Blood Pressure is Elevated in Children with Primary Snoring

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Objectives To compare ambulatory blood pressure (ABP) in nonoverweight, prepubertal children with and without primary snoring (PS), and to investigate whether PS is a part of the dose-response relationship between sleep-disordered breathing (SDB) and BP in children.

Study design This was a cross-sectional community-based study involving 190 children age 6 to 13 years. Each participant underwent an overnight sleep study and ABP monitoring after completing a validated sleep symptoms questionnaire. Individual systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial BP were calculated for wake and sleep periods. Subjects were hypertensive if mean SBP or DBP was > 95th percentile (relative to sex and height) of reference.

Results A total of 56 nonsnoring controls, 46 children with PS, 62 children with an apnea-hypopnea index (AHI) of 1 to 3, and 26 children with an AHI > 3 were identified. The daytime and nighttime BP increased across the severity spectrum of SDB. The dose-response trends for the proportion of subjects with nighttime systolic and diastolic hypertension also were significant. Nighttime DBP was significantly higher in the children with PS compared with controls after adjusting for age, sex, and body mass index.

Conclusions PS was demonstrated to be an aspect of the dose-response relationship between SDB and BP in children and should not be considered completely benign. *(J Pediatr 2009;155:362-8)*.

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Snoring signifies a degree of narrowing in the upper airway, and habitual snoring (snoring >3 nights per week), which affects around 10% of the pediatric population,[1,2] is the most common symptom associated with obstructive sleep apnea (OSA). Subjects with habitual snoring but normal overnight polysomnography (PSG) often are designated as having primary snoring (PS).

Previous studies in both adults[3] and children[4-8] have suggested a positive association between OSA and elevated systemic blood pressure (BP). This has important clinical implications, because elevated BP in childhood has been linked to the development of hypertension and the metabolic syndrome in adulthood.[9] Whether a similar positive relationship also exists between PS and systemic BP in children remains unclear. A previous adult study found that PS, at the beginning of the severity spectrum of sleep-disordered breathing (SDB), is an aspect of the dose-response relationship between SDB and BP.[10] Two pediatric studies comparing BP in children with and without PS reported conflicting results.[11,12] Kwok et al[11] studied 30 children with PS and a cohort of age-, sex-, and body size–matched healthy controls and found significantly increased systolic, diastolic, and mean BP in the children with PS. In a subsequent study using a community-based sample, Kaditis et al[12] found no relationship between BP and snoring. Both studies had some major design limitations, however. First, casual "on-the-spot" measurements were used to document BP. Ambulatory blood pressure (ABP) measurement is now considered a better diagnostic tool, because it eliminates the effect of "white coat hypertension" and thus provides a more reliable evaluation of BP changes.[13] In addition, those 2 studies did not perform overnight PSG in all participants. A more recent small-scale pediatric study compared 24-hour BP in children with PS, mild OSA, and moderate-to-severe OSA and found no significant difference among the 3 groups; however, this study lacked a nonsnoring control group for comparison, and the results were heavily confounded by obesity.[14]

Obesity is an important predisposing factor for the development of cardiovascular consequences in adulthood and childhood, and is also a major confounder in most studies dealing with SDB.[15] Pubertal growth accelerates the elevation in childhood BP; a recent study found that pubertal growth is associated with a 3- to 6-fold increase in BP in boys and a 2- to 4-fold increase in girls.[16] To control for these 2 factors, in the present study we included only nonoverweight, nonobese prepubertal

ABP	Ambulatory blood pressure	OSA	Obstructive sleep apnea
AHI	Apnea-hypopnea index	PS	Primary snoring
BMI	Body mass index	PSG	Polysomnography
BP	Blood pressure	SBP	Systolic blood pressure
DBP	Diastolic blood pressure	SD	Standard deviation
IQR	Interquartile range	SDB	Sleep-disordered breathing
MAP	Mean arterial pressure	SpO_2	Oxyhemoglobin saturation
ODI	Oxygen desaturation index		

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subjects to investigate the relationship of PS with BP and to evaluate whether PS is an aspect of the dose-response relationship between SDB and BP.

Methods

Subjects for this study were drawn from our childhood OSA epidemiologic study, which involved children age 6 to 13 years recruited from 13 schools chosen at random. Parents of these children were asked to complete a validated OSA screening questionnaire[17] that stratified the children into high risk or low risk for OSA. Snoring frequency was included in the questionnaire with the following response options: never, less than 1 night per month, 1 to 2 nights per month, 1 to 2 nights per week, and 3 or more nights per week. All children at high risk for OSA and a randomly selected sample from the low-risk group were invited to undergo overnight PSG and ABP monitoring. Children with an intercurrent illness within 4 weeks of PSG; with a cardiac, renal, or neuromuscular disorder or a chromosomal abnormality; or previous upper airway surgery were excluded from the study. Children receiving medications that could affect BP measurement, such as diuretics, also were excluded. Anthropometric variables, including weight, height, waist, and hip circumference, were measured on the day of PSG. Body mass index (BMI) was translated to BMI *z*-score.[18] In this study, only prepubertal (Tanner stage 1 for breasts or genitalia and pubic hair) and normal-weight children (BMI *z*-score < 1.036, corresponding to the 85th percentile relative to age and sex) were included.

Polysomnography

A single overnight PSG was performed in a dedicated sleep laboratory with a CNS 1000P polygraph (CNS Inc, Chanhassen, Minnesota).[19] All computerized sleep data were manually edited by experienced PSG technologists and clinicians according to standardized criteria.[20] Subjects with an obstructive apnea-hypopnea index (AHI) $\geq$ 1 were designated abnormal.[21] Those subjects were further subdivided into those with an AHI of 1 to 3 and those with an AHI > 3. PS was diagnosed in those subjects reported to snore 3 or more nights per week in whom PSG revealed an AHI < 1, an oxygen desaturation index (ODI) < 1, and an oxyhemoglobin saturation (SpO_2) nadir $\geq$ 90%. Healthy controls were those reported to snore less than 3 nights per week, with no snoring detected during PSG, which revealed an AHI < 1, an ODI < 1, and a SpO_2 nadir $\geq$ 90%. The study design was approved by the Ethics Committee of the Chinese University of Hong Kong, and written consent was obtained from parents of all subjects.

Ambulatory Blood Pressure Monitoring

ABP was monitored on the same day as the overnight PSG was performed, using an oscillometric monitor (model 90217; SpaceLabs Medical, Redmond, Washington) that has been validated for use in children.[22] Systolic BP (SBP), diastolic BP (DBP), and mean arterial BP (MAP) were measured every hour during the period from 2130 to 0700 hours and every half-hour out of this period. The cuff was placed on the nondominant arm, with cuff size based on the subject's arm length. The exact cutoff time dividing awake BP and asleep BP was defined individually according to the PSG tracings. Recordings were considered adequate and were included in the analysis when they had a minimum of 7 successful readings during active wakefulness and at least 7 successful readings during sleep. Individual mean SBP, DBP, and MAP were calculated for the awake and asleep periods. All mean BP variables were converted into BP *z*-scores using the LMS reference values (relative to sex and height) published by Wuhl et al.[23] Hypertension was defined as mean SBP or DBP values > 95th percentile of the ABP norm.[24] Nocturnal dipping of SBP, DBP, and MAP were derived by calculating the difference between mean awake BP and mean asleep BP and expressed as a percentage of mean awake BP. Subjects with nocturnal BP dip of < 10% were defined as "nondippers."[25]

Statistical Analysis

Parametric data are expressed as mean $\pm$ standard deviation (SD); nonparametric data, as median (interquartile range [IQR]); and categorical data, as number (percentage). Parametric and nonparametric data were compared using 1-way analysis of variance and the Krustal-Wallis test, respectively. The Tukey or Games-Howell test was used for post hoc pairwise comparisons, with adjustments made depending on the agreement of the assumption of variance. The Fisher exact test or χ^2 test was used to investigate the difference in proportions between groups. Multiple χ^2 tests with adjusted *P* values were used for 6 pairwise comparisons ($P < .05/6 = .008$). All of the analyses were performed using SPSS version 13.0 for Windows (SPSS Inc, Chicago, Illinois) or Prism version 4.00 for Windows (GraphPad Software, San Diego, California).

Results

A total of 619 subjects were admitted for PSG, but only 466 of them had completed the ABP recording. This was because 4 subjects were admitted for PSG every working day, but our unit only had 3 ABP recording machines. Thus, 3 of 4 subjects were randomly selected for recording, none of whom refused.

Of the 466 subjects who underwent both PSG and ABP recording, 190 nonoverweight prepubertal children (mean age, 10.0 $\pm$ 1.5 years) satisfied the inclusion criteria for this study and were included in the final analysis (**Figure 1**). Apart from the obvious differences in OSA variables, there were no significant differences in demographic, anthropometric, and PSG characteristics between the 4 study groups (**Table I**).

The median (IQR) total recording time for all subjects was 16.1 (15.0 to 22.6) hours. The median (IQR) number of BP readings during wakefulness and sleep were 12 (10 to 20) and 9 (8 to 9), respectively. There were no significant differences in the characteristics of ABP recording among the groups (**Table II**; available at www.jpeds.com).

During both wakefulness and sleep, SBP, DBP, and MAP all exhibited an increasing trend across the severity spectrum of SDB, from healthy controls without snoring to subjects with PS and to subjects with increasing severity of OSA (Table III). This trend remained significant after the BP levels were converted into *z*-scores. Subjects with PS had significantly higher nighttime DBP compared with nonsnoring healthy subjects (mean difference = 3.2 mmHg; 95% confidence interval = 0.4 to 5.9 mmHg; $P = .016$). No significant differences in any BP measurements were found among children with PS, those with an AHI of 1 to 3, and those with an AHI > 3.

SBP and DBP during both wakefulness and sleep were adjusted for age, sex, and BMI (Figure 2). After the adjustment, significant increasing trends for daytime diastolic, and nighttime systolic and diastolic BP were seen ($P = .010$, .0008, and .0002, respectively). Subjects with an AHI >3 had significantly higher adjusted daytime DBP ($P = .03$) and nighttime SBP ($P = .005$) and DBP ($P = 0.0003$) compared with nonsnoring controls. Those with PS also had significantly higher nighttime DBP than nonsnoring controls ($P = 0.013$).

For the comparison of the proportion of subjects with daytime hypertension, no significant increasing trend could be identified across the severity spectrum. In contrast, for nighttime hypertension, a significant increasing trend was found for both systolic and diastolic hypertension. The control group had a significantly smaller proportion of subjects with nighttime diastolic hypertension compared with either the subjects with PS or those with an AHI >3.

For nocturnal BP dipping, significant decreasing trends were found across the severity spectrum (Table III). Subjects with AHI >3 had a significantly less MAP dipping than controls ($P < .05$). These results remained the same after adjusting for age, sex, and BMI (Figure 3; available at www.jpeds.com). In addition, the proportion of MAP nondippers increased across groups (P for trend = .029)

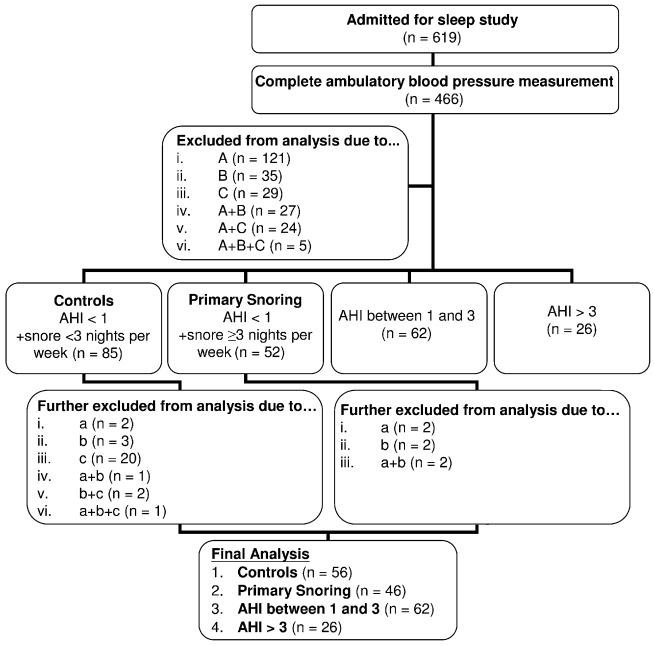

Figure 1. Flow diagram documenting the recruitment of subjects. A total of 619 subjects were admitted for the sleep study, of whom 466 also had ABP measurements. A total of 241 subjects were excluded from the analysis because they were overweight, in puberty, or had inadequate ABP readings. Twenty-nine controls were further excluded because of an ODI >1, an SpO_2 nadir <90%, or snoring recorded during PSG. Six subjects with PS also were excluded because of an ODI > 1 or an SpO_2 nadir <90%.

Discussion

Our findings demonstrate that PS is an aspect of the dose-response relationship between SDB and BP in our cohort of nonoverweight prepubertal children. Daytime and nighttime BP increased and nocturnal BP dipping decreased across the severity spectrum from no snoring to PS and to increasing OSA severity. This relationship remained statistically significant even after adjusting for age, sex, and BMI. The dose-response trends for the proportion of subjects with nighttime systolic and diastolic hypertension also were significant. Our data suggest that PS could be the beginning of the severity spectrum of SDB and, most importantly, that the condition should no longer be considered entirely benign.

Although the difference in BP between the subjects with PS and controls was small, a recent pediatric study[26] found that a similar difference in BP levels was associated with significant left ventricular abnormalities, which are important markers of future cardiovascular adverse events.[27] Moreover, the literature suggests that elevated childhood BP mediates adulthood hypertension and the metabolic syndrome.[9] In addition, elevated BP during childhood is associated with increased carotid artery intima-media thickness and arterial stiffness, which precede the development of atherosclerosis.[28] Thus, our findings of only slightly elevated BP still have important long-term health implications.

Previous prospective studies found a worse prognosis in terms of cardiovascular events in nondippers compared with dippers.[13,29] Nondipping also has been associated with a greater risk of diabetic nephropathy in subjects with normotensive type 1 diabetes.[30] Our results demonstrate that nocturnal BP dipping decreased and the prevalence of MAP nondippers increased significantly across the severity spectrum of SDB, possibly indicating a higher cardiovascular risk for more severe SDB.

In this study we used ABP monitoring to evaluate the relationship between PS and systemic BP in children. Previous studies measured casual "on-the-spot" BP changes.[11,12] Kwok et al[11] compared BP obtained from an automatic oscillometric device in 30 children with PS and a group of age-, sex-, and body size–matched healthy controls and found that the PS group had significantly higher daytime SBP, DBP and mean BP. Those authors also demonstrated that the presence of snoring was a significant determinant of systemic BP. Their healthy controls did not undergo PSG assessment, however. A negative response from parents to the

Table I. Demographic, anthropometric, and PSG data

	Controls (n = 56)	PS (n = 46)	AHI 1 to 3 (n = 62)	AHI > 3 (n = 26)	*P*
Demographic and anthropometric data					
Age, years	10.0 ± 1.6	9.9 ± 1.6	10.0 ± 1.5	10.2 ± 1.4	.87
Male sex, n (%)	34 (60.7)	29 (63.0)	47 (75.8)	20 (76.9)	.20
Body height, cm	136.6 ± 9.4	134.3 ± 9.4	134.7 ± 9.0	137.0 ± 8.2	.44
Body weight, kg	30.1 ± 6.5	29.4 ± 5.8	29.9 ± 6.2	31.4 ± 5.8	.61
BMI, m/kg^2	16.0 ± 1.7	16.1 ± 1.5	16.3 ± 1.9	16.6 ± 1.6	.46
BMI *z*-score	-0.19 ± 0.73	-0.07 ± 0.80	-0.08 ± 0.85	0.05 ± 0.72	.62
Waist circumference, cm	57.3 ± 5.6	57.8 ± 4.9	57.8 ± 5.4	59.5 ± 6.0	.41
Hip circumference, cm	68.9 ± 6.8	68.5 ± 5.9	68.2 ± 5.9	70.6 ± 5.9	.42
Waist-to-hip ratio	0.83 ± 0.04	0.85 ± 0.04	0.85 ± 0.04	0.84 ± 0.04	.23
PSG data					
Total sleep time, hours	8.1 ± 1.0	7.8 ± 0.9	8.0 ± 1.0	8.3 ± 1.0	.10
Rapid eye movement sleep, %	21.3 ± 4.1	21.1 ± 3.9	21.6 ± 3.2	21.7 ± 3.4	.85
Slow wave sleep, %	23.3 ± 4.5	24.2 ± 5.3	23.5 ± 4.8	23.8 ± 4.2	.79
Sleep efficiency, %	84.4 ± 9.8	81.2 ± 9.6	83.8 ± 9.8	86.8 ± 9.8	.13
AHI, /hour	0.1 (0 to 0.3)	0.3 (0 to 0.5)	1.7 (1.3 to 2.3)	6.6 (4.1 to 8.3)	< .0001
ODI, /hour	0.1 (0 to 0.3)	0.1 (0 to 0.3)	0.5 (0.1 to 1.0)	1.0 (0.4 to 3.2)	< .0001
Arousal index, /hour	5.5 (4.5 to 7.4)	5.9 (4.4 to 8.2)	6.6 (5.4 to 7.9)	8.9 (7.2 to 13.0)	< .0001
SpO_2 nadir, %	93 (92 to 94)	93 (92 to 95)	92 (91 to 93)	91 (90 to 92)	< .0001

Parametric data are expressed as mean ± SD; nonparametric data, as median (IQR); and categorical data, as number (percentage).

question of nocturnal snoring was the inclusion criterion used for normality. Parental reporting of symptoms related to children's sleep may be unreliable.[31] The community-based study of Kaditis et al[12] found no differences in morning SBP and DBP between children with and without habitual snoring; however, none of their subjects had laboratory confirmation of OSA status. In the present study, we performed overnight PSG in all subjects, to allow us to define nonsnoring controls and primary snorers with more stringent criteria and thus avoid cross-contamination. Some children with OSA possibly could have been misclassified as having PS by a single-night PSG. Our previous study found that about 85% of subjects with OSA were captured by the first-night PSG.[32] This possible error was further minimized by the use of more stringent criteria to define normal PSG. Another possible source of error could be the misclassification of subjects with upper airway resistance syndrome as primary snorers. Because we did not perform esophageal manometry

Table III. Daytime and nighttime BP measurements in patients with SDB

	Controls (n = 56)	PS (n = 46)	AHI 1 to 3 (n = 62)	AHI > 3 (n = 26)	*P* (trend)
Daytime BP measurements					
SBP, mmHg	107.5 ± 6.8	110.4 ± 7.4	109.9 ± 7.8	110.8 ± 5.3	.042
DBP, mmHg	69.6 ± 3.9	71.7 ± 5.2	71.2 ± 4.3	72.6 ± 4.5*	.008
MAP, mmHg	82.3 ± 4.1	84.2 ± 5.4	83.8 ± 4.7	85.3 ± 4.1*	.014
SBP z-score	-0.67 ± 0.85	-0.23 ± 1.02	-0.33 ± 1.04	-0.23 ± 0.76	.042
DBP *z*-score	-0.41 ± 0.63	-0.06 ± 0.87	-0.15 ± 0.72	0.09 ± 0.75*	.008
MAP *z*-score	-0.31 ± 0.58	-0.01 ± 0.84	-0.10 ± 0.71	0.11 ± 0.64	.019
Systolic hypertension, n (%)	0 (0)	2 (4.3)	4 (6.5)	0 (0)	.39
Diastolic hypertension, n (%)	0 (0)	2 (4.3)	1 (1.6)	1 (3.8)	.39
Nighttime BP measurements					
SBP, mmHg	95.4 ± 6.9	97.6 ± 7.9	98.2 ± 7.8	101.8 ± 8.8†	.0009
DBP, mmHg	56.5 ± 4.9	59.6 ± 5.9*	59.0 ± 4.5*	61.7 ± 6.4‡	.0001
MAP, mmHg	70.9 ± 4.7	73.2 ± 5.8	73.2 ± 4.7	76.3 ± 6.0‡	.0001
SBP z-score	-0.26 ± 0.85	0.06 ± 0.96	0.14 ± 0.99	0.54 ± 1.08†	.0005
DBP *z*-score	0.19 ± 0.82	0.75 ± 0.99†	0.65 ± 0.77*	1.05 ± 1.09‡	.0001
MAP z-score	0.28 ± 0.71	0.64 ± 0.82	0.64 ± 0.69*	1.03 ± 0.86‡	< .0001
Systolic hypertension, n (%)	1 (1.8)	1 (2.2)	4 (6.5)	4 (15.4)	.013
Diastolic hypertension, n (%)	1 (1.8)	9 (19.6)§	5 (8.1)	8 (30.8)§	.005
Nocturnal dipping					
SBP dipping, %	11.2 ± 4.7	11.5 ± 5.7	10.6 ± 5.6	8.1 ± 5.6	.038
DBP dipping, %	18.8 ± 5.9	16.6 ± 7.7	17.0 ± 5.6	15.0 ± 7.7	.021
MAP dipping, %	13.8 ± 4.4	12.9 ± 6.2	12.5 ± 5.0	10.5 ± 6.5*	.013
SBP nondipper, n (%)	28 (50.0)	18 (39.1)	23 (37.1)	15 (57.7)	.93
DBP nondipper, n (%)	3 (5.4)	9 (19.6)	8 (12.9)	5 (19.2)	.13
MAP nondipper, n (%)	11 (19.6)	13 (28.3)	20 (32.3)	11 (42.3)	.029

Data are expressed as mean ± SD for parametric data and as number (%) for categorical data.
*Tukey honestly significant difference (HSD) test, $P < .05$, significantly different from nonsnoring healthy controls.
†Tukey HSD test, $P < .01$, significantly different from nonsnoring healthy controls.
‡Tukey HSD test, $P < .001$, significantly different from nonsnoring healthy controls.
§Fisher exact test, $P < .005$, significantly different from nonsnoring healthy controls.

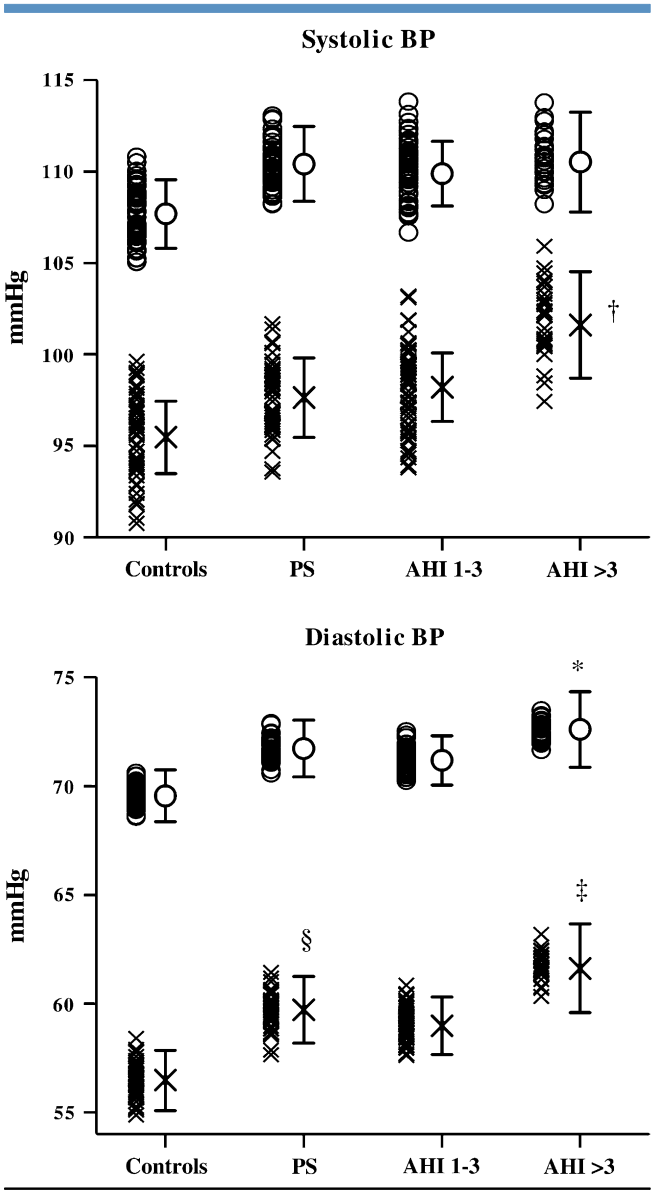

Figure 2. Daytime and nighttime SBP and DBP adjusted for age, sex, and BMI. The scatterplots were constructed based on the predicted values of a model adjusted for age, sex, and BMI. The error bars show the adjusted mean with 95% confidence intervals. Circles (○) and crosses (×) represent daytime and nighttime BP, respectively. Subjects with an AHI >3 had significantly higher daytime DBP (*P = .03) and nighttime SBP (†P = .005) and DBP (‡P = .0003) compared with nonsnoring controls. Subjects with PS also had a significantly higher nighttime DBP than nonsnoring controls (§P = .013).

in our sleep laboratory, we could not properly identify upper airway resistance syndrome. We tried to minimize such potential sources of error by excluding subjects with any PSG abnormalities (ie, AHI ≥ 1, SpO2 nadir < 90%, or ODI ≥ 1) and obtaining a group of primary snorers with an arousal index similar to that of the controls.

The underlying mechanism of BP elevation in the subjects with PS remains unclear. The present study as well as a previous adult study both suggest that PS is an aspect of a dose-response relationship between SDB and systemic BP.[10] This might imply that PS and OSA operate with a similar mechanism in causing BP elevation.[33,34] However, we were not able to find any significant differences in AHI, ODI, SpO2 nadir, or arousal index between primary snorers and normal controls. A possible explanation for this is that primary snorers experience more microarousals (shorter than 3 seconds), greater sleep fragmentation, and/or more episodes of subthreshold oxygen desaturation compared with normal controls. Mograss et al[35] reported that children often experience movement arousals of < 3 seconds duration, sufficient to reestablish airway patency. Moreover, another previous study found that a significant proportion of arousals detected by peripheral arterial tonometry (a sensitive measure of moment-to-moment changes in sympathetic activitiy) were not accompanied by visual EEG arousals.[36] These sleep alterations that are not detected and accounted for by routine PSG might contribute to the BP changes in children with PS.

Nighttime DBP was the only measure significantly elevated in the subjects with PS compared with healthy controls. Diastolic hypertension is a specific pattern of hypertension associated with OSA in which sympathetic overactivity leads to changes in vascular tone and an increase in peripheral vascular resistance, leading to DBP elevations.[37,38] A similar mechanism could operate in PS to cause changes in DBP. A previous study found decreased arterial distensibility in children with PS, providing evidence for vascular reactivity in these children.[11]

Clinical practice guidelines published by the American Academy of Pediatrics suggest that PS may be considered a benign entity.[39] Even though the difference in absolute BP values between the subjects with PS and healthy controls was small in the present study, BP does track with time, and this BP difference may possibly persist or even worsen over time. Some previous studies also have documented increased numbers of neurocognitive deficits in children with PS compared with healthy controls.[40,41] Thus, this entity should no longer be considered entirely benign.

Many subjects in the present study were unwilling to comply with monitoring over a 24-hour period because of school or other social commitments, and we were unable to offer home BP recording because of resource constraints. Nonetheless, all of our sleep BP measurements satisfied the criteria for adequate ABP monitoring,[22] and 7 readings during wakefulness were shown to be representative in our previous report.[8] Another limitation of the present study is related to the use of an normal ABP reference. Because local reference values were not available, we used normal data from a German cohort to define hypertension in this study. Because racial differences might be present, the prevalences of hypertension in our 4 study groups should be interpreted carefully. But despite these limitations, the present study has major advantages over previous published pediatric studies. First, we avoided sampling bias by recruiting subjects from the community instead of from the hospital. This minimized bias or other unknown factors that influence referral to hospital

clinics. We had performed overnight PSG on all participants, allowing us to adjust for possible discrepancies in sleep data. Finally, we minimized the potential confounding effect of obesity and puberty on systemic BP by excluding overweight, obese, and pubertal subjects from the study cohort.

In conclusion, our findings demonstrate that PS is an aspect of the dose-response relationship between SDB and BP measurements in children. These findings may be clinically relevant and important, because BP elevation is a known risk factor for future adverse cardiovascular events. PS in children should not be considered purely benign and, when resources allow, should be monitored for regularly. ■

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50 Years Ago in THE JOURNAL OF PEDIATRICS

Comments on Current Literature: Favism

Blattner RJ. J Pediatr 1959;55:531-3

In this 1959 article, Blattner describes favism as an acute illness with the findings of hemolytic anemia, hemoglobinuria, and jaundice developing in susceptible individuals who inhale the pollen of the flowering fava bean plant or ingest mature fava beans. A familial tendency was noted, affecting both male and female patients. Hay fever, asthma, petechiae, ecchymosis, and even blindness were also attributed to favism. Although the mechanisms leading to hemolysis were not understood, an immune process was implicated, with possible erythrocyte autoimmunization and autosensitization and a hemagglutinating antibody.

Today we know that favism occurs in persons who have glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder affecting >400 million people worldwide. Favism is most common in young children and usually presents as acute hemolytic anemia hours after eating fava beans. Anemia can be severe, leading to renal failure and necessitating blood transfusion in some patients. In 1956, Carson et al discovered that individuals in whom hemolytic anemia developed after exposure to primaquine had low levels of G6PD activity in their red blood cells.[1] That same year, Crosby noted similarities between hemolytic anemia induced by primaquine and hemolytic anemia associated with ingestion of fava beans.[2] Soon after, a low activity of G6PD in individuals with earlier favism were reported in Italy and Germany. About 140 distinct genetic mutations, mostly single base changes leading to amino acid substitutions in the G6PD enzyme, have been described to date. Favism is usually associated with the severe Mediterranean variant of G6PD deficiency and, as with other clinical manifestations, is seen primarily in male patients. All individuals who experience favism are G6PD deficient; however, many individuals who are G6PD deficient can eat fava beans without experiencing any problems. The factors leading to hemolysis in the susceptible subpopulation of subjects who are G6PD deficient are still not known. Divicine, isouramil, and convicine are considered to be the toxic constituents of fava beans and increase the activity of the hexose-monophosphate shunt, promoting hemolysis in patients who are G6PD-deficient. The best approach for persons with severe G6PD deficiency is avoidance of fava beans, with prompt medical attention for signs of hemolysis.

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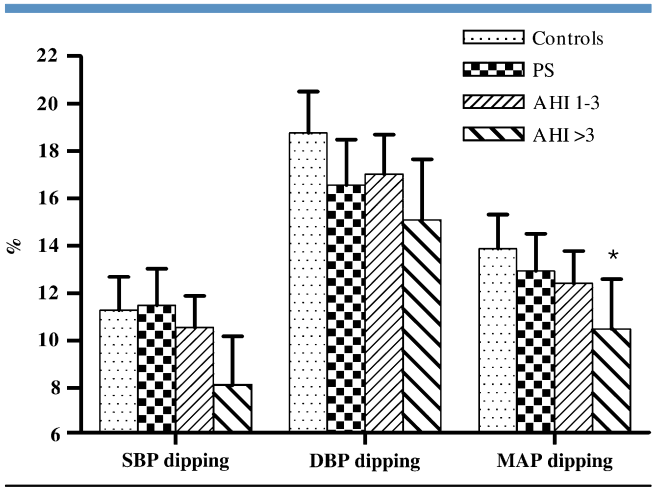

Figure 3. Nocturnal BP dipping adjusted for age, sex, and BMI. *P* values (trend) for adjusted SBP dipping, DBP dipping, and MAP dipping were .009, .032, and .008, respectively. The Tukey HSD test indicated that subjects with an AHI >3 had significantly less MAP dipping than the control group (*$P < .05$).

Table II. Characteristics of BP recordings

	Controls (n = 56)	PS (n = 46)	AHI 1 to 3 (n = 62)	AHI > 3 (n = 28)
Total recording time, hours	16.0 (15.1 to 22.6)	16.2 (15.0 to 22.1)	16.7 (14.9 to 23.1)	16.0 (14.5 to 18.8)
Recording start time	16:21 (15:24 to 17:17)	16:52 (16:04 to 17:48)	16:29 (15:37 to 17:37)	16:50 (16:08 to 17:41)
Recording end time	8:41 (8:17 to 11:36)	8:58 (8:27 to 15:00)	8:44 (8:16 to 13:50)	8:41 (8:10 to 10:34)
Total number of BP readings	21 (20 to 31)	21.5 (19 to 28)	22 (19 to 29)	22 (18 to 25)
Number of BP readings during wakefulness	12.5 (11 to 22)	12 (10 to 18)	13 (10 to 21)	12 (9 to 17)
Number of BP readings during sleep	9 (8 to 9)	9 (8 to 9)	9 (9 to 10)	9 (9 to 10)

Data are expressed as median (IQR).