level of significance was established at  $p \leq 0.002$ , after dividing the usual level of 0.05 by the number of tests done on the same variable (24, one for each hourly mean). The daily (24-h), diurnal, and nocturnal means of BP were further compared among groups by repeated measures analysis of variance. Additionally, the demographic and clinical characteristics in Table 1 were compared among groups by analysis of variance. Comparisons within each treatment group for each variable included in Table 1 measured before and after three months of intervention were performed by paired *t* test.

## RESULTS

**Demographic and analytic characteristics.** The baseline characteristics of the three groups of subjects (Table 1) were similar in age, height, weight, body mass index (BMI), waist and hip perimeters, and clinic SBP and DBP (average of the six morning measurements obtained just before ABPM). Moreover, there were no statistically significant changes in weight, BMI, and the waist and hip perimeters in either group after three months of intervention. Clinic BP mea-

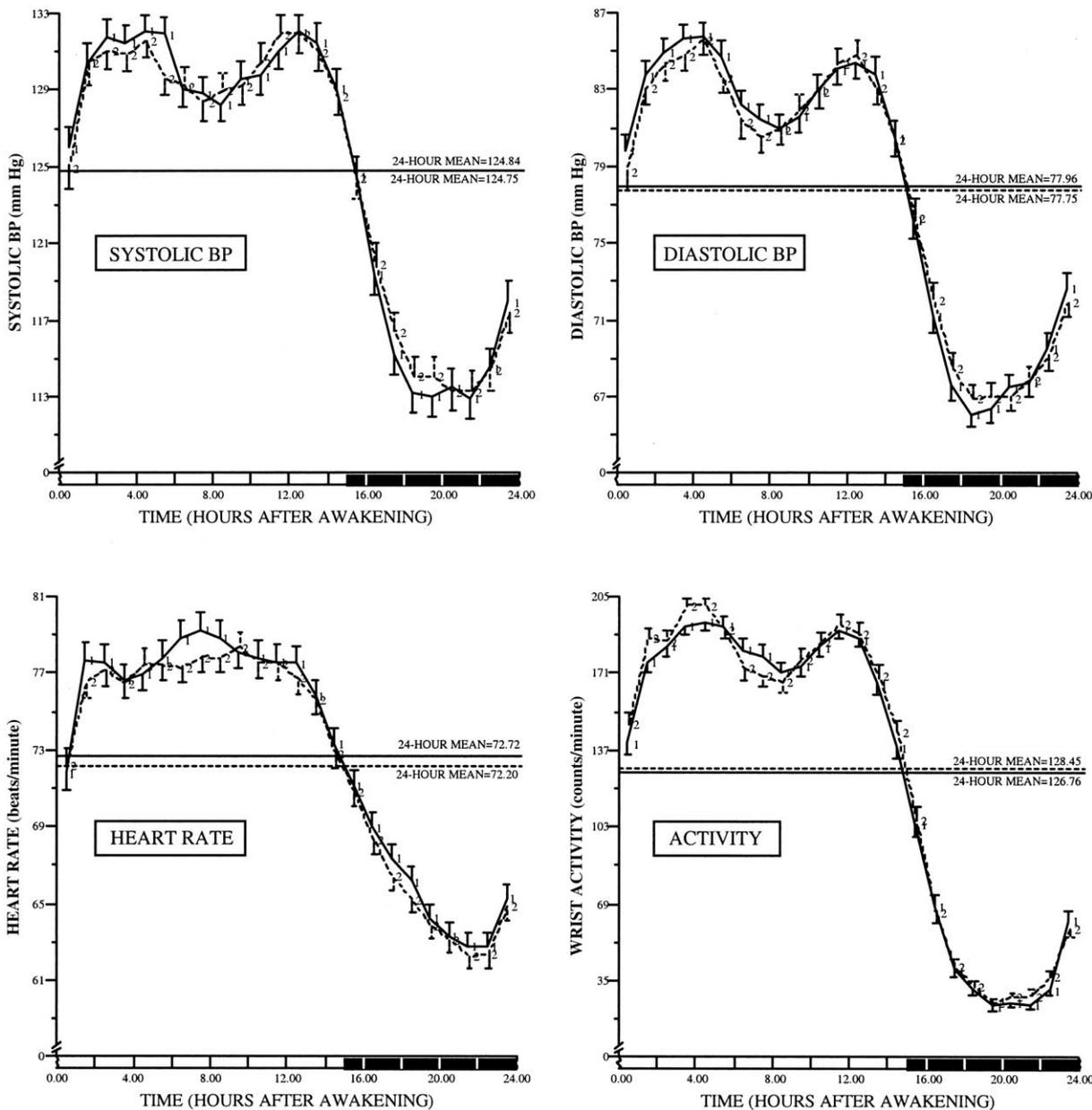
surements were slightly but statistically reduced from baseline ones (4.1 and 3.1 mm Hg in SBP and DBP,  $p < 0.001$ ) only in the group receiving ASA before bedtime. The serum values of glucose, creatinine, uric acid, cholesterol, triglycerides, fibrinogen, sodium, potassium (Table 1), and other laboratory chemistry variables of the three treatment groups were comparable at baseline and were unchanged after three months of intervention. The use of the low dose of 100 mg/day of ASA did not modify the baseline values of hemoglobin at any time of administration tested here (Table 1). Sodium and potassium from 24-h urine samples were not significantly modified in any group.

**ABPM characteristics.** The circadian variation of SBP, DBP, HR, and wrist activity in untreated mild hypertensive patients measured by 48-h ABPM before and after three months of nonpharmacologic HDR is depicted in Figure 1. Results indicate no significant change in diurnal, nocturnal, and 24-h means of BP or HR after three months of nonpharmacologic intervention ( $p > 0.394$  in all cases). Physical activity monitored before and after three months of intervention also remained unchanged (Fig. 1, bottom right).

There was no statistically significant change in the diurnal means of BP, HR, or activity after three months of 100 mg/day ASA ingested on awakening (Fig. 2). Blood pressure slightly but significantly increased during nocturnal resting hours (3.4 and 2.0 mm Hg for SBP and DBP,  $p < 0.005$ ). Accordingly, there was a significant decrease in the diurnal/nocturnal ratio of BP ( $p = 0.012$ ), and an increase from 35% to 47% in the prevalence of nondipper subjects (patients with <10% decline in the nocturnal relative to the diurnal BP mean [31]).

Figure 3 shows the significant reduction compared to baseline of 6.8 and 4.6 mm Hg in the 24-h mean of SBP and DBP, respectively ( $p < 0.001$ ), after 3 months of 100 mg/day ASA taken at bedtime. Blood pressure was homogeneously reduced during the hours of diurnal activity and nocturnal rest. Figure 3 further indicates that the mean reduction in BP at each clock time during the 24-h dosing interval was statistically significant ( $p$  always  $< 0.05$  after correcting for multiple testing). A reduction in BP was observed in 87% of the patients in this group. Only one patient experienced a significant BP elevation after treatment. Despite the significant effect on BP, HR and physical activity remained unchanged after three months of intervention (Fig. 3).

The comparison of results provided in Figures 1 to 3 indicates the lack of statistically significant differences in BP at baseline among the three intervention groups ( $p = 0.492$  for comparison of 24-h mean of SBP among groups;  $p = 0.734$  for DBP). The 24-h mean of HR was also equivalent at baseline among groups ( $p = 0.335$ ). After intervention, results indicate a highly significant reduction in the 24-h mean of BP after ASA ingested before bedtime in comparison to the other two groups ( $p < 0.001$  for SBP and DBP).



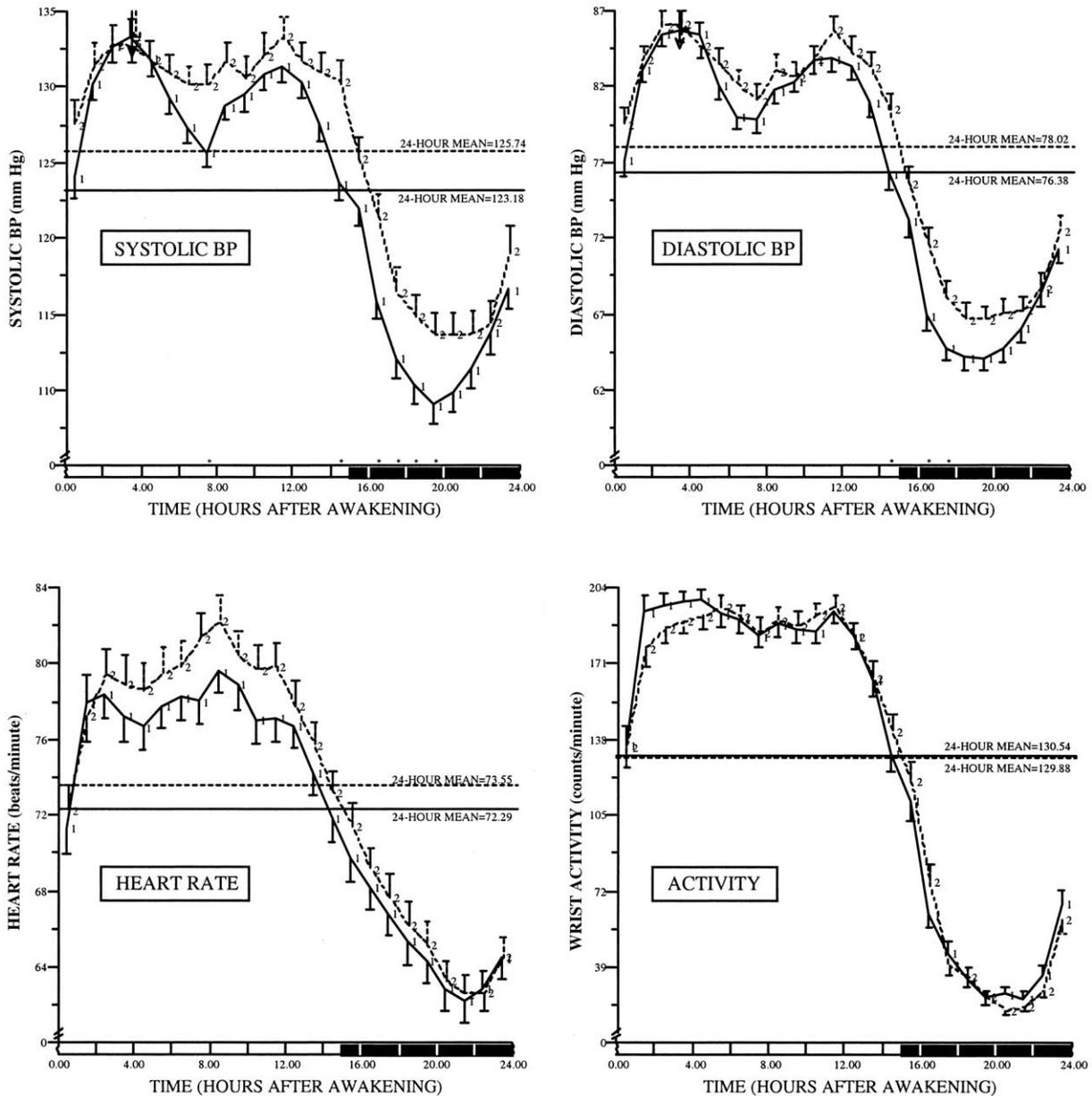
**Figure 1.** Changes in blood pressure (BP), heart rate, and wrist activity after three months of hygienic-dietary intervention in patients with mild hypertension sampled by 48-h ambulatory monitoring. Each graph shows hourly means and standard errors of data collected before (continuous line) and after (dashed line) three months of nonpharmacological intervention. Dark shading along the lower horizontal axis of the graphs represents average hours of nocturnal sleep across the patients.

## DISCUSSION

The major result from this study is that ASA selectively decreases BP as a function of the timing of its administration in relation to the rest-activity cycle of each individual subject. The administration time-dependent effects of ASA on BP demonstrated here are fully in agreement with conclusions found earlier in clinically healthy normotensive subjects as well as in hypertensive patients using the same low-dose of 100 mg/day ASA but for the much shorter time of just one week (19,20). A higher dose of ASA (500 mg/day), however, showed a pressor effect, even when administered before bedtime (20). Similar conclusions re-

garding the time-dependent influence of ASA on BP were also corroborated in pregnant women who used 100 mg/day of ASA for most of their pregnancy (21). In the present study, low-dose ASA given before bedtime not only significantly reduced the mean BP from ABPM, but also conventional BP measurements. Further results from Table 1 indicate the poor compliance with HDR among all three groups of patients, inasmuch as there was no significant change in weight, waist and hip perimeters, serum glucose, cholesterol, or triglycerides after three months of intervention.

There is extensive literature on the effects of ASA, mainly in the prevention of cardiovascular events (2-5). Although

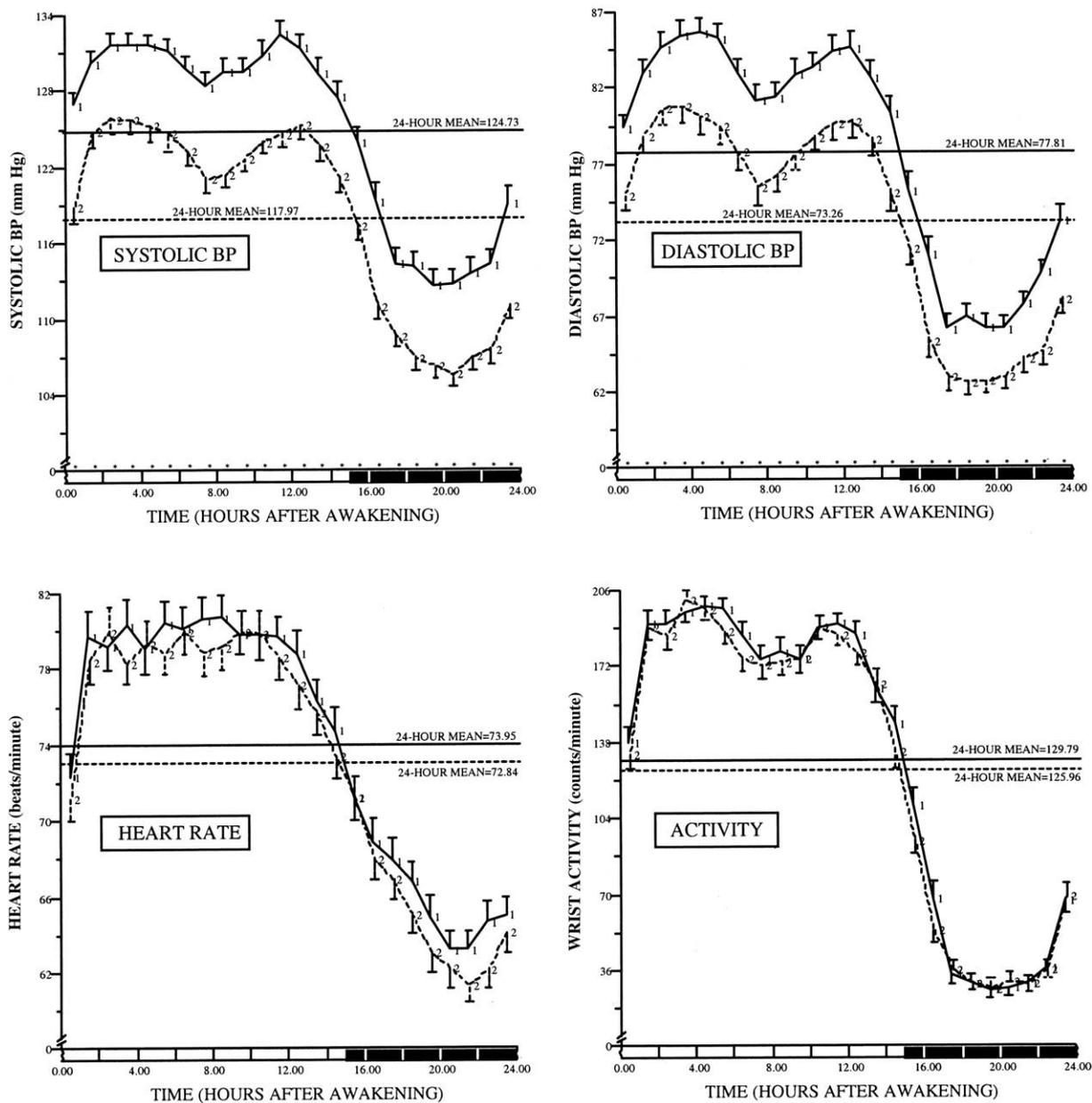


**Figure 2.** Changes in blood pressure (BP), heart rate, and wrist activity after aspirin (100 mg/day) administered on awakening in patients with mild hypertension sampled by 48-h ambulatory monitoring. Each graph shows hourly means and standard errors of data collected before (**continuous line**) and after (**dashed line**) three months of aspirin administration. **Dark shading** along the lower horizontal axis of the graphs represents average hours of nocturnal sleep across the patients. \* $p < 0.05$  from  $t$  test adjusted for multiple testing.

some of these studies reported average values of office BP measurements for the patients before and after long-term administration of ASA or placebo, the study of a possible effect from ASA on BP was not a primary objective. In fact, the effect of ASA on BP was evaluated only in a few small studies (20,22,32,33). It has been reported that NSAIDs may increase BP both in normotensive and hypertensive subjects (32,34-36). The effects appear more marked in hypertensives under treatment (32,34). The mechanisms whereby an NSAID may increase BP are not fully understood, nor it is known whether the increase in BP is a long-term effect. In any event, the dose of ASA regularly used to show anti-inflammatory effects is markedly larger

than the dose used as anticoagulant (37) and recommended for prevention of cardiovascular events (2-5).

With respect to the potential mechanism(s) involved in the responsiveness of BP to ASA administered at different times according to the rest-activity cycle, ASA has been shown to provide a significant inhibition of angiotensin II dependent on the dose and circadian time of ASA administration (18). Moreover, ASA is known to acetylate a variety of proteins, including COX-2; COX-2 inhibition has also been shown to decrease renin content and to lower BP in a model of renovascular hypertension (38). These results may be relevant inasmuch as ASA given at the end of the activity cycle could thus target the nocturnal peak of



**Figure 3.** Changes in blood pressure (BP), heart rate, and wrist activity after aspirin (100 mg/day) administered before bedtime in patients with mild hypertension sampled by 48-h ambulatory monitoring. Each graph shows hourly means and standard errors of data collected before (**continuous line**) and after (**dashed line**) three months of aspirin administration. **Dark shading** along the lower horizontal axis of the graphs represents average hours of nocturnal sleep across the patients. \* $p < 0.05$  from  $t$  test adjusted for multiple testing.

plasma renin activity, while enhancing the nocturnal trough in the production of nitric oxide (9,10), hypotheses that deserve further investigation.

From the clinical point of view, the effects of ASA on BP demonstrated here indicate the need to identify patients using both ASA and antihypertensive medication, as well as the time of ingestion of ASA, due to the possible confounding effects of ASA on BP that could result from its use in conjunction with other drugs. Recent studies have shown no influence of low-dose ASA on BP in hypertensive patients under pharmacologic therapy (39,40), yet the time of ingestion of ASA (presumably morning [29]) has not been reported. Whether or not ASA enhances the effects of

antihypertensive medication or if such a possible influence is circadian-time-dependent are further issues of clinical interest that should be addressed in future research.

Apart from these limitations, one could also discuss the potential risks of ASA administered at different times of the day. Compliance was not different in this trial between morning and night dose. With respect to tolerability and potential side effects, a previous endoscopic trial on volunteers who took high-dose ASA (1,300 mg) at different times of the day has shown that the evening dose, in comparison to the morning, produced 37% fewer gastric hemorrhagic lesions (41). Although low-dose ASA would be generally associated with lower potential risks as com-

pared to higher doses, prior studies have concluded that nighttime administration of ASA is better tolerated than morning administration (41).

The results from this prospective trial in untreated patients with mild hypertension corroborate earlier findings on the administration time-dependent influence of low-dose ASA on BP. Apart from the documented benefits of ASA in the secondary prevention of cardiovascular disease, results indicate that the timed administration of low-dose ASA with respect to the rest-activity cycle of each individual patient could provide a valuable approach for BP control of patients with mild essential hypertension and poor compliance with hygienic and/or dietary recommendations. Apart from the BP lowering effect, low-dose ASA administered at bedtime, but not on awakening, has also been shown to be protective against preeclampsia, gestational hypertension, intrauterine growth retardation, and preterm delivery in high-risk pregnant women (21). Whether or not low-dose ASA administered at the end of the activity cycle is able to provide further cardiovascular protection in hypertensive patients beyond documented findings (2) deserves prospective investigation.

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