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Making Minds Matter

Ambulatory blood pressure monitoring

Effects of physical activity

Marinel Cavelaars

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Effects of physical activity

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Effecten van lichamelijke activiteit

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Contents

CHAPTER 1

General introduction

Ambulatory blood pressure monitoring

The development of non-invasive ambulatory blood pressure monitoring (ABPM) devices has enabled routine assessment of 24 h blood pressure profiles away from the medical environment. This technique has been a great impetus to hypertension research in the past 25 years, which has resulted in the definition of new diagnostic entities, such as the white coat effect and the non-dipping or extreme dipping blood pressure pattern. In this chapter, the main directions of research involving ABPM are outlined and examined on aspects that needed further study.

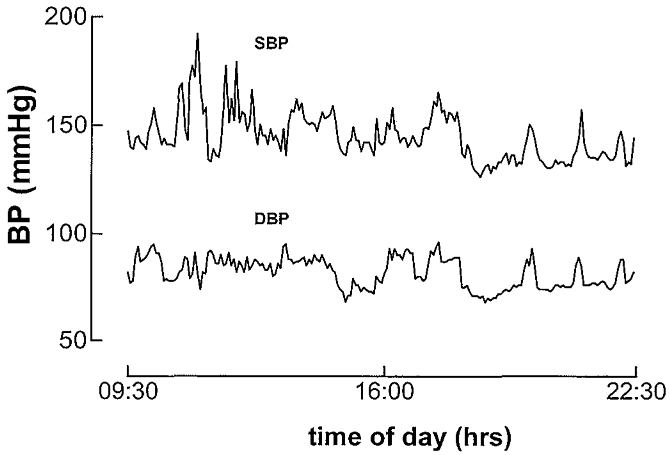
Research with direct clinical implications

Development of a representative measure of blood pressure

Variability of blood pressure

Blood pressure (BP) fluctuates considerably during the day in response to a variety of environmental and behavioural factors (Fig. 1).

Figure 1



Profiles of ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) during a normal day.

Factors that influence BP include physical activity, posture, mental activity, emotional state, social interaction, eating, talking, temperature, etc. [1-4]. A factor of particular interest is the presence of a physician during BP measurement, causing a clinically relevant BP rise. This alerting reaction occurs in some people and is known as the 'white-coat effect'. The inherent variation in BP and the white-coat effect limit the ability of isolated office readings to characterize the individual's true blood pressure.

The prognostic value of office BP and ABPM have been compared in many studies [5-12]. Overall, these studies indicate that ABPM provides a better predictor of cardiovascular risk than one or a few office BP readings [13,14]. A limitation of most of these studies is that they were conducted in either the general population or in subjects with essential hypertension who were not yet treated or in whom BP was poorly controlled by treatment at the time ABPM was performed. Another limitation is that most studies predicted outcome on the basis of surrogate markers such as left ventricular hypertrophy, microalbuminuria and arterial stiffness [10-12].

In a recently published large-scale prospective study, Clement and co-workers have addressed the question whether ABPM is a predictor of cardiovascular events in subjects already treated for hypertension [15]. That study showed that in patients with treated hypertension a higher ambulatory systolic or diastolic pressure predicts cardiovascular events even after adjustment for office measurement of BP. These findings are a further demonstration of the superiority of ABPM over office BP readings in predicting cardiovascular risk.

Despite the growing evidence in favour of ABPM, this technique is still not widely used for diagnosis and management of hypertension. An important reason is that interpretation of data gathered under ambulatory conditions is not as straightforward as is the interpretation of office measurements. This is partly because one does not know the behavioural conditions during measurements, and their effects on BP. Furthermore, the equipment for performing ABPM is rather expensive and the technique may cause discomfort and disturbance of sleep.

Effect of physical activity on ambulatory blood pressure

As the type and duration of behaviour during ABPM may substantially influence the average daily BP, they may need to be taken into account when interpreting ABPM. There is evidence that physical activity and posture are particularly important determinants of BP variation during normal daily life [1-3,16,17]. Most studies aiming to explain BP variability during the day focused on the effect of physical activity.

The first reports on the relationship between physical activity and ambulatory BP were based on self-reported activity. This method to measure physical activity highly depends on the subject's co-operation, and often lacks reliability and accuracy [18]. With the advent of electronic accelerometer devices, a better and more objective investigation of the effect of activity on BP has become feasible.

Studies applying wrist-actigraphy, reported that the average correlation between physical activity and ambulatory BP is low during daytime [19-22]. Body posture, on the other hand, was reported to significantly influence BP during the day, with standing pressures being higher than sitting pressures, which in turn are higher than reclining pressures, and to explain a substantial proportion of BP variation during the day [3,23]. These postural effects may be a reflection of differences in activity, since posture and activity are closely related (lying and sitting being associated with low levels, while standing is associated with high levels of activity).

Information about the relationship between posture and activity, and about the interdependence of the effects of both factors on BP during everyday life, are lacking. In view of the low correlation between wrist-actigraph measures of physical activity and BP, it is questionable whether quantification of wrist movements is a valid method to measure total body activity. Also, wrist-actigraphy does not give information about posture.

Reproducibility of BP measurements

It has been well established that repeated BP measurements provide a more accurate reflection of the true BP than one or a few office readings. In line to this knowledge are the many reports showing that average 24 h and daytime BPs obtained by ambulatory monitoring are better reproducible than office BP readings [24-28]. Instructions for improved reproducibility of standard office BP measurements include a need for multiple measurements repeated throughout each of several visits [29]. These instructions, however, are often not observed. Knowing this, questions were raised on the quality of office measurements in studies comparing the prognostic value of office measurements with the prognostic value of ABPM. Fagard and Staessen reviewed relevant studies, and concluded that the quality of the conventional BP measurements left much to be desired in studies on left ventricular mass, but was reasonably good in studies that had cardiovascular morbidity and/or mortality as outcomes [30].

In an attempt to increase BP reproducibility, alternative ways to measure BP have been evaluated. It was shown that nurse-measured BP values obtained after 5 min of sitting in rest by the subject may be as reproducible as the average daytime ambulatory BP [31]. Mancia *et al.* [32] reported that the average of 25 BP readings, obtained in the outpatient clinic under supine resting conditions at 3 min intervals by an automated sphygmomanometer, was as reproducible as the average 24 h BP obtained by ambulatory monitoring.

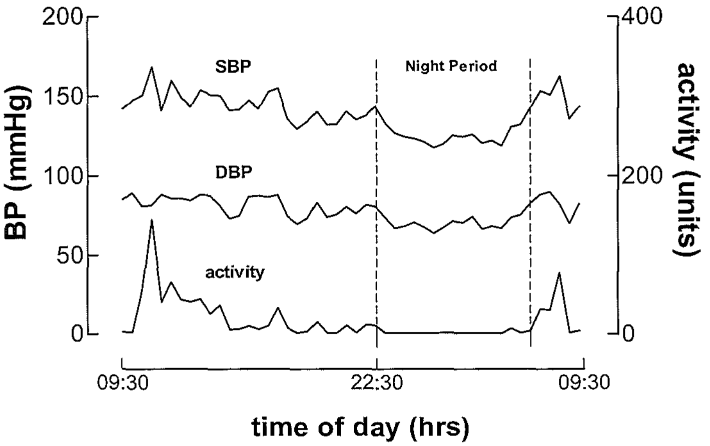
A challenge for ABPM in the near future is further improvement of its reproducibility. To improve reproducibility, it has been suggested that ABPM should be performed on like-days, for example on working or recreational days. It has also been suggested to use a diary card to record symptoms and events that may influence ABPM [33]. Whether reproducibility of ABPM improves with correction for factors like physical activity and body position, has not been studied yet.

Clinical value of diminished nocturnal BP decrease

One of the most specific advantages of ABPM is the possibility to monitor the 24 h cycle of BP. BP normally shows a diurnal pattern with lower values during the night when subjects are asleep than during the day when subjects are active (Fig. 2).

Individuals who exhibit a diminished nocturnal decline in BP ('non-dippers') have been reported to have more cardiovascular target-organ damage than those with normal nocturnal decline in BP ('dippers') [34-36]. The relevance of a diminished nocturnal fall in BP has been controversial, but recent evidence from prospective studies indicates that this feature is a strong independent risk factor for cardiovascular morbidity and mortality [6,8,37]. Importantly, this risk is present, not only in hypertensive, but also in normotensive subjects [8,37].

Figure 2



Twenty-four hour profiles of ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP) and physical activity. Physical activity was measured by means of accelerometry.

The classification of subjects into dippers and non-dippers has been criticized because of its low reproducibility over time, which suggests that dipping status cannot be reliably determined [38-40]. Several factors influencing the day-night BP difference may play a role in the poor reproducibility. One of these factors is the definition of the night-time period [41,42]. In most studies, fixed time periods were used to define daytime and night-time. Weston *et al.* [43] demonstrated that the reproducibility of the nocturnal fall in BP improves when definition of night-time is based on times noted in a diary.

Another factor that influences the day-night BP difference is physical activity. One study reported that the levels of daytime and night-time physical activity are independently predictive of the magnitude of the nocturnal BP fall [44]. Others found that higher night-time activity is associated with a smaller day-night BP difference [45,46]. As quality and pattern of sleep influence nocturnal BP, these factors may also significantly influence the day-night BP difference [47,48].

Finally, supine body position may influence nocturnal BP readings as it may cause hydrostatic pressure differences between the heart and the arm-cuff. It has indeed been shown that variation in resting body position can induce considerable variation in BP readings [49].

Basic research

ABPM is being used in basic hypertension research to gain insight into mechanisms of cardiovascular control and into haemodynamics that underlie BP variation during everyday life. The automated devices used for ambulatory monitoring in clinical practice are not suitable for these purposes as they record BP at relatively large intervals, varying from 15 to 60 minutes. Another disadvantage of these devices is that they do not allow movement while readings are taken, and therefore cannot provide information about the direct effect of physical activity on BP. With continuous BP monitoring, however, short-term BP variation can be measured under truly ambulatory conditions and insight can be gained into mechanisms of cardiovascular control (e.g., baroreflex sensitivity) during everyday life.

From pressure waveforms, obtained with continuous monitoring, haemodynamic variables that underlie BP can be computed. Using a pulse contour method or the more sophisticated three-element model of arterial input impedance, developed by Wesseling and co-workers, stroke volume can be computed from the pressure signal [50,51]. In several studies, this methodology has been applied to study the diurnal variation of systemic haemodynamics in healthy and hypertensive subjects as well as in cardiac transplant recipients [52-55].

Aim and outline of the present thesis

The present thesis deals with the effects of physical activity and body posture on ambulatory BP and systemic haemodynamics in normotensive and hypertensive individuals. The Activity Monitor, i.e., the method used to measure physical activity and posture, is the constant factor in the presented studies. The Activity Monitor is a combination of acceleration sensors mounted on the trunk and legs, a portable data recorder, and analysis software. With this technique, which has been validated in previous studies, physical activity can be quantified and posture (lying, sitting, standing) and type of activity (e.g., general movement, walking) can be automatically detected [56,57]. The method used to measure BP varies between the presented studies. BP was measured intermittently and non-invasively in studies aiming to improve interpretation of ABPM in clinical practice, whereas BP was measured continuously and invasively in studies aiming to determine in detail the effects of physical activity and posture on BP and systemic haemodynamics.

In chapter 2, a study aimed at quantifying the responses of non-invasively measured BP and heart rate to physical activity is presented. The effects of age, gender, body mass index, mean BP or heart rate level, and the use of antihypertensive medication on these responses were determined. It was assessed whether correlation between physical activity, as quantified by the Activity Monitor, and BP is higher than correlations presented in earlier reports based on wrist-actigraph measures of activity.

In chapter 3, a study is presented that provides deeper insight into the relationships between physical activity, BP, and heart rate during everyday life. The role of posture in these relationships was determined, and systemic haemodynamics underlying BP responses were computed.

Chapter 4 deals with the reproducibility of ABPM. A study is described, aimed to determine the effects of differences in physical activity, posture and sleep quality between recording days on the reproducibility of daytime and night-time BP.

Chapter 5 reports about the effect of supine body position on nocturnal BP readings, and about the influence of this effect on the reproducibility of nocturnal BP.

Chapter 6 describes a study, in which the effects of daytime and night-time physical activity on the diurnal variation of BP and systemic haemodynamics were assessed. Also, diurnal haemodynamic profiles were compared between dippers and non-dippers.

In the final chapter, the main findings of the studies are summarized and briefly discussed.

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CHAPTER 2

Determinants of ambulatory blood pressure response to physical activity

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J Hypertens 2002; 20:2009-2015.

Abstract

Objectives: Previous studies reported that the association between physical activity, measured with a wrist-worn accelerometer, and ambulatory blood pressure is rather weak and that the inter-individual variation in the degree of association is high. The aim of the present study was to quantify the responses of ambulatory blood pressure (BP) and heart rate (HR) to physical activity, and to determine the effect of age, gender, body mass index, mean BP and HR level and the use of antihypertensive medication on these responses.

Patients and methods: Twenty-seven subjects (24 hypertensive) underwent 24 h ambulatory monitoring of BP, HR and physical activity. Physical activity was measured with four accelerometers mounted on the trunk and legs. The daytime BP and HR responses to physical activity and the possible modulating effects of the various subject characteristics on these responses were estimated with Random Regression Models.

Results: Increasing physical activity from a very low level (e.g., watching television) to a moderate level (e.g., shopping) caused an average response of systolic blood pressure (SBP) of 11.6 mmHg, of diastolic blood pressure (DBP) of 7.0 mmHg and of HR of 16.1 beats/min. The SBP response to activity was about 2 mmHg larger for the overweight subjects than for subjects with normal weight, and the SBP, DBP and HR responses increased about 0.8 mmHg, 0.6 mmHg and 0.7 beats/min, respectively, with every 10 years increase in age. The between-subjects variances in estimated responses were low and were almost completely explained by differences in overweight and age between subjects. The average within-subject variances, however, were high.

Conclusions: Normal daily physical activity explains only a small part of the BP and HR variability. The BP and HR responses to activity are modestly affected by age. Overweight has a small effect on the SBP response to activity.

Introduction

Ambulatory blood pressure (ABP) monitoring is increasingly being used in clinical research and practice because it provides a more representative measure of blood pressure than traditional office readings. It has been shown that average 24 h ABP is a better reproducible parameter [1] and a better predictor of future cardiovascular events [2] than office readings. Despite these promising findings, the interpretation of ambulatory readings is hampered by the influence of several exogenous factors on blood pressure (BP), of which physical activity is particularly important.

Several studies have shown that the average correlation between electronically monitored physical activity and ABP is weak, and that the inter-individual variation in the degree of correlation is high [3-6]. One of the factors that may have contributed to the weakness of the correlation is the method used to measure physical activity. The studies cited used a wrist actigraph to measure physical activity. This is a rather crude method, as movements of the wrist may occur without body movements. In the recently developed portable Activity Monitor, a combination of four accelerometers, mounted on the trunk and legs, is used to measure both physical activity and body position [7-10]. With this validated technique, a more refined measure of physical activity is obtained and corresponding body positions and activities can be determined.

In earlier research, few attempts have been made to explain the large individual differences in the degree to which physical activity and ABP are associated. Four studies presented contradictory findings [2-4,11]. Two studies concluded that the differences were not associated with age and gender [4,11] and mean BP level [4] or body mass index (BMI) [11]. In contrast, two other studies found that gender and overweight affected the relationship between systolic blood pressure (SBP) and physical activity [5], and that individual differences in the relationship between physical activity and the SBP-heart rate (HR) product were associated with age [6].

The aim of the present study was to quantify the responses of BP and HR to physical activity under real-life ambulatory conditions, and to determine the effects of age, gender, BMI, mean BP or HR level and the use of antihypertensive medication on these responses.

Methods

Subjects

Twenty-seven subjects (23 hypertensive, 13 male) participated in the study. The average (mean ± SD) age of the subjects was 49.5 ± 13.5 years and average BMI was 26.7 ± 4.2 kg/m^2. Fifteen subjects were overweight (BMI $\geq$ 25 kg/m^2). Subjects were considered to be hypertensive if they received antihypertensive medication or had an office BP of at least 140/90 mmHg, measured on at least three separate occasions. Twenty-one subjects used antihypertensive medication. Patients using α- or β-adrenoceptor blocking agents were excluded from the study.

Procedures and measurements

Twenty-four-hour ambulatory measurements of BP and physical activity were performed for each subject. Subjects arrived in the research clinic in the morning before 10:00 h to have the measurement devices fitted, after which they left the clinic. Participants were instructed to follow their normal daily routine and to minimize movements during each BP measurement. The monitors were returned after 24 hours and the stored data were downloaded into a PC.

An automatic ambulatory non-invasive device (SpaceLabs model 90207; SpaceLabs Medical, Inc., Redmond, Washington, USA) was used for the BP and HR measurements, which were made on the non-dominant arm at intervals of 15 min between 07:00 h and 11:00 h and of 20 min between 11:00 h and 07:00 h.

Physical activity and body position were measured with four uni-axial acceleration sensors (IC-3031; Temec Instruments, Kerkrade, The Netherlands). The alternating current (AC) component of the output voltage of each sensor is associated with the actual acceleration of the sensor, while the direct current (DC) component is associated with the angle of the sensor relative to the gravitational axis [12]. Two sensors were mounted perpendicular to each other on the skin over the sternum. In the upright standing position, one sensor was sensitive parallel to the field of gravity (the longitudinal axis) and one sensor was sensitive along the sagittal axis. Two sensors were placed on the upper legs with the axes perpendicular to the surface, being sensitive along the sagittal axis [7-10]. The acceleration signals were recorded by means of a portable digital recorder (Vitaport System; Temec Instruments) and were digitally stored on a memory card with a sampling frequency of 32 Hz. The recorder was carried on a belt around the waist. The SpaceLabs monitor was connected to the digital recorder by means of a pressure transducer in order to prevent timing discrepancies between both devices.

Analysis

The DC and AC components of the raw acceleration signals were separated by means of lowpass (0.3 Hz) and bandpass (0.3-16 Hz) filtering.

The bandpass filtered accelerosignals were rectified and averaged over a fixed window of 1 s to yield an activity signal at 1 Hz, which was expressed in arbitrary units. Total physical activity was computed by averaging the four activity signals. Average total activity was computed over three different periods: 3, 9 and 15 min preceding each BP measurement.

The angles of the sensors with respect to the gravitational axis were computed from the lowpass filtered signals. A range of reference values for the lowpass and bandpass filtered signals were employed to determine posture (standing, sitting and lying) and dynamic activity (general movement, walking, running, cycling). With the currently used Activity Monitor (the combination of four accelerometers, portable data recorder and the analysis software), several validation studies have been performed, showing high percentages of agreement between the output of the Activity Monitor and the classification of postures on the basis of visual analysis of simultaneously recorded videotapes [7-10].

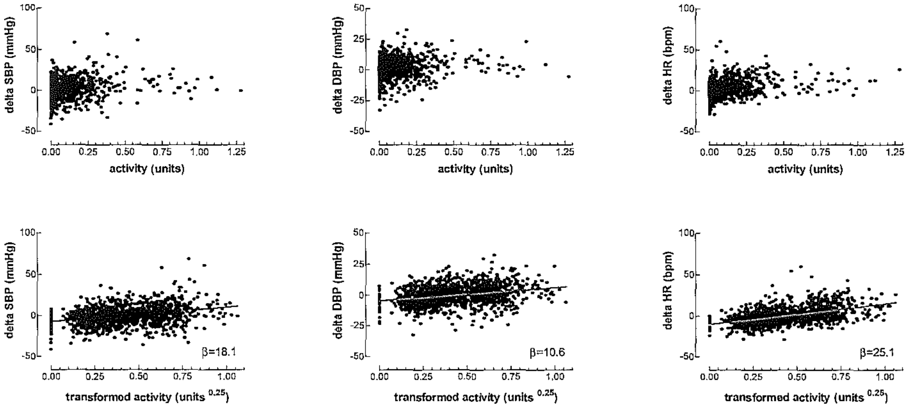
Only daytime values were analysed. Recordings of the second day (the day the monitors were returned) were excluded from the analysis. The night-time period was defined as the period during which subjects were lying down, as identified by the Activity Monitor.

Statistics

Values are presented as means ± SD or as median values with interquartile range. The distributions of the three activity measures were positively skewed. Spearman's rank correlation coefficients were computed for each individual to investigate the strength of the association between the activity values and SBP, diastolic blood pressure (DBP) and HR in the three different periods. The activity measure that showed the highest degree of association with these haemodynamic variables was used for further analysis.

The BP and HR responses to physical activity and the possible modulating effects of age, gender, BMI, mean daytime BP or HR level and use of antihypertensive medication on these responses were estimated with Random Regression Models (RRMs) for continuous data. These models were used to estimate the linear trend in the relationships. As the investigated relationships were not linear, a quartic root transformation was applied to the the activity data (Fig. 1).

Figure 1



Relationships between physical activity and the differences between the actual and the subject's mean daytime values of systolic blood pressure (delta SBP), diastolic blood pressure (delta DBP) and heart rate (delta HR), before and after transformation of the activity data. The regression coefficients (β) of the different relationships are indicated in the scatter plots.

Regression analysis was performed with the procedure Proc Mixed in SAS (Statistical Analysis Systems for Windows, release 8.0). In this procedure, a mixed linear regression model is fitted, which is the appropriate model for analysis of repeated measurements.

The differences between the actual and the subject's mean daytime values of BP and HR (delta SBP, delta DBP and delta HR) were the dependent variables in the regression models. The slopes of the delta BP and delta HR values regressed against transformed activity were assumed to be random. The random regression approach uses data from individuals augmented by information from the total study population to estimate the mean slopes and the between-subjects and within-subjects variances of the slopes of the linear relationships between the dependent variables and physical activity. Special features of the RRMs are their ability to handle missing values and unbalanced data.

In determining which subject characteristics modify the BP and HR responses to activity, we used a two-step approach: first, the different characteristics were entered separately in the model; and second, all characteristics that significantly affected the relationship were analysed simultaneously. $P<0.05$ was considered to indicate a significant effect.

Results

An average of 51.9 ± 4.4 BP readings were taken per subject of which, on average, 49.5 ± 5.7 were successful. Mean daytime SBP, DBP and HR were 142.7 ± 15.0 mmHg, 88.5 ± 12.6 mmHg and 79.0 ± 8.9 beats/min, respectively. The median daytime activity level computed before BP measurement was 24.1 mU (interquartile range, 117.8) over the 3-min period, 49.4 mU (interquartile range, 145.6) over the 9-min period and 60.7 mU (interquartile range, 141.6) over the 15-min period.

Association between activity and BP or HR

Table 1 presents the median values and ranges of the individual Spearman's rank correlation coefficients between the activity values, averaged over the three different periods, and BP and HR values. Highest correlation coefficients were found for HR. The SBP correlated slightly stronger with activity than did the DBP. In all cases, a large inter-individual variation in the strength of the correlation was present. In 63% of the subjects, activity over the 3-min period correlated significantly with SBP. For the 9-min and 15-min periods, these percentages were 56 and 52%, respectively. For DBP, these percentages were 56, 48 and 44% and for HR of 96, 93 and 93%, respectively.

Table 1 Median Spearman's rank correlation coefficients with ranges

	Median r_s (range)		
Period preceding	Activity–SBP	Activity–DBP	Activity–HR
3 min	0.37 (-0.17–0.67)	0.35 (-0.11–0.76)	0.53 (0.13–0.75)
9 min	0.33 (-0.19–0.71)	0.25 (-0.14–0.70)	0.54 (0.20–0.79)
15 min	0.34 (-0.24–0.65)	0.24 (-0.15–0.71)	0.54 (0.13–0.75)

Period preceeding, period over which activity values are averaged; r_s, Spearman's rank correlation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

BP and HR responses to activity

The average physical activity levels in the 3-min period preceding each BP and HR measurement were used in the regression analyses, since they correlated best with BP and HR (Table 1).

Activity values in the 3-min period

The output of the Activity Monitor allowed us to determine which postures and dynamic activities corresponded to the different activity levels. For different levels of activity, a description of corresponding posture and dynamic activity is presented in Table 2.

Table 2 Description of posture and type of physical activity for different activity levels

Activity level (mU)	Posture and physical activity	Example of action
Minimum = 0	Lying down, no movement	Resting
5th percentile = 0.33	Lying or sitting, minimal movement	Resting, watching television
25th percentile = 5.4	Lying or sitting, little movement	Watching television, reading
50th percentile = 24.1	Sitting moving regularly, also combined with standing	Having a conversation, desk work
75th percentile = 123	Standing, moving around a bit	Preparing dinner, doing the dishes
95th percentile = 342	Walking, also combined with standing or sitting	Shopping, tidying the house
Maximum = 1277	Walking briskly the whole period	Walking

Activity had a significant effect on SBP, DBP and HR ($p < .0001$). Figure 1 shows the activity values of the total group, before and after transformation, plotted against delta SBP, delta DBP and delta HR. Average BP and HR responses to activity were computed from the regression coefficients (β values indicated in Fig. 1) and are expressed as the differences between levels at the 95th and 5th percentiles of activity. The average SBP, DBP, and HR responses to activity were 11.6 mmHg, 7.0 mmHg, and 16.1 beats/min, respectively.

Effects of subject characteristics on the responses to activity

Age affected the slope of the relationship between activity and SBP ($p = 0.034$). The effect of BMI was not significant ($p = 0.07$). When subjects were divided into the two categories of those with normal weight (BMI < 25 kg/m^2) and those being overweight (BMI ≥ 25 kg/m^2), there was a significant difference in the slopes between these two groups ($p = 0.017$). In combined analysis, the effects of age and overweight remained statistically significant ($p = 0.020$ and 0.011, respectively). The relationships between activity and DBP and between activity and HR were affected by age ($p = 0.006$ and 0.005, respectively), but not by BMI or overweight. None of the investigated relationships were modified by gender, use of antihypertensive medication or mean daytime SBP, DBP or HR level.

Table 3 shows the effects of age and overweight on the responses to activity, again expressed as differences between levels at the 95th and 5th percentiles of activity.

Effects of modifying characteristics on the variances in the slopes

Addition of age and overweight to the model reduced the variance between subjects in the estimated slope of the relationship between transformed activity and delta SBP from 4.8 to 0.17. For delta HR, the between-subjects variance in the estimated slope decreased from 1.0 to 0.0 after addition of age to the model. The between-subjects variance in the estimated slope of the relationship between transformed activity and delta DBP was 0.0 in the initial model and remained 0.0 after addition of age.

The within-subjects variances in the slopes were much higher than the between-subjects variances. The average within-subject variances in the slopes of the relationships between transformed activity and delta SBP, delta DBP and delta HR were 116.0, 57.4 and 84.3, respectively.

Table 3 Average responses to activity adjusted for modifying subject characteristics

Subject characteristics	Average	95% Confidence interval
	SBP response (mmHg)	
Normal weight, age 50 years	10.4	8.4 – 12.4
Overweight, age 50 years	12.6	10.6 – 14.6
10 years age increase	0.76	0.15 – 1.37
	DBP response (mmHg)	
Age 50 years	7.0	5.7 – 8.3
Age increase 10 years	0.59	0.17 – 1.02
	HR response (beats/min)	
Age 50 years	16.1	14.5 – 17.7
Age increase 10 years	0.73	0.22 – 1.25

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Discussion

In the present study, we have introduced a novel technique to measure intensity and type of physical activity in order to assess the BP and HR responses to activity under real-life ambulatory conditions. In this small study, the average correlation coefficients indicate a rather weak relationship between physical activity and BP or HR. However, the average BP and HR responses to a modest increase in activity were quite substantial. We found that increasing physical activity from a very low level (e.g., watching television) to a moderate level (e.g., shopping) causes an average increase of SBP of 11.6 mmHg, an increase of DBP of 7.0 mmHg and an increase of HR of 16.1 beats/min. The response of SBP to activity was greater for the overweight subjects and increased with increasing age. Age also increased the DBP and HR responses to activity.

The large differences between the waking and sleeping period in activity, BP, and HR could spuriously elevate the correlation between these variables if the entire 24 h period was analysed. Therefore, we have assessed the relationships between activity and haemodynamic variables during the waking period only. Three recent studies presented average correlation coefficients between BP or HR and physical activity, measured with a wrist-worn accelerometer, in the waking period. Leary *et al.* [5] studied 431 normotensive and hypertensive subjects, and found mean correlation coefficients of 0.33, 0.29 and 0.42 between physical activity and SBP, DBP and HR, respectively. Shapiro and Goldstein [4] found no significant correlation between activity and BP in a group of 119 healthy elderly subjects. In this group, the correlation between activity and HR was statistically significant, with a correlation coefficient of 0.30. Stewart *et al.* [3] studied 30 hypertensive patients and found average correlation coefficients between activity and BP of 0.25 for SBP and 0.34 for DBP.

In contrast to these studies mentioned, we performed a non-parametric correlation analysis, as the distribution of the transformed activity data was not perfectly normal. This analysis yielded median Spearman's rank correlation coefficients of 0.37, 0.35 and 0.53 between physical activity and SBP, DBP and HR, respectively. For comparison, average Pearson correlation coefficients of 0.34, 0.28 and 0.52 were computed on this data set between transformed activity (activity $^{0.25}$) and SBP, DBP and HR, respectively. The present correlation coefficients are comparable with earlier findings [3-5]. The variation between subjects in the degree of correlation was large, which also is in agreement with previous studies [3-5].

In attempting to explain the large variation between subjects in the degree of correlation, we estimated the effect of several subject characteristics on the haemodynamic responses to activity with RRMs. The activity data were transformed (quartic root) in order to obtain linear relationships with BP and HR. Such linear relationships were crucial for evaluating the effects of the various subject characteristics on these relationships, since the distributions of the activity data differed between subgroups. Male subjects, younger subjects (age $\leq$ 50 years) and subjects with normal weight reached higher activity levels than female subjects, older subjects (age > 50 years) and overweight subjects. Estimation of the linear trend in the relationships would result in lower regression coefficients for individuals that reached higher levels of activity, as the shapes of the relationships were parabolic (Fig. 1). It should be realized that the appropriate transformation was found by trial and error.

The variance between subjects in the estimated slopes of the relationships between activity and BP or HR was low and was further reduced by addition of the modifying subject characteristics to the different models. The average variance within subjects with respect to the estimated slopes, however, was high. Therefore, it can be concluded that the large variation between subjects in the degree of correlation mainly originated from large differences between subjects in variation of the data around the regression line, as opposed to differences between subjects in the estimated regression lines themselves. This complies with the finding that subject characteristics had only a small effect on the BP and HR responses (Table 3).

The presently reported effect of overweight is in agreement with earlier studies [5,11]. It has been reported that, for heavier individuals, the SBP [5] and DBP [11] responses to physical activity are greater than for individuals with normal weight, although the differences did not reach statistical significance. In our study, the BP and HR responses to activity increased with increasing age. To our knowledge, no previous studies found an effect of age on SBP or DBP responses to activity, and only one study reported an effect of age on the HR response to activity during normal daily life. This study [5] reported greater regression coefficients for the reactivity of HR to activity for subjects aged 50 years or younger than for those older than 50 years. Furthermore, the reactivity of HR was also greater for subjects not using antihypertensive medication compared with those who did use antihypertensives. Subgroup analysis revealed that the effect of antihypertensive medication was mainly explained by the action of β-blockers. As 30% of the older group and only 15% of the younger group used β-blockers, the lower reactivity of HR to activity seen in those older than 50 years may have been confounded by medication. Studies during dynamic exercise generally showed that, with ageing, the HR response to increasing levels of exercise is reduced [13] and that the SBP and DBP responses to increasing levels of exercise are increased [14]. The decrease in exercise HR with increasing age could be due to a decrease in ß-adrenergic responsiveness [15], while the greater increase in BP during exercise with ageing is usually explained by loss of elasticity in the aorta and large peripheral arteries [16]. The presently reported effect of ageing on the HR response to activity is in contradiction with the findings during exercise. However, it is uncertain whether cardiovascular adaptations to exercise are comparable with adaptations to the lower levels of activity seen during normal daily life.

We expected that activity of the trunk and legs, as quantified by the Activity Monitor, would be stronger associated with BP and HR than activity measured with an accelerometer attached to the wrist. This appeared not to be the case, as the present correlation coefficients are comparable with earlier findings. Wrist and waist movements are highly correlated [11], from which it can be concluded that movements of the wrist represent both a local and a body movement. However, it seems obvious that movements of the trunk and legs are a better measure of body movements than wrist movements. The fact that movements of the trunk and legs are not higher associated with haemodynamic parameters than movements of the wrist may result from the fact that, at a given oxygen uptake, arm work results in higher BP and HR than work performed with the legs [17-18]. Possibly higher degrees of association can be found if movements of additional body segments are integrated in the current measure of physical activity.

Some other methodological factors may have led to underestimation of the degree of association between activity and ambulatory BP or HR. Body movements recorded with the Activity Monitor do not always have a physical origin. During transport, high activity levels (up to the 75th percentile level) were recorded, which were mainly caused by movements of the vehicle. Furthermore, static exercise does not result in body movements, while at a given cardiac output this type of exercise has a larger effect on BP than dynamic exercise [19].

In general, ABPM is associated with reduced physical activity during the monitoring day [20]. This is partly caused by the need for participants to keep their arm still during cuff inflation and may furthermore be caused by reluctance to perform normal duties while wearing the BP monitor [20]. The BP and HR responses to activity as computed in the present study are likely to be lower than responses during a non-monitoring day, because of lower levels of physical activity.

The possibility of finding high degrees of association between physical activity and ambulatory-monitored BP or HR using automated sphygmomanometers is limited, mainly by two factors. First, under real-life ambulatory conditions, BP and HR are subject to a variety of stimuli besides physical activity. These stimuli include emotional status, mental activity, talking and ingestion of vasoactive substances. Second, intermittent sampling of BP and HR at a frequency typically used with ambulatory monitors yields values that are not highly representative, given the relatively large variation in BP and HR that can occur in a short period of time, even a minute [4,21]. Continuous monitoring of BP and HR will greatly improve the likelihood of finding higher degrees of association between activity and BP or HR if such higher degrees of association are indeed present.

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CHAPTER 3

Haemodynamic responses to physical activity and body posture during everyday life

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Abstract

Objective: To determine the relationships between body posture and physical activity and systemic haemodynamics during everyday life.

Patients and methods: Continuous measurements were performed in 34 subjects (16 hypertensive, 12 male), aged 49 ±13 (mean ± SD) years. Blood pressure (BP) was measured in the brachial artery. Physical activity and posture were measured with four accelerometers. Beat-to-beat values of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were computed from the pressure waveforms. Multiple correlation coefficients (*R*) between activity and haemodynamic variables were computed and responses to physical activity were estimated with Random Regression Models.

Results: The overall percentages of variance in SBP, DBP, HR, SV, CO and SVR explained by activity (R^2) were 32, 28, 56, 44, 74, and 45%, respectively. The SBP and HR increased linearly with increasing levels of activity (19 mmHg and 30 beats/min when activity increased 90 percentiles). Other variables showed parabolic relationships. The initial decrease in SV and CO (14 ml and 0.5 l/min) and increase in DBP and SVR (9 mmHg and 2 mmHg.min/l) with increasing levels of activity coincided with changes in posture (lying–sitting–standing). The subsequent SV and CO increase (23 ml and 3.7 l/min) and DBP and SVR decrease (8 mmHg and 8 mmHg.min/l) coincided with changes in activity (standing–moving generally–walking).

Conclusions: Our findings show that normal daily posture and activity are only moderate determinants of BP, but main determinants of HR and CO variation.

Introduction

Blood pressure (BP) fluctuates considerably during the day in response to a variety of environmental and behavioural factors. Studies involving ambulatory BP monitoring have indicated that BP varies as a function of physical and mental activity, body posture, location, social interaction and emotional state. There is evidence that physical activity [1,2] and posture [3] are particularly important determinants of BP variation. However, several studies showed that the correlation between BP and normal daily physical activity is rather weak [4-8]. Automated sphygmomanometers used in these studies record the BP and heart rate (HR) at relatively large intervals, varying from 15 to 30 min. The obtained values are not highly representative, given the large variation in BP and HR that can occur in a short period of time, even within 1 min [5,9]. Moreover, sphygmomanometer devices do not allow movement while readings are taken. In the period between cuff inflation and actual measurement the BP and HR are likely to drop, which reduces the possibility of finding high degrees of association between these variables and preceding physical activity.

Since body posture is related to physical activity (low levels being associated with lying down and sitting, while high levels are associated with the standing position) and also affects haemodynamics (for instance, redistribution of blood volume when body position changes), it may play a role in the relationships between activity and BP or HR. Studies that reported an effect of posture on ambulatory BP and HR [3,10] did not record concomitant activity. Therefore, it is uncertain whether the effects are attributable to posture or to activity.

The recently developed portable Activity Monitor, a combination of four accelerometers, data recorder and analysis software, makes it possible to measure both physical activity and body posture under ambulatory conditions [11-14].

In the present study, we performed direct continuous BP measurements and simultaneously monitored physical activity and body posture under real-life ambulatory conditions. With these measurements we expected to find higher correlation coefficients between activity and BP or HR than previously reported.

As we were interested in haemodynamic changes that underlie BP responses, we also studied relationships between activity and stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR). Furthermore, we assessed the effect of posture on these relationships. Finally, the effects of age, gender, body mass index (BMI) and daytime BP on the haemodynamic responses to activity were studied.

Methods

Subjects

Thirty-six (14 male) apparently healthy normotensive (n=19) and hypertensive subjects were studied. The age of the subjects was 48.8 ± 12.9 years (mean ±SD) and the BMI was 26.8 ± 3.6 kg/m^2. Subjects were considered to be hypertensive if they received antihypertensive medication (n=15) or had an office BP ≥140/90 mmHg, measured on at least three separate occasions. Eight of the patients used a ß-blocker, 6 patients a diuretic, 2 patients a calcium entry blocker, 2 patients an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, and 1 patient a central-acting antihypertensive agent. Four of the patients used two antihypertensive agents. All antihypertensive medications were discontinued two weeks prior to measurements. All subjects gave informed consent to participate in the study, which was approved by the medical ethics committee of the Erasmus MC, University Medical Centre, Rotterdam

Procedures and measurements

BP, physical activity and body posture were measured continuously under ambulatory conditions during 24 hours in each subject. Measurements started at about 10:00 h. During the first two hours subjects remained in the research clinic to perform activities according to a protocol. These activities consisted of lying down, sitting, standing and walking. Subjects left the clinic at about 12:30 h and were instructed to follow their normal daily routine. Driving a car and riding a bicycle were prohibited during measurements for safety reasons. Subjects returned to the clinic the next morning at about 09:30 h.

The BP was recorded directly in the brachial artery of the non-dominant arm. A catheter was inserted in the artery and was connected to a pressure transducer (Becton Dickinson Infusion Therapy Systems Inc., Sandy, Utah, U.S.A.) by means of a pressure tube (length 75 cm; Ohmeda Inc, Murray Hill, New Jersey, U.S.A.). The pressure transducer was mounted on the chest at heart level. Air bubbles were carefully removed from the tubing-transducer system before connecting it to the catheter. The catheter-tubing-transducer system was flushed every 90 s by means of an ambulatory infusion pump (CADD-1, model 5100 HFX; Pharmacia Deltec Inc., St. Paul, Minnesota, U.S.A.) with a heparinized saline solution to prevent clotting. The infusion pump (380 gr) was carried on a belt around the waist. The dynamic response of the catheter-tubing-transducer system was tested during each measurement by tapping on the pressure tube with the medial part of the index finger during the diastolic phase of the pressure wave. From the resulting distortion in the BP signal, the natural frequency and the damping coefficient were computed [15]. The average natural frequency and damping coefficient were 19.5 ± 5.0 Hz and 0.03 ± 0.01, respectively. The BP signal was calibrated during each measurement against an air-pressure column (Ametek / Texim 5093 PM; Tradinco BV, Berkel, The Netherlands).

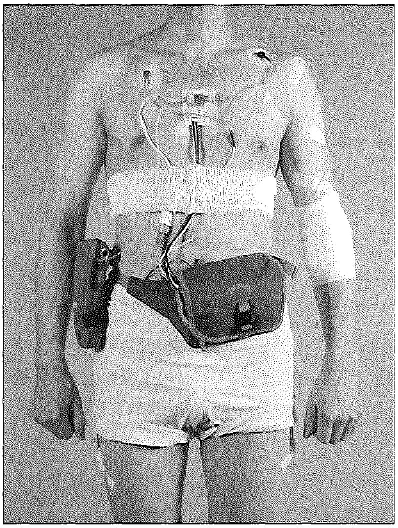
Physical activity and body posture were measured with four acceleration sensors (ADXL 202 JQC; Analog Devices, Norwood, Massachusetts, U.S.A.), weighing about 3 gr each. Two sensors were mounted perpendicular to each other on the skin over the sternum. In the upright standing position, one sensor was sensitive parallel to the field of gravity (the longitudinal axis) and one sensor was sensitive along the sagittal axis. Two sensors were placed on the upper legs with the axes perpendicular to the surface, being sensitive along the sagittal axis [11-14].

The BP and acceleration signals were recorded by means of a portable digital recorder (Vitaport System; Temec Instruments, Kerkrade, The Netherlands) and digitally stored on a memory card with frequencies of 128 Hz and 32 Hz, respectively. The recorder (820 gr) was carried on a belt around the waist. Also a three-lead electrocardiogram (ECG) was recorded in each subject (Fig. 1). The ECG recordings were not used in the present study.

Analysis

The arterial pressure waveforms were analysed with the BeatScope software package, version 1.1 (TNO BMI, Amsterdam, The Netherlands). We used this package to compute beat-to-beat systolic blood pressure (SBP), diastolic pressure (DBP), HR, SV, CO and SVR. DBP was taken as the minimum pressure in diastole just before the starting upstroke (end-diastolic pressure). SV was computed with the Modelflow method (a model-based and validated method to compute the aortic flow waveform from an arterial BP waveform), which is included in the BeatScope software [16]. CO was computed as SV*HR and SVR as the mean arterial pressure/CO. For all subjects the body surface area (BSA) was calculated according to the Dubois formula [17] and the SV, CO and SVR were normalized to a BSA of 1.73 m^2. Artefacts in the BP signal were edited off-line, based on visual inspection by a trained operator. Values were manually replaced by missing values when observing the following phenomena: extrasystolic beats, absence of a pulse signal and artefacts caused by touching the

Figure 1



Subject wearing the catheter-tubing-transducer system, the ambulatory infusion pump, the acceleration sensors, the cardiogram electrodes and the recorder.

pressure tube or body movement. Disturbance of the pressure waveform was considered an artefact if: 1) frequency in SBP, DBP, HR or SV deviated from the frequency in the surrounding 30 s, and 2) the amplitude of the variation was larger than the amplitude in the surrounding 30 s.

The accelerometer signals were analysed with a kinematic software package (Temec Instruments). Activity signals were computed from each accelerometer signal after subsequent high-pass filtering at 0.3 Hz and computation of RMS amplitude over 1 s. The average of the four activity signals was used as a measure of physical activity and was expressed in gravitation units (g). In order to determine posture and type of activity, two additional feature signals were derived from each accelerometer signal. An angular signal was created after low-pass filtering (cut-off frequency 0.3 Hz), averaging over 1 s intervals and conversion to angles via an arcsine transformation. A frequency signal was created after band-pass filtering (0.3-2 Hz for the legs and 0.6-4 Hz for the trunk), frequency analysis and averaging over 1 s intervals. A preset range of reference values for the activity, angular and frequency signals were employed to determine posture (lying, sitting and standing) and type of activity (general movement, walking, running, cycling) [18]. With the currently used Activity Monitor (the combination of four accelerometers, a portable data recorder and the analysis software) several validation studies have been performed, showing high agreement between the output of the Activity Monitor and the classification of postures on the basis of visual analysis of simultaneously recorded videotapes [11-14].

During transportation, movements of the vehicle often caused high-frequency variation in the acceleration signals with a low amplitude. This characteristic combination of features in the acceleration signals was identified by means of visual inspection, and subsequently signals were replaced by missing values.

Only daytime values (collected in the period between start of measurements and night rest) were analysed. The night-time period was defined as the period during which subjects were lying down, as identified by the Activity Monitor. Values were averaged over 100 s. If more than 75 s out of 100 s were missing, the average was noted as missing value. A natural logarithmic transformation was applied to the averaged activity values ($\text{activity}_{\ln}$) to reduce the positive skew of the distribution and to make it more symmetric.

Statistics

Distributions of variables are summarized by means ± SDs or by medians and interquartile ranges. Estimated effects are presented with standard error (SE).

Multiple correlation coefficients (R) were computed for each individual to investigate the degree of association between $\text{activity}_{\ln}$ and the different haemodynamic parameters. In the individual multiple regression model, $\text{activity}_{\ln}$ and $(\text{activity}_{\ln})^2$ were defined as the independent variables. An estimate of the mean (overall) R^2 and variance of R^2 across all subjects was obtained after weighing the individual R^2 values with the individual variances of the dependent variable as weights. The variance of R is calculated from the variance of R^2 using the delta method. The relationships between physical activity and haemodynamic variables were further investigated with Random Regression Models (RRMs) for continuous data [19]. The random regression approach uses data from individuals augmented by information from the total study population to estimate the mean slopes and intercepts of the relationships between the dependent variables and $\text{activity}_{\ln}$. Special features of RRMs are their ability to handle missing values and unbalanced data [20]. Random regression analysis was performed with the procedure Proc Mixed in SAS (Statistical Analysis Systems for Windows, release 8.0; SAS inc., Cary, North Carolina, USA). In the RRMs the slopes and the intercepts obtained from regressing the haemodynamic variables on $\text{activity}_{\ln}$ and $(\text{activity}_{\ln})^2$ were assumed to be random across the subjects. The estimated RRMs were used to predict the mean values of the haemodynamic variables for different levels of $\text{activity}_{\ln}$ (minimum, 5th, 25th, 50th, 75th, 95th percentiles, maximum and, in case of a parabolic relationship, level at peak or trough). In order to assess the effect of body posture on the relationships between physical activity and haemodynamic variables, the following parameters were computed: for different postures and activities (lying, sitting, standing, general movement and walking) the logarithm of the median and interquartile range of activity, and the mean of the haemodynamic variables. The original (before averaging over 100 s) individual data were used for these computations, and values were weighed for duration.

RRMs were also used to estimate the possible modifying effects of age, gender, BMI, mean daytime SBP and mean daytime DBP on the haemodynamic responses to activity. First, the various potential modifiers were entered separately in the model and, second, all modifiers that significantly affected the relationship were entered simultaneously. A value of $p< 0.10$

was considered to indicate a significant modifying effect, in all other cases significance was taken at $p<0.05$.

Results

The results are based on 34 subjects (18 normotensive, 12 male; age, 48.6 ± 13.0 years; BMI, 26.9 ± 3.7 kg/m^2). Recordings of two subjects were excluded from the study because of frequent extrasystolic beats, especially during physical activity, in one subject, and because of a low natural frequency of the BP measurement system (< 10 Hz) in the other subject [15]. The average daytime period lasted 13 hours and 14 min (± 58 min). Artefacts in the BP signal caused on average 3.0%, and transport caused on average 2.5% of this period to be missing. Totally, 4.4% of the 100 s averages were missing. Subjects were lying down, sitting, standing, moving generally and walking during 14.9, 47.1, 19.6, 1.5 and 14.4% of the accepted daytime period. The respective average daytime SBP, DBP, HR, SV, CO and SVR were 136 ± 18 mmHg, 75 ± 11 mmHg, 85 ± 9 beats/min, 69 ± 10 ml, 5.9 ± 0.9 l/min and 18.3 ± 4.3 mmHg.min/l.

Relationships between activity, posture and haemodynamic variables

In all subjects, activity$_{\mathrm{ln}}$ correlated significantly ($p<0.001$) with each of the haemodynamic variables. A high overall correlation coefficient was found for CO, with a low variation between subjects. Lowest overall correlation coefficients were found for BP (Table 1).

Table 1 Correlation between activity$_{\mathrm{ln}}$ and haemodynamic variables

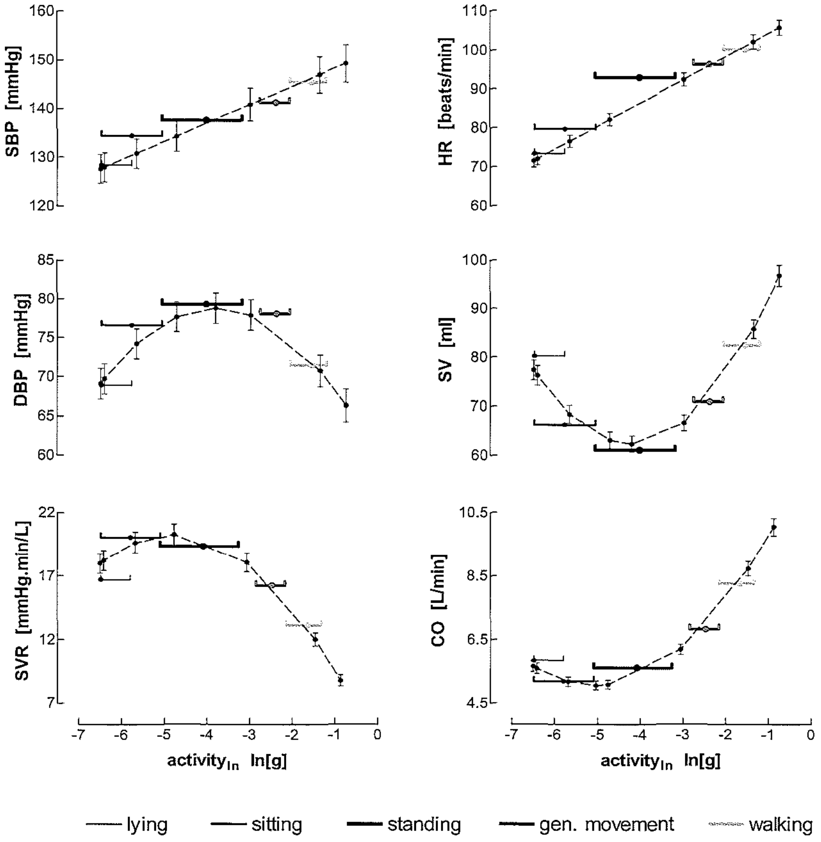
	Overall *R*	Standard deviation	Overall $R^2 \times 100$ (%)
Systolic blood pressure	0.57	0.15	32
Diastolic blood pressure	0.53	0.13	28
Heart rate	0.75	0.08	56
Stroke volume	0.67	0.14	44
Cardiac output	0.86	0.07	74
Systemic vascular resistance	0.67	0.12	45

R, multiple correlation coefficient; $R^2 \times 100\%$, percentage explained variance.

SBP and HR increased linearly with increasing levels of activity, while the other variables showed parabolic relationships (Fig. 2). The initial decrease in SV and CO with increasing levels of activity coincided with changes in posture (lying–sitting–standing), while the subsequent increase coincided with changes in activity (standing–moving generally–walking).

DBP and SVR showed opposite responses to activity; an initial increase (coinciding with posture transitions) was followed by a decrease (coinciding with activity transitions).

Figure 2



Estimated relationships between activity$_{ln}$ and different haemodynamic variables. For different levels of activity$_{ln}$ (minimum, 5th, 25th, 50th, 75th and 95th percentile, maximum and, if present, level at peak or trough) the estimated values of the different haemodynamic variables are plotted with SE. For different postures (lying, sitting, standing) and activities (general movement, walking) the natural logarithm of median and interquartile range of activity is plotted against the corresponding mean of the haemodynamic variable. SBP, systolic blood pressure; HR, heart rate; DBP, diastolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; CO, cardiac output.

Haemodynamic responses to posture and activity, and effect of subject characteristics

Haemodynamic responses to posture and activity are expressed as differences between levels at the 95th and 5th percentiles of activity. For haemodynamic variables that showed a parabolic relationship with activity, the difference between the peak or trough and the level at the 5th percentile of activity$_{\ln}$ is referred to as response to posture. The difference between the level at the 95th percentile of activity$_{\ln}$ and the peak or trough is referred to as response to activity (Table 2).

Table 2 Estimated responses to postural change and/or activity

		Response	Standard error of response	Unit	Relative response (%)
SBP	Posture and activity	+19.0	1.7	mmHg	+15
DBP	Posture	+9.1	0.8	mmHg	+13
	Activity	-8.0	0.6		-11
HR	Posture and activity	+29.9	1.1	beats/min	+42
SV	Posture	-14.0	0.8	ml	-18
	Activity	+23.4	1.1		+31
CO	Posture	-0.53	0.05	l/min	-10
	Activity	+3.67	0.13		+66
SVR	Posture	+1.9	0.3	mmHg.min/l	+11
	Activity	-7.6	0.4		-45

Relative response, the response expressed as percentage of level at the 5th percentile of activity; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance.

The SBP, DBP, HR and SVR responses to activity were affected by age. The SBP response was also affected by BMI and daytime SBP, while the DBP and HR responses were also modified by gender. Gender affected the SV response as well. The SVR and CO responses to activity were affected by daytime SBP, while the latter response was also affected by daytime DBP. When all modifiers were analysed simultaneously, only effects of age and most effects of gender remained significant. Table 3 presents the magnitude of these modifying effects on the different responses to posture and activity, together with significance levels.

Table 3 Estimated effects of modifying characteristics on responses to posture and/or activity

					P level	
		Response	SE	Unit	(activity$_{ln}$)	(activity$_{ln}^{2}$)
Age: effect of 10 years increase						
SBP	Posture and activity	+3.7	1.2	mmHg	0.004	
DBP	Posture	+1.5	0.6	mmHg	0.013	0.008
	Activity	-0.8	0.5			
HR	Posture and activity	-1.4	0.8	beats/min	0.085	
SVR	Posture	+0.54	0.19	mmHg.min/l	0.0001	0.0003
	Activity	-0.81	0.25			
Gender: effect of female, relative to male						
HR	Posture and activity	+3.9	2.2	beats/min	0.082	
SV	Posture	+1.0	1.7	ml	0.043	0.078
	Activity	-5.2	2.2			

SE, standard error of response; P level, significance level of modifying effect; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance.

Discussion

The presently performed continuous measurements yield detailed insight into the effects of both physical activity and body posture on haemodynamic variables under real-life conditions. SBP, DBP and HR appear to be more closely correlated to physical activity than previously reported, and especially high correlation coefficients were found between physical activity and CO.

Four recent studies in which BP was measured intermittently with an arm-cuff device have shown lower correlations between activity and BP than observed in the present study [4-7], whereas one study even failed to find a correlation [5]. Although the correlation coefficients were relatively high in the present study, only 32% of SBP and 28% of DBP variation could be explained by physical activity. A larger effect was seen on HR, where 56% of variation was explained by physical activity. A remarkably high correlation was found for

CO, as 74% of its variability was explained by physical activity. CO was measured as SV × HR, and SV was estimated from the arterial pressure signal using the Modelflow method [16]. In the present study SV was much less correlated with activity than CO. Therefore, it is unlikely that the high correlation coefficient between activity and CO was a consequence of the model used to estimate SV.

Since the Activity Monitor records dynamic activity of the trunk and legs, it mainly provides information about the activity of large muscle groups. This kind of activity is associated with an increase in CO and a decrease in SVR, and consequently a smaller effect on BP [21-23]. This could explain why the correlation between BP and activity was low compared with correlation between CO and activity.

As shown in figure 2, the relationships between activity and haemodynamic variables were linear for SBP and HR, but parabolic for the other parameters. The initial decrease in SV, CO and increase in DBP and SVR with increasing levels of activity coincided with changes in body position. With transition from the lying to the sitting or standing position, venous blood is pooled in the lower body, which reduces venous return to the heart and thereby reduces SV. A decrease in BP was prevented by an increase in HR and SVR due to activation of baroreceptor reflexes. The DBP increase in response to posture has been previously reported [3,24,25] and, apart from the increase in SVR, can probably be explained by the increase in HR, impairing the roll-off of BP to a lower level.

Several studies using indirect ambulatory BP recording reported that daily activity increases DBP [4,6,7]. These DBP responses may have been caused mainly by postural changes, as the effect of activity will have been diminished during the resting period preceding the BP reading. Dynamic exercise studies in which BP was measured directly have reported increments and decrements in DBP [26-29].

For the haemodynamic variables showing parabolic relationships with activity, two responses were estimated. The difference between the peak or trough and level at the 5th percentile of $\text{activity}_{\ln}$ was referred to as response to posture, whereas the difference between the level at the 95th percentile of $\text{activity}_{\ln}$ and the peak or trough was referred to as response to activity. Under ambulatory conditions, response to posture cannot be strictly separated from response to activity, as postural changes are accompanied by changes in activity. Nevertheless, we speak of response to posture because we think that the initial haemodynamic response was almost completely caused by postural changes. The subsequent response to activity is no longer influenced by postural changes, as these levels of activity were performed in the standing position. For SBP and HR, increasing linearly with increasing levels of activity, responses to posture could not be distinguished from responses to activity. Therefore, the reported responses of these two parameters comprise responses to posture and activity.

As shown in Table 2, the average SBP and HR responses to activity were 19.0 mmHg and 29.9 beats/min, respectively. In a previous study [7] using the same activity monitoring system, but indirect BP monitoring, respective average SBP and HR responses of 11.5 mmHg and 16.1 beats/min were computed. The levels of activity preceding BP measurement were similar in both studies. These differences in response indicate that SBP and HR drop considerably in the resting period preceding the non-invasive BP readings and that the responses of BP and HR to activity are underestimated when BP and HR are measured with an arm-cuff device.

In a previous study SV was computed from intra-brachial arterial pressure by the Modelflow method and was compared with thermodilution-determined SV [30]. The SV decrease in response to transition from the lying to standing position was reported to be underestimated by the Modelflow method by about 25%. Therefore, the presently computed SV decrease in response to postural change may have been underestimated as well.

With increasing age the HR response to activity decreased and the SBP, DBP and SVR responses to activity increased. The effect of age on the HR response to activity agrees with a previous ambulatory study [4], although the authors mentioned that this effect might have been confounded by the action of ß-blockers in the older subjects. Dynamic exercise studies have also shown decreased HR and increased SBP responses with increasing age [27,31]. The decrease in HR response to activity with increasing age could be due to a decrease in ß-adrenergic receptor responsiveness [32], while the greater increase in SBP may be explained by loss of elasticity in the aorta and large arteries [33].

At present lower SV and higher HR responses to posture and activity were found for female subjects than for male subjects. A previous study also reported a lower SV response for females as compared with males when posture changed from lying to standing, and a tendency for a greater HR response [24]. For these observed gender differences we do not have an explanation.

In conclusion, our findings show that posture and activity are the main determinants of HR and CO variation during everyday life. Although the responses of directly measured BP to activity are considerable, only about one-third of daytime BP variation is explained by these factors. Our findings further indicate that the effect of activity on BP and HR is underestimated if BP is measured intermittently with an arm-cuff method.

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CHAPTER 4

Reproducibility of intra-arterial ambulatory blood pressure: effects of physical activity and posture

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J Hypertens; in press.

Abstract

Objective: To examine the effects of physical activity, body posture and sleep quality on the reproducibility of continuous ambulatory blood pressure monitoring.

Patients and methods: Measurements were performed in 35 subjects (18 hypertensive, 11 male), age 49 ±13 (SD) years. BP was measured in the brachial artery, and beat-to-beat values of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were computed. Physical activity and posture were continuously measured with 5 accelerometers. Subjective quality of sleep was assessed with a questionnaire. Reproducibility was expressed as intraclass correlation coefficient (ICC) and as SD of the within-subject differences (SDD).

Results: Posture and activity significantly influenced the BP and HR. From lying to sitting, the SBP, DBP and HR increased 6 mmHg, 8 mmHg and 8 beats/min, respectively. From sitting to standing these respective increases were 4 mmHg, 2 mmHg and 13 beats/min. Further rise in activity (from standing to moving generally or walking) increased SBP by 7 mmHg, HR by 7 beats/min and decreased DBP by 8 mmHg. For daytime SBP, DBP and HR the ICC (SDD) values were 0.93 (7.2 mmHg), 0.94 (3.8 mmHg) and 0.90 (4.1 beats/min). For night-time these respective values were 0.98 (4.4 mmHg), 0.97 (2.5 mmHg) and 0.96 (2.2 beats/min). Correction for physical activity level and posture hardly improved reproducibility of daytime BP and HR. Reproducibility of night-time BP and HR was not improved by correction for physical activity, supine position or self-reported sleep quality.

Conclusions: Within-subject differences between ambulatory BP recordings cannot be explained by differences in physical activity and body posture.

Introduction

Several studies have shown that ambulatory blood pressure monitoring (ABPM) provides a better predictor of cardiovascular risk than one or a few standard office measurements of blood pressure (BP), as reviewed by Verdecchia [1] and White [2] and as recently confirmed by a large-scale prospective study [3]. In response to this finding, questions were raised on the quality of office measurements used in these studies. Fagard and Staessen reviewed relevant studies and concluded that the quality of the conventional BP measurements left much to be desired in studies on left ventricular mass, but that it was reasonably good in studies that had cardiovascular morbidity and/or mortality as outcomes [4].

The average 24 h or daytime BP obtained by ambulatory monitoring is better reproducible, and hence more representative, than office BP [5-8], which may be an important explanation for its higher prognostic value. Indeed, a report from the HARVEST study indicates that ABPM is a better predictor of target-organ damage than office BP, but only in subjects with good blood pressure reproducibility [9]. Although the reproducibility of ABPM is good compared with office BP, it is far from perfect. Several studies reported reproducibility values of daytime systolic ABPM (expressed as the SD of the differences between repeat recordings, SDD) of 10 mmHg, while the corresponding night-time values ranged from 8 to 15 mmHg [8,10-12].

Differences in physical activities between recording days may play a role in the limited reproducibility of ABPM. Recently, we studied the effect of physical activity and body posture on daytime BP under real-life conditions by means of intra-arterial recordings [13]. We reported an average systolic blood pressure (SBP) increase of 19 mmHg when activity increased from sitting quietly to walking. Diastolic blood pressure (DBP) increased 9 mmHg when activity levels increased from sitting to standing. The correlation between physical activity and BP has been reported to be stronger during the night than during the day [14], and therefore physical activity may also influence the reproducibility of nocturnal BP. Whether the association of night-time activity to night-time BP reflects differences in sleep quality is unknown [14].

In the present study, we performed direct continuous BP measurements and simultaneously monitored physical activity and body posture under real-life ambulatory conditions. Subjective quality of sleep was also assessed. The aim was to examine the effects of differences in physical activity, body posture and sleep quality between recordings on the reproducibility of daytime and night-time ABPM.

Methods

Subjects

Thirty six (14 male) apparently healthy hypertensive (n=18) and normotensive subjects participated in the study. The age of the subjects was 50.0 ± 13.1 years (mean ±SD) and BMI was 26.9 ± 3.6 kg/m^2. Subjects were considered to be hypertensive if they received antihypertensive medication (n=16) or had an office BP ≥140/90 mmHg, measured on at least three separate occasions. All antihypertensive medications were discontinued two weeks prior to measurements. All subjects gave informed consent to participate in the study, which was approved by the medical ethics committee of Erasmus MC, University Medical Centre, Rotterdam.

Procedures and measurements

BP, physical activity and body posture were measured continuously under ambulatory conditions during 48 hours in each subject. The daytime recordings of the first 24 h period were also used in a previous report [13]. On both days, subjects stayed in the research clinic from about 10:00 until 12:00 h to perform activities according to a protocol. These activities consisted of lying down (total 20 min), sitting (total 35 min), standing (total 20 min) and walking (total 35 min). Subjects left the clinic at about 12:30 h and were instructed to follow their normal daily routine. Driving a car and riding a bicycle were prohibited during measurements for safety reasons.

BP was recorded directly in the brachial artery of the non-dominant arm. Offline analysis of the BP signals (Beatscope software package, version 1.1, TNO BMI, Amsterdam, the

Netherlands) yielded beat-to-beat SBP, DBP, mean arterial pressure (MAP) and heart rate (HR).

Physical activity and body posture were measured with four acceleration sensors. Two sensors were mounted perpendicular to each other on the skin over the sternum and two were placed on the upper legs. In order to determine the supine position (lying on the back, right side, left side or prone), a fifth sensor was placed on the skin over the sternum, perpendicular to the other two sensors. The accelerometer signals were analysed offline with a kinematic software package (Temec Instruments, Kerkrade, The Netherlands). Preset ranges of reference values for different feature channels (each derived from the accelerometer signals) were employed to determine posture (lying, sitting and standing) and type of activity (general movement, walking) [15].

The BP and acceleration signals were recorded by means of a portable digital recorder and digitally stored on a memory card with frequencies of 128 Hz and 32 Hz, respectively. Measurement and analysis of BP and accelerometer signals are described in detail in a previous report [13].

Subjective quality of sleep was assessed by means of a sleep quality questionnaire, which yielded a score from 0 to 11 [16]. The questionnaire was completed by all subjects each morning after breakfast. The day period was defined as the period from the start of the activity protocol in the morning until night rest. The night-time period was defined as the period during which subjects were lying down.

Statistical analysis

Variables that were normally distributed were summarized by means ± SD. The distribution of physical activity level was positively skewed. Therefore, each subject's daytime physical activity level was summarized by the median value. The median value of night-time activity level was the same for all subjects and for both nights. The 95th percentile was chosen as measure of night-time activity because it was the lowest percentile with a value higher than the median value in the majority of subjects. The paired t-test was used to evaluate within-subject differences. A value of $p< 0.05$ was considered to indicate a significant effect. In case of multiple testing, the Hochberg procedure was applied [17].

Reproducibility of daytime and night-time measurements was expressed as intraclass correlation coefficient (ICC) [18] and as SD of the within-subject differences (SDD). Note that we define here reproducibility directly as the SDD, while usually it is defined as the SDD multiplied by 2 (or actually 1.96), representing the 95th percentile of the distribution of the absolute value of within-subject differences under reproducibility conditions. In some cases, the coefficient of variation (CV) was presented instead of the SDD. CV was computed as SDD divided by the average value of both recordings. The ICC was computed as the variance between subjects divided by the total variance (sum of between and within-subjects variance), and the SDD was computed as the square root of twice the within-subject variance. It is generally accepted that the reproducibility of measurements is high when the ICC is higher than 0.90. The ICC and SDD were estimated with the Variance Components procedure in SPSS (release 9.0 for Windows).

In order to assess the effect of within-subjects differences in physical activity on the reproducibility of daytime measurements, daytime physical activity was entered as covariate in the Variance Components procedure. Night-time physical activity and sleep quality were entered as covariates to assess their effects on reproducibility of nocturnal measurements. The resulting SDDs are adjusted for within-subjects variability of the covariates, and ICCs are adjusted for between as well as within-subjects variability of the covariates. In order to rule out the effect of within-subject differences in body position, reproducibility of daytime and night-time values was also computed for different body positions separately.

Results

The recordings of one subject were excluded because of a low natural frequency of the BP measurement system (< 10 Hz). In another subject, the recordings failed during the second night due to a technical problem. Therefore, reproducibility of daytime values was assessed in 35 subjects, and reproducibility of night-time values in 34 subjects.

Table 1 Average (SD) daytime and night-time BP and HR

	Daytime		Night-time					
			Overall		Lying back		Lying side	
	(n=35)		(n=34)		(n=27)			
Day number	1	2	1	2	1	2	1	2
SBP (mmHg)	136.8	136.0	124.4	124.4	121.3	121.7	123.8*	123.2
	(18.2)	(19.6)	(19.6)	(20.1)	(17.9)	(19.2)	(17.5)	(17.9)
DBP (mmHg)	75.5	75.2	68.8	68.9	66.2	66.2	70.5*	70.1*
	(11.2)	(11.2)	(11.0)	(10.6)	(10.8)	(10.9)	(10.9)	(10.3)
MAP (mmHg)	99.5	99.2	91.4	91.5	88.5	88.7	92.1*	91.5*
	(13.9)	(14.3)	(14.2)	(14.1)	(13.4)	(13.8)	(13.2)	(12.8)
HR (beats/min)	85.5	85.0	66.3	66.5	65.1	65.4	65.0	65.3
	(9.4)	(9.1)	(7.4)	(7.7)	(7.2)	(7.3)	(7.0)	(7.7)

N, number of subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; * value significantly different from value during lying back.

Summary of daytime and night-time values

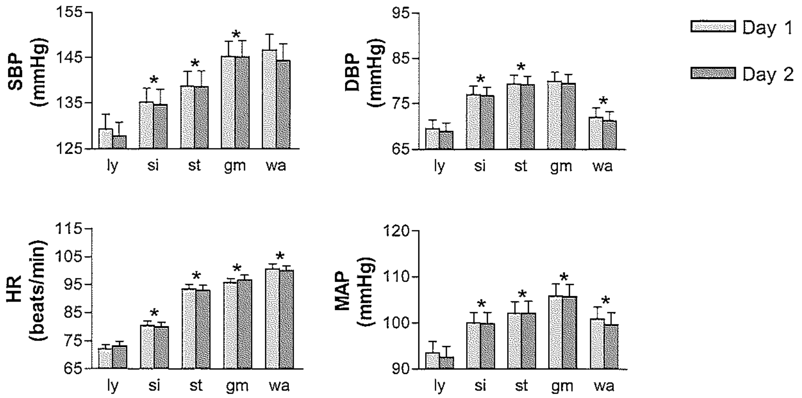
The average first daytime period lasted 13 hours and 16 min (± 59 min). On average, 3% of this period was rejected because of artefacts in the BP signal. The average second daytime period lasted 13 hours and 29 min (± 52 min), of which on average 3.3% was rejected.

Subjects were lying down, sitting, standing, moving generally and walking during 14, 50, 19, 2 and 15%, respectively, of the first daytime period. During the second daytime period these percentages were 16, 50, 18, 2 and 14%, respectively. On group level, there was no difference between both days in degree of physical activity.

The respective first and second night lasted 8 hours (± 60 min) and 8 hours (± 42 min). On average, 1.8 and 1.7% of these respective periods were rejected because of artefacts in the BP signal. Subjects were lying down (on the back, and on the side) during 99% (60, and 39%) of the first night time period and during 99% (56, and 43%) of the second night-time period. There was no difference in degree of physical activity between both nights. The quality of sleep was significantly lower ($p<0.01$) during the first night (score 5.2 ± 3.8) than during the second night (score 7.1 ±3.2).

The average daytime and night-time BP and HR values are presented in Table 1. Values did not differ significantly between both days or between both nights.

Figure 1



Average SBP, DBP, HR and MAP during lying (ly), sitting (si), standing (st), general movement (gm) and walking (wa). Significant differences with previous postures/activities are indicated (* $p<0.05$).

As the pressure transducer was mounted on the chest, it was likely to measure lower BP values while subjects were lying on the back than on the side. Average BP and HR values were computed for both positions in subjects that spent at least 10% of both night-time periods lying in each of these positions (Table 1). DBP and MAP were significantly lower when subjects were lying on the back than on the side. For SBP this was only the case during the first night. HR values did not differ between both positions. During both nights the DBP difference between both lying positions was significantly larger than the corresponding SBP difference ($p<0.001$).

For both days, the activity during standing was higher than during sitting ($p<0.001$), and activity during sitting was higher than during lying ($p<0.001$). Average BP and HR values for different daytime postures and activities during the first and second day are plotted in Fig. 1. HR and MAP differed significantly between all successive postures and activities during both days. For SBP all successive differences, except between general movement and walking, were significant. For DBP all successive differences were significant, except between standing and general movement.

Reproducibility of daytime and night-time values

The reproducibility of daytime and night-time BP and HR is illustrated in Fig. 2A and 2B. For all variables the reproducibility was high. Highest ICC values, accompanied by lowest SDD values, were observed during the night (Table 2).

Table 2 Reproducibility of daytime and night-time BP and HR, before and after correction

			SBP		DBP		MAP		HR	
			ICC	*SDD [mmHg or beats/min]*	ICC	*SDD*	ICC	*SDD*	ICC	*SDD*
Daytime	N=35	Overall	0.93	*7.2*	0.94	*3.8*	0.94	*5.0*	0.90	*4.1*
		Activity correction	0.93	*7.2*	0.95	*3.7*	0.94	*5.0*	0.92	*3.8*
		Sitting	0.92	*7.5*	0.93	*4.1*	0.93	*5.3*	0.91	*3.8*
		Standing	0.94	*6.9*	0.96	*3.2*	0.95	*4.5*	0.90	*4.6*
		Walking	0.94	*7.0*	0.96	*3.2*	0.96	*4.5*	0.93	*3.8*
Night-time	N=34	Overall	0.98	*4.4*	0.97	*2.5*	0.97	*3.3*	0.96	*2.2*
		Activity correction	0.98	*4.2*	0.97	*2.5*	0.97	*3.2*	0.96	*2.2*
		Sleep qual correction	0.97	*4.5*	0.97	*2.6*	0.97	*3.3*	0.96	*2.2*
		Preferred position	0.96	*5.3*	0.96	*2.8*	0.96	*3.8*	0.95	*2.5*

ICC, intraclass correlation coefficient; SDD, SD of differences; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; N, number of subjects.

The reproducibility values of daytime physical activity and body posture were lower than those of BP and HR. The respective ICC and CV of daytime physical activity were 0.87 and 38%. The ICC values of the duration (expressed as percentage of the total daytime period) of sitting, standing and walking were 0.61, 0.80 and 0.75, respectively. The corresponding SDD values were 10.8 %, 4.3% and 3.2%, respectively.

Figure 2A

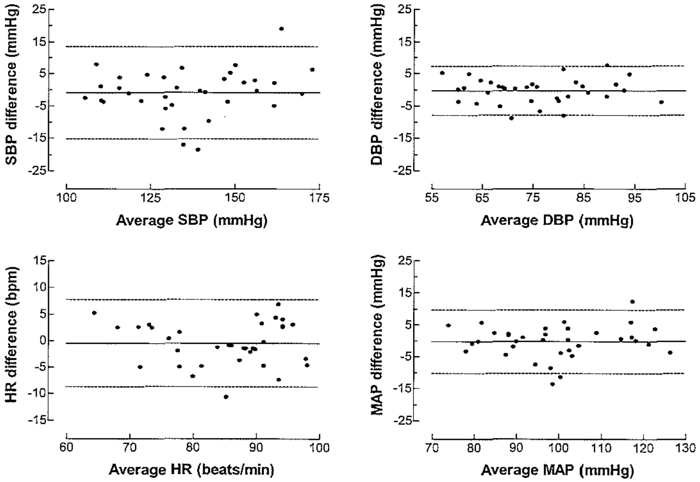
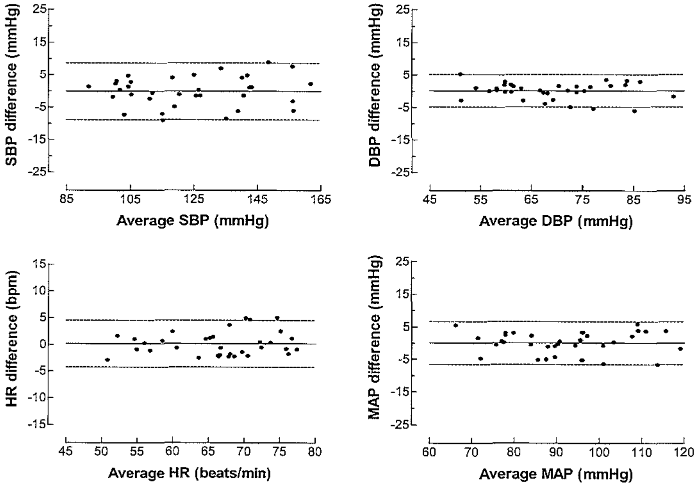


Figure 2B



Bland-Altman plots of daytime (2A) and night-time (2B) SBP, DBP, HR and MAP values. The continuous lines indicate the mean differences between days or nights; the dotted lines indicate the limits of agreement between the two days or nights (mean ± 2SDD).

The reproducibility of night-time physical activity and sleep quality were low. The ICC and CV of night-time physical activity were 0.45 and 63%. For self-reported sleep quality, the ICC and SDD were 0.37 and 3.8, respectively.

In order to compute the reproducibility of night-time body position, the position in which subjects spent most of the first night (referred to as the preferred position) was determined. This position was lying back in 65% of the subjects, and lying on the side in 35% of the subjects. We computed the reproducibility of the preferred position. The respective ICC and SDD were 0.72 and 12%. On average, 72% of the first night and 69% of the second night was spent in the preferred position.

In general, reproducibility of daytime and night-time BP and HR was hardly improved by correction for activity, posture or sleep quality (Table 2). Correction for daytime activity resulted in some improvement of HR reproducibility, but hardly any improvement of BP reproducibility. Correction for posture had a greater positive effect on daytime BP reproducibility than correction for activity. The reproducibility of night-time BP and HR was not improved by correction for physical activity, body position or self-reported sleep quality. The reproducibility of daytime and night-time BP and HR was comparable for normotensive and hypertensive subjects (Table 3).

Table 3 Reproducibility of daytime and night-time BP and HR for normotensive and hypertensive subjects

		ICC *CV (%)*							
		SBP		DBP		MAP		HR	
Day-time	Normotens. (n=17)	0.88	5.2	0.88	*5.2*	0.89	*5.2*	0.92	*4.9*
	Hypertens. (n=18)	0.90	5.2	0.92	*4.8*	90.0	*4.9*	0.87	*4.7*
Night-time	Normotens. (n=16)	0.96	*3.4*	0.96	*3.5*	0.96	*3.5*	0.96	*3.5*
	Hypertens. (n=18)	0.96	*3.7*	0.96	*3.7*	0.96	*3.7*	0.95	*3.2*

ICC, intraclass correlation coefficient; CV, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; n, number of subjects.

Discussion

Differences in physical activity, body position and quality of sleep have often been mentioned as possible explanations for the limited reproducibility of BP during the day and the night [10,11,19]. However, in the present study the reproducibility of daytime ambulatory BP and HR was hardly improved by correction for physical activity. Correction for body posture had a small effect on BP reproducibility and, interestingly, reproducibility of BP tended to be higher during standing and walking than during sitting. This may indicate that other factors influencing BP, like mental activity, social interaction and emotional state, have more effect on BP during sitting than during standing and walking. The reproducibility of night-time BP was high, and did not improve by correction for physical activity, supine position or self-reported sleep quality.

Effect of activity and sleep quality

The finding that correction for daytime physical activity did not improve BP reproducibility and only slightly improved HR reproducibility, is surprising when considering the substantial effect of posture and activity on BP and HR (Fig. 1). To some extent, this may be explained by the rather high reproducibility of physical activity itself. It further indicates that, besides activity and posture, other factors influencing BP and HR are important determinants for the within-subjects differences in BP and HR between recording days.

In the present study, night-time physical activity was low and median night-time activity did not differ within or among subjects. As a consequence, correction for median levels of activity would not influence BP reproducibility. Instead of the median levels of night-time activity, the 95th percentile of activity, which differed within and between subjects, was used to estimate the effect of night-time activity on BP reproducibility. Despite its low reproducibility, correction for night-time activity did not improve night-time BP or HR reproducibility. Correction for the self-reported sleep quality, which like night-time activity had a poor reproducibility, also did not improve the reproducibility of night-time BP and HR.

There are some studies indicating that night-time physical activity does affect night-time BP [14,20,21], but to our knowledge studies looking at the effect of different physical activities between nights on BP and HR reproducibility have not been reported. Physical activity during the night may be related to sleep quality [22]. However, in our study no correlation between subjective sleep quality and physical activity during the first or second night could be established. Also, within-subject differences in subjective sleep quality and activity between nights were not correlated (data not presented).

Effect of transducer position

As the pressure transducer was mounted on the skin over the sternum, a hydrostatic pressure difference between lying on the back (underestimation of BP) and lying on the side was anticipated. The DBP difference between these two positions was larger than the corresponding SBP difference. If the conversion factor, as proposed by Block *et al.* [23], is applied, the DBP difference corresponded to 5.5 cm while the SBP difference between both positions corresponded to 2.7 cm height difference. This observation suggests that, apart from hydrostatic pressure, one or more other factors influence the BP differences between different supine positions, as has been reported previously [24]. In search of these factors, we wondered whether the side on which subjects were lying down (right or left side) played a role. This appeared not to be the case, as neither SBP nor DBP differed between lying on the left and right side in 15 subjects who spent at least 10% of one night-time period in these two positions.

Effect of continuous monitoring

Compared with other reproducibility studies, using intermittent non-invasive recordings, we found a considerably higher reproducibility of night-time BP. Also, daytime BP reproducibility was high compared with most previous reports. Only one study reported lower daytime SDD values, but coefficients of variation were similar (Table 4).

Table 4 Reproducibility of daytime and night-time ABPM: Non-invasive studies compared with present invasive study

Reference	Interval between visits	Number nor / hyp	SDD SBP/DBP (mmHg)		CV SBP / DBP (%)	
			Daytime	Night-time	Daytime	Night-time
Wendelin-Saarenhovi *et al.*[29]	4-12 m	19 / 7	8.1 / 3.6	8.4 / 5.6	6.3 / 4.6	7.7 / 8.2
van der Steen *et al.*[11]	2-3 w	0 / 45	12 / 6	16 / 8	8.3 / 6.7	12.7 / 10.5
Weston *et al.*[30]	9 w	32 / 0	6.0 / 3.9	6.1 / 4.2	5.1 / 4.9	5.8 / 5.9
Musso and Lotti[12]	8 m	0 / 91	9.6 / 7.3	8.1 / 6.6	7.2 / 8.6	6.7 / 9.0
James *et al.*[10]	2 m	7 / 35	11.2 / -	13.5 / -	7.3 / -	9.4 / -
Palatini *et al.*[31]	3 m	0 / 508	8.8 / 6.9	10.5 / 7.5	6.6 / 8.3	9.0 / 10.3
Mansoor *et al.*[8]	15 m	0 / 25	10.7 / 5.8	7.7 / 5.2	7.4 / 6.5	6.3 / 7.1
Present study	-	17 / 18	7.2 / 3.8	4.4 / 2.5	5.3 / 5.0	3.5 / 3.6

Nor, normotensive; hyp, hypertensive; SDD, SD of differences; CV, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, months; w, weeks.

An obvious factor that may have played a role in the higher reproducibility is the minimal interval between the two measurement days in the present study. With longer intervals, factors such as changes in diet, body weight and seasonal influences can affect BP, and hence reproducibility. However, when considering the studies presented in Table 4, there is no evidence that reproducibility is affected by the interval of measurements.

A second factor in the higher reproducibility of BP might be the larger number of values on which the average BP is based. The influence of sampling rate on BP reproducibility has been assessed by Trazzi *et al.* [7]. The authors reported that SDD values of 24-h intra-arterial BP progressively decreased as the value on which the mean was calculated increased, but no further decrease in SDD was observed for SBP and DBP when more than 12 and 96 values, respectively, were considered. Therefore, the higher sampling rate is not a likely explanation for the higher BP reproducibility. Using continuous finger BP measurements in 8 normotensive and 10 hypertensive subjects, Voogel and van Montfrans [25] reported SDD values of daytime SBP/DBP of 2.9/3.2 mmHg for normotensive subjects and 6.6/4.7 mmHg for hypertensive subjects, whereas night-time values were, respectively, 4.4/2.7 and 12.5/6.5 mmHg. In their study, subjects stayed in the hospital during measurements, and meals and all other activities were fully standardized, which probably contributed to the very high reproducibility of daytime BP.

The high reproducibility of night-time BP in the present study, as compared with the reproducibility obtained from non-invasive ambulatory BP recordings, is possibly attributable to less disturbance of sleep. Disturbance of sleep due to cuff inflation during non-invasive ambulatory BP recordings has been reported to occur in two-thirds of patients [26]. A study applying polysomnography showed that cuff inflations during sleep resulted in arousals [27]. In response to these arousals, BP may increase, depending on sleep stage [28].

In conclusion, the presently performed continuous ambulatory BP recordings were better reproducible than recordings in other studies, based on intermittent arm-cuff readings. This suggests that the method used to measure BP plays a role in the reproducibility of ABPM. Although physical activity and posture have a considerable effect on BP, our findings do not indicate that these factors significantly influence reproducibility of BP recordings. Therefore, routine assessment of physical activity to improve interpretation and hence clinical value of ABPM seems not warranted.

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CHAPTER 5

Assessment of body position to quantify its effect on nocturnal blood pressure under ambulatory conditions

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Abstract

Background: Nocturnal blood pressure readings may be influenced by body position because of variation in the vertical distance between heart and cuff level.

Objectives: To quantify the effect of body position on nocturnal blood pressure and to assess whether this effect influences the reproducibility of nocturnal blood pressure.

Patients and methods: In 16 subjects (3 normotensive and 13 hypertensive) 24 h ambulatory measurement of blood pressure and body position was performed twice, separated by an interval of 2-6 weeks. Body position was measured with 5 acceleration sensors, which were mounted on the trunk and legs.

Results: During the first night 43 ±31% of blood pressure values were measured while subjects were in the supine position, 29 ±28% when they were lying on their side with the cuffed arm down and 28 ±29% when they were lying on their side with the cuffed arm up. During the second night these percentages were 40 ±29%, 32 ±29% and 28 ±25% respectively. Blood pressure readings obtained while subjects were lying with the cuffed arm up were about 10 mmHg lower than those obtained with the subject in either the supine position or lying with the cuffed arm down. After correction for the underestimation attributable to ‘cuff-up’ readings, nocturnal blood pressure increased by 3 mmHg and the number of non-dippers increased from two to four. Correction did not affect the reproducibility of nocturnal blood pressure measurements (standard deviation of the differences 8.3 mmHg for systolic and 6.0 mmHg for diastolic blood pressure after correction). Dipping status was reproduced in 88% of subjects before correction, and in 87% after correction.

Conclusions: Under ambulatory conditions, a highly variable but sometimes substantial number of blood pressure readings are taken with the arm-cuff above heart level. These readings result in underestimation of nocturnal blood pressure and hence influence dipping classification. However, body position does not seem to have an important effect on the reproducibility of nocturnal blood pressure or dipping status.

Introduction

The most important and consistent source of blood pressure (BP) variation is the diurnal change associated with the sleep-wake cycle. This diurnal variation in BP may be of prognostic value. Several studies have demonstrated that hypertensive damage to target organs is more severe in individuals who do not exhibit a nocturnal decline in BP (non-dippers) [1-3]. It has also been shown that non-dippers have an increased risk of cardiovascular morbidity and mortality compared with individuals who experience a normal nocturnal decline in BP (dippers) [4,5].

Although classification of subgroups of patients with and without a dipping BP pattern may be useful in large-scale studies of cardiovascular risk, in individual cases the classification of a patient as a dipper or non-dipper very much depends on how reliable the decrease in nocturnal BP can be measured. In order to assess this reliability, several studies have been conducted in which the reproducibility of the nocturnal BP and the nocturnal BP decrease was tested [6-14]. Most of these studies indicated that the reproducibility of the nocturnal BP and the dipping phenomenon is rather poor [8-14].

Factors known to influence the nocturnal BP include the definition of the night-time period, the quality and pattern of sleep, and the position of the arm relative to the heart [6,15-21]. Body position may influence BP readings during the night because of variation in the vertical distance between heart and cuff level; it has been shown that variation in resting body position can induce changes of about 10 mmHg in the recorded BP [21]. The recent development of a portable Activity Monitor has made it possible to measure body position in 'real-life' ambulatory situations [22-25].

The present study was designed to quantify the effect of body position on nocturnal BP readings during non-invasive 24 h BP monitoring and to assess whether this effect influences the reproducibility of nocturnal BP measurements.

Methods

Subjects

Thirteen hypertensive and 3 normotensive subjects (8 men), aged between 28 and 68 years (mean age 49.5 years), participated in the study. They had no diabetes mellitus and no neurological or sleep disorders. All hypertensive subjects used their usual antihypertensive medication during both measurements. Patients using α- or ß-adrenoceptor blocking agents were excluded from the study. All those included gave informed consent to participate in the study, which was approved by the medical ethics committee of the Erasmus MC, University Medical Centre, Rotterdam.

Procedures and measurements

In each subject, 24 h ambulatory measurements of BP and body position were performed twice, separated by an interval of 2-6 weeks. Subjects entered the research clinic in the morning before 10:00 h to have the measurement devices fitted, after which they left the clinic. No limitations were applied to their daily routine. The monitors were returned after 24 hours and the stored data were downloaded into a personal computer. On both recording days, the same procedures were followed and the same measurement devices were used. At least one week before the first measurement, each subject underwent a 24 h ambulatory BP recording (BP device only) in order to become habituated to the regular cuff inflation.

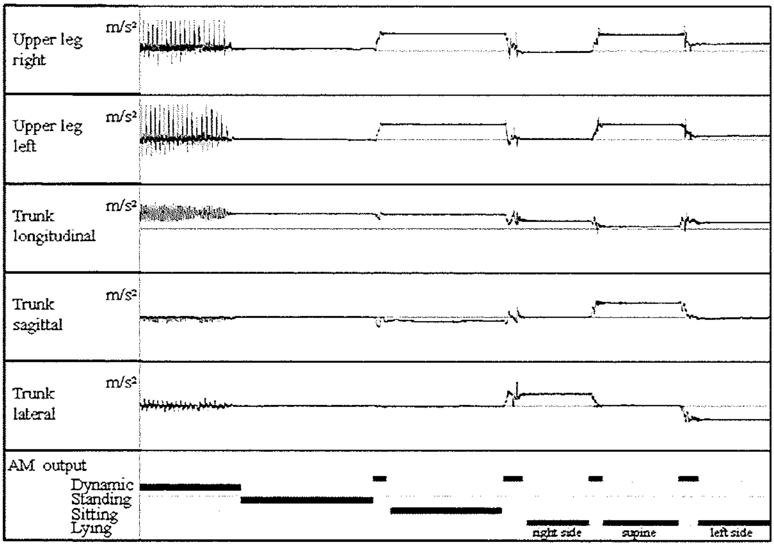
An automatic ambulatory non-invasive device (SpaceLabs model 90207) was used for the BP measurements, which were made in the non-dominant arm (left arm in 13 and right arm in 3 subjects) at intervals of 15 min between 07:00 h and 23:00 h and 20 minutes between 23:00 h and 07:00 h.

Body position was measured with 5 uni-axial acceleration sensors (IC-3031). The alternating current (AC) component of the output voltage of each sensor is associated with the actual acceleration of the sensor, whereas the direct current (DC) component is associated with the angle of the sensor relative to the gravitational axis [26]. Three sensors were mounted perpendicular to each other on the skin over the sternum. In the upright standing position, one sensor was sensitive parallel to the field of gravity (the longitudinal axis), one sensor was sensitive along the sagittal axis, and one sensor was sensitive along the lateral axis. Two sensors were placed on the upper legs with the sensitive axes perpendicular to the surface, being sensitive along the sagittal axis [22-25]. The acceleration signals were recorded by means of a portable digital recorder (Vitaport System; Temec Instruments, Kerkrade, The Netherlands) and digitally stored on a memory card, using a sample frequency of 32 Hz. The recorder was carried on a belt around the waist. The SpaceLabs monitor was connected to the digital recorder by means of a pressure transducer in order to synchronize both recordings.

Analysis

The DC and AC components of the raw acceleration signals were separated by means of low-pass (0.3 Hz) and band-pass (0.3-16 Hz) filtering. The angles of the sensors with respect to the gravitational axis were computed from the low-pass filtered signals. A range of reference values for four low-pass and four band-pass filtered signals (from the ‘longitudinal’ and ‘sagittal’ trunk sensor and both leg sensors) were used to determine postures (standing, sitting and lying). With the currently used Activity Monitor (the combination of four accelerometers,

Figure 1



Two minute tracings of the five raw accelerometer signals (two leg sensors, three trunk sensors) and the corresponding output of the Activity Monitor (AM).

portable data recorder and the computer analysis software), several validation studies have been performed, showing high agreement between the output of the Activity Monitor and the classification of postures on the basis of visual analysis of simultaneously recorded videotapes [22-25]. An example of the classification of postures on the basis of the raw accelerometer signals is depicted in Figure 1.

During the periods when body position was classified as lying, the angle of the trunk in the transverse plane was computed from the low-pass filtered signals of the trunk sensors that were sensitive along the sagittal and lateral axes. Angles of 90 ± 45° were deemed to represent the subject lying on the left side, 180 ± 45° as the supine position, 270 ± 45° as lying on the right side, and 360 ± 45° as the prone position.

Average daytime and nocturnal BPs were calculated for each subject. Dipping was defined as a decrease in nocturnal systolic or diastolic BP of at least 10% of the daytime value [5]. The night-time period was defined as the period during which subjects were lying down, as identified by the Activity Monitor (daytime rest was excluded). Each subject's average BP for each body position while lying down was calculated whenever the subject had four or more readings in that position.

Statistics

Values are presented as means ± standard deviation (SD). The paired t-test was used to compare BP values that were measured with the subjects in different body positions and to compare the nocturnal BPs of the two recordings. Reproducibility was assessed in terms of the SD of the within-subject differences (SDD) and examination of Bland-Altman plots [27]. Analysis of covariance was performed to determine the effect of age and gender on the circadian blood pressure variation (percentages nocturnal decrease in SBP and DBP) and on the reproducibility of nocturnal BP (absolute BP differences between nights). A value $p < 0.05$ was considered to indicate a significant effect.

Results

Number of BP readings and day- and night-time values

The number of daytime and night-time BP readings were, respectively, 60.0±5.8 and 23.3±4.0 during the first and 59.9±7.0 and 22.7±4.8 during the second recording.

Average day- and night-time BPs (systolic/diastolic) during the first and second recording were similar. Values were 138.6±15.0/86.3±12.0 mmHg and 117.8±15.7/68.8±12.6 mmHg during the first recording and 138.8±10.1/85.8±9.5 mmHg and 121.9±13.6/71.2±11.4 mmHg during the second recording. The percentages of nocturnal systolic and diastolic BP decrease were not related to age or to gender. During the first night, 43.3±30.6% of the BP readings were obtained while the subjects were in the supine position, 29.2±28.4% were obtained while they were lying on their side with the cuffed arm down (cuff-down), and 27.5±29.4% were obtained while they were lying on their side with the cuffed arm up (cuff-up). During the second night, these respective proportions were 39.6±29.0, 32.1±28.6 and 28.3±24.8%. No readings were obtained while the subjects were lying prone.

Table 1 BP differences between different body positions during the first and the second night

	BP difference (mmHg)			
	Night 1		Night 2	
Body positions compared	SBP / DBP Mean (SD)	*n*	SBP / DBP Mean (SD)	*n*
Sup / cd	1.5 / -0.1 (4.7 / 5.4)	9	0.7 / 1.3 (4.6 / 1.9)	7
Sup / cu	10.4** / 11.4** (5.9 / 5.9)	8	8.9** / 8.5** (5.4 / 6.4)	9
Cd / cu	12.5* / 13.7** (11.5 / 9.7)	7	12.2** / 11.7** (8.4 / 7.1)	7

n, number of subjects; sup, supine position; cd, lying on the side with the cuff down; cu, lying on the side with the cuff up. * $P<0.05$, ** $P<0.01$, BP compared between body positions.

Effect of body position on nocturnal BP readings

The effect of the different body positions on the outcome of the nocturnal BP readings is presented in Table 1. The number of readings in one or both of the specified positions was sometimes fewer than four, so that between-position differences in BP could not be calculated for each individual. As expected, the BP measured when the subject was in the cuff-up position was significantly lower than when measured in the supine or cuff down-position. BPs measured when subjects were in the supine and cuff-down positions were similar, therefore readings obtained in these two positions were pooled and the average of the pooled values

Table 2 Difference between uncorrected and corrected nocturnal BP during the first and the second night

	SBP/DBP (mmHg)	*P*†	*n*
Night 1	-3.4 ±7.0 / -3.4 ±5.6	0.04 / 0.02	15
Night 2	-2.6 ±3.1 / -2.6 ±3.4	0.002 / 0.004	16

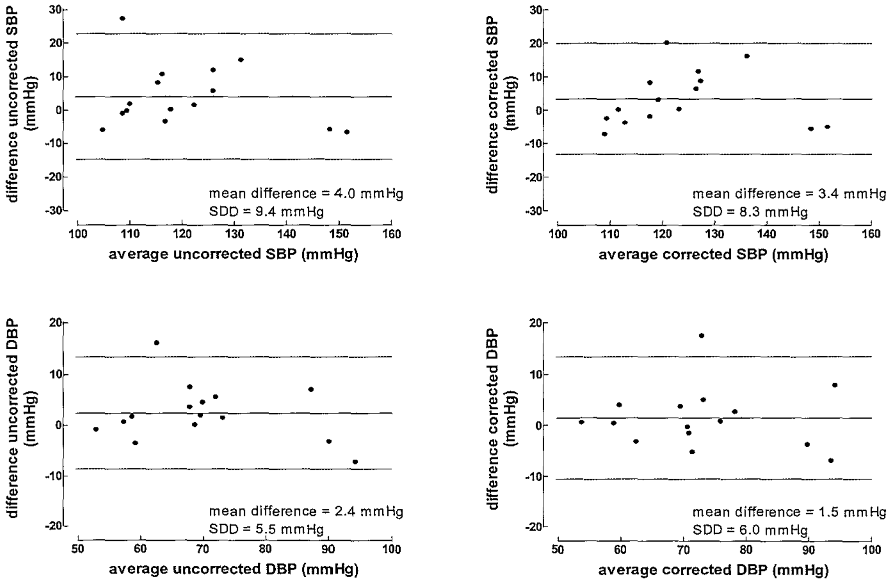
†One-tailed significance level of the difference between the uncorrected nocturnal SBP/DBP and the corrected nocturnal SBP/DBP.

(referred to as *corrected BP*) was calculated for each subject. Differences (systolic/diastolic) between the corrected BP values and the values measured with the subject in the cuff-up position were 12.4±10.4/13.1±8.2 mmHg ($p<0.01$) during the first recording and 10.7±6.6/10.4±7.4 mmHg ($p<0.001$) during the second recording.

Effect of body position on average nocturnal BP and dipping status

During the first and second recordings, the average nocturnal systolic and diastolic BP was underestimated by about 3 mmHg because of readings obtained when the subject was in the cuff-up position (Table 2). This underestimation of the true nocturnal BP influenced the number of subjects identified as having a non-dipping BP pattern. When nocturnal BP was not corrected for the measurements obtained with the subject in the cuff-up position, the numbers of non-dippers were 1 of 16 subjects (6.3%) and 3 of 16 subjects (18.8%) during the first and second recordings, respectively. After correction for the cuff-up measurements, the number of non-dippers increased to 4 of 15 individuals (26.7%) during the first recording and

Figure 2



Bland-Altman plots of uncorrected and corrected systolic blood pressure (SBP) and diastolic blood pressure (DBP). In each plot, the average BP of both nights is depicted on the *X*-axis and the BP difference between night 2 and night 1 is depicted on the *Y*-axis. The continuous lines indicate the mean BP difference between nights; the dotted lines indicate the limits of agreement between the two nights (mean ± 2SDD) [27].

to 4 of 16 individuals (25%) during the second recording (during the first recording, corrected BP could not be calculated in one participant because only one reading was obtained in the cuff-down or supine position).

Effect of body position on reproducibility of nocturnal BP and dipping status

Correction for body position did not change the reproducibility of either systolic or diastolic BP (Fig 2). The group mean BP values (uncorrected and corrected) did not differ between the two nights. The SDDs in the male and female groups were similar (8.3 and 8.9 for systolic and 5.4 and 6.7 for diastolic BP, respectively) and the absolute BP differences between both nights were not related to age or gender. Correction for body position also did not affect the reproducibility of dipping status: on the basis of the uncorrected BPs, dipping status reproduced in 14 of 16 subjects (88%), and on the basis of the corrected BPs, it reproduced in 13 of 15 subjects (87%).

Discussion

Accelerometry in combination with a portable recorder makes it possible to measure the position of the body under ambulatory conditions [22-25]. We have applied this new technique to assess the influence of body position on nocturnal ambulatory BP readings. Our study shows that nocturnal BP was underestimated by about 3 mmHg and that the number of non-dippers was underestimated by about 13% because of BP readings obtained when the subject was in the cuff-up position. Correction of the nocturnal BP for the cuff-up readings did not affect either the reproducibility of the nocturnal BP or the reproducibility of the dipping status.

No readings were obtained while subjects were lying prone, most probably because the activity recorder was worn ventrally. The BP differences found between the remaining body positions (supine, lying with the cuffed arm up and lying with the cuffed arm down) were comparable with those reported by Schwan and Pavek [21], who investigated the effect of changes in recumbent body positions on BP while subjects were awake. BPs with the individual in the supine and the cuff-down position were about 10 mmHg higher than those in the cuff-up position. These differences were similar for SBP and DBP, owing to a common hydrostatic origin.

Contrary to expectations, the BPs obtained when the subjects were in the cuff-down position were not higher than those obtained in the supine position. In their study, moreover, Schwan and Pavek [21] found that SBP, but not DBP, was 5 mmHg higher in subjects in the supine position than in those in the cuff-down position. The absence of a difference between BPs measured when subjects were in the supine and cuff-down positions suggests that the vertical distance between the heart and the cuff is similar in these two positions. Possibly, subjects placed their arm in a more comfortable position close to heart level when lying with the cuffed arm down, so that BP readings obtained when they were in this position did not differ from the readings obtained when they were supine.

During both recording days, about 28% of the nocturnal BP readings were obtained in individuals in the cuff-up position, which resulted in an average underestimation of the nocturnal BP by about 3 mmHg. However, as the interindividual variation in percentage of cuff-up readings was large (ranging from 0% to 95%), the differences between the uncorrected (all readings included) and corrected (cuff-up readings excluded) nocturnal BPs also varied considerably between subjects. As a consequence, not only did some of the borderline dippers become non-dippers after correction for body position, but also one of the subjects with a relatively high nocturnal BP decrease before correction became a non-dipper after correction.

The reproducibility of the nocturnal BP, expressed as the SDD, was 9.4 mmHg for the systolic and 5.5 mmHg for the diastolic BP. These values are comparable with those reported in a number of other studies [7-10]. The reproducibility of the dipping status was better in this study than in other studies [6, 9-12]. This may be explained by the more correct definition of the night-time period as the time during which subjects were lying down, as determined by the Activity Monitor. For example, in a study by Weston *et al.* [6] the percentage of subjects who changed their dipping status between visits decreased from 33% to 0% when night-time was defined by diary instead of as a fixed night period from 22:00 to 07:00 h. We anticipated that the reproducibility of the nocturnal BP and dipping status would improve after correction for readings obtained when the subject was in the cuff-up position. This appeared not to be the case, since the SDDs were 8.3 mmHg for systolic and 6.0 mmHg for diastolic BP for the corrected nocturnal BPs, and the number of subjects who changed their dipping status remained the same after correction. The absence of improvement of the reproducibility after correction for cuff-up readings may be explained by the finding that, in the majority of subjects, the percentage of cuff-up readings reproduced well.

The fact that the reproducibility of the nocturnal BP did not improve after correction for body position implies that the reproducibility of nocturnal BP is determined by other factors also. In the present study, the period of night-time rest was identified objectively by means of the Activity Monitor, thereby excluding possible influences arising from unreliable definitions of the period that might affect reproducibility [6, 15-18]. Furthermore, all participants underwent a 24 h ambulatory BP recording at least one week before the first recording, in order to become habituated to the regular cuff inflation, and the same BP monitor was used in the same subject on both occasions. Finally, the period between the first and the second measurement was relatively short, so that changes in external factors such as seasonal influences and body weight could not have been very large. Quality and pattern of sleep influence nocturnal BP, and even minor variations in these parameters can lead to marked changes in the hypotensive effect [19,20]. In the present study we did not measure sleep pattern. It can not be ruled out that these parameters varied from one occasion to the other and in this way affected the reproducibility of nocturnal BP.

We conclude that nocturnal BP readings which are obtained while subjects are lying with the arm-cuff above heart level result in a lower average nocturnal BP and thereby will influence the classification of a subject as a dipper or non-dipper. Because of the uncertainty as to how many of the nocturnal BP readings are taken with the arm in the cuff-up position during routine ABPM, it seems prudent to use more stringent criteria to define a subject as a non-dipper, as was recently recommended by others [28,29]. In the present small study, the rather poor reproducibility of nocturnal BP did not improve when we discarded readings that were obtained while the arm-cuff was above heart level, indicating that factors other than body position, such as sleep patterns, are also involved.

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CHAPTER 6

Physical activity, dipping and haemodynamics

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Submitted.

Abstract

Objective: To determine the effect of physical activity on diurnal BP and haemodynamic variation.

Patients and methods: Ambulatory measurements were performed during 24 hours in 36 subjects (18 hypertensive, 13 male), age 49.7±13.5 years. BP was recorded in the brachial artery. Physical activity and posture were measured with five acceleration sensors.

Results: Of the subjects 50% were dippers (nocturnal decrease in systolic or diastolic BP ≥10%). Dippers and non-dippers had similar daytime BP, daytime, night-time, and day-night difference in physical activity, subjective sleep quality, and nocturnal cardiac output decrease (14.9±9.6% and 16.0±5.9%). In non-dippers vascular resistance increased from day to night by 9.7±8.3%, while it remained unchanged (-1.0±13.9%) in dippers. Day-night changes in heart rate and cardiac output were correlated with day-night changes in physical activity (r=0.39 and 0.43), whereas day-night changes in systolic BP were correlated with night-time activity (r=-0.34). By selection of the active (i.e., walking) and inactive (i.e., not walking) periods during the day, we showed that physical activity has a large potential effect on dipping status and diurnal haemodynamic variation underlying BP variation. Depending on the BP taken (systolic or diastolic, respectively) the proportion of dippers increased to 81% or decreased to 25% if only the walking, whereas it decreased to 36% or increased to 53%, if only the non-walking period was considered.

Conclusions: Non-dippers differ from dippers by an increase of vascular resistance during the night. The degree of physical activity normally encountered during ambulatory monitoring has little influence on the diurnal BP profile or dipping status, but significantly influences underlying haemodynamics. Related to the different effects of posture and activity on systolic and diastolic BP, dipping classification may vary with the BP index taken.

Introduction

Blood pressure (BP) normally shows a diurnal pattern with a lower BP during the night when subjects are asleep than during the day when subjects are active. When the nocturnal fall in BP is diminished, the risk of cardiovascular morbidity and mortality is increased as has been demonstrated now in several prospective studies [1-3]. This risk is not only present in hypertensive, but also in normotensive subjects [2,3].

From studies exploring the effects of physical activity and physical rest on BP, it has been concluded that the diurnal variation in physical activity plays an important role in the diurnal BP variation [4,5]. One study reported that the levels of daytime and night-time physical activity are independently predictive of the magnitude of the nocturnal BP fall [6]. Others found that higher night-time activity is associated with smaller day-night BP differences [7,8]. However, the correlation between the diurnal pattern in physical activity and diurnal BP pattern appeared to be weak.

The methods used to measure BP may have contributed to the weakness of the correlation. In a previous study, we demonstrated that the correlation between daytime physical activity and daytime BP is considerably higher when BP is measured continuously instead of intermittently [9]. In order to assess whether the same counts for the day-night pattern in these parameters, the continuous 24 h profiles of intra-arterial BP and physical activity were monitored under real-life ambulatory conditions. As we were interested in haemodynamic changes that underlie diurnal BP variation, the continuous 24 h profiles of stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) were determined as well. Additionally, we monitored body posture to assess in more detail the effect of physical activity on diurnal haemodynamic variation and to compare this variation with haemodynamic changes in response to daytime supine rest.

Methods

Subjects

Thirty-six (13 male) apparently healthy hypertensive (n=18) and normotensive subjects participated in the study. The age of the subjects was 49.7 ± 13.5 years (mean ±SD) and BMI was 26.9 ± 3.6 kg/m^2. Subjects were considered to be hypertensive if they received antihypertensive medication (n=16) or had an office BP ≥140/90 mmHg, measured on at least three separate occasions. All antihypertensive medications were discontinued two weeks prior to measurements. All subjects gave informed consent to participate in the study, which was approved by the medical ethics committee of Erasmus MC, University Medical Centre, Rotterdam.

Procedures and measurements

BP, physical activity and body posture were measured continuously under ambulatory conditions during 24 hours in each subject. Measurements started at about 10:00 h. During the first two hours subjects remained in the research clinic to perform activities according to a protocol. These activities consisted of lying down (total 20 min), sitting (total 35 min), standing (total 20 min) and walking (total 35 min). Subjects left the clinic at about 12:30 h and were instructed to follow their normal daily routine. Driving a car and riding a bicycle were prohibited during measurements for safety reasons. Subjects returned to the clinic the next day at about 9:30 h.

BP was measured directly in the brachial artery of the non-dominant arm. Physical activity and body posture were measured with five piezo-resistive acceleration sensors (three on the skin over the sternum and two on the upper legs). The BP and acceleration signals were recorded by means of a portable digital recorder, and digitally stored on a memory card with frequencies of 128 and 32 Hz, respectively.

Offline analysis of the BP signals (Beatscope software package, version 1.1, TNO BMI, Amsterdam, the Netherlands) yielded beat-to-beat systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), SV, CO and SVR. Activity signals were derived from the accelerometer signals by means of offline analysis with a kinematic software package (Temec Instruments, Kerkrade, the Netherlands). The average of four activity signals (two trunk and two leg signals) was used as a measure of physical activity and was expressed in gravitation units. Preset ranges of reference values for different feature channels (each derived from the accelerometer signals) were employed to determine posture (lying, sitting, and standing) and type of activity (general movement, walking) [10]. Measurement and analysis of BP and accelerometer signals and artefact rejection are described in a previous publication [9]. A logarithmic transformation was applied to the activity values (activity$_{ln}$) to reduce the positive skew of the distribution and to make it more symmetric. Activity$_{ln}$ is expressed in units.

Subjective quality of sleep was assessed by means of a sleep quality questionnaire, which yielded a score from 0 to 11 [11]. All subjects completed the questionnaire in the morning and noted the time they went to bed at night and rose in the morning. The night-time period was defined as the period during which subjects were lying down to sleep, and was identified by combined analysis of posture and subjects' reported sleeping times. Subjects were classified as dippers if their nocturnal SBP or DBP level was at least 10% lower than their daytime values [1].

Statistical analysis

Distributions of variables are summarized by means ± SD. Haemodynamic day-night differences were expressed as percentages of the daytime values. Paired t-tests were used to

Table 1 Characteristics of dippers and non-dippers

		Dippers (n=18)	Non-dippers (n=18)
Age (years)		48.1 ± 14.5	51.2 ± 12.6
Gender (female / male)		12 / 6	11 / 7
BMI (kg/m^2)		26.2 ± 3.9	27.6 ± 3.2
Hypertensive / normotensive		8 / 10	10 / 8
Sleep quality		6.1 ± 3.7	4.4 ± 3.9
Mean Daytime	SBP (mmHg)	135.4 ± 18.8	139.2 ± 18.0
	DBP (mmHg)	75.3 ± 10.9	76.6 ± 11.7
	HR (beats/min)	87.2 ± 9.6	85.5 ± 9.3
	Activity$_{ln}$ (units)	-4.64 ± 0.40	-4.63 ± 0.40
Mean Night-time	SBP (mmHg)	115.8 ± 17.9	132.1 ± 17.1 *
	DBP (mmHg)	64.4 ± 10.3	72.6 ± 10.1 *
	HR (beats/min)	66.1 ± 8.4	65.7 ± 6.4
	Activity$_{ln}$ (units)	-6.33 ± 0.07	-6.30 ± 0.07

Values are presented as average ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. * $P<0.05$ *vs.* dippers.

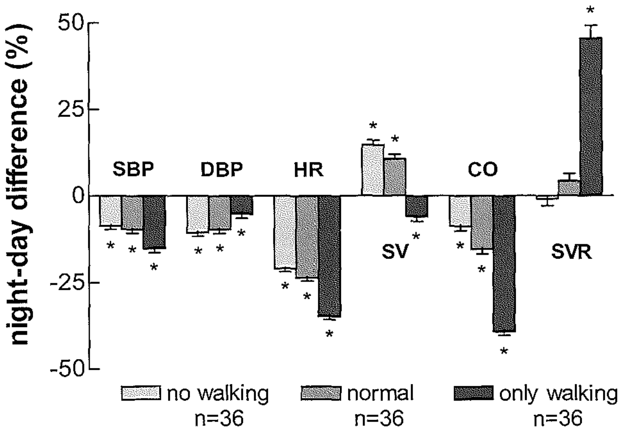
Determinants of diurnal variation of haemodynamics

Physical activity

The day-night changes in HR and CO, but not in SBP, DBP, SV and SVR were correlated with the day-night changes in physical activity (r=0.39 and 0.43, respectively). The correlations that were found were largely attributable to the effect of daytime physical activity, as HR and CO decrease were correlated with daytime (r=0.36 and 0.41, respectively), but not with night-time physical activity. The nocturnal SBP decrease was correlated with night-time physical activity (r =-0.34), but not with daytime physical activity. Non-dippers did not differ from dippers with respect to nocturnal activity decrease, daytime activity or night-time activity.

To further assess the effect of physical activity on diurnal haemodynamic variation and dipping status, daytime was divided into periods during which subjects were walking or not. The walking period compared with the whole daytime period was associated with increased diurnal variation of SBP, HR, CO, and SVR and decreased variation of DBP and SV. Confining daytime to the period during which subjects were not walking, resulted in decreased diurnal variation of SBP, HR, CO and SVR, and increased diurnal variation of DBP and SV (Fig. 3). The changes in diurnal variation were significant in all cases. The proportion of subjects with a nocturnal SBP fall of ≥ 10% of daytime value increased, whereas the proportion of subjects with a nocturnal DBP fall of ≥ 10% of daytime value decreased when the period during which subjects were walking increased (Table 2).

Figure 3



Mean differences between night-time and daytime systemic haemodynamics, expressed as percentage of daytime values. Daytime was based on the whole daytime period (normal), daytime period while walking (only walking), and daytime period while not walking (no walking). Error bars indicate the SEM. * P<0.05 night-time *vs.* daytime.

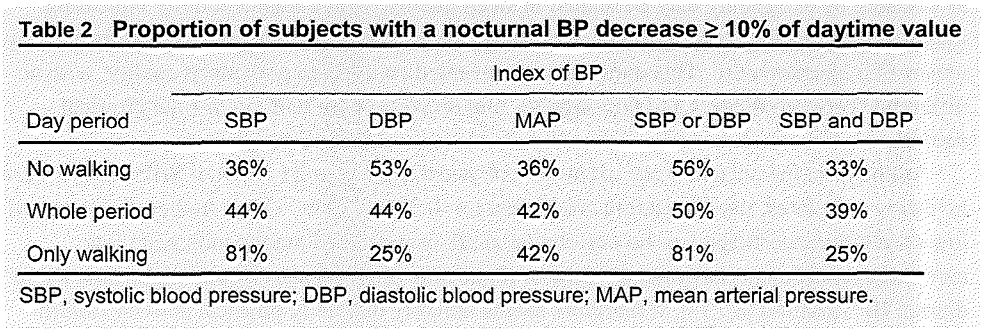


Table 2 Proportion of subjects with a nocturnal BP decrease ≥ 10% of daytime value

	Index of BP				
Day period	SBP	DBP	MAP	SBP or DBP	SBP and DBP
No walking	36%	53%	36%	56%	33%
Whole period	44%	44%	42%	50%	39%
Only walking	81%	25%	42%	81%	25%

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Sleep quality

None of the haemodynamic day-night differences correlated with self-reported sleep quality. Also, sleep quality did not differ between dippers and non-dippers. Sleep quality was also not correlated with night-time physical activity.

Supine body position

BP differences between lying on the back and lying on the side were computed for subjects that spent at least 10% of the night-time period in both positions (n=29). While lying on the back, SBP, DBP and MAP were significantly lower (3.2 mmHg, 4.6 mmHg and 4.0 mmHg, respectively) than while lying on the side. However, the day-night BP differences were not correlated with the percentages of the night-time period that were spent in one of the two supine positions (i.e., lying on the back or on the side). Also, these percentages did not differ between dippers and non-dippers.

Discussion

The main findings of this study are that: 1) the decrease in overall physical activity from day to night is a determinant for the nocturnal decrease in HR and CO, but not for the decrease in BP; 2) the day-night difference in overall physical activity does not differ between dippers and non-dippers, but increased night-time activity is associated with a smaller nocturnal SBP decrease; 3) non-dippers have a similar decrease in CO as dippers, but as opposed to dippers they have a nocturnal increase in SVR; 4) dipping status partly depends on which index of BP is chosen, and 5) the haemodynamic profile underlying the nocturnal decrease in BP may vary considerably depending on the degree of daytime physical activity.

Effects of physical activity on diurnal BP variation and dipping

Various studies have applied wrist or waist actigraphy and non-invasive BP monitoring to assess the effects of diurnal variation of physical activity on the diurnal variation of BP [6-8,12,13]. Most of these studies, like the present study, showed that higher night-time physical activity is associated with a smaller nocturnal BP decline [6-8,12]. Night-time physical activity as assessed by actigraphy may be related to sleep quality, with a higher activity indicating impaired sleep quality [14]. In the present study, sleep quality was subjectively determined by means of a questionnaire. This questionnaire revealed on average poor sleep quality, with no difference between dippers and non-dippers, and no correlation with night-time physical activity.

Although in the present study night-time physical activity and nocturnal SBP decline were inversely correlated, the correlation coefficient ($r=-0.34$) was low. Other studies also reported low correlation coefficients or no correlation at all, or presented graphs indicating low correlation coefficients between daytime or night-time physical activity and night-time BP or diurnal BP variation [6,7,13]. It therefore seems unlikely that daily physical activity *usually* performed during ambulatory BP monitoring by itself is an important determinant of the diurnal BP profile. In fact, in the present study daytime and night-time physical activity did not differ between dippers and non-dippers.

Although physical activity is a determinant of BP, previous studies have shown that between subjects the correlation between normal daily activity and BP is highly variable and on average weak [12,15-17]. In a recently reported study, we found that daytime physical activity was strongly correlated with HR and CO, but weakly with systolic and diastolic BP [9]. This accords with the present finding that the day-night difference in physical activity correlated with the day-night difference in HR and CO, but not with the day-night difference in BP.

With the method presently used to monitor physical activity, we had the opportunity to subdivide the daytime period in periods subjects were either walking or not, and to explore how these different levels of physical activity influence diurnal BP variation and dipping status. The day-night SBP difference increased when daytime was confined to the period during which subjects were walking, and decreased when daytime was confined to the period during which subjects were not walking. As expected, and in agreement with another study using a different experimental approach (i.e., BP recordings during a more and a less active day) [18], this way of analysis revealed that the proportion of subjects with a nocturnal SBP fall of ≥ 10% of daytime value may vary considerably from as low as 36% to as high as 81%. Interestingly, opposite results were obtained if the DBP fall was considered. As reported previously, DBP, contrary to SBP, is non-linearly related to physical activity [9]. When posture changes from lying to sitting and standing, DBP increases and subsequently, when physical activity further increases from standing to general movement and walking, DBP declines. This approach suggests that, besides the magnitude of the nocturnal BP decline, the index of BP selected for dipping classification (systolic, diastolic, mean, or combinations) has to be taken into account as well.

Diurnal profile of systemic haemodynamics

In agreement with a number of other reports, the nocturnal decrease in CO was the principal haemodynamic alteration underlying the nocturnal decrease in BP [19-22]. This nocturnal decrease in CO was caused by a pronounced decrease in HR, whereas SV increased only modestly and to a similar extent in both dippers and non-dippers. Dippers and non-dippers differed, however, with respect to the nocturnal change in SVR. As compared with daytime values, nocturnal vascular resistance did not change in dippers, whereas it increased in non-dippers.

In dippers, the haemodynamic changes in response to daytime supine rest were only quantitatively dissimilar to the changes in response to night-time supine rest: compared with the nocturnal haemodynamic changes, decrements in BP, HR and CO were smaller. Interestingly, the haemodynamic changes in response to daytime supine rest were similar in dippers and non-dippers. These findings suggest that on the basis of haemodyamic responses to daytime supine rest, which on average lasted almost two hours in our study, no simple distinction can be made between dippers and non-dippers.

As far as we know, only one other study compared diurnal haemodynamic profiles in dippers and non-dippers [20]. Contrary to our findings, in that study non-dippers differed from dippers by a smaller nocturnal decrease in cardiac index, which in turn was caused by opposite nocturnal changes in stroke index, with a tendency for an increase in non-dippers and a decrease in dippers. A possible explanation for the difference in diurnal haemodynamic profiles in dippers and non-dippers between our and the cited study, may be differences in physical activity, as discussed later.

Under physiological conditions, a reduction in sympathetic tone is considered to be an important mediator for the nocturnal decline in BP, which is supported by observations that concentrations of catecholamines in either plasma or urine and muscle sympathetic nerve activity are lower during the night than during the day [23-25]. If a decrease in sympathetic tone was causal for the nocturnal decrease in BP in our study population, nocturnal sympathetic tone must have been higher in non-dippers than dippers. As a reflection of this higher sympathetic tone, we would, contrary to our findings, expect a higher nocturnal HR and/or a smaller nocturnal HR decline in non-dippers compared with dippers. Also, overall nocturnal physical activity, which partly and indirectly determines nocturnal sympathetic tone, did not differ between dippers and non-dippers. It remains therefore doubtful whether a more or a less pronounced nocturnal decrease in sympathetic tone was the principal determinant for a dipping or non-dipping BP profile in our study population.

Although studies monitoring diurnal haemodynamics have shown a decrease in CO as the principal alteration underlying the nocturnal decrease in BP, the magnitude of the reported nocturnal decrease in CO varies between different studies [19-22]. For instance, in the study reported by Takakuwa *et al.* [20], performed in hypertensive subjects, CO declined by 17% in dippers and by 11% in non-dippers. In the study reported by Veerman *et al.*, performed in healthy subjects, CO decreased on average by 29% and SVR increased by 22% from day to night [21]. As suggested by our findings (Fig. 3), these differences can partly be explained by differences in daytime physical activity. If, instead of the whole daytime period, only the period was selected during which subjects were walking, the haemodynamic profile underlying the nocturnal BP decrease changed dramatically. An explanation is that in response to walking the increase in MAP is on average small, whereas increments in HR, SV, and hence in CO, and decrements in SVR are considerable [9]. As a consequence, the nocturnal decline in CO is enhanced and SVR, instead of remaining unchanged as compared with daytime values, will markedly increase. These findings have consequences for the correct interpretation of diurnal haemodynamic profiles that underlie diurnal BP profiles. For instance, if during daytime non-dippers are less active than dippers, it may be anticipated that their nocturnal decline in CO is smaller and their nocturnal increase in SVR, as observed in the present study, is similar to the increase observed in active dippers. This lower decline in CO may then be mistaken as related to non-dipping, while the difference in nocturnal SVR between dippers and non-dippers may not be noticed, as it is offset by differences in daytime activity.

We conclude that physical activity, usually performed during ABPM, has a negligible effect on the diurnal BP variation, and therefore is clinically irrelevant. However, for a correct interpretation of diurnal haemodynamic variations underlying the 24-hour BP profiles, and especially for the comparison of these profiles in different populations, information about daytime physical activity, preferentially obtained by objective physical activity monitoring, is mandatory.

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CHAPTER 7

Summary and general discussion

Summary

The aim of the studies presented in this thesis, was to determine the effects of physical activity and posture on various aspects of ambulatory BP recordings. We investigated whether the interpretation of non-invasive ABPM can be improved by simultaneous monitoring of physical activity and posture. Using continuous invasive ABPM, the effects of activity and posture on blood pressure were assessed in greater detail. The main findings of our investigations are summarized in this chapter.

Effect of physical activity and posture on ambulatory BP

Interpretation of ABPM is not as straightforward as is interpretation of office blood pressure measurements, which is related to the fact that one does not know the behavioural conditions during ambulatory measurements, and to what extent these conditions influence blood pressure. As physical activity and posture are considered particularly important determinants of blood pressure variation during normal daily life [1-3], we assessed their effects on non-invasive ABPM **(chapter 2)**. We found that the overall level of physical activity in our study population during the daytime was quite low, i.e., corresponding to sitting or standing with little movement. The average activity level during the 3-min periods preceding BP measurements was lower than the activity level averaged over longer periods (i.e., 9 or 15 min) preceding measurements, reflecting that movement was not allowed while readings were taken. Physical activity computed over the 3-min periods correlated best with the actual BP, but could only explain about 13% of the daytime BP variation.

Between subjects, large variations in the correlation coefficients between physical activity and BP were present, which could not be explained by the between-subject variation in the magnitude of BP response to activity. The systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) responses to activity increased slightly with age, and SBP responses to activity were also slightly higher in overweight than in normal weight subjects. Previous studies, using wrist actigraphy to measure physical activity, reported similar correlation coefficients between activity and blood pressure as presently found [4-6]. This may indicate that wrist or arm movements represent both a peripheral and a total body movement. It may also indicate that arm movements have a relatively large effect on BP, as reported previously [7,8].

The influence of physical activity on BP during everyday life is probably underestimated when BP is measured with the arm-cuff method, as BP is likely to drop in the period between cuff inflation and actual measurement. To test this hypothesis, and to determine the relationship between the effects of posture and activity on BP, we performed continuous monitoring of all variables concerned **(chapter 3)**. Indeed, this study showed that during everyday life BP and activity are more closely related than suggested by discontinuous cuff readings, as about 30% of daytime variation in BP was explained by physical activity. A remarkably high correlation was found for cardiac output (CO), with 74% of its variability being explained by physical activity.

Posture did not significantly influence the relationships of physical activity with SBP and HR. However, the relationships of physical activity with DBP, stroke volume (SV), CO, and systemic vascular resistance (SVR) were influenced by posture. Changing posture from lying to sitting and standing, was associated with an increase of physical activity, and resulted in an increase of DBP and SVR, and a decrease of SV and CO. A further increase of activity, without postural changes, resulted in opposite haemodynamic responses: DBP and SVR decreased, whereas SV and CO increased.

With increasing age, the SBP and DBP responses to activity increased, while, as opposed to the study described in chapter 2, the HR response to activity decreased. Dynamic exercise studies have also shown increased SBP and decreased HR responses to activity with increasing age [9,10], which probably can be explained by loss of elasticity in the large arteries and decreased responsiveness of cardiac ß-adrenoceptors, respectively [11,12]. As opposed to the study described in chapter 2, the HR response to activity was influenced by gender, with females having higher responses than males.

Effect of physical activity and posture on reproducibility of ambulatory BP

It has been suggested that physical activity, posture and quality of sleep can easily vary from one recording session to another, and thereby adversely effect the reproducibility of daytime and night-time BP [13-16]. To test this assumption, we continuously monitored BP, physical activity and posture during 48 hours, and assessed subjective sleep quality **(chapter 4)**.

Daytime BP reproducibility was high compared with most previous studies that used intermittent non-invasive recordings [14,15,17-21]. The reproducibility was hardly improved by correction for physical activity, which most likely is explained by the rather high reproducibility of daytime physical activity itself, and the modest effect of physical activity on daytime BP, as reported in chapter 3. Posture had a small effect on daytime BP reproducibility. Reproducibility tended to be better during standing and walking than during sitting, which may indicate that other factors influencing BP, like mental activity, social interaction and emotional state, have a larger effect on BP during sitting than during standing and walking, as has been reported previously [3].

Night-time BP reproducibility was considerably higher than previously reported [14,15,17-21], and was not improved by correction for physical activity, supine position or self-reported sleep quality. Night-time physical activity was very low, and median levels were the same during both nights in all subjects, which may explain why it did not influence reproducibility of night-time BP. Although Self-reported sleep quality did not reproduce well, correction for this variable did not influence reproducibility of night-time BP.

A factor that may have played a role in the presently reported higher reproducibility of daytime and night-time BP as compared with previous studies is the larger number of values on which the average BP is based. The influence of sampling rate on BP reproducibility has been assessed by Trazzi *et al.* [22]. These authors reported that reproducibility of 24-h intra-arterial BP improved as the number of values on which the mean was calculated increased, but no further improvement of reproducibility was observed for SBP when more than 12, and for DBP when more than 96 values were considered. Therefore, the higher sampling rate is not a likely explanation for the higher BP reproducibility. The high reproducibility of night-time BP in the present study as compared with the reproducibility obtained from intermittent non-invasive recordings is possibly attributable to less disturbance of sleep. In other studies, disturbance of sleep due to cuff inflation has been reported to occur in two-thirds of patients [23]. Polysomnography has showed that cuff inflations during sleep result in arousals, which, depending on sleep stage, may cause an increase in BP [24,25].

Effect of physical activity and body position on diurnal BP variation

Recent evidence from prospective studies indicates that individuals who exhibit a diminished nocturnal decline in BP ('non-dippers') are at higher risk of developing fatal and non-fatal cardiovascular disease than those with a normal nocturnal decline in BP ('dippers') [26-28]. The classification of subjects into dippers and non-dippers has been criticized because of its low reproducibility over time [14,15,29]. Several factors influencing the day-night BP difference may play a role in the poor reproducibility.

Supine body position

If BP is measured with an arm-cuff method, supine body position may cause erroneous nocturnal readings because hydrostatic pressure differences may exist between heart and cuff level [30]. We assessed the effect of supine body position on nocturnal BP readings during ambulatory monitoring with an arm-cuff method, and the influence of this effect on the reproducibility of nocturnal BP readings **(chapter 5)**. On average, 41% of BP readings were taken while subjects were lying supine, 31% while lying on the side with the cuff down and 28% while lying on the side with the cuff up. BP readings in the supine and 'cuff-down' positions were similar, but BP readings in the 'cuff-up' position were about 12 mmHg lower than BPs measured in the supine and cuff-down positions. As a consequence of the cuff-up readings, nocturnal systolic and diastolic BP was underestimated by 3 mmHg and the proportion of non-dippers by 13%. Differences in supine body position between nights did not influence the reproducibility of nocturnal BP or dipping status in our population.

Physical activity and sleep quality

Other factors that may influence the day-night BP difference are physical activity and quality and pattern of sleep [25,31-33]. We assessed the effects of daytime and night-time physical activity and subjective sleep quality on the diurnal variation of BP and systemic haemodynamics **(chapter 6)**. Fifty percent of the subjects were classified as dippers and 50% as non-dippers. Non-dippers had higher night-time BP than dippers, but similar daytime BP. Non-dippers also differed from dippers with respect to diurnal SVR variation; in non-dippers SVR increased, while in dippers it did not change significantly from day to night.

Self-reported sleep quality was not correlated with night-time BP or diurnal BP variation. Larger differences between daytime and night-time physical activity were weakly associated with larger diurnal variations of HR and CO, but not of BP. Higher night-time activity, however, was weakly associated with a smaller diurnal SBP variation. These findings are in agreement with studies that also reported low or non-significant correlation coefficients between daytime or night-time physical activity and diurnal BP variation or night-time BP [31,32,34]. By selection of the active (i.e., walking) and inactive periods (i.e., not walking) during the day, we showed that physical activity has a large potential effect on dipping status and diurnal variation of systemic haemodynamics. As walking increases SBP, but decreases DBP (see chapter 3), active periods as well as inactive periods had opposite effects on diurnal variations of SBP and DBP.

General discussion

Daytime BP variation

Since physical activity and posture can have a large effect on BP, we expected that these factors would be strong determinants of daytime BP variation during normal daily life. However, our results indicate that this is not the case, as only about 13 % of daytime BP variation could be explained by physical activity. The main explanation for this finding is that the intensity of physical activity normally encountered during ABPM is rather low. This may partly be caused by BP monitoring itself. Costa *et al.* [35] reported that physical activity is lower during a day of ABPM using a sphygmomanometer than during a day without BP monitoring, possibly due to reluctance to perform normal activities while wearing the BP monitor. Secondly, as sphygmomanometer devices do not allow movement while readings are taken, the use of these devices will lead to underestimation of the effect of physical activity on BP. With invasive BP recordings, we demonstrated that this indeed is true. However, even during invasive recordings physical activity could only explain 30% of daytime BP variation.

Diurnal BP variation

Because of the low correlation between physical activity and ambulatory BP, daytime physical activity is not likely to be an important determinant of the diurnal BP profile. In fact, in our study, daytime physical activity was not at all significantly related to the diurnal BP profile. Apart from the low levels of activity during daytime, this can be explained by the relative unimportance of daytime BP for the diurnal BP profile. We found that night-time BP, but not daytime BP, was correlated with the diurnal BP variation, and that non-dippers had higher night-time BP than dippers, but similar daytime BP. Higher night-time physical activity was associated, although only weakly, with a smaller nocturnal fall in systolic BP.

We confirmed that the use of an arm-cuff device to measure BP may lead to erroneous nocturnal readings, depending on the body position of the subject. In our study, the average nocturnal BP as well as the number of non-dippers were modestly underestimated due to readings that were taken while subjects were lying on their side with the cuff above heart level.

Reproducibility of BP

Correction for physical activity and posture hardly improved the reproducibility of daytime invasive BP, and did not improve the reproducibility of night-time invasive BP in our study. Again, this indicates that physical activity and posture have only a relatively small effect on BP during everyday life, although it should be noted that the reproducibility of activity was rather high in our study.

The presently performed continuous invasive BP recordings were better reproducible than recordings in other studies, based on intermittent arm-cuff readings. This suggests that the method used to measure BP plays a role in the reproducibility of ABPM.

Haemodynamic variation

As opposed to BP, the haemodynamic variables underlying daytime and diurnal BP variation (i.e., heart rate, stroke volume, cardiac output, and systemic vascular resistance) are greatly influenced by physical activity and posture. We demonstrated that physical activity and posture are the main determinants of daytime variation of heart rate and cardiac output, as 56% and 74% of these respective variations could be explained by these factors. The relationships between physical activity and stroke volume, cardiac output, and vascular resistance were influenced by posture, which is related to pooling of blood in the lower body when posture changes from lying to sitting or standing.

The opposite responses of vascular resistance and cardiac output to postural changes are likely mediated by the baroreceptor reflexes, aiming to maintain BP when cardiac output decreases. The decline in vascular resistance in response to physical activity is explained by a vasodilator response triggered by an increased metabolic demand of the active muscles. In this case, the change in vascular resistance plays a permissive role, allowing cardiac output to increase during physical activity.

As expected, daytime physical activity had a considerably larger effect on the diurnal variation of heart rate, stroke volume, cardiac output, and vascular resistance than on the diurnal variation of BP. Night-time physical activity, however, did not influence the diurnal variation of systemic haemodynamics underlying BP. This suggests that the correlation between night-time physical activity and the nocturnal fall in SBP is not caused by a direct effect of activity, but merely reflects the effect of another factor on nocturnal SBP, possibly diminished sleep quality.

Main conclusions

1. Physical activity is only a weak determinant of daytime BP variation during ABPM.
2. The effect of physical activity on diurnal BP variation during ABPM is not clinically relevant.
3. Variation in supine body position causes errors in arm-cuff BP readings, and thereby influences dipping classification.
4. Physical activity and posture hardly influence reproducibility of ABPM under normal ambulatory conditions.
5. Physical activity has a relatively large effect on the haemodynamic variables underlying BP (i.e., heart rate, stroke volume, cardiac output, and vascular resistance).
6. Posture influences most of the relationships between physical activity and haemodynamics.

Implications for clinical practice and research

- Routine assessment of physical activity to improve interpretation of ABPM, and hence the clinical value of ABPM, is not warranted.
- Monitoring of the vertical distance between the arm-cuff and the right atrium during nocturnal ABPM is essential for reliable dipping classification.
- Activity monitoring is essential for the interpretation of diurnal variation of haemodynamics underlying diurnal BP variation.

Suggestions for future research

One of the most specific advantages of ambulatory BP monitoring over office or home BP readings is the possibility to monitor nocturnal BP. Recent evidence strongly points to nocturnal hypertension, or non-dipping, as an independent risk factor for cardiovascular complications in hypertensive as well as normotensive subjects. Non-dipping remains a poorly understood phenomenon, and much research still needs to be carried out to elucidate the underlying pathophysiologic mechanism, or mechanisms.

The theory that non-dipping simply is caused by physical inactivity during the day is rejected in the present thesis. Two alternative hypotheses for the cause of nocturnal hypertension are: 1) a raised sympathetic tone during the night [36], and 2) an increased renal reabsorption of sodium and water, necessitating a higher BP during the night to drive pressure natriuresis and diuresis [37]. The frequent occurrence of a non-dipping BP profile in patients with renal disease is in keeping with the latter hypothesis [38-40]. Furthermore, some studies have shown a significant relationship between nocturnal BP and nocturnal sodium excretion, or the restoration of a dipping diurnal BP profile in non-dipping hypertensive patients given a low salt diet [37,41]. Besides being related to the high rate of cardiovascular complications in renal disease or diabetes mellitus, nocturnal hypertension may also accelerate the progression of renal disease. Therefore, elucidation of the mechanisms that underlie nocturnal hypertension in these conditions is relevant, not merely from a scientific, but also from a clinical point of view, as it may lead to the development of treatment for nocturnal hypertension in these conditions.

A first step towards insight into nocturnal hypertension, or a non-dipping BP profile, in these conditions would be monitoring of diurnal variation of heart rate, stroke volume, cardiac output, and vascular resistance by means of continuous ambulatory BP monitoring. From these recordings it can be concluded whether the non-dipping BP profile is related predominantly to a relatively high nocturnal vascular resistance or a high nocturnal cardiac output. If vascular resistance is increased, it indicates that vasoconstrictor mechanisms, such as, for instance, an increased sympathetic tone, play a role in the presence of nocturnal hypertension. If, on the other hand, cardiac output is increased, it indicates that volume-dependent factors are involved in the nocturnal hypertension. Determination of plasma and extracellular volume, venous compliance and venous tone, and the response of cardiac output to changes in preload may then further indicate the way in which volume-dependent factors influence the day-night variations in cardiac output.

A different approach to elucidate the mechanisms of nocturnal hypertension, is to investigate the determinant of the minimal BP during the night. It has been suggested that the perfusion of specific centres in the brainstem is the critical determinant for the minimal nocturnal BP [42]. A diminished perfusion of these centres may therefore cause a high nocturnal BP. Whether brain perfusion is involved in nocturnal hypertension, and, if so, via which mechanism, can be investigated by monitoring the diurnal variation of BP and underlying haemodynamics in patients with a high degree stenosis of the common or internal carotid artery, before as well as after correction of the stenosis.

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Samenvatting en algemene discussie

Samenvatting

De ontwikkeling en introductie van automatische ambulante bloeddrukmeters voor klinisch gebruik hebben het mogelijk gemaakt om het 24-uurs bloeddrukprofiel van personen te meten tijdens hun dagelijkse bezigheden. In het algemeen zijn ambulante gemeten waarden representatiever voor iemands bloeddruk dan incidentele metingen tijdens het spreekuur. Zo is in verschillende studies aangetoond dat de gemiddelde 24-uurs ambulant gemeten bloeddruk een betere voorspeller is van hart- en vaatziekten dan enkele spreekuurbloeddrukmetingen [1-3]. Ondanks dit voordeel wordt in de praktijk van alledag nog relatief weinig gebruik gemaakt van ambulante bloeddrukmetingen. Een belangrijke reden hiervoor is dat de ambulant gemeten bloeddruk aanzienlijk kan variëren tijdens de dag, waardoor interpretatie van deze metingen niet altijd eenvoudig is. Er is nog weinig bekend over de oorzaken van deze bloeddrukvariatie, vooral in kwantitatief opzicht. Er zijn echter aanwijzingen dat lichaamshouding en lichamelijke activiteit belangrijke factoren zijn [4-6].

In de studies beschreven in dit proefschrift zijn de effecten van houding en lichamelijke activiteit op de ambulante bloeddruk bestudeerd. Onderzocht is of de interpretatie van niet-invasieve ambulante bloeddrukmetingen verbeterd kan worden door gelijktijdige registratie van lichaamshouding en lichamelijke activiteit. Daarnaast is onderzocht in hoeverre dag-nacht verschillen in houding en activiteit van invloed zijn op dag-nacht verschillen in bloeddruk en in onderliggende hemodynamische parameters, zoals hartminuutvolume en perifere vaatweerstand. Om houding en activiteit betrouwbaar te kunnen meten, is gebruik gemaakt van de Activiteiten Monitor. Dit instrument bestaat uit een combinatie van versnellingssensoren die op de huid zijn bevestigd, een draagbare datarecorder en analyse software. Met deze techniek, die is gevalideerd in eerdere studies, kan lichamelijke activiteit gekwantificeerd worden en kunnen houding (liggen, zitten, staan) en type activiteit (b.v. algemeen bewegen, lopen en fietsen) automatisch herkend worden [7,8]. De belangrijkste bevindingen van onze studies zijn samengevat in dit hoofdstuk.

Effecten van houding en activiteit op ambulante bloeddruk

In de eerste studie is het effect van lichamelijke activiteit op niet-invasieve intermitterende ambulante bloeddrukmetingen onderzocht **(hoofdstuk 2)**. De lichamelijke activiteit overdag was laag in onze onderzoekspopulatie; overeenkomend met zitten, of staan met weinig beweging. De gemiddelde activiteit gedurende de 3 minuten voorafgaand aan iedere bloeddrukmeting was lager dan de gemiddelde activiteit gedurende periodes van 9 en 15 minuten. De meest waarschijnlijke verklaring hiervoor is dat beweging niet was toegestaan tijdens de bloeddrukmetingen omdat dit de meting kan verstoren. Lichamelijke activiteit tijdens de 3-minuten periode voorafgaand aan de bloeddrukmetingen correleerde het best met de actuele bloeddruk, maar kon slechts 13% van de bloeddrukvariatie overdag verklaren.

De mate waarin bloeddrukvariatie verklaard kon worden door variatie in lichamelijke activiteit, verschilde sterk tussen individuen; de bloeddrukresponsen op activiteit vertoonden daarentegen weinig interindividuele variatie. De systolische en diastolische bloeddrukresponsen en de hartfrequentieresponsen op activiteit namen toe, zij het in lichte mate, met het stijgen van de leeftijd. De systolische bloeddrukresponsen op activiteit waren eveneens iets groter voor personen met overgewicht dan voor personen met een normaal gewicht. Eerdere studies, waarin polsactometers werden gebruikt om lichamelijke activiteit te meten, rapporteerden vergelijkbare correlatiecoëfficiënten tussen activiteit en bloeddruk als in onze studie zijn berekend [9-11]. Dit kan erop wijzen dat pols- en/of armbewegingen zowel perifere als totale lichaamsbeweging representeren. Het kan er ook op wijzen dat dergelijke bewegingen een relatief groot effect hebben op bloeddruk, zoals eerder is beschreven [12,13].

De invloed van lichamelijke activiteit op bloeddruk tijdens het dagelijkse leven wordt vermoedelijk onderschat wanneer de bloeddruk met een manchet rondom de bovenarm wordt gemeten, omdat de bloeddruk mogelijk daalt in de periode tussen het oppompen van de manchet en de feitelijke meting. Om deze hypothese te toetsen, en om de relatie te bepalen tussen de effecten van houding en activiteit op bloeddruk, werden de genoemde variabelen continu geregistreerd **(hoofdstuk 3)**. Inderdaad kon worden aangetoond dat tijdens het dagelijkse leven bloeddruk en activiteit sterker gerelateerd zijn dan tot nu toe was vastgesteld op grond van intermitterende manchetmetingen. De continue metingen lieten zien dat ongeveer 30% van de bloeddrukvariatie overdag verklaard kon worden door lichamelijke activiteit. Hartminuutvolume en lichamelijke activiteit waren opmerkelijk sterk gecorreleerd; vierenzeventig procent van de variabiliteit in hartminuutvolume werd verklaard door lichamelijke activiteit.

Houding had geen significante invloed op de relatie tussen lichamelijke activiteit en systolische bloeddruk of hartfrequentie. Echter, de relaties tussen lichamelijke activiteit en diastolische bloeddruk, slagvolume, hartminuutvolume en vaatweerstand werden wel significant beïnvloed door houding. Houdingsveranderingen van liggen naar zitten, en van zitten naar staan, waren geassocieerd met een toename van lichamelijke activiteit en resulteerden in een stijging van diastolische bloeddruk en vaatweerstand en een daling van slagvolume en hartminuutvolume. Verdere toename van activiteit, zonder houdingsverandering, resulteerde in tegenovergestelde hemodynamische effecten: diastolische bloeddruk en vaatweerstand daalden, terwijl slagvolume en hartminuutvolume stegen.

Met het stijgen van de leeftijd namen de systolische en diastolische bloeddrukrespons op activiteit toe, terwijl, in tegenstelling tot de studie beschreven in hoofdstuk 2, de hartfrequentierespons afnam. Deze effecten van leeftijd bevestigen de bevindingen van eerdere studies [14,15], en kunnen hoogstwaarschijnlijk verklaard worden door enerzijds een leeftijdsafhankelijke afname van elasticiteit van de geleidingsarteriën en anderzijds door een leeftijdsafhankelijke verminderde gevoeligheid van de cardiale β-adrenerge receptoren [16,17]. Eveneens in tegenstelling tot de studie beschreven in hoofdstuk 2, werd in de invasieve studie de hartfrequentierespons op activiteit beïnvloed door geslacht, waarbij er een grotere respons werd gezien voor vrouwen dan voor mannen.

Effecten van houding en activiteit op reproduceerbaarheid van ambulante bloeddruk

In verschillende studies is een matige reproduceerbaarheid van ambulante bloeddruk overdag en 's nachts gevonden, waarbij gesuggereerd is dat verschillen in houding, lichamelijke activiteit en slaapkwaliteit hieraan ten grondslag liggen [18-21]. Om hierin meer inzicht te krijgen, werden bij 36 normotensieve en hypertensieve individuen bloeddruk, houding en lichamelijke activiteit continu geregistreerd en werd middels een vragenlijst informatie verkregen over de slaapkwaliteit **(hoofdstuk 4)**. In vergelijking met eerdere onderzoeken, waarbij de bloeddruk intermitterend en niet-invasief werd gemeten, was in onze studie de reproduceerbaarheid van de bloeddruk zowel overdag als 's nachts hoog [19,20,22-26].

Wanneer gecorrigeerd werd voor lichamelijke activiteit, werd de reproduceerbaarheid van de bloeddruk overdag nauwelijks verbeterd. Verklaringen hiervoor zijn enerzijds de redelijk hoge reproduceerbaarheid van de activiteit zelf en anderzijds het relatief kleine effect van activiteit op bloeddruk, zoals beschreven in hoofdstuk 3. Houding had een klein effect op de reproduceerbaarheid van de bloeddruk overdag. De reproduceerbaarheid leek hoger te zijn tijdens staan en lopen dan tijdens zitten, wat er mogelijk op wijst dat andere factoren die van invloed zijn op de bloeddruk, zoals mentale activiteit, sociale interactie en emotionele gesteldheid, een groter effect hebben op de bloeddruk tijdens zitten dan tijdens staan en lopen [6].

In vergelijking met de resultaten van andere studies was in onze studie de reproduceerbaarheid van de nachtelijke bloeddruk opvallend hoog [19,20,22-26]. Correctie voor lichamelijke activiteit, lighouding of subjectieve slaapkwaliteit had geen invloed op deze reproduceerbaarheid. De lichamelijke activiteit 's nachts was extreem laag, met gelijke waarden voor alle personen tijdens beide nachten. De lage lichamelijke activiteit 's nachts verklaart waarom correctie voor activiteit de reproduceerbaarheid van de nachtelijke bloeddruk niet beïnvloedde. De reproduceerbaarheid van subjectieve slaapkwaliteit was laag. Correctie hiervoor had evenmin invloed op de reproduceerbaarheid van de nachtelijke bloeddruk.

Een factor die een rol kan hebben gespeeld bij de hoge reproduceerbaarheid van de dag- en nachtbloeddruk in de huidige studie in vergelijking met eerdere studies, is het grotere aantal waarden waarop de gemiddelde bloeddruk is gebaseerd. De invloed van het aantal metingen op de reproduceerbaarheid van bloeddruk is onderzocht door Trazzi *e.a.* [27]. Deze auteurs rapporteerden dat de reproduceerbaarheid van de 24-uurs intra-arteriële bloeddruk verbeterde met de toename van het aantal waarden waarop het gemiddelde was gebaseerd. Echter, de reproduceerbaarheid van de systolische en diastolische bloeddruk verbeterde niet verder wanneer meer dan respectievelijk 12 en 96 waarden werden gebruikt. Daarom is het hogere aantal bloeddrukwaarden waarschijnlijk niet de verklaring voor de huidige hogere reproduceerbaarheid. De hoge reproduceerbaarheid van de nachtelijke bloeddruk in de huidige studie in vergelijking met studies waarbij bloeddruk intermitterend en non-invasief is gemeten, kan mogelijk worden toegeschreven aan minder verstoring van de slaap. In een eerdere studie is vastgesteld dat de slaap bij tweederde van de patiënten wordt verstoord ten gevolge van het oppompen van de bloeddrukmanchet [28]. Met polysomnografie is bovendien aangetoond dat het oppompen van de manchet resulteert in "arousals" die, afhankelijk van het slaapstadium, een verhoging van de bloeddruk kunnen veroorzaken [29,30].

Effecten van houding en lichamelijke activiteit op dag-nacht variatie van bloeddruk

Recente prospectieve studies hebben aangetoond dat personen met een verminderde nachtelijke bloeddrukdaling ('non-dippers') een hoger risico hebben op het ontwikkelen van hart- en vaatziekten dan personen met een normale nachtelijke bloeddrukdaling ('dippers') [31-33]. De dipping-classificatie is echter bekritiseerd wegens zijn slechte reproduceerbaarheid [19,20,34]. Verschillende factoren die het dag-nacht bloeddrukverschil beïnvloeden, kunnen een rol spelen bij deze lage reproduceerbaarheid.

Lighouding

Indien bloeddruk met een manchet rondom de arm wordt gemeten, kan de lighouding foutieve nachtelijke bloeddrukmetingen veroorzaken doordat een hydrostatisch drukverschil kan bestaan tussen het hart en de manchet [35]. Wij hebben het effect van lighouding op nachtelijke manchetbloeddrukmetingen onderzocht tijdens ambulante registraties. Eveneens is de invloed van dit effect op de reproduceerbaarheid van nachtelijke bloeddrukmetingen onderzocht **(hoofdstuk 5)**. Gemiddeld werden 41% van de bloeddrukmetingen uitgevoerd terwijl personen op hun rug lagen, 31% terwijl zij op hun zij lagen met de bloeddrukmanchet naar beneden en 28% terwijl zij op hun zij lagen met de manchet naar boven. De metingen tijdens liggen op de rug waren vergelijkbaar met die tijdens liggen op de zij met de manchet naar beneden. Echter, de metingen tijdens liggen op de zij met de manchet naar boven waren ongeveer 12 mmHg lager dan de metingen in de andere posities. Als gevolg van deze 'manchet-boven' metingen, werden de nachtelijke systolische en diastolische bloeddruk onderschat met gemiddeld 3 mmHg en het aantal non-dippers met 13%. De reproduceerbaarheid van de nachtelijke bloeddruk en van de dipping-status werden niet beïnvloed door houdingsverschillen tussen nachten.

Lichamelijke activiteit en slaapkwaliteit

Andere factoren die mogelijk het dag-nacht verschil in bloeddruk beïnvloeden, zijn lichamelijke activiteit en kwaliteit en patroon van de slaap [30,36-38]. Wij hebben de effecten onderzocht van lichamelijke activiteit overdag en 's nachts en van subjectieve slaapkwaliteit op het dag-nacht verschil in bloeddruk en op de onderliggende hemodynamische variabelen **(hoofdstuk 6)**. Vijftig procent van de deelnemers werden geclassificeerd als dippers en 50% als non-dippers (nachtelijke systolische en diastolische bloeddrukdaling minder dan 10% van de dagwaarden). Non-dippers hadden een hogere nachtelijke bloeddruk dan dippers, maar de twee groepen hadden overdag een vergelijkbare bloeddruk. De hogere nachtelijke bloeddruk bij non-dippers werd veroorzaakt door een hogere vaatweerstand; bij non-dippers nam de vaatweerstand 's nachts toe, terwijl de vaatweerstand gelijk bleef bij dippers.

Subjectieve slaapkwaliteit was niet gecorreleerd met de nachtelijke bloeddruk of het dag-nacht bloeddrukverschil. Toename van het dag-nacht verschil in activiteit was in lichte mate gerelateerd aan een toename van het dag-nacht verschil in hartfrequentie en hartminuutvolume, maar niet in bloeddruk. Echter, toename van nachtelijk activiteit was wel zwak gerelateerd aan afname van het dag-nacht verschil in systolische bloeddruk. Deze bevindingen zijn in overeenstemming met eerdere studies, die eveneens lage of niet significante correlatiecoëfficiënten lieten zien tussen activiteit overdag of 's nachts en het dag-nacht bloeddrukverschil of de nachtelijke bloeddruk [36,37,39]. Door selectie van de actieve (d.w.z. lopen) en inactieve (d.w.z. niet lopen) perioden tijdens de dag kon worden aangetoond dat lichamelijke activiteit potentieel een groot effect heeft op de dipping-status en op het dag-nacht verschil in hartfrequentie, slagvolume, hartminuutvolume en vaatweerstand. Doordat lopen de systolische bloeddruk verhoogt maar de diastolische bloeddruk verlaagt (zie hoofdstuk 3), hadden zowel de actieve als de inactieve periode een tegengesteld effect op het dag-nacht verschil in systolische en diastolische bloeddruk.

Algemene discussie

Bloeddrukvariatie overdag

Aangezien lichamelijke activiteit en houding een groot effect op bloeddruk kunnen hebben, was onze verwachting dat deze factoren in sterke mate de bloeddrukvariatie overdag zouden bepalen tijdens het dagelijkse leven. Onze resultaten tonen echter aan dat dit niet het geval is, aangezien slechts 13% van de bloeddrukvariatie overdag verklaard kon worden door lichamelijke activiteit. De belangrijkste verklaring voor deze bevinding is dat de lichamelijke activiteit tijdens ambulante bloeddrukregistratie gemiddeld vrij laag is. Wellicht wordt dit deels veroorzaakt door de bloeddrukregistratie zelf. Costa *e.a.* [40] rapporteerden dat lichamelijke activiteit lager is tijdens ambulante bloeddrukregistratie met een armmanchet dan tijdens een normale dag. Blijkbaar worden er tijdens het dragen van de bloeddrukmonitor minder activiteiten ontplooid. Voorts leidt het gebruik van een armmanchet onvermijdelijk tot onderschatting van het effect van lichamelijke activiteit op bloeddruk, aangezien bij deze techniek niet bewogen mag worden tijdens een meting. Met onze invasieve bloeddrukregistraties kon dit inderdaad worden aangetoond, waarbij moet worden aangetekend dat ook met deze metingen niet meer dan 30% van de bloeddrukvariatie overdag verklaard kon worden door lichamelijke activiteit.

Dag-nacht bloeddrukverschil

Gezien de zwakke correlatie tussen lichamelijke activiteit en ambulant gemeten bloeddruk, is het niet waarschijnlijk dat lichamelijke activiteit een belangrijke bepalende factor is voor het dag-nacht bloeddrukprofiel. In onze studie was lichamelijke activiteit overdag zelfs helemaal niet gerelateerd aan het dag-nacht bloeddrukverschil. Naast de gemiddeld lage activiteitsniveaus kan dit worden verklaard door het feit dat de bloeddruk overdag relatief onbelangrijk is voor het dag-nacht bloeddrukverschil. Wij vonden dat de nachtelijke bloeddruk, maar niet de bloeddruk overdag, gecorreleerd was met het dag-nacht bloeddrukverschil en dat non-dippers een hogere nachtelijke bloeddruk hadden dan dippers, maar een vergelijkbare bloeddruk overdag. Hogere lichamelijke activiteit tijdens de nacht was gerelateerd, hoewel slechts zwak, aan een kleiner dag-nacht verschil in systolische bloeddruk.

Wij hebben bevestigd dat gebruik van een bloeddrukmanchet kan leiden tot meetfouten, afhankelijk van de lighouding van de persoon. In onze studie werden zowel de gemiddelde nachtelijke bloeddruk als het aantal non-dippers enigszins onderschat ten gevolge van metingen die plaatsvonden terwijl personen op hun zij lagen met de manchet boven hartniveau.

Reproduceerbaarheid van de bloeddruk

Correcties voor verschillen in houding en lichamelijk activiteit hadden een minimaal gunstig effect op de reproduceerbaarheid van de invasief gemeten dagbloeddruk en geen effect op de reproduceerbaarheid van de nachtbloeddruk. Wederom wijst dit erop dat houding en activiteit slechts in geringe mate de bloeddruk beïnvloeden tijdens gebruikelijke dagelijkse bezigheden, hoewel aangetekend moet worden dat de reproduceerbaarheid van activiteit zelf tamelijk hoog was in onze studie. De reproduceerbaar van de huidige continue invasieve bloeddrukregistraties was beter dan de gerapporteerde reproduceerbaarheid van registraties waarbij bloeddruk intermitterend werd gemeten met een armmanchet. Dit suggereert dat reproduceerbaarheid van ambulante bloeddrukregistraties afhankelijk is van de meetmethode.

Hemodynamische variatie

In tegenstelling tot bloeddruk, worden de hemodynamische variabelen die ten grondslag liggen aan de bloeddruk (hartfrequentie, slagvolume, hartminuutvolume en vaatweerstand) in sterke mate beïnvloed door houding en lichamelijke activiteit. Wij hebben aangetoond dat houding en lichamelijke activiteit de belangrijkste bepalende factoren zijn voor de variatie overdag van hartfrequentie en hartminuutvolume. Niet minder dan 56% van de dagvariatie in hartfrequentie en 74% van de dagvariatie in hartminuutvolume konden verklaard worden door houding en lichamelijke activiteit. De relaties tussen lichamelijke activiteit en slagvolume, hartminuutvolume en vaatweerstand werden in belangrijke mate beïnvloed door lichaamshouding, wat verklaard kan worden door de 'pooling' van bloed in het onderlichaam wanneer de houding verandert van liggen naar zitten, of van zitten naar staan.

Hartminuutvolume en vaatweerstand reageerden tegengesteld op houdingsveranderingen en veranderingen in lichamelijke activiteit. Wanneer, ten gevolge van houdingsveranderingen, het hartminuutvolume daalt, stijgt de vaatweerstand om zodoende de bloeddruk constant te houden. Deze stijging van de vaatweerstand wordt gemedieerd door de baroreflex. De daling van de vaatweerstand bij toenemende lichamelijke activiteit wordt verklaard door vaatverwijding in antwoord op de toegenomen metabole vraag van de actieve spieren. Deze daling van de vaatweerstand is, samen met een toename van de cardiale sympathicustonus, verantwoordelijk voor de stijging van het hartminuutvolume tijdens lichamelijke activiteit.

Zoals verwacht, had lichamelijke activiteit overdag een aanzienlijk groter effect op het dag-nacht verschil in hartfrequentie, slagvolume, hartminuutvolume en vaatweerstand dan op het dag-nacht verschil in bloeddruk. Nachtelijke lichamelijke activiteit had geen invloed op de dag-nacht variatie van de hemodynamische variabelen die ten grondslag liggen aan bloeddruk. Dit suggereert dat de relatie tussen lichamelijke activiteit 's nachts en de nachtelijke systolische bloeddrukdaling niet wordt veroorzaakt door een direct effect van activiteit, maar louter een weerslag is van het effect van een andere factor op de nachtelijke systolische bloeddruk, zoals mogelijk verminderde slaapkwaliteit.

Belangrijkste conclusies

1. Lichamelijke activiteit verklaart slechts een klein deel van de bloeddrukvariatie overdag.
2. Het effect van lichamelijke activiteit op het dag-nacht verschil in bloeddruk is klinisch niet relevant.
3. Variatie in lighouding veroorzaakt foutieve machetbloeddrukmetingen en beïnvloedt daardoor de dipping-classificatie.
4. Houding en lichamelijke activiteit beïnvloeden nauwelijks de reproduceerbaarheid van ambulante bloeddrukmetingen.
5. Lichamelijke activiteit heeft een relatief groot effect op de hemodynamische variabelen die ten grondslag liggen aan bloeddruk (zoals hartfrequentie, slagvolume, hartminuutvolume en vaatweerstand).
6. Lichaamshouding beïnvloedt de meeste relaties tussen lichamelijke activiteit en hemodynamische variabelen.

Implicaties voor de klinische praktijk en wetenschappelijk onderzoek

- Registratie van lichamelijke activiteit is niet nodig tijdens ambulante bloeddrukmetingen, aangezien het de interpretatie ervan niet verbetert.
- Registratie van de verticale afstand tussen de bloeddrukmanchet en het rechter atrium tijdens de nacht is nodig voor een betrouwbare dipping-classificatie.
- Registratie van lichamelijke activiteit is nodig voor de interpretatie van dag-nacht variatie van hemodynamische variabelen die ten grondslag liggen aan de dag-nacht variatie van bloeddruk.

Suggesties voor verder onderzoek

Een van de meest specifieke voordelen van ambulante bloeddrukregistratie boven spreekkamer of thuis-bloeddrukmetingen is de mogelijkheid om de nachtelijke bloeddruk te meten. Recent onderzoek heeft aangetoond dat nachtelijke hypertensie, of non-dipping, een onafhankelijke risicofactor is voor het ontstaan van hart- en vaatziekten, zowel bij individuen met een hoge bloeddruk als bij individuen met een normale bloeddruk [31-33].

Non-dipping is nog steeds een slecht begrepen fenomeen. De theorie dat non-dipping simpelweg wordt veroorzaakt door lichamelijke inactiviteit overdag is verworpen in het huidige proefschrift. Twee alternatieve hypothesen voor de oorzaken van nachtelijke hypertensie zijn: 1) een toegenomen nachtelijke sympathicustonus [41] en 2) een toegenomen renale natrium en water re-absorptie [42]. Het frequente voorkomen van een non-dipping bloeddrukprofiel bij patiënten met nierziekten is een ondersteuning voor deze laatste hypothese [43-45]. Bovendien is er een verband aangetoond tussen de nachtelijke bloeddruk en de nachtelijke renale natriumuitscheiding, en zijn er aanwijzingen dat een non-dipping bloeddrukprofiel kan overgaan naar een dipping bloeddrukprofiel middels natriumbeperking [42,46]. Behalve dat nachtelijke hypertensie of non-dipping een risicofactor is voor hart- en vaatziekten bij patiënten met een verminderde nierfunctie, zijn er aanwijzingen dat deze afwijking de nierfunctieverslechtering kan versnellen. Vanuit klinisch oogpunt is het relevant om de mechanismen die ten grondslag liggen aan nachtelijke hypertensie op te helderen, omdat het kan bijdragen aan het ontwikkelen van strategieën om nachtelijke hypertensie beter te behandelen.

Door middel van continue ambulante bloeddrukregistraties kan worden vastgesteld of een non-dipping bloeddrukprofiel bij bepaalde aandoeningen vooral berust op relatief hoge nachtelijke vaatweerstand of hoog nachtelijk hartminuutvolume. Indien de vaatweerstand verhoogd is, wijst dit erop dat vooral vasoconstrictoire mechanismen, zoals een verhoogde sympathicustonus, een rol spelen bij de nachtelijke hypertensie. Indien vooral het hartminuutvolume 's nachts verhoogd is, is dit een aanwijzing dat vooral volume-afhankelijke factoren een rol spelen bij de nachtelijke hypertensie. Bepaling van plasmavolume en extracellulair volume, veneuze tonus en de respons van het hartminuutvolume op veranderingen van de voorbelasting van het hart, kunnen vervolgens meer inzicht geven in de wijze waarop volume-afhankelijke factoren de dag-nacht veranderingen in hartminuutvolume beïnvloeden.

Een andere benadering om de mechanismen van nachtelijke hypertensie op te helderen, is de factor te onderzoeken die de minimale bloeddruk tijdens de nacht bepaalt. Gesuggereerd is dat perfusie van bepaalde centra in de hersenstam de kritische factor is voor de minimale nachtelijke bloeddruk [47]. Een verminderde perfusie van deze centra kan daardoor een hoge nachtelijke bloeddruk veroorzaken. Of perfusie van de hersenen een rol speelt bij nachtelijke hypertensie, en zo ja, via welk mechanisme, kan onderzocht worden door de dag-nacht variatie in bloeddruk en onderliggende hemodynamische variabelen te registreren bij patiënten met een ernstige vernauwing van de halsslagader, zowel voor als na herstel van de vernauwing.

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Curriculum Vitae
Publicaties

Curriculum Vitae

Marinel Cavelaars werd op 2 oktober 1967 geboren te Leuvenheim, gemeente Brummen. Lager onderwijs genoot zij aan de PiusX school te Didam. In 1986 behaalde zij het VWO diploma aan het Liemers College te Zevenaar. In hetzelfde jaar begon zij de studie gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen. Gedurende een jaar volgde zij aanvullende vakken ergonomisch ontwerpen aan de Technische Universiteit Twente, Faculteit Werktuigbouwkunde. Als afstudeerrichting werd gekozen voor bewegingswetenschappen. De afstudeerprojecten betroffen onderzoek naar reflexmodulatie in de M. Gastrocnemius tijdens het lopen, verricht bij het Laboratorium voor Medische Fysica en Biofysica van de Katholieke Universiteit Nijmegen, en onderzoek naar compensatie-mechanismen tijdens het gaan met een onderbeenprothese, verricht bij Roessingh Research and Development te Enschede. De studie werd in 1993 met succes afgerond. Van 1996 tot 1998 heeft zij wetenschappelijk onderzoek verricht bij de afdelingen Fysiotherapie en Longziekten van het Academisch Ziekenhuis VU Amsterdam naar hemodynamische responsen tijdens inspanning bij patiënten met chronische obstructieve longziekten en eveneens naar de validiteit van impedantiecardiografie tijdens inspanning. In januari 1998 startte zij haar promotie onderzoek naar de invloed van lichaamshouding en lichamelijke activiteit op arteriële bloeddruk tijdens ambulante registraties, bij de afdelingen Inwendige Geneeskunde en Medische Informatica van het huidige Erasmus MC te Rotterdam. Dit proefschrift doet verslag van dit onderzoek.

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