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Diurnal Blood Pressure Variations Are Associated with Changes in Distal–Proximal Skin Temperature Gradient

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It is generally assumed that skin vascular resistance contributes only to a small extent to total peripheral resistance and hence to blood pressure (BP). However, little is known about the impact of skin blood flow (SBF) changes on the diurnal variations of BP under ambulatory conditions. The main aim of the study was to determine whether diurnal patterns of distal SBF are related to mean arterial BP (MAP). Twenty-four-hour ambulatory measurements of BP, heart rate (HR) and distal (mean of hands and feet) as well as proximal (mean of sternum and infraclavicular region) skin temperatures were carried out in 51 patients (men/women = 18/33) during a 2-d eye hospital investigation. The standardized ambulatory protocol allowed measurements with minimal interference from uncontrolled parameters and, hence, some conclusive interpretations. The distal minus proximal skin temperature gradient (DPG) provided a measure for distal SBF. Individual cross-correlation analyses revealed that the diurnal pattern of MAP was nearly a mirror image of DPG and hence of distal SBF. Scheduled lunch and dinner induced an increase in DPG and a decline in MAP, while HR increased. Low daytime DPG (i.e. low distal SBF) levels significantly predicted sleep-induced BP dipping ($r = -.436$, $p = .0014$). Preliminary path analysis suggested that outdoor air temperature and atmospheric pressure may act on MAP via changed distal SBF. Changes in distal SBF may contribute to diurnal variation in MAP, including sleep-induced BP dipping and changes related to food intake. This finding might have an impact on individual cardiovascular risk prediction with respect to diurnal, seasonal and weather variations; however, the underlying mechanisms remain to be discovered.

Keywords: Blood pressure, Diurnal variation, Distal skin blood flow, Heart rate, Skin temperatures

INTRODUCTION

Arterial blood pressure (BP) usually undergoes diurnal variations including a dominant sleep-induced decline by 10–20% from daytime level (Degaute et al., 1991; Hermida et al., 2007; Perez-Lloret et al., 2004; Stergiou et al., 2002). In addition, a smaller daytime trough in the afternoon has been found situated between two maxima occurring in the morning and evening, respectively (Degaute et al., 1991; Hermida et al., 2007; Perez-Lloret et al., 2004; Stergiou et al., 2002). Diurnal variation of BP is influenced by exogenous masking effects such as physical activities, food intake, posture change and largely by sleep; however, an endogenously driven circadian oscillation seems to play an additional role (Scheer et al., 2010; Shea et al., 2011). The diurnal variation in BP may be linked to an increased incidence of many cardiovascular events, including stroke, sudden cardiac death and myocardial infarction (Manfredini et al., 2005; Stergiou et al., 2002). Additionally, changes in diurnal BP variations, either characterized as increased, decreased or inverse day–night difference, are related to the individual's risk of cardiovascular morbidity and mortality. For instance, nocturnal non-dipping (decline in BP <10% of daytime level) is associated with an increased risk of cardiac, kidney and vascular target organ injury, independent of the 24-h mean BP level. All these diurnal phenomena have been associated with important hemodynamic and neuro-hormonal changes, e.g. in blood viscosity, blood volume, heart rate (HR), vascular tone, catecholamines and sympathetic and parasympathetic nervous activity (Birkenhager & van den Meiracker, 2007; Grassi et al., 2010).

A reproducible endogenous circadian pattern has been described for HR even under stringent controlled constant routine resting supine conditions (sleep not allowed; minimum during night phase, peak–trough

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difference: 6 bpm) (Anders et al., 2010; Kerkhof et al. 1998; Kräuchi & Wirz-Justice, 1994; Shea et al., 2011; Van Dongen et al., 2001). Under real-life conditions, the endogenous circadian rhythm in HR is usually reinforced or weakened by the so-called masking effects such as physical activity, relaxation, posture change, food intake, mental stress etc., increasing and decreasing HR.

BP is mainly determined by systemic vascular resistance (VR) and cardiac output. However, under normal life conditions, only BP and HR are measurable without major detraction. In controlled laboratory conditions, the gradient between core body temperature and distal skin temperature (e.g. toe) has been proposed as an indirect measure for systemic VR (Schey et al., 2010). However, it is known that VR of the skin contributes rather little to total VR. Skin temperatures, and assumed also skin blood flow (SBF), are highly variable in normal life conditions and crucially rely on many factors, such as environmental temperature, postural changes, physical activity etc. Nevertheless, reproducible intra-individual patterns have been described (Gompper et al., 2010; van Marken Lichtenbelt et al., 2006; Sarabia et al., 2008). Until now, there is no direct non-invasive measure available for distal SBF under ambulatory real-life conditions. The DPG may provide a reliable, valid and non-invasive measure, which is positively correlated with distal SBF (Akata et al., 2004; Greif et al., 2003; Rubinstein & Sessler, 1990). Low DPG values (i.e. negative values = distal skin temperatures are lower than proximal) indicate low distal SBF and hence centralization of blood. Furthermore, cutaneous blood circulation in distal regions consists of two components: capillary flow (partially nutritional) and arteriovenous shunts (AVA, mostly thermoregulatory) (Hales & Molyneux, 1988; Rowell, 1977). Proximal skin regions are lacking AVA providing therefore an intra-individual reference to distinguish thermoregulatory-induced changes from nutritional blood flow mirrored in changes of DPG. Since the invention of small skin temperature probes with high accuracy and long storage capacity, it has become possible to measure skin temperatures, and hence, indirectly, distal SBF under real-life conditions. Because changes in blood flow within a large, densely vascularized skin area is likely to impact VR, an effect on systemic BP is to be expected from changes in DPG. However, no study addressed the question whether changes in distal SBF, as measured by DPG, could contribute to changes in the daily time course of BP, including sleep-induced BP dipping.

The main aim of the study was to analyze the temporal association between diurnal patterns in BP, HR and skin temperatures, as well as the relationship between amplitudes of these patterns in subjects under ambulatory conditions. It can be expected that subjects with low daytime DPG values markedly drop their BP once this peripheral vasoconstriction is released during sleeping hours. Specifically, the hypothesis that sleep-induced dipping in BP can be predicted from diurnal changes in DPG was tested, i.e. the higher diurnal amplitude in DPG, the larger nocturnal dipping. Additionally, possible environmental influences (e.g. atmospheric pressure, outdoor air temperature) on DPG and MAP were examined using bivariate correlation and multivariate path analyses. In order to minimize variance between different individual daily life routines, a sample of patients was studied under standardized activities including the same schedule of non-invasive eye investigations and meal times during a 2-d stay at the University Eye Hospital of Basel.

METHODS

Population

Participants comprised 51 subjects who stayed at the University Eye Hospital of Basel for a 2-d screening investigation (Table 1). Each subject signed an informed consent form approved by the local ethics committee. All experimental procedures used during the screening investigation were also approved by the local ethics committee (Ethikkommission beider Basel). The sample represents a heterogeneous group with respect to age, BMI, medication and final medical diagnosis, which have to be considered as possible confounding effects on the findings. The participant demographics are outlined in Table 1.

Ambulatory Measurements of Skin Temperatures, BP and HR

Ambulatory 24 h patterns of BP and HR were measured in 30 min intervals using an automated oscillometric BP monitoring system (Mobil-o-Graph®, IEM GmbH, Stolberg, Germany). Wireless temperature sensors (DS 1922L, Thermochron, iButtons®; resolution: .0625°C, accuracy: .5°C; Maxim, Dallas, USA) were used to record skin temperatures continuously in 1 min intervals. The iButtons® were fixed to the skin with thin, air-permeable adhesive surgical tape (Fixomull®; Beiersdorf, Hamburg, Germany) on the left and right side of the body: ankle (inner side, between talus and Achilles'

TABLE 1. Demographic data of the study population

Variable	Mean (SD) or ratios
Gender (men/women):	18/33
Age (y):	57.6 (13.9)
Body mass index (kg/m^2):	25.34 (4.31)
Normal weight/overweight/obese:	27/18/6
Any medication (yes/no):	33/18
Antihypertensiva (yes/no):	21/30
Smoker (yes/no):	4/47
Ophthalmologic diagnosis (NTG/OAG/other):	22/12/17
non-dipper/dipper	20/31

Normal tension glaucoma = NTG; OAG = open-angle glaucoma; non-smoker = 0 cigarettes/d; normal weight: >18 and ≤25 kg/m^2, overweight: >25 and <30 kg/m^2, obese: ≥30 kg/m^2.

tendon above the shoes), wrist (palmar side), infraclavicular region and one temperature sensor on the sternum. "Proximal skin temperature" is defined as averaged skin temperatures of infraclavicular region (mean of left and right) and sternum. The mean skin temperatures of the wrists and ankles constitute the "distal skin temperature".

Protocol and Data Analysis

The study met the ethical standards of the journal (Portaluppi et al., 2010). Study participant entered the University Eye Hospital for eye investigations usually at 10 AM. Skin temperatures, BP and HR were recorded during a 2-d ambulatory protocol under structured daytime conditions including three timed meals (breakfast 07:30–08:00 h; lunch 11:30–12:15 h; dinner 17:30–18:15 h) and scheduled eye investigations, mostly in sitting body position and walks between different laboratory rooms. Participants could freely choose their bedtime; however, all were awakened at 07:00 h. Such a structured daily schedule allowed cardiovascular and thermophysiological measurements to be obtained without much external interference, e.g. sports. Skin temperature probes were mounted in the afternoon of the first day and the equipment for cardiovascular measures (BP and HR) was installed at 10 h in the morning of the second day. Data sets of the last 24 h were used for statistical analyses. All subjects finished the two screening days without any complaints.

Outdoor Air Temperature and Atmospheric Pressure

The study was carried out over 1 yr, therefore environmental conditions, such as outdoor air temperature and atmospheric pressure, varied within the sample. This circumstance could be used to get information whether these variables co-varied with skin temperatures, HR and BP. The daily profiles of the meteorological data were provided by the Institute of Meteorology (University of Basel).

Statistical Analyses

Time courses were statistically tested by analyses of variance for repeated measures (rANOVA) using Greenhouse–Geisser's correction. Following rANOVA, all *p*-values were based on Greenhouse–Geisser-corrected degrees of freedom (reported are original degrees of freedom). Post-hoc analyses used Tukey's test to compare means between pairs. Intra-individual phase relationships between skin temperatures and mean arterial BP (MAP) were determined by cross-correlation analyses, using 24 h time series of 48×30 min data (skin temperature data binned in 30 min) (Kräuchi et al., 2006). Mean cross-correlation curves were plotted after Fisher *z*-transformation of *r*-values, which were retransformed. The relation between two variables was statistically tested by least-squares regression analysis. In order to test how BP and DPG could be related to air temperature and atmospheric pressure, path analysis with an a priori formulated model structure was performed. The critical alpha-level of statistical significance was set at $p = .05$. Group data are expressed as mean ± SEM. ANOVA were performed using Statistica™ 6 software package (StatSoft, Tulsa, OK, USA) and cross-correlations by R version 2.12.0 using the function ccf() in package "stats". Path analysis was carried out using Mplus Version 5.2 (Muthén & Muthén, 2007). To adjust for the non-normal distributions of some variables, path models were estimated by using the robust maximum likelihood estimator.

RESULTS

In a first analysis, we tested the prerequisite of internal consistency within the variables, distal and proximal skin temperatures' by calculation of individual correlations between wrist vs. ankle skin temperatures and infraclavicular vs. sternum skin temperatures [($p < .0001$), $N = 1440$ 1-min measures/subject, $N = 51$ subjects, median *r*-values: .72 (.19, IQR) and .70 (.24, IQR), respectively]. Additionally, no significant differences between right and left sided probes were found (1440 1-min measures/subject, one-sample sign test, hypothesized difference = 0). These findings demonstrate good internal consistency within the pooled skin regions.

Diurnal Phase Relationships

The diurnal pattern of DPG exhibited maximal values during the sleep phase and lowest values during the wake phase (Figure 1, top panel; Table 2a). During the wake phase, a bimodal pattern of DPG occurred with a peak in the early afternoon and two troughs in the morning and late afternoon, respectively. The diurnal pattern of MAP showed nearly a mirror image of DPG, including the bimodal daytime pattern (Figure 1, middle panel; Table 2a). This was statistically verified by individual cross-correlation analyses showing an overall cross-correlogram with a minimum at lag 0, or in other words, the 24 h patterns are inversely in phase (Figure 2, black dots). The diurnal pattern of HR exhibits a distinct three-modal pattern including a minimum during the sleep phase and two minor minima during the wake phase at 11 and 15 h (Figure 1, bottom panel; Table 2a). Three peaks are found during the wake phase, with a major peak early in the morning, a second peak around noon and a third peak late in the afternoon. Cross-correlation analyses of the 24 h patterns between HR and DPG revealed a minimum at lag –15 min, indicating a slightly delayed and inverse time course of DPG by 15 min with respect to HR (Figure 2, open dots).

Diurnal Variations and Sleep-induced Dipping

The relationship between MAP and DPG was additionally tested with respect to amplitude of their 24 h patterns by regression analyses. Data between 10 and 17 h were selected and averaged for the time segment "daytime". During this time segment, daily activities were most stringently controlled (e.g. eye investigations). Data between 24 and 7 h were averaged for "sleep" values and the

differences between "daytime" and "sleep" values (=Δd-s) were taken as a measure of diurnal amplitude. Mean ± SD of "daytime', "sleep' and Δd-s -values are shown in Table 3. All parameters excluding atmospheric pressure exhibited significant differences between "daytime" and "sleep" values. Furthermore, Δd-s of DPG correlated significantly with sleep-induced MAP dipping expressed as Δd-s in % from "daytime' MAP (%Dipp; data pairs of 51 subjects; $r = -.362$, $p < .009$). "Daytime" DPG values (d-DPG) correlated highly with Δd-s of DPG ($r = .830$, $p < .0001$), demonstrating that d-DPG alone can be used as a measure of diurnal amplitude of DPG. In fact, linear regression analysis showed that d-DPG correlated significantly with %Dipp ($r = -.436$, $p < .0014$; Figure 3, Table 4). "Sleep" DPG values did not correlate with % Dipp ($r = -.149$, n.s.), indicating that specifically d-DPG can be used as a predictor for the following sleep-induced MAP dipping.

In order to analyze in detail physiological changes during daytime, effects of the two major meals (lunch and dinner) on HR, MAP and DPG were calculated with respect to pre-meal value at –30 min (dense scores; Figure 4, Table 2b). Both meals induced similar effects with a rapid increase in HR (significant increase 30min after starting the meals) followed by an increase in DPG (i.e. less negative DPG values and increase in distal SBF) and a decline in MAP (significant increase 60 min after starting the meals). Taken together, the response

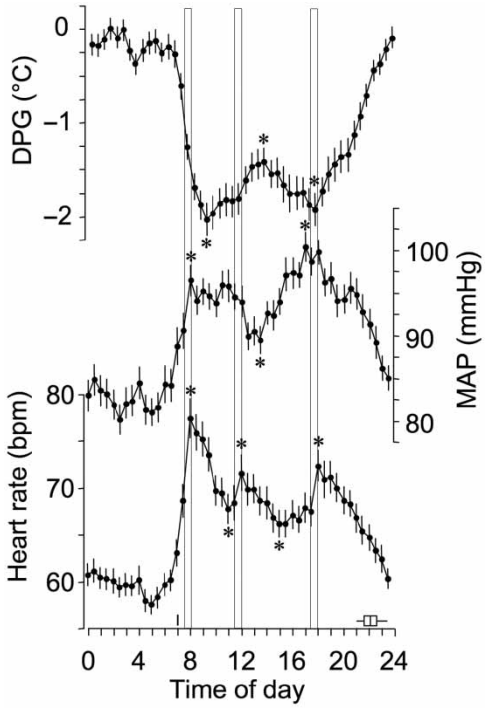

FIGURE 1. Time course of ambulatory measured data (mean ± SEM, $N = 51$ subjects) of DPG (top panel, 30 min bins), MAP (middle panel, 30 min intervals) and HR (lower panel, 30 min intervals). Vertical open columns indicate meal times (breakfast, lunch, dinner). The vertical line above time axis indicates rising time and the horizontal box plot (10%, 25%, median, 75%, 90% percentiles) marks bedtime. Asterisk indicates a significant difference ($p < .05$) between peak to the nearest trough and vice versa. Note: DPG and hence distal SBF exhibit an inverse time course to MAP.

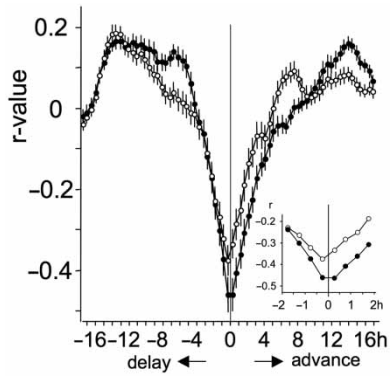

FIGURE 2. Cross-correlation curves (mean ± SEM after Fisher's z-transformation, retransformed values are plotted; $N = 51$ subjects) calculated between DPG and MAP (black dots; DPG is lagged with respect to MAP) and between DPG and HR (open dots; DPG is lagged with respect to HR) over the entire 24 h pattern. In the insert, mean cross-correlation curves are shown between time lag –2 h and +2 h. Note: DPG exhibits an inverse time course to MAP, both are in phase (maximal negative lag at lag 0); however, DPG exhibits a slight phase delay with respect to HR (maximal negative lag at lag –15 min).

TABLE 2. ANOVA tables ($N = 51$ subjects)

	Time	
Variable	$F(47,2350)$	p
(a) Diurnal 24 h patterns (Figure 1)		
HR (beats per minute)	24.8	.0001
MAP (mmHg)	28.2	.0001
DPG (°C)	40.9	.0001

(b) Effects of lunch and dinner (Figure 3)

Variable	Meal		Time		Meal × time	
	$F(1,50)$	p	$F(5,250)$	p	$F(5,250)$	p
HR	.13	.73	5.21	.0001	.34	.89
MAP	.15	.70	14.1	.0001	.47	.80
DPG	.09	.76	13.8	.0001	.26	.93

TABLE 3. Comparisons of mean "daytime" and "sleep" phase values ($N = 51$ subjects)

Variable	Daytime (d), mean (SD)	Sleep (s), mean (SD)	Δd-s, mean (SD)	ANOVA, $F(1,50)$, p
HR (beats per minute)	68.3 (9.0)	59.7 (6.6)	8.7 (6.1)	102.4, <.0001
MAP (mmHg)	93.9 (9.1)	82.8 (10.4)	11.2 (6.7)	140.8, <.0001
DPG (°C)	−1.66 (1.01)	−.17 (.58)	−1.49 (.98)	118.1, <.0001
Outdoor air temperature (°C)	15.5 (7.6)	12.2 (6.7)	3.3 (2.0)	142.7, <.0001
Atmospheric pressure (mmHg)	983.0 (6.7)	983.0 (6.9)	0 (2.6)	.02, n.s.

profile of HR after food intake clearly differs to that of sleep induction; however, that of MAP and DPG was similarly inverted.

Correlation Analyses and Path Analysis

Inspection of the correlation matrix (Table 4) revealed significant negative correlations of daytime atmospheric pressure (d-AP) with daytime MAP (d-MAP) and d-DPG, and tendentially of daytime outdoor air temperature (d-OT) with d-DPG values ($p < .1$). d-MAP correlated with BMI and d-AP, but not significantly with d-DPG or age. The outcomes of these bivariate analyses were more or less confirmed in a multivariate data analysis. To test how the environmental and physiological variables could combine together, a path model was formulated with %Dipp as a purely endogenous variable (indicated as squares in Figure 5), d-DPG and d-MAP as partially endogenous variables and BMI, d-OT and d-AP as purely exogenous variables (indicated as circles in Figure 5). This model structure was based on hypothesized (e.g. %Dipp is dependent on d-DPG) or well-known and accepted relationships (e.g. higher BMI is associated with higher MAP; skin cooling reduces skin temperatures and increases MAP). The chi-square test statistic of this path model ($\chi^2 = 4.820$, df = 5, $p = .4382$) clearly did not reach significance, which is a desirable result indicating that the model fits the data well. A further indication for a good model fit represent the four different fit indices, CFI (=1.000), TLI (=1.015), RMSEA (=.000) and SRMR (.067). As expected, a significant direct path leads from d-DPG to %Dipp. Additionally, there are significant indirect paths from d-AP (−.155, $p = .014$) and d-OT −.133, $p = .019$) via d-DPG to %Dipp. No significant direct paths from d-MAP, d-OT, d-AP or BMI to %Dipp were found underlining the selectivity of the relationship between d-DPG and %Dipp. This finding indicates that d-DPG seems to be the crucial factor which has to be modulated to influence %Dipp. Furthermore, outcomes of the model revealed d-MAP as a purely endogenous variable receiving significant direct inputs from BMI, d-DPG and d-AP. Additionally, D-AP (.133, $p = .038$), and to a weaker extent d-OT (−.114, $p = .054$), show indirect paths to d-MAP via d-DPG. Here again, d-DPG seems to be a crucial factor that influences d-MAP. Despite these interesting findings, important limitations have to be mentioned. The

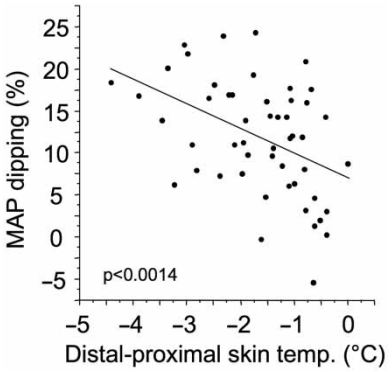

FIGURE 3. Inter-individual ($N = 51$ subjects) correlation between sleep -induced dipping of MAP [difference between daytime (13 – 17 h) and sleep phase (24 – 07 h) values expressed as % of daytime value] and daytime values of DPG. Note: Lower d-DPG values and hence lower daytime distal SBF is associated with higher sleep-induced dipping of MAP.

TABLE 4. Bivariate correlation matrix

	d-HR	d-MAP	d-DPG	d-OT	d-AP	%Dipp	Age	BMI
Daytime HR (d-HR)	1							
d-MAP	−.117	1						
d-DPG	−.143	−.223	1					
d-OT	−.020	−.123	.238 $^+$	1				
d-AP	.081	−.313*	−.298*	.190	1			
%MAP dipping (%Dipp)	.270 $^+$	.032	−.436*	.035	.256$^+$	1		
Age	−.183	.249$^+$	.203	.212	−.167	−0.168	1	
BMI	−.324*	.284*	.113	−.135	−0.051	−.125	.227	1

Values are Pearson's correlation coefficients (r) of $N = 51$ subjects.
$^+p < .1$
$^*p < .05$

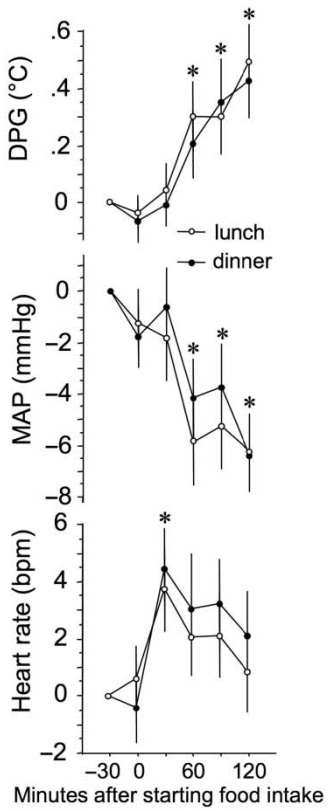

FIGURE 4. Effects of meals on DPG (30 min data bins; e.g. averaged DPG values within time segment −15 to +15 min is plotted at 0 min), MAP (recorded in 30 min intervals) and HR (recorded in 30 min intervals) for lunch and dinner (mean ± SEM, $N = 51$ subjects). Data are adjusted to pre-meal values (−30 min). Asterisk indicates a significant difference ($p < .05$) to time 0. Note: An increase in DPG indicates an increase in distal SBF. Changes in HR occur first followed by DPG and MAP which exhibit an inverse time course (no differences between lunch and dinner in all variables).

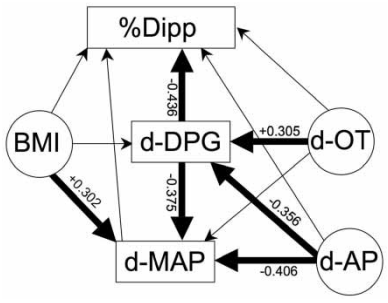

FIGURE 5. Path diagram showing the relation between d-OT, d-AP, d-MAP, d-DPG, body mass index (BMI) and % sleep-induced MAP dipping (%Dipp). Daytime: mean values between 10 and 17 h. Significant paths ($p < .05$, indicated by thick arrows) are shown with standardized path coefficients beside the path arrows (thin lines represent non-significant paths). Note: d-DPG appears as the only variable for relaying environmental influences to %Dipp.

analyzed sample size ($N = 51$) is rather small (low power) in relation to the number of tested variables; thus, the suggested model has to be regarded with caution (see Discussion).

DISCUSSION

The time course of DPG (Figure 1), but also those of distal and proximal skin temperatures (data not shown), resembles the outcome of our previous study in young women (Gompper et al., 2010). A key finding of the present study is that the diurnal pattern of MAP is nearly mirror-imaged to DPG and hence distal SBF. This inverse relationship has been examined by cross-correlation analyses of the entire 24 h patterns of MAP with DPG and by correlation of their diurnal amplitudes. Furthermore, detailed analysis of the patterns of MAP and DPG during daytime revealed also an inverse time course, e.g. food intake increases DPG and declines MAP. How can these changes in MAP and DPG induced by different behaviors (sleep, food intake) be explained?

Diurnal Phase Relationships

Cross-correlation analyses revealed an inverse 24 h pattern of MAP and DPG with maximal negative correlation value at lag 0 (Figure 2). The inverse temporal relationship between these variables is in line with Darcy's law. According to this law, it can be concluded that when two of its compartments are changed the third must also be changed, i.e. when MAP is reduced and DPG increased during sleep distal skin VR is also reduced. Further, the inverse temporal relationship between these variables may suggest a contribution of distal SBF to the regulation of diurnal MAP variation, or vice versa; however, the causality remains to be clarified in future studies (see Limitations). The temporal association between HR and DPG was slightly different showing a maximal phase delay of DPG by 15 min with respect to HR. Under very controlled laboratory conditions, similar temporal associations between these variables have been found, however, with larger time lag (Kräuchi & Wirz-Justice, 2001; Kräuchi et al., 2000, 2006). This phase relationship can be explained by increased HR and cardiac output to supply higher blood flow to the inner organs where oxygen consumption rate and heat production are enhanced during the circadian day (Kräuchi & Wirz-Justice, 1994). The circadian rhythm in heat loss is phase delayed in relation to heat production, and core body temperature is placed in between the lag arises because transport of heat takes time (Aschoff et al., 1974; Kräuchi et al., 2000). Therefore, the slightly different temporal relationships between changes in HR and DPG found in this study could be explained from a thermophysiological point of view.

Diurnal Variations and Sleep-induced Dipping

Our data provide insight to the day-to-night changes in BP. It has been described that sleep at any circadian phase induces vasodilatation mainly in distal skin regions, but also, to a lesser extent, in proximal skin regions (Kräuchi et al., 1999, 2004, 2006; Schey et al., 2010). This leads to a DPG value of ±0°C, a level where both distal and proximal skin temperatures are similar

(Kräuchi et al., 1999, 2004, 2006; Gompper et al., 2010; Schey et al., 2010). Sleep initiation is also associated with an increase in forearm and leg SBF measured by plethysmography under supine lab conditions – in addition, a significant decrease in MAP and HR occurs (Casiglia et al., 1996). Similar to the decline in BP (Baumgart, 1991; Manfredini et al., 2005), the sleep-induced cutaneous vasodilatation take place at all circadian phases (Kräuchi et al., 2006), whereby the autonomic nervous system activity seems to be crucial for both skin vasodilatation and reduction in BP.

The skin sympathetic nervous system activity (SSNA) seems to play a crucial role in blood flow regulation in the skin, and the muscle sympathetic nervous activity (MSNA) in muscles (Mano et al., 2006; Wallin & Charkoudian, 2007). During sleep, burst properties of SSNA resemble those of MSNA and both are suppressed during non-REM sleep (Somers & Grassi, 2003; Takeuchi et al., 1994; Wallin & Charkoudian, 2007). However, the relationship between SSNA and MSNA is rather complex and still not fully understood (Bernjak et al., 2012; Kodama et al., 1998). During wake state, it is well known that cutaneous microcirculation is mainly controlled by SSNA triggered by thermal and non-thermal stimuli, such as deep inspiratory gasps, pain and mental or emotional stressors (Kistler et al., 1998). In contrast to MSNA, SSNA is independent of baroreceptor and chemoreceptor-reflex activity (Mano et al., 2006; Wallin & Charkoudian, 2007). This suggests that the skin, primarily distal sites, may serve as an ideal reservoir for redistributed blood from the core to the shell in warm environmental conditions without baroreflex-induced feedback changes in skin vascular tone. In contrary, thermoregulatory vasoconstriction in distal skin regions is the primary defense against cold environmental temperature, which is mainly mediated by increased SSNA (Grassi et al., 2003; Wallin & Charkoudian, 2007). Besides the reflex thermoregulatory control (via thermal afferents and sympathetic efferents), direct effects of warming and cooling on the level of SBF play an additional role (e.g. via nitric oxide system, postsynaptic alpha-2c-adrenoceptors changes) (Johnson & Kellogg, 2010). In any case, cold application to the skin can lead to centralization of blood and increased BP (Hess et al., 2009; Kregel et al., 1992). Further studies have to clarify whether these mechanisms causally contribute to the reported increase in BP and the worsened cardiovascular risk in the winter (Abrignani et al., 2009; Alperovitch et al., 2009; Barnett et al., 2007; Hayashi et al., 2008) (see also discussion below).

How are the diurnal changes in distal SBF related to sleep-induced dipping in MAP? This study revealed that lower d-DPG levels are significantly associated with larger sleep-induced MAP dipping, confirming our initial suggestion that high diurnal amplitudes in DPG predict larger MAP dipping during sleep. Our sample was collected throughout a year leading to different environmental conditions. In a further analysis, we could show that, in fact, outdoor temperature significantly affected d-DPG, and hence %Dipp (see below). In subjects who started distal vasodilatation in the evening from a lower d-DPG level exhibited a larger %Dipp, whereas sleep phase values were indistinguishable in all subjects. This led to an overall greater vasodilatation from day to night levels in subjects with a larger sleep-induced decline in MAP. Reduced d-DPG levels indicate a stronger centralization of blood (e.g. to the splanchnic region) than in non-dippers and during sleep core blood is redistributed mainly to the distal skin regions (Kräuchi & Wirz-Justice, 2001; Kräuchi et al., 2004). Given that the SSNA is essential for the distal vasoconstrictory level, our findings support the concept that withdrawal of sympathetic traffic to the skin blood vessels may play a crucial role in mediating sleep-induced dipping (Narkiewicz et al., 2002; Sherwood et al., 2002). A similar interpretation has been reported in a study showing that increased digital vasoconstriction before induction of anesthesia leads to a greater fall in BP after induction (Sakai & Sumikawa, 2009). Since DPG can be considered as a measure of distal SBF (Rubinstein & Sessler, 1990), and indirectly of distal SSNA (Kistler et al., 1998), the diurnal pattern in MAP may be primarily caused by diurnal changes in SSNA, and hence by changes in distal skin VR. Diverse studies have demonstrated that disturbed sleep and increased activity during sleep (e.g. measured by wrist activity devices) are associated with increased BP during that phase and reduced BP dipping (Agarwal, 2010; Mansoor et al., 2000). However, these findings could not be confirmed in our sample; HR during sleep was neither associated with MAP during sleep ($r = .009$, n.s.) nor with %Dipp ($r = .041$, n.s.). Taken together, sleep-induced dipping can be understood as an amplitude measure of the overt diurnal MAP rhythm, which may be linked directly to the diurnal amplitude of SSNA and distal vasoconstriction, which remains to be demonstrated by direct measurements of SSNA.

A second line of evidence for a close relationship between MAP and DPG concerns the inverse daytime patterns. The time courses of MAP, HR and DPG showed typical changes during daytime, which can be explained by the structured daytime behaviors. Directly around awakening MAP and HR increased, while DPG declined. Since breakfast was scheduled 30 min after standing up from supine posture, effects of these changes are temporally overlapped and cannot be separated. However, in spite of the fact that daytime activities were not optimally controlled (e.g. no baseline condition including days with no meal; constant posture), physiological changes occurring with lunch and dinner can plausibly be explained by the structured daytime activities, i.e. scheduled meals and ocular investigations. It is well known that diet-induced thermogenesis increases oxygen consumption, HR and core body temperature, followed by an increase in thermoregulatory heat loss mainly via distal skin regions (Ahuja et al., 2009; Roth & Sheard, 1950). This pattern has been found for both lunch and dinner. Interestingly, DPG followed the rise in HR, whereas the rise in DPG was exactly in phase

with a fall in MAP, a finding similar to the temporal relationship between their 24 h patterns (Figure 2). A comparable "post-prandial dipping" pattern has been described mainly in older individuals (Stergiou et al., 2002; Van Orshoven et al., 2010), which corresponds to the average age range of our study sample.

Relationship to Outdoor Air Temperature and Atmospheric Pressure

Multivariate (path analysis; summarized in Figure 5) and bivariate data analysis (Table 4) revealed d-DPG as a central variable to affect %Dipp and d-MAP. In addition to the often found association between increased BMI and elevated d-MAP (Table 4 and thick arrows in Figure 5), the other two tested exogenous variables d-OT and d-AP relayed their effects on %Dipp and d-MAP via d-DPG, as indicated by significant indirect paths (thick arrows in Figure 5). This confirms, at least partially, previous studies showing increased %Dipp (Murakami et al., 2011) and increased d-MAP on cool days in comparison to warm days (Abrignani et al., 2009; Alperovitch et al., 2009; Barnett et al., 2007; Hanna, 1999). It has also been found that decreased outdoor and indoor temperatures may independently elevate BP (Barnett et al., 2007). During the study days, our subjects mostly stayed inside, they only went outside for a few minutes. In a previous study carried out over 1 yr, we have shown that indoor temperatures in the eye hospital (no air conditioning) are significantly correlated with outdoor temperature ($r = .682$, $p < .0001$, $N = 257$) (Kräuchi et al., 2008). However, individual measurements of environmental temperature directly outside the subject's clothes are needed to improve understanding the described associations. Based on the finding that %Dipp was significantly correlated with sleep MAP values ($r = -.607$, $p < .0001$), but not with d-MAP ($r = .032$, n.s.; Table 4 and thin arrows in Figure 5), we support the notion that dipping patterns mainly depend on the nocturnal decline in BP (Birkenhager & van den Meiracker, 2007; Dolan et al., 2005; Modesti et al., 2006; de la Sierra et al., 2009). There are many studies showing higher BP values and increased cardiovascular-related mortality in the cold winter months, particularly in older adults (Abrignani et al., 2009; Alperovitch et al., 2009; Barnett et al., 2007). It has been suggested that a major component of seasonal change in BP, and hence VR is due to temperature changes (Alperovitch et al., 2009; Hanna, 1999). Associations between increased cardiovascular-related mortality and cold temperatures may be mediated, in part, by acute physiological responses to cold, which include elevated plasma norepinephrine, blood viscosity, peripheral and visceral vasoconstriction, elevated BP and diuresis (see discussion above; Keatinge et al., 1984; Wilson et al., 2007) (discussion concerning sympathetic nervous activity see above). Recently, an augmented increase in BP has been reported during mild cold exposure in elderly subjects (Hess et al., 2009). In our sample, however, no significant age effects were found (Table 4).

In contrast to these often-described influences of environmental temperature on BP and cardiovascular events, an association with atmospheric pressure is less consistently reported (Hanna, 1999; Jehn et al., 2002; Jimenez-Conde et al., 2008; McArthur et al., 2010; Murakami et al., 2011). Similar to an older study, carried out in the same city as the present study (Weinbacher et al., 1996), we could demonstrate a negative correlation between atmospheric pressure and BP ($r = -.323$, $p < .05$ and thick arrows in Figure 5). The physiological mechanisms to explain the relationship between atmospheric pressure and cardiovascular events are still not fully understood (McArthur et al., 2010). It has been suggested that changes in atmospheric pressure lead to changes in pressure across blood vessels and, thus, predispose to rupture and bleeding complications. Variations in AP may exert an influence on vessel walls and their endothelial function by endogenous inflammatory mechanisms (Jimenez-Conde et al., 2008). Further evaluations are therefore needed to better understand the relationship between atmospheric pressure and BP.

Limitations

Some limitations should be considered. The present study was not designed to clarify the mechanisms responsible for diurnal BP variations. Nevertheless, it could be shown that these variations significantly co-vary in an inverse manner to DPG, which is the first step to illustrate potential causal effects. Thus, further studies are needed to investigate whether the influence of food intake in fact reduces MAP by increasing DPG, or whether artificial environmental cooling in the afternoon/evening, and hence declining DPG, can enhance sleep-induced dipping. To better understand the underlying mechanisms, additional direct measurements are necessary of SSNA and MSNA (Grassi, 2009; Grassi et al., 2010) in response to diverse specific stimuli such as passive cooling and warming. Furthermore, we also cannot rule out the possibility that a different composition of the study sample (with respect to, for example, age, gender, medication) could reveal different temporal association between DPG and MAP. However, the heterogeneity of the present patient group bears the statistical advantage of increased inter-subject variability of the variables, which in turn increases the chance to find a potential association between them. In spite of the convincing findings of the path analysis, the relatively low number of study subjects represents a further limitation of the present study, which hinders conclusive interpretations; they need further validation in prospective studies with larger sample sizes.

CONCLUSION

Reduced sleep-induced decline in BP, the so-called "non-dipping' BP pattern, is regarded as a risk for

cardiovascular events and target organ damage. However, the pathophysiological mechanism(s) of a non-dipping pattern is still not fully understood but might involve abnormalities in VR regulation. Until now, no devices are available to record information about VR under ambulatory conditions. Skin temperature measurements by calculating DPG may serve a simple tool to collect a valid and non-invasive measure of distal SBF in addition to conventional ambulatory BP monitoring. Thus, the two measures in conjunction permit interpretation of distal skin VR, which is usually not available from convention ambulatory BP measurements. The present study provides evidence that the diurnal pattern of DPG exhibits an inverse temporal relationship to MAP, which provides evidence that not only MAP and distal SBF undergo diurnal variations but also distal skin VR. The standardized ambulatory study protocol allows interpretations about thermophysiological and cardiovascular effects of diurnal activities. For example, daytime food intake and warm "outdoor temperature" were associated with increased DPG and hence distal SBF and reduced MAP. Interestingly and of potential clinical relevance could be the finding that increased sleep-induced dipping in MAP can be predicted from reduced daytime level of DPG (i.e. reduced distal SBF). It is in line with the notion that changes in distal skin VR and distal SBF may contribute to the diurnal modulation of MAP. Our study does not address directly any causal nature of the associations we describe. However, these findings suggest how environmental changes may influence the diurnal BP profile including sleep induced dipping, namely via changes in distal skin VR and distal SBF. They further suggest that the assessment of diurnal pattern of DPG, in addition to the conventional ambulatory BP monitoring, might have an impact on improved individual cardiovascular risk prediction with respect to diurnal, environmental and seasonal variations. These findings further suggest that outdoor temperature and atmospheric pressure should also be recorded, improving additionally the interpretability of BP measurements (Barnett et al., 2007).

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