

Arterial Hypertension Determined By Ambulatory Blood Pressure Profiles: Contribution To Microalbuminuria Risk In A Multicenter Investigation In 2105 Children And Adolescents With Diabetes Mellitus Type 1

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Running title: Blood pressure profiles and microalbuminuria in diabetic children

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ABSTRACT

Objective: Arterial hypertension is a key player in the development of diabetic complications. We used a nationwide database to study risk factors for abnormal 24-hour blood pressure (BP) regulation and microalbuminuria in children and adolescents with diabetes type 1.

Research design and methods: Ambulatory blood pressure monitoring (ABPM) was performed in 2105 children and adolescents from 195 pediatric diabetes centers in Germany and Austria. Individual LMS-SD scores were calculated for diurnal and nocturnal systolic (SBP), diastolic (DBP) and mean arterial BP (MAP) according to normalized values of a reference population of 949 healthy German children. The nocturnal BP reduction (dipping) was calculated for SBP as well as DBP.

Results: In diabetic children, particularly nocturnal BP was significantly elevated (SBP +0.51, DBP +0.58 and MAP +0.80 LMS-SDS) and dipping of SBP, DBP and MAP was significantly reduced ($p < 0.0001$). Age, diabetes duration, gender, body mass index (BMI), HbA1c and insulin dose were related to altered blood pressure profiles; dipping, however, was only affected by age, female gender and HbA1c. The presence of microalbuminuria was associated with nocturnal diastolic BP ($p < 0.0001$) and diastolic dipping ($p < 0.01$).

Conclusions: Our observations revealed a clear link between the quality of metabolic control and altered BP regulation even in pediatric patients with short diabetes duration. Particularly, the nocturnal BP seems to contribute mainly to diabetic complications such as microalbuminuria.

Arterial hypertension is a major risk factor for microvascular and macrovascular complications in type 1 diabetes mellitus.

Diabetic vascular complications can be regarded as endpoints of a long lasting pathological process, involving metabolic and possibly genetic factors. Recently, a high age-dependent prevalence of atherogenic risk factors like obesity, dyslipidemia, smoking, poor glycemic control and arterial hypertension was reported in a large cross-sectional study of children and adolescents with type 1 diabetes (1).

Many studies have shown increased BP levels in adult diabetic patients (2) and an impact of BP regulation on the development of albuminuria and vice versa (3). So far, however, systematic investigations on BP regulation and cardiovascular complications in diabetic children and adolescents have been performed only on a limited number of patients and with conflicting results. Up to 30% of children and adolescents with type 1 diabetes showed arterial hypertension in an investigation in Poland (4) whereas only 2% of the boys and 7% of the girls of a French cohort of diabetic children were hypertensive (5).

Several factors are known to influence BP profile in diabetic patients such as age, gender, body weight, diabetes duration, insulin dosage, metabolic control and microalbuminuria (6).

Ambulatory blood pressure monitoring (ABPM) permits the observation of BP throughout day and night in a non-medical environment, and to quantify the circadian BP variability (7). ABPM is better related to end organ damage and cardiovascular morbidity from hypertension than office BP readings (8, 9). Consistently, impairment of nocturnal

BP regulation has been reported in adolescents and young adults with type 1 diabetes (10, 11). However, the contribution of increased systolic or diastolic BP to an altered BP profile and the development of end organ damage remains controversial.

Identifying factors that initiate and accelerate the development of vascular complications and controlling such factors is crucial for the prevention of these long term consequences of diabetes mellitus. Therefore, we studied the influence of potential risk factors on the quantitative development of hypertensive BP profiles and microalbuminuria in a prospective cohort of diabetic children from 195 pediatric diabetes centers in Germany and Austria.

RESEARCH DESIGN AND METHODS

A total of 31278 patients with type 1 diabetes under 18 years were consecutively registered at 195 centers for Pediatrics and Internal medicine using the national quality initiative DPV (Diabetes software for prospective documentation). The data were locally generated, documented and transmitted in anonymous form to the University of Ulm for central evaluation and analysis as described earlier (1, 12).

Study population. From January 1994 until October 2006, 5982 24-hour BP recordings were obtained.

Only pediatric patients between 5 and 18 years and the most recent ambulatory BP recording for each patient were included in this cross-sectional investigation. The patients with antihypertensive treatment were excluded (9.2% of the patients). Thus, BP profiles of 2105 children and adolescents (1101 boys and 1004 girls) were analysed. 74%

of the recordings were generated in 6 major centers.

Control population. Normalized reference values were obtained from cross-sectional ABPM data in 949 healthy children and adolescents (464 boys, 485 girls). Their age ranged from 5 – 20 (mean 11.1) years, their height from 101 to 198 cm (mean 150 cm). Only healthy children with no history of disease affecting BP and without current antihypertensive medication or other BP-affecting drugs were included in this investigation performed by the German Working Group on Pediatric Hypertension (7). Using the LMS method, gender-specific L, M and S reference values were calculated for 24 hours, daytime and nighttime mean values of systolic, diastolic and mean arterial BP relative to age and height. These reference values enable to calculate SDS (standard deviation score) values in individual patients for each of the above mentioned ABPM recordings (see below).

Measurements. HbA1c values were determined in each center and standardised according to the Diabetes Control and Complication Trial (DCCT) reference range of 4.05-6.05% (1).

BMI were compared by SDS values based on a cohort of 34422 healthy German children (17147 boys, 17275 girls) (13).

Blood pressure profiles. Ambulatory 24-hour BP monitoring was performed by oscillometry with adapted cuff size. Daytime blood pressure was measured every 20 minutes between 08:00 and 20:00 o'clock, nighttime BP was recorded once per hour between 0.00 and 6.00 o'clock. Each patient recorded his daily routine, in case of changes in active and sleeping times the BP reading were individually adjusted. Only ABPM

recordings with at least 75% reliable readings were further analysed.

Mean systolic (SBP) and diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were calculated separately for day and nighttime, as well as the nocturnal reduction of SBP and DBP (dipping).

Age and sex dependency of BP were corrected for by using SDS values for SBP, DBP and MAP.

As the use of pediatric ABPM reference values is comprised by the non-Gaussian distribution of 24-hour BP in children we used the LMS method to calculate appropriate SDS values for ABPM. The LMS method describes the distribution of a measurement Y by its median (M), the coefficient of variation (S), and a measure of skewness (L) required to transform the data to normality. The reference values of L, M, S can be used to calculate individual LMS transformed SD Scores (LMS-SDS) by the following equation (7):

$$\text{LMS-SDS} = [(Y / M(t))^{L(t)} - 1] / (L(t) \times S(t))$$

Y is the child's individual BP value

L(t), M(t), S(t) represent gender-specific reference values of L, M and S interpolated for the child's height.

The individual LMS-SDS values were compared to the published reference population of healthy German children (7, 14).

BP profiles (SBP, DBP, MAP) were considered pathological when the LDS-SDS exceeded 1.65 corresponding to the 95th percentile (7).

The nocturnal reduction of BP (dipping) was calculated as follows:

$$\text{daytime BP} - \text{nighttime BP} / \text{daytime BP}$$

The generally accepted definition of normal systolic dipping is a nocturnal

SBP reduction of more than 10% (15), whereas pathological diastolic dipping is controversially defined as a nocturnal reduction of less than 10% (16) or less than 20% (15). Therefore, prevalence will be given for both definitions.

Albuminuria. Persistent microalbuminuria was defined according to the guidelines of the International Society for Pediatric and Adolescent Diabetology (ISPAD) as a minimum of two positive out of three consecutive urine specimens at least 4 weeks apart (17) with an albumin excretion rate (AER) of 20-200 $\mu\text{g}/\text{min}$ in timed overnight urine collections or 30-300 $\text{mg}/24\text{h}$ in 24-h urine collections and an albumin/creatinine ratio (ACR) of 2.5-25 mg/mmol or 30-300 mg/g in the morning spot urine. Each of the participating centers decided independently which method to use. BP profiles were compared to the urinary albumin excretion rates taken within ± 3 months of the ABPM recording.

Statistical analysis. Statistical analysis was performed with the statistic package SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Group specific differences were compared by parametric testing (t-test) after testing for Gaussian distribution (Kolmogorov-Smirnov) and otherwise by non-parametric Wilcoxon test.

Age (years), diabetes duration (years), gender, HbA1c (%), BMI-SDS and the insulin dose (IU/kg bodyweight/day) were compared to the BP LMS-SDS as independent variables by multiple linear regression analysis. Potential factors contributing to microalbuminuria were studied by stepwise multiple logistic regression analysis. We did not correct for the multiple tests. Therefore, all reported p-values are nominal. Unless stated otherwise data are presented as

mean \pm SD. $P < 0.05$ was considered as significant, $p < 0.01$ as highly significant.

RESULTS

Characteristics of the study population. The mean age of the children included in this investigation was 14.05 ± 2.95 years, the mean diabetes duration 5.15 ± 4.02 years, the mean BMI-SDS 0.49 ± 0.90 and the average HbA1c $8.0 \pm 1.8\%$. The subjects required an average insulin dosage of 0.83 ± 0.28 U/kg BW/d.

The boys were significantly older than the girls (14.2 ± 0.09 years vs. 13.9 ± 0.1 years; $p = 0.021$, Wilcoxon test) and had a shorter diabetes duration (4.9 ± 0.12 years vs. 5.4 ± 0.13 years; $p = 0.001$, Wilcoxon test), BMI-SDS was significantly higher in girls than in boys (0.57 ± 0.03 vs. 0.42 ± 0.03 ; $p < 0.0001$; Wilcoxon test). HbA1c ($p = 0.06$) and insulin dosage ($p = 0.56$) did not differ between girls and boys.

Blood pressure profiles. At daytime mean LMS-SDS in diabetic patients was higher by 0.06 ± 0.83 for systolic BP and by 0.11 ± 0.97 for mean arterial BP LMS-SDS, whereas LMS-SDS for diastolic BP was reduced by 0.12 ± 1.08 compared to the reference population ($p < 0.0001$ for all three variables; Fig. 1).

More pronounced results were found for the nocturnal BP: mean LMS-SDS was increased by 0.51 ± 1.20 for the systolic BP, by 0.58 ± 1.10 for the diastolic BP and by 0.80 ± 1.20 for the mean arterial BP in the study population ($p < 0.0001$ for all three variables; Fig. 1).

Mean dipping was significantly reduced in the diabetic children compared to the reference population ($10.0 \pm 5.7\%$ vs. $13.0 \pm 6.0\%$, respectively for systolic dipping and $16.8 \pm 8.1\%$ vs. $23.0 \pm 9.0\%$ for diastolic dipping, $p < 0.0001$; Fig. 2).

The prevalence for pathological BP at daytime was 5.1% for SBP, 4.3% for DBP and 5.7% for MAP and during the night 14.6% for SBP, 14.7% for DBP and 19.0% for MAP.(Fig. 1). Pathological dipping was found in 49.1% for SBP and in 17.5% for DBP using a cut-off of 10% and in 64.9% for DBP using a cut-off of 20%.

Diabetes associated risk factors for arterial hypertension. Using multiple regression analysis, insulin dosage, female gender, BMI-SDS, HbA1c and diabetes duration were significantly associated with increased BP (table 1).

Increased SBP was strongly related to diabetes duration, female gender and BMI-SDS, both, for the diurnal and nocturnal values. Age and HbA1c were not associated with SBP.

DBP was strongly related to diabetes duration, female gender and HbA1c. Diurnal DBP was additionally associated with BMI-SDS, nocturnal DBP with age and insulin dosage.

Diabetes duration, female gender, BMI-SDS and insulin dose were significantly correlated with the mean arterial pressure (MAP), age and HbA1c, however, only with the nocturnal MAP.

Nocturnal BP reduction was linked to age and HbA1c, the diastolic dipping additionally to female gender and insulin dosage.

Albumin excretion and blood pressure. 24-hour BP profiles and data on urinary albumin excretion were available for 1670 patients. 101 patients (6.1%) had a persistent microalbuminuria which was significantly associated with nocturnal DBP ($p<0.0001$) and impaired diastolic dipping ($p<0.01$).

SBP, MAP, HbA1c, age, diabetes duration, gender, BMI-SDS and insulin dose were not related to microalbuminuria.

CONCLUSIONS

In this binational multicenter investigation, diabetic children showed an abnormal BP profile, particularly affecting the nocturnal BP. Mean LMS-SDS values of BP in diabetic children differed from the control population by +0.51 to +0.80.

The prevalence of arterial hypertension in the diabetic population is 1.5 to 3 times higher than that of non-diabetic age-matched groups (18), approximately 75% of adult diabetic patients have a BP above 140/90 mmHg (19). Age related changes in BP regulation were observed in both, diabetic and non-diabetic subjects, but the changes seem to occur 15 – 20 years earlier in type 1 diabetic patients compared to controls suggesting accelerated vascular ageing (20). Compared with the non-diabetic population, type 1 diabetes is associated with a deleterious BP pattern in adult patients even in the absence of diabetic kidney disease (20). In the Strong Heart Study (21), prehypertension is more prevalent in diabetic patients, the risk for cardiovascular disease is increased 2.9 fold in subjects with diabetes type 1 alone and 3.7 fold in diabetic patients with prehypertension. Our data demonstrate that this fatal development already starts in children and adolescents at an early stage of type 1 diabetes.

Particularly, the nocturnal arterial hypertension and nondipping seems to be associated with cardiovascular disease in the general population. Systemic arterial vascular tone is increased in patients with essential hypertension during the night compared to normotensive control subjects. This increased vascular tone might contribute to the well-known changes of arterial structure in essential hypertension and eventually lead to cardiovascular disease (22).

Non-dippers experience a greater incidence of stroke and myocardial infarction compared to people with normal dipping (23). As our diabetic children showed impaired nocturnal BP regulation they might have an increased risk for macrovascular complications even after short diabetes duration (24). Therefore, an early detection of alterations in BP regulation is crucial for an adequate diabetes management and sufficient antihypertensive therapy. Performing AMBP in diabetic patients might provide valuable informations on early alterations in BP regulation (25).

BMI mostly influenced systolic BP, but had no effect on BP dipping as the most prominent sign of altered BP regulation in these diabetic patients. Performing 24-hour ambulatory BP measurements, Wühl et al. (7) demonstrated a significant association between systolic BP and BMI-SDS accounting for about 10.7 % of the total variability in systolic BP in healthy children and adolescents. The contribution of increased BMI on systolic BP variability in our patients was less pronounced with a maximum of 5.6 %.

BMI was significantly associated with the systolic BP-SDS in children with type 1 diabetes participating in the Oxford Regional Prospective Study (26).

Elevated BMI is associated with peripheral insulin resistance leading to higher insulin requirements similar to a type 2-like metabolic situation. Metabolic syndrome is a frequent finding in type 1 diabetes and increases with inadequate glycaemic control (27). Even short term hyperglycaemia of 48 hours may disturb vascular function, so prolonged and repeated episodes of hyperglycaemia could lead to permanent vascular dysfunction (28).

Both, hyperglycaemia and hyperinsulinemia stimulate different

pathophysiological pathways which result in altered BP regulation and endothelial dysfunction.

In our diabetic children, female gender predisposed to early BP alterations, probably due to an increased weight gain and a higher risk for insulin resistance during puberty. Adolescent non-diabetic girls are less insulin sensitive than boys, but compensate for decreased sensitivity by increasing their insulin secretion (29). Thus, an elevated BMI is probably a major cause for higher insulin resistance in pubertal girls with type 1 diabetes (30). Increased insulin resistance resulting in hyperinsulinemia and hyperglycemia and elevated BMI substantially contribute to the increased rate of arterial hypertension in diabetic girls.

Alterations in nocturnal BP regulation contribute to microalbuminuria and might enhance the development of diabetic nephropathy even in children with type 1 diabetes. Development of microalbuminuria is linked to insufficient BP control and a progressive increment of glucose values in non-diabetic with mild hypertension (31, 32). The Oxford Regional Prospective Study confirmed the link between microalbuminuria and arterial hypertension in children followed from diagnosis of type 1 diabetes. In young adults with type 1 diabetes, an increase in systolic BP during nighttime preceded the development of microalbuminuria. The risk of microalbuminuria for diabetic subjects with a normal pattern of nocturnal BP was 70% lower than the risk for patients with abnormal pattern (33). In accordance, our cross-sectional data suggest that impairment of BP regulation begins at nighttime with a higher prevalence than microalbuminuria. However, office BP did not rise before the onset of microalbuminuria (26, 27).

Therefore, metabolic state, body weight and insulin dosage need to be optimised at the onset of diabetes in order to avoid negative impact on BP regulation and vasculature. Age, female gender and diabetes duration also affected BP regulation as non-modifiable risk factors. However, these factors classify patients at a higher risk for arterial hypertension requiring special monitoring.

Our data suggest that ABPM might be a valuable tool in monitoring pediatric patients with diabetes type 1, thus enabling vascular-directed preventive intervention at the earliest possible time.

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TABLE 1. Results of the multiple linear regression analysis for systolic (SBP), diastolic (DBP) and mean (MAP) BP values during daytime and nighttime as well as for nocturnal dipping.

		SBP			DBP			MAP		
	Parameter	Estimate	95% CI	p	Estimate	95% CI	p	Estimate	95% CI	p
DAYTIME	Age	-0.007	-0.200 - -0.006	0.3134	0.009	-0.008 - 0.026	0.2996	-0.008	-0.023 - -0.008	0.3384
	Diabetes Duration	0.026	0.016 - 0.036	<0.0001	0.039	0.026 - 0.052	<0.0001	0.026	0.014 - 0.038	<0.0001
	Gender	-0.166	-0.236 - -0.951	<0.0001	-0.163	-0.255 - -0.071	0.0005	-0.270	-0.354 - -0.184	<0.0001
	HbA1c	-0.006	-0.026 - 0.015	0.5697	0.038	0.011 - 0.065	0.0054	0.015	-0.010 - 0.039	0.2364
	BMI-SDS	0.138	0.099 - 0.177	<0.0001	0.082	0.031 - 0.133	0.0017	0.131	0.083 - 0.178	<0.0001
	Insulin dose	0.170	0.035 - 0.304	0.0136	0.175	-0.001 - 0.351	0.0509	0.307	0.146 - 0.468	0.0002
		SBP			DBP			MAP		
	Parameter	Estimate	95% CI	p	Estimate	95% CI	p	Estimate	95% CI	p
NIGHTTIME	Age	0.018	-0.001 - 0.036	0.0535	0.047	0.030 - 0.065	<0.0001	0.032	0.013 - 0.0519	0.0011
	Diabetes Duration	0.029	0.015 - 0.042	<0.0001	0.027	0.014 - 0.040	<0.0001	0.021	0.006 - 0.035	0.0067
	Gender	-0.363	-0.459 - -0.265	<0.0001	-0.226	-0.318 - -0.134	<0.0001	-0.188	-0.293 - -0.829	0.0005
	HbA1c	0.008	-0.020 - 0.036	0.572	0.081	0.054 - 0.107	<0.0001	0.056	0.026 - 0.086	0.0003
	BMI-SDS	0.237	0.183 - 0.291	<0.0001	0.029	-0.022 - 0.080	0.2690	0.080	0.021 - 0.139	0.0078
	Insulin dose	0.272	-0.088 - 0.456	0.0037	0.323	0.148 - 0.498	0.0003	0.393	0.194 - 0.594	0.0001
		SBP			DBP			MAP		
	Parameter	Estimate	95% CI	p	Estimate	95% CI	p	Estimate	95% CI	p
NOCTURNAL DIPPING	Age	-0.177	-0.270 - -0.084	0.0002	-0.215	-0.347 - -0.083	0.0014			
	Diabetes Duration	0.006	-0.065 - 0.076	0.8722	0.049	-0.051 - 0.149	0.3347			
	Gender	0.007	-0.492 - 0.506	0.9772	-0.808	-1.512 - -0.104	0.0245			
	HbA1c	-0.183	-0.328 - -0.039	0.0127	-0.430	-0.633 - -0.226	<0.0001			
	BMI-SDS	0.045	-0.233 - 0.324	0.7488	0.332	-0.060 - 0.725	0.0970			
	Insulin dose	-0.325	-1.272 - 0.622	0.5017	-1.682	-3.020 - 0.345	0.0137			

Estimated coefficient values, the 95th confidence interval (95% CI) and the level of significance are given (p<0.05 is marked in bold); gender is coded as 0 for female, and 1 for male.

FIGURE LEGENDS

Figure 1. Mean LMS transformed BP values in diabetic children. Systolic (SBP), diastolic (DBP) and mean arterial BP (MAP) was significantly elevated compared to the control group ($p < 0.0001$), diurnal DBP was significantly reduced ($p < 0.0001$). Mean LMS-SDS of the control population is represented by the baseline (LMS-SDS 0.0). Values are given as mean \pm SD. The prevalence of pathological BP values is shown below.

Figure 2. Absolute dipping values in the group of diabetic children. Systolic (SBP) and diastolic (DBP) dipping were significantly reduced compared to the control population ($p < 0.0001$, **). Values are given as mean \pm SD.

FIGURE 1

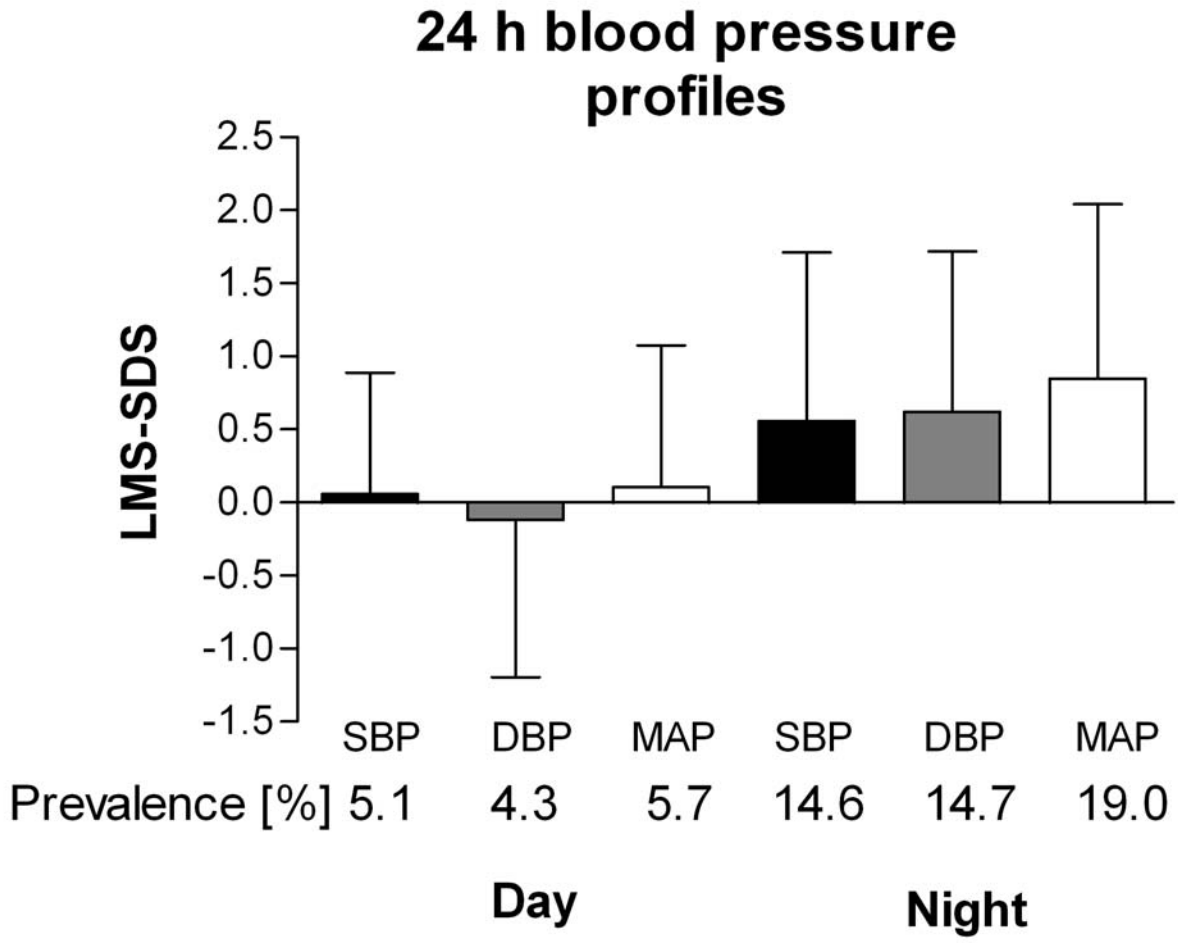


FIGURE 2

