

# Time of day to monitor ambulatory blood pressure affects the outcome

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**Objectives** The reproducibility of blood pressure variables from ambulatory blood pressure monitoring (AMBP) initiated at the same time of day (SAME: 1700–1900 h) was compared with the reproducibility of blood pressure variables when monitoring was initiated at opposite times of day (OPP: randomized, morning=0700–0900 h and evening=1700–1900 h). It was hypothesized that the reproducibility for SAME ( $n=18$ ) would be no different than the reproducibility for OPP ( $n=13$ ).

**Methods** The order of AMBP sessions was randomized. The Accutacker II was used to determine average blood pressures, Crest (CrBP), Trough (TrBP), and TrBP:CrBP ratio; Averages were divided into 24-h, daytime (0600–2200 h), and night-time (2200–0600 h) for both systolic and diastolic blood pressures. A paired *t*-test with an intraclass correlation was used to determine the reproducibility of AMBP for both SAME and OPP. A chi-square was used to compare the distribution of reproducible AMBP variables between SAME and OPP. Significance was at  $P<0.05$ .

**Results** The reproducibility of AMBP variables for SAME and OPP was a significantly different for systolic blood

pressure. All of the ambulatory systolic variables measured in the SAME group were reproducible except for the TrBP:CrBP, whereas only the systolic night-time averages of the OPP group were reproducible. Similarly all of the ambulatory diastolic variables measured in the SAME group were reproducible except for TrBP:CrBP, whereas 24-h, night-time averages, and TrBP were reproducible in the OPP group.

**Conclusions** Ambulatory blood pressure variables were consistently higher when the monitoring session began in the morning hours. *Blood Press Monit* 10:43–50 © 2005 Lippincott Williams & Wilkins.

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**Key words:** ambulatory blood pressure monitoring, reproducibility, time of day

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## Introduction

Ambulatory blood pressure monitoring is considered to be a valuable tool in the assessment of blood pressure under a variety of free-living conditions [1] and throughout extended periods of time [2]. In addition, ambulatory monitoring has a higher accuracy [3–5], less variability [6], and a higher correlation with end-organ damage [3,7] compared to clinical blood pressures.

A high accuracy and reproducibility of ambulatory technology has been found for normo- and hypertensive adults during activities of daily living [3,5,8–14]. In fact, the reproducibility of ambulatory blood pressure measurements has been reported to be higher than clinic measurements [10,13,14]. Designs of these studies varied from the observation of 2–4 separate 24-h monitoring conditions [9–11,14] to a single 48-h condition [13]. Statistical methods used to report reproducibility in ambulatory blood pressure monitoring have been simple correlations [2,9,14], paired *t*-tests [13], or an analysis of variance (ANOVA) [10,11,13]. The correlation

coefficient between two 24-h ambulatory measurement periods has been reported to range from 0.81 to 0.91, depending on the ambulatory variable measured [9]. Correlations are lower for diastolic, than for systolic blood pressure [2]. When using an ANOVA instead of correlation coefficients, no significant differences were reported among repeat measurements in hypertensive adults [10].

Blood pressure rhythms are on a 24-h cycle [15]. In theory, the time to initiate measurement of the 24-h cycle should not influence the outcome as long as the whole 24-h cycle is measured. In the reproducibility studies cited above, James and colleagues [10] and Trazzi and colleagues [14] did not report the time of day the monitoring began; Hietanen and Saarenhovi [9] reported 'morning'; Musso and colleagues [11] reported 1000 h; and Prasad [13] and colleagues reported between 0900 h and 1600 h. Although there is a variation in the time of day to begin monitoring, it was believed that the time of day for monitoring had no influence on the 24-h blood pressure outcome during activities of daily living.

However, our studies focusing on a separate problem have provided data that indicate otherwise. In a series of studies we developed to observe the influence of the time of day for exercise on the ambulatory blood pressure reduction [16–21], we discovered that the time of day to begin the ambulatory blood pressure monitoring may affect the blood pressure outcome when monitoring during activities of daily living. We found the time of day to begin monitoring resulted in statistically significant differences in selected ambulatory blood pressure variables in our control data, not associated with the exercise intervention. To further investigate this phenomenon, we compared the reproducibility of ambulatory blood pressure monitoring between sessions beginning at the same time of day and sessions beginning at opposite periods of the day (i.e., morning versus evening). We hypothesized that the reproducibility between two ambulatory blood pressure monitoring sessions beginning at the same time of day would be no different from the reproducibility between two sessions beginning at different times of day (i.e., morning versus evening). All sessions measured ambulatory blood pressure during activities of daily living.

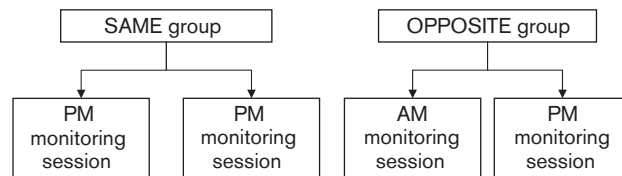
## Methods

The design of this study is illustrated in Figure 1. Utilizing existing data from two separate studies [16,19], the reproducibility of ambulatory blood pressure monitoring between two monitoring sessions initiated at the same time of day was compared with the reproducibility of ambulatory blood pressure monitoring between two monitoring sessions initiated at opposite times of day (i.e., morning versus evening). Two sets of subjects were grouped by those who performed two ambulatory blood pressure monitoring sessions beginning at the same time of day (SAME) [16] and those who performed two sessions beginning at the opposite times of the day (OPP) [19]. Procedures included: (1) blood pressure screening and (2) two ambulatory blood pressure monitoring sessions. The Committee for Protection of Human Subjects at Indiana University approved all procedures.

## Subjects

Thirty-one hypertensive middle-aged adults were identified for this study; 18 were in the SAME group and 13 were in the OPP group. Hypertensive subjects were defined by one of the following: (1) having had a previous diagnosis of hypertension by a primary physician; (2) having a mean systolic blood pressure  $\geq 140$  mmHg and/or a mean diastolic blood pressure  $\geq 90$  mmHg taken from at least two readings on 2 days, 3 days apart [22] (taken with a random zero sphygmomanometer); or (3) exhibiting a mean daytime ambulatory blood pressure of  $\geq 135/85$  mmHg [3]. Subject exclusion criteria included: (1) significant cardiovascular disease; (2) significant dysrhythmias; (3) brachial artery bruits; (4) cardiac or

Fig. 1



Design of the study. Subjects in the SAME group were monitored twice, beginning in the evening whereas subjects in the OPPOSITE group were monitored once, beginning in the morning and once, beginning in the evening.

renal transplant patients; (5) sleep apnea, and (6) taking antihypertensive medications. A physician clearance by each subject's primary physician was required prior to participation in the study. Under the supervision of their primary physician, subjects who were taking antihypertensive medications were removed from those medications for a period of 1 month, at least 2 weeks prior to the beginning of the treatments.

## Blood pressure screening

For all subjects, three clinic blood pressures were taken on two separate days, 3 days apart (a total of six measurements). On the first day, blood pressures were taken in both arms. The arm with the highest blood pressure was used for the screening. This screening was also used to confirm non-medicated hypertensive pressures (systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg) based on the definitions of the World Health Organization [22]. Ambulatory blood pressure monitoring was conducted to confirm high blood pressure in selected subjects whose screening pressures did not meet our criteria ( $n = 3$ ; SAME = 2 and OPP = 1).

## Twenty-four hour blood pressure monitoring

Ambulatory blood pressures were measured on two separate weekdays, 2–3 days apart. For the subjects in the SAME group, ambulatory blood pressures were measured beginning in the evening (1700–1900 h). For the subjects in the OPP group, the ambulatory blood pressure monitoring sessions were randomized to begin in the morning (0700–0900 h) or the evening (1700–1900 h). All of these sessions were conducted on days in which the subject participated in activities of daily living.

The Accutracker II (Suntech Medical Instruments, Inc., Raleigh, NC, USA) was used for all ambulatory measurements. The sampling interval was randomized to take a reading on the average of every 15 min  $\pm 5$  min for daytime hours (0600–2200 h) and on the average of every 30–45  $\pm 5$  min for night-time hours (2200–0600 h). One repeat measurement was taken if the first measurement was unsuccessful during the daytime hours and two

repeat measurements were taken during the night-time hours. The inflation of the cuff for each measurement was programmed to inflate 30 mmHg greater than the previous reading. The cuff deflation rate was programmed at 3 mmHg/s.

Subjects were asked to document: (1) time of sleeping; (2) time at work; (3) time of meals; and (4) time at leisure activities. Subjects were asked to go to bed between 2000–2400 h and get up between 0600–1000 h. Subjects were instructed: (1) not to exercise; (2) not to take a shower; and (3) to relax and straighten out the arm during each recording interval for the entire 24-h period.

The blood pressure monitor was worn on the non-dominant arm. Electrode wires and blood pressure tubing were taped securely to the chest. The subjects were given the option to secure the recording unit with a belt or the shoulder strap provided. A roll of micropore tape was given to each subject to re-tape areas if needed. Phone numbers of the investigators were provided to the subjects in case they had any problems with the device during the course of the monitoring.

Individual blood pressure measurements were reviewed for missing and erroneous readings. Readings were purged if: (1) data were missing; (2) systolic blood pressure was lower than diastolic pressure or if  $> 240$  mmHg or  $< 50$  mmHg; (3) if diastolic pressure was  $> 140$  mmHg or  $< 40$  mmHg; or (4) if pulse rate was  $> 150$  or  $< 40$  per min in accordance with Staessen *et al.* [23]. System tagged data were purged if: (1) systolic pressures deviated  $\pm 50$  mmHg; (2) diastolic pressures deviate  $\pm 20$  mmHg; or (3) heart rates deviated  $\pm 30$  beats from the surrounding values.

#### Data management of ambulatory blood pressure

Dependent variables for ambulatory blood pressure monitoring included average blood pressures (mmHg), crest blood pressure (CrBP), trough blood pressure (TrBP), and TrBP:CrBP ratio, for both systolic and diastolic pressures. Average pressures were divided into 24-h, daytime (0600–2200 h), and night-time (2200–0600 h) time periods.

The CrBP was calculated as the time-weighted mean blood pressure of the period of at least 6 h with the highest time-weighted mean pressure [24]. The TrBP was calculated as the time-weighted mean blood pressure of the period of at least 6 h with the lowest time-weighted mean pressure [24]. The trough to crest ratio (TrBP:CrBP) was calculated as the ratio of TrBP to CrBP.

#### Statistical methods

A paired *t*-test confirming non-significance between trials with a significant intraclass correlation was used to determine the reproducibility of ambulatory blood

**Table 1** Demographics of subjects in the SAME and OPP groups. Data are reported as means  $\pm$  standard error

Variable	SAME	OPP
Number	18	13
Sex distribution (men/women)	7/11	6/7
Height (cm)	173.8 $\pm$ 2.14	169.8 $\pm$ 2.62
Weight (kg)	88.1 $\pm$ 5.21	79.2 $\pm$ 4.47
Age (years)	52.1 $\pm$ 2.51	56.1 $\pm$ 1.83
BMI (kg/m <sup>2</sup> )	29.0 $\pm$ 1.41	29.8 $\pm$ 2.59
Screening or clinic blood pressure (mmHg)	143.7 $\pm$ 2.89/92.3 $\pm$ 1.77	142.5 $\pm$ 2.86/89.2 $\pm$ 1.55
Number (%) of subjects removed from antihypertensive medications:	10 (55.6%)	7 (53.8%)
Beta-blockers	6 (33.3%)	2 (15.4%)
Diuretics	3 (16.7%)	
Calcium-channel blockers	1 (5.6%)	3 (23.1%)
Vasodilators		2 (15.4%)

pressures taken either at the same time of day or taken at the opposite times of day. The significant values of intraclass correlations have been defined by Landis and Koch [25]. Values of  $< 0.40$ ,  $0.4–0.75$ , and  $> 0.75$  represent poor, fair-to-good, and excellent agreement respectively. For this study, only excellent intraclass correlations would be considered reproducible. A chi square test was used to compare the distribution of reproducible variables among the six ambulatory variables (three average variables and three diurnal variables) observed between SAME and OPP groups for systolic and diastolic blood pressures respectively. A two-way ANOVA (condition  $\times$  trial) with repeated measures was used to compare ambulatory blood pressure outcomes when the reproducibility could not be demonstrated. Significance was set at  $P < 0.05$ .

#### Results

The demographics of the subjects are presented in Table 1. There was no significant difference in any demographic variable between the two groups. Although the medications were different, a similar percentage of subjects in each group were taken off antihypertensive medications.

Table 2 summarizes the intraclass correlation coefficients and summarizes the variables that met the different criteria. Reproducibility was defined as a non-significant *t*-test with an excellent intraclass correlation ( $> 0.75$ ) between trials. For systolic blood pressures, all of the ambulatory variables measured in the SAME group were reproducible except the TrBP:CrBP ratio for systolic blood pressure, whereas none of the ambulatory variables measured in the OPP group were reproducible, except night-time average systolic pressure. For diastolic blood pressure, all of the ambulatory variables measured in the SAME group were reproducible except TrBP:CrBP ratio,

**Table 2 Ambulatory variables meeting the criteria for reproducibility. Reproducibility was defined as exhibiting a non-significant paired *t*-test with a significant intraclass correlation between trials**

Group	Variable	Paired <i>t</i> -test <i>P</i> value	Intraclass correlation	Reproducibility
Systolic blood pressure				
SAME				
	Averages			
	24-h	0.257	0.9102*	Yes
	Daytime	0.131	0.9044*	Yes
	Night-time	0.693	0.8751*	Yes
	Crest	0.537	0.7961*	Yes
	Trough	0.966	0.8792*	Yes
	Trough:crest	0.634	0.7040	No
OPPOSITE				
	Averages			
	24-h	0.044 <sup>#</sup>	0.7369	No
	Daytime	0.153	0.5381	No
	Night-time	0.214	0.8025*	Yes
	Crest	0.702	0.5395	No
	Trough	0.011 <sup>#</sup>	0.9287*	No
	Trough:crest	0.178	0.7256	No
Diastolic blood pressure				
SAME				
	Averages			
	24-h	0.240	0.8640*	Yes
	Daytime	0.392	0.8515*	Yes
	Night-time	0.623	0.8149*	Yes
	Crest	0.423	0.8862*	Yes
	Trough	0.560	0.8712*	Yes
	Trough:crest	0.331	0.7339	No
OPPOSITE				
	Averages			
	24-h	0.406	0.7725*	Yes
	Daytime	0.271	0.6455	No
	Night-time	0.467	0.8640*	Yes
	Crest	0.458	0.6886	No
	Trough	0.305	0.9207*	Yes
	Trough:crest	0.382	0.6190	No

\*Excellent intraclass correlation. <sup>#</sup>Significant *t*-test.

whereas 24-h average, night-time average, and TrBP were reproducible for the OPP group. There was a significant difference in the number of reproducible variables measured at the same time of day versus the opposite time of day ( $\chi^2 = 5.3$ ) for systolic pressure, but not for diastolic pressures ( $\chi^2 = 1.5$ ). Figures 2 and 3 illustrate the ambulatory blood pressures found for the monitoring sessions for both groups. Average 24-h and TrBP were significantly higher for systolic blood pressures when the ambulatory monitoring session began in the morning hours, whereas no differences were found between diastolic blood pressure variables.

## Discussion

The purpose of this investigation was to compare the reproducibility of ambulatory blood pressure monitoring between sessions beginning at the same time of day and sessions beginning at opposite periods of the day. It was hypothesized that the reproducibility of two sessions beginning at the same time of day would be no different from the reproducibility between two sessions beginning at opposite times of day. Unexpectedly, for systolic blood pressure the reproducibility of ambulatory blood pressure monitoring appeared to be influenced by the time of day the session began. When monitoring began at the same time of day, ambulatory blood pressure variables measured were reproducible whereas variables monitored at

the opposite times of day were not. More specifically, the TrBP and average 24-h pressure were significantly higher for systolic blood pressures when the monitoring session began in the morning than when the session began in the evening. On the other hand, reproducibility of diastolic blood pressure variables was similar between the SAME and OPP conditions.

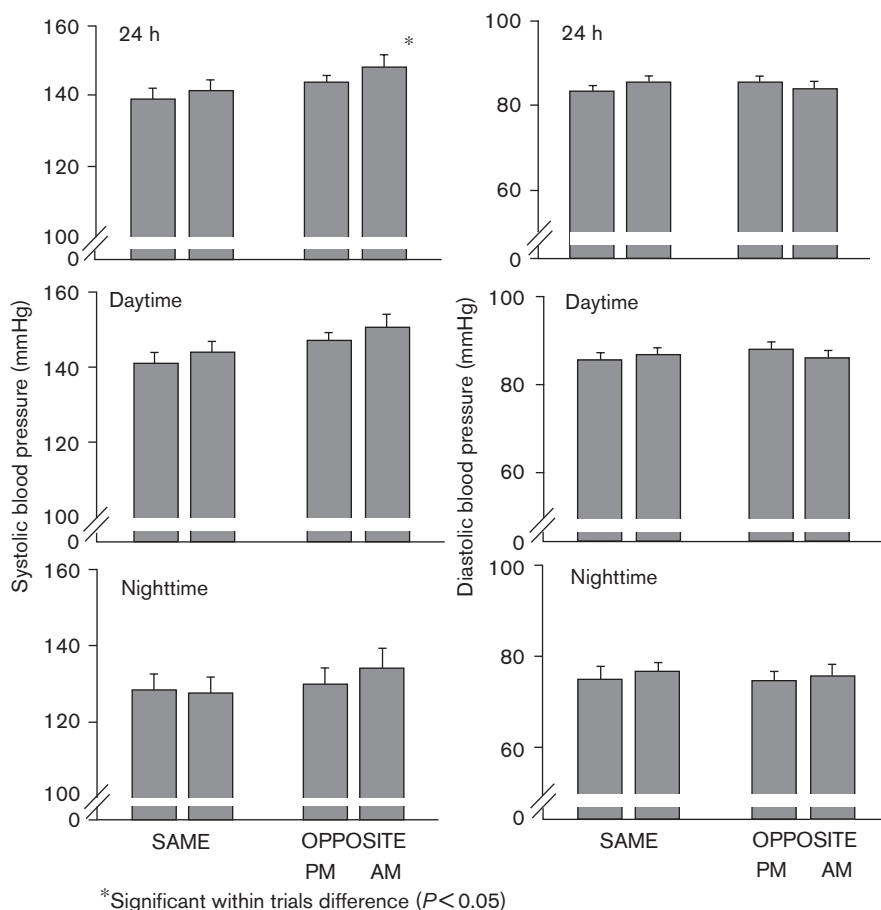
The reproducibility found for ambulatory blood variables in this study were different than that reported in the literature [2,9–11,13,14]. Most investigators, however, reported the reproducibility for both systolic and diastolic blood pressure to range from good [10] to excellent [11]. Similar to the work of Reeves and colleagues [2], the correlations were lower for diastolic variables than for systolic variables. Yet, the reproducibility of diastolic blood pressures was statistically similar between the two treatment conditions. However, these results should be viewed with caution. Only 50% of the diastolic variables measured in the OPP group demonstrated reproducibility.

The only ambulatory blood pressure variable that exhibited a consistent lack of reproducibility for every condition and for both systolic and diastolic pressures was the TrBP:CrBP ratio. A similar trough-to-peak ratio has been recommended to evaluate the efficacy of antihypertensive medications [26]. Even though the trough-to-peak ratio has been reported to be reproducible [27], the ratio has been the topic of criticism [28] and has been modified since its inception [29] to improve its sensitivity.

Statistical methods used to report reproducibility in ambulatory blood pressure monitoring have been simple correlations [2,9,14], paired *t*-tests [13], or ANOVA [10,11,13]. Both a non-significant paired *t*-test and an excellent intraclass correlation between trials were used in this study to define reproducibility. The intraclass correlation would establish a significant relationship between the two trials whereas the non-significant paired *t*-test would confirm no differences between the two trials. The intraclass correlation was chosen instead of simple correlations because intraclass correlations measure the relative homogeneity of the scores within the class in relation to the total variation, whereas simple correlations measure interclass relationships and are not considered to be a measure of reproducibility.

One criticism of the study design could be the separate subject groups. The same subjects did not receive all four treatments. Two separate groups of subjects comprised the SAME and OPPOSITE groups. The two subject groups were recruited in separate studies, 3 years apart. Subjects volunteered for the different studies as they were advertised. There was no bias in the placement of subjects in the SAME or OPP groups. Each treatment

Fig. 2



Reproducibility of average ambulatory blood pressure initiated at the same time of day versus opposite times of day.

within the SAME and OPP groups was presented in a randomized order. In addition, there was no significant difference in the demographics between the two groups, as summarized in Table 1. Thus, the two groups of subjects appeared to be similar. To confirm similarities between groups for the ambulatory blood pressure variables, a two-way ANOVA (condition  $\times$  time) with repeated measures was used. The only between-group difference for the six ambulatory blood pressure variables was found for CrBP. No other ambulatory variable differed between the two groups.

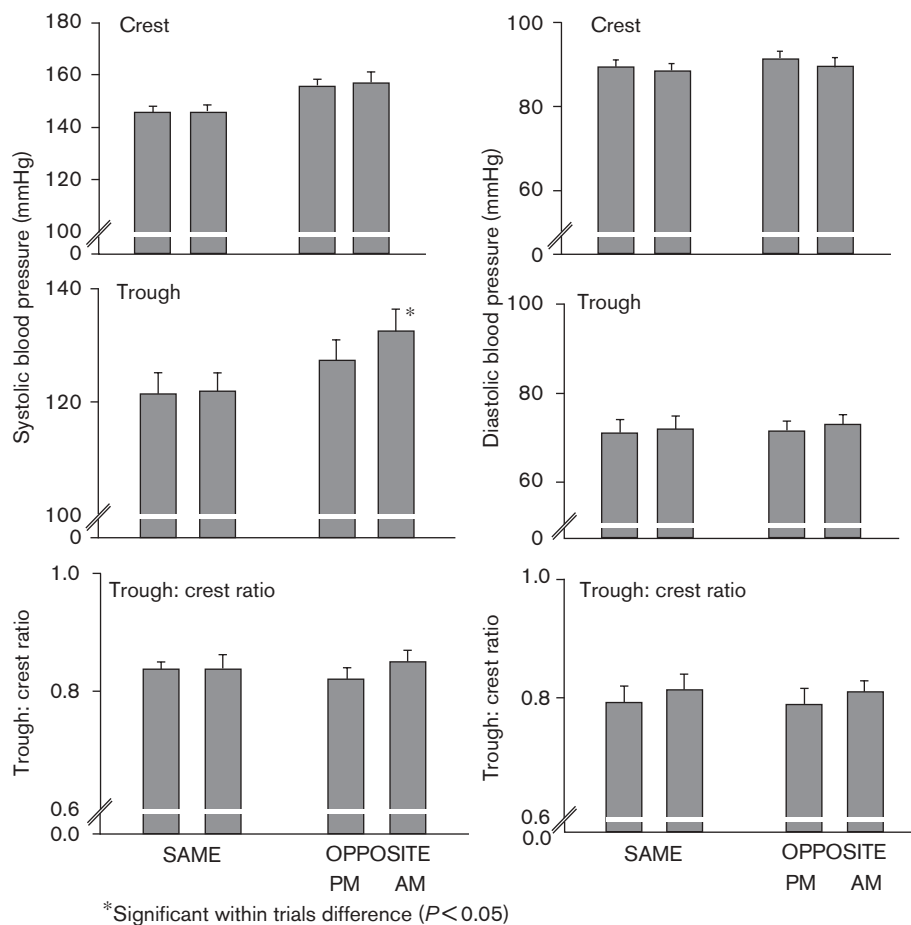
Because the groups were separated by 3 years, the quality control of measurement technique and instrumentation as well as the technicians can also be in question. The same equipment was used for screening and monitoring in all studies. In addition, the ambulatory blood pressure monitors were sent back to the factory for calibration before each major study. Technicians undergo rigorous training and exhibited reproducibility in blood pressure monitoring as well as editing of ambulatory data ( $r > 0.9$ ).

In addition, the protocol for editing ambulatory data remained consistent [23].

In our design, there was only one SAME group. There could have been two; one starting both sessions in the morning and another starting both sessions in the evening. Our database only had one SAME group, namely the one starting in the evening. By itself, the observation of the OPP group would have been adequate to illustrate the primary findings in this study because the treatments were randomized within the OPP group. However, the differences in blood pressure outcomes become stronger when the two groups were compared. Adding a second SAME group that started in the morning may not have added more information in terms of reproducibility.

Blood pressure rhythms are on a 24-h cycle [15]. In theory, the time to initiate measurement of the 24-h cycle should not influence the outcome as long as the whole 24-h cycle is measured. Recently, it has been reported that the ambulatory blood pressure monitoring

Fig. 3



Reproducibility of ambulatory crest and trough blood pressures initiated at the same time of day versus opposite times of day.

may interfere with daily blood pressures by producing a pressor response [30]. Our data appear to support these new findings. Beginning the monitoring session in the morning hours may contribute to the pressor response. Calvo [30] and Hermida [31] and colleagues found that the first 12 h of 48 h of ambulatory monitoring sessions exhibited significantly higher systolic and diastolic blood pressures in > 800 subjects. Both investigators began blood pressure monitoring sessions in the morning.

Similarly, Prasad and colleagues [13] reported a significant elevation in systolic and diastolic pressures, but only for the first 2 h of one 48-h monitoring session in 50 subjects. The duration of the pressor response may have been diminished in Prasad's study due to smaller numbers of subjects and the time of day the blood pressure monitoring began. Some monitoring began as early as 0900 h, whereas others began as late as 1600 h. In our study, subjects who began monitoring in the morning exhibited higher ambulatory systolic blood pressure

variables than those who began monitoring in the evening. Perhaps the pressor effect was exhibited during the morning hours when the monitoring began in the morning. The pressor response may have not been triggered during the nadir of the diurnal rhythm. After all, it is more difficult to detect an interventional change in blood pressures in subjects who exhibit normal blood pressures [32]. In any case, the identification of mechanisms for the differences found in this study warrants further investigation.

What is the significance of this phenomenon? The two categories of ambulatory blood pressure variables were the focus of this study because they are reported to have clinical significance. Average blood pressure variables have been used to diagnose hypertension [33] and to identify white-coat syndrome [1]. Crest and trough data have been utilized in pharmacological studies to investigate the effects of antihypertensive medications [26,34] as well as to investigate the dose intervals [28]. The time

of day to begin monitoring was found to affect the reproducibility of these commonly used variables. It is quite possible for any of these diagnostic and therapeutic outcomes to be influenced by the time of day the ambulatory monitoring began.

The 2.9% increase in 24-h average systolic pressure for the morning monitoring session was significantly different from the evening monitoring session. Similarly, the 3.3% increase in the trough blood pressure for systolic pressure was statistically higher for the morning session than the evening. These differences would be considered physiologically significant had a blood pressure treatment been given and the changes would have been attributed to that intervention. However, no intervention was given in this study. The difference could only be attributed to the method of the ambulatory blood pressure measurement.

Clinicians and researchers not only need to consider the time of day to begin the ambulatory blood pressure measurements, but other clinical or design issues to insure valid and reliable outcomes. Calvo [30] and Hermida [31] and colleagues have recommended several 48-h monitoring sessions instead of one 24-h monitoring session to control for the pressor effect in the evaluation of the diurnal rhythm. To control for these phenomenon, researchers may also need to consider sample sizes as well as implications in interpreting data from the control or placebo group.

Ambulatory blood pressure monitoring has been used: (1) to diagnose hypertension [2]; (2) to evaluate white-coat syndrome [1]; (3) to investigate the efficacy of antihypertensive medications [35]; and (4) to investigate the efficacy of exercise treatment [36,37]. Because the time of day to begin the ambulatory monitoring appears to influence the outcome, the time of day to begin the monitoring must now be considered an additional factor to be controlled in these studies.

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