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Correlation between the morning hypertension on ambulatory blood pressure monitoring and the left ventricular mass in children

Hyun Jung Kim, MD[1], Kyung Hee Kim, MD[2], Hong Ryang Kil, MD[2]

[1]Department of Pediatrics, Eulji Universitiy School of Medicine, Daejeon, [2]Department of Pediatrics, Chungnam University School of Medicine, Daejeon, Korea

Purpose: Although high morning blood pressure (BP) is known to be associated with the onset of cardiovascular events in adults, data on its effects in children with hypertension are limited. Our retrospective study aimed to define the clinical characteristics of children with morning hypertension (MH) and to determine its associated factors.

Methods: We reviewed 31 consecutive patients with hypertension, confirmed by the ambulatory blood pressure monitoring (ABPM). We divided these patients into 2 groups: the MH group (n=21, 67.7%), morning BP above the 95th percentile for age and height (2 hours on average after waking up) and the normal morning BP group (n=10, 32.3%). We compared the clinical manifestations, laboratory results, and echocardiographic findings including left ventricular hypertrophy (LVH) between the groups.

Results: The early/atrial (E/A) mitral flow velocity ratio in the MH group was significantly lower than that in the normal morning BP group. In addition, LV mass was higher in the MH group than in the normal morning BP group, although the difference was not statistically significant. The age at the time of hypertension diagnosis was significantly higher in the MH group than in the normal morning BP group (*P*=0.003). The incidence of hyperuricemia was significantly higher in the MH group than in the normal morning BP group.

Conclusion: Older patients and those with hyperuricemia are at higher risk for MH. The rise in BP in the morning is an important factor influencing the development of abnormal relaxation, as assessed by echocardiography. Clinical trials with longer follow-up periods and larger sample sizes are needed to clarify the clinical significance of MH.

Key words: Ambulatory blood pressure monitoring, Hypertension, Left ventricular hypertrophy

Corresponding author: Hong Ryang Kil, MD
Department of Pediatrics, Chungnam National University Hospital, Chungnam University School of Medicine, 282 Munhwa-ro, Jung-gu, Daejeon 301-721, Korea
Tel: +82-42-280-7251
Fax: +82-42-255-3158
E-mail: gilhong@cnu.ac.kr

Introduction

Noninvasive techniques of ambulatory blood pressure monitoring (ABPM) make it possible to assess the blood pressure (BP) variability and to measure the early morning BP[1,2]. Morning hypertension (MH) defined by ABPM or home BP measurements has been reported to be associated with a significant cardiovascular event in adults[3]. In addition, the prognostic value as well as the baseline characteristics of adult patients with MH have been well documented. That is, the old age, male gender, a more pronounced use of diverse types of antihypertensive drugs, a more prevalent use of β-blockers and a higher clinic BP are major factors that are responsible for the difference in the BP between the morning and evening[4]. It has also been shown that the morning BP surge on the ABPM is associated with the old age, elevated fasting blood glucose levels and a higher 24-hour systolic BP[5].

Levels of BP were higher beginning in childhood, changed adversely through adulthood,

and associated with condition of prehypertension and hypertension in adulthood. However, little is known about the baseline characteristics of children and adolescents with MH. In addition, there is a paucity of evidence supporting the association of high morning BP and the target organ damage in children and adolescents with hypertension. Given the above background, we evaluated the baseline characteristics of 31 hypertensive patients for whom we performed the ABPM and then analyzed its correlation with echocardiography and laboratory findings.

Materials and methods

1. Patients

We performed a retrospective pooled analysis of the data collected from Eulji University Hospital and Chungnam National University Hospital during a period ranging from March of 2006 to March from 2013. We excluded the patients with secondary hypertension, arrhythmias, a history of heart failure or coronary artery disease, renal insufficiency or chronic inflammatory diseases. The current study was approved by the Institutional Review Board of Eulji University Hospital and Chungnam National University Hospital.

2. The measurement of BP

The office BP was measured with the patients in a sitting position after a period of quiet for 5 minutes. The definition of casual hypertension used in this study followed the normative BP references for Korean children and adolescents[6].

ABPM was performed according to the standard institutional policy and procedure using (GEMS IT Cardiosoft V4.2, Freiburg, Germany). The patients filled out a 24-hour diary to report daily activities and rest, including the sleep period. We defined the MH as the morning BP (two hours on average after waking up) above the 95th percentile for age and height. We compared the clinic BP, 24-hour systolic and diastolic BP, night dip and the heart rates between the two groups.

3. Definition of variables

We recorded fasting serum laboratories including glucose, insulin and complete lipid panels. Based on commonly used gender-based cutoffs, we defined hyperuricemia as serum levels of uric acid of ≥6 mg/dL in women and ≥7 mg/dL in men[7]. In addition, we defined dyslipidemia as serum triglyceride of ≥110 mg/dL or high-density lipoprotein (HDL) of ≤40 mg/dL[8].

4. Echocardiography

Echocardiography was performed using the Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway) and a transducer probe of 3 or 5 MHz in frequency in the initial evaluation. The echocardiographic examination was used to evaluate the valve regurgitation, quantitative cardiac contractile function and the presence of left ventricular mass index (LVMI). As described by de Simone et al.[9], we used the height ($m^{2.7}$) to express the LVMI. Thus, we attempted to standardize the LVM for body size. In addition, we defined the left ventricular hypertrophy (LVH) as LVMI>51 $g/m^{2.7}$, as recommended by the working group. We calculated the relative wall thickness (RWT) of the LV as twice the posterior wall thickness divided by the end-diastolic LV dimension[10].

We defined the concentric LVH as the LVH with a RWT of ≥ 0.42[11]. We classified the pattern of LV geometry into the following[12]:
  1) Normal geometry, no LVH and RWT<0.42
  2) Concentric remodeling, no LVH and RWT≥0.42
  3) Eccentric LVH, LVH and RWT<0.42
  4) Concentric LVH, LVH and RWT≥0.42

5. Statistical analysis

All the data was expressed as median unless otherwise stated. We compared the categorical variables between the two groups using a two-tailed Fisher exact test. We used the Mann-Whitney test to analyze the continuous variables. In addition, we performed the Spearman rank correlation analysis to identify the correlation between the variables.

Results

1. Baseline characteristics of the patients

We performed a pooled analysis in a total of 31 patients (children and adolescents) for whom we measured the casual BP, ABPM, echocardiography and fasting laboratory values. Our clinical series of patients comprise 26 boys and 5 girls, whose mean age at diagnosis was 14.4 years (range, 10–19 years). In addition, they were followed up during a mean period of 11.8 months.

The most common chief complaint was headache in 15 patients (48.3%). This was followed by subclinical hypertension that had been detected from the regular school medical check-up, and it was seen in 10 patients (32.2%). Moreover, there were eight patients (26%) with a family history of parental hypertension for which the medication was needed (7 in MH group vs 1 in normal morning BP group) (Table 1).

2. BP measurements

MH group had a significantly high systolic and diastolic BP in night-time compared to normal morning BP group ($P<0.001$). However, in casual BP, only systolic BP was significantly higher in the MH group ($P=0.001$). Twenty-four-hour systolic and dia-

stolic BP was significantly higher in the MH group (*P*<0.001 for systolic BP, *P*=0.003 for diastolic BP). No statistical difference was found in night dips between the two groups (Table 2).

3. Laboratory findings

We measured the serum levels of uric acid in 28 patients; this showed that hyperuricemia was seen in 47.6% of the patients of the MH group and 20% of those of the normal morning BP group. The median serum level of uric acid was higher in the MH group (6.9 mg/dL vs. 5.9 mg/dL, *P*=0.064), but which did not reach a statistical significance. However, the proportion of the patients with hyperuricemia was significantly higher in the MH group as compared with the normal morning BP group (*P*=0.037). Blood glucose levels were measured in 100% of the patients. The median glucose level was 95 mg/dL in the MH group and 101.5 mg/dL in the normal morning BP group (*P*=0.173). In addition, the median insulin level was 14.6 IU/mL in the MH group and 17.6 IU/mL in the normal morning BP group (*P*=0.562). Serum triglyceride levels were measured in 30 patients; this showed that hypertriglyceridemia was seen in 40% of total patients. The median triglyceride level was 105 mg/dL in the MH group and 98.5 mg/dL in the normal morning BP group (*P*=0.746). The HDL was

measured in 26 patients; this showed that there were only two patients with serum HDL levels of <40 mg/dL (Table 3).

4. Echocardiographic parameters

The early/atrial (E/A) mitral flow velocity ratio was significantly lower in the MH group as compared with the normal morning BP group (1.5 vs. 1.74, *P*=0.026). But there were no significant differences in the fractional shortening and the early transmitral flow velocity (E)/the early diastolic velocity of mitral valve annulus (e') ratio between the two groups. LVM (gm) was higher in the MH group as compared with the normal morning BP group, but which did not reach a statistical significance (*P*=0.172). There were no significant differences in the LVMI and RWT between the two groups (Table 4). We also compared the distribution of the LV geometric patterns between the two groups. This showed that the concentric LVH was more prevalent in the MH group (23.8%) as compared with the normal morning BP group (10%), which did not reach a statistical significance (Table 5).

5. Treatment of hypertension

The MH group were more likely to take antihypertensive medication than the normal morning BP group (*P*=0.013). That is, the proportion of the patients taking antihypertensive medication was 80.9% (17/21) in the MH group and 30.0% (3/10) in the normal morning BP group. With regard to the antihypertensive drug class prescribed, there were 15 patients who used angiotensin converting enzyme (ACE) inhibitors, seven who did calcium channel blockers and three on diuretics (Table 3). If BP still was not controlled, a second agent was added in 8 patients. The median duration of antihypertensive medication was 4 months in the MH group and this was statistically significant longer compared with the normal morning BP group (*P*=0.001).

Table 1. Baseline characteristics by chief complaint (n=31)

Characteristic	No. of patients (%)
Family history of essential hypertension	8 (25.8)
Chief complaint	
Headache	15 (48.3)
No symptom*	10 (32.2)
Obesity with elevated liver enzyme	4 (12.9)
Chest pain	2 (6.4)

*Suspected hypertension on school regular checkup.

Table 2. Comparison of blood pressure

Variable	Patients with MH (n=21)	Patients without MH (n=10)	*P* value	BP difference*
Office BP (mmHg)				
Systolic BP	143.0 (130–170)	135.5 (130–150)	0.025	7.5
Diastolic BP	90.0 (62–110)	86.0 (70–100)	0.574	4.0
ABPM				
Day-systolic BP	139.5 (129.2–167.8)	126.3 (113.4–139.1)	<0.001	13.2
Day-diastolic BP	83.8 (75.4–109.8)	78.9 (61.2–88.9)	0.009	4.9
Night-systolic BP	128.2 (105.3–169.6)	115.8 (102.7–121.6)	<0.001	12.4
Night-diastolic BP	73.7 (63.3–97.0)	64.2 (51.9–77.0)	<0.001	9.4
Night dip (%)	10.4 (2.7–16.3)	14.3 (1.7–16.7)	0.217	
24-Hour systolic BP	138.3 (125.3–168.2)	121.5 (111.1–133.0)	<0.001	16.8
24-Hour diastolic BP	81.6 (74.0–106.1)	74.4 (61.4–82.0)	0.003	7.1

Values are presented as median (range).
BP, blood pressure; MH, morning hypertension; ABPM, ambulatory blood pressure monitoring.
*BP difference: (BP of the patients with morning hypertension)–(BP of the patients without morning hypertension)

Table 3. Demographic and laboratory data of patients with and without morning hypertension

Variable	Patients with MH (n=21)	Patients without MH (n=10)	P value
General characteristics			
Age (yr), median (range)	16.0 (12.0–19.0)	13.0 (10.0–17.0)	0.003
Male sex	18	8	1.000
Height (cm), median (range)	173.0 (140.7–187.6)	156.7 (149.0–169.0)	0.001
Body mass index (kg/m^2), median (range)	25.2 (19.3–36.4)	23.2 (18.9–33.9)	0.233
Antihypertensive medication			0.013
ACEIs	12	3	
Calcium channel blockers	7	0	
Diuretics	3	0	
Angiotensin receptor blockers	2	0	
β-Blockers	1	0	
Xanthine oxidase inhibitors	1	0	
Duration of antihypertensive medication (mo), median (range)	4 (0–40)	0 (0–3)	0.001
Laboratory data			
Fasting glucose (mg/dL)	95.0	101.5	0.173
Fasting insulin (IU/mL)	14.6	17.6	0.562
Serum creatinine (mg/dL)	0.75	0.7	0.159
Serum uric acid (mg/dL)	6.9	5.9	0.064
Total cholesterol (mg/dL)	156.0	160.0	0.819
Triglyceride (mg/dL)	105.0	98.5	0.746
LDL-C (mg/dL)	94.8	89.9	0.196
HDL-C (mg/dL)	49.0	55.0	0.586

MH, morning hypertension; ACEI, angiotensin converting enzyme inhibitor; LDL-C, low density lipoprotein-cholesterol, HDL-C, high density lipoprotein-cholesterol.

Table 4. Echocardiographic parameters of the patients

Parameter	Patients with MH (n=21)	Patients without MH (n=10)	P value
LV mass (g)	158.0 (129–236)	124.0 (95.8 –183.3)	0.172
LV mass index (g/m$^{2.7}$)	40.6 (36.9–53.4)	38.3 (30.6–54.8)	0.859
Relative wall thickness	0.42 (0.33–0.62)	0.43 (0.33–0.58)	0.884
LV fractional shortening (%)	34.3 (28.7–40.2)	36.9 (29.4–43.0)	0.151
E/A ratio	1.50 (1.28–1.64)	1.74 (1.47–1.80)	0.026
E/e' ratio	6.95 (5.6–11.1)	8.40 (6.9–10.3)	0.181

Values are presented as median (range).
MH, morning hypertension; LV, left ventricle; E, base peak early diastolic E-wave velocity (cm/sec); A, base peak early diastolic A-wave velocity (cm/sec); e', peak early diastolic myocardial velocity (cm/sec).

Table 5. Left ventricular geometry in the patients

Variable	Patients with MH (n=21)	Patients without MH (n=10)	P value
Normal geometry	6	3	0.521
Concentric remodeling	9	4	–
Eccentric LVH	1	2	–
Concentric LVH	5	1	–

MH, morning hypertension; LVH, left ventricular hypertrophy.

6. Factors affecting the LVMI

There was a significant correlation between the LVMI and the casual systolic BP in the MH group (r=0.457, P=0.037). The LVMI also had a significant correlation with the body mass index (BMI) in patients without MH (r=0.827, P=0.006). In addition, the LVMI also had a significant correlation with the age and body mass index (BMI) in patients without MH (age: r=−0.635; P=0.066; BMI: r=0.827, P=0.006). But there were no significant correlations between the LVMI and the laboratory findings in both groups (Table 6).

Table 6. Spearman correlation coefficients between the clinical parameters and left ventricular mass index

Variable	Patients with MH		Patients without MH	
	r	P value	r	P value
Age	0.132	0.569	−0.635	0.066
Body mass index	−0.163	0.481	0.827	0.006
Blood pressure				
Office				
Systolic BP	0.457	0.037	−0.022	0.935
Diastolic BP	0.226	0.325	−0.218	0.572
Morning				
Systolic BP	−0.124	0.593	0.535	0.138
Diastolic BP	0.178	0.441	−0.320	0.398
Heart rate				
Day-time	−0.419	0.059	0.382	0.310
Night-time	−0.426	0.054	0.315	0.490
Latoratory data				
Fasting glucose (mg/dL)	0.318	0.160	0.208	0.591
Fasting insulin (IU/mL)	−0.273	0.445	0.631	0.179
Serum creatinine (mg/dL)	0.055	0.812	−0.204	0.599
Serum uric acid (mg/dL)	−0.063	0.803	−0.045	0.908
Total cholesterol (mg/dL)	−0.161	0.487	0.359	0.342
Triglyceride (mg/dL)	0.189	0.425	0.168	0.666
LDL-C (mg/dL)	−0.043	0.880	0.568	0.110
HDL-C (mg/dL)	−0.157	0.561	−0.491	0.170

MH, morning hypertension; BP, blood pressure; LDL-C, low density lipoprotein-cholesterol, HDL-C, high density lipoprotein-cholesterol.

Discussion

ABPM allows a better understanding of BP fluctuations over 24 hours than simple clinic measurements. The ambulatory BP is usually several mmHg lower than office pressure[13]. The ambulatory BP level is also increased during the period from night to early morning. The renin-angiotensin-aldosterone system is activated in the early morning before arousal, with increased production of renin and angiotensin II, as a result of activation of the sympathetic nervous system. In the healthy individual, this is a physiological adjustment to compensate for the change from a horizontal to a vertical position and consequent increased cardiovascular demand. It is subject to change depending on various psychological and physical stress conditions[14]. In normal individuals, the BP at night drops by 10%–20% when compared with mean daytime readings. A high percentage of patients with essential hypertension show "dipping" whereas all those with secondary hypertension do not[15]. In our study, decreased nocturnal dipping was observed in MH group compared to normal morning BP group (10.4% vs. 14.3%, P=0.217), although there was no statistical significance.

There are two types of MH: the nocturnal hypertension and the morning BP surge. The nocturnal hypertension (nondipper) is characterized by the persistent high BP from night-time to morning. The morning BP surge is associated with the extreme dipping status of nocturnal BP[16]. If MH is defined as a morning-evening systolic or diastolic BP difference exceeding 10 mmHg[17], the nocturnal hypertension type could be missed. Therefore, we defined the MH as a condition in which the BP is above the 95th percentile for age and height in the morning (two hours on average after waking up). It has been reported that the morning rise of BP may be a predictor of hypertensive target organ damage irrespective of the actual morning BP level[18,19]. To date, however, few reports have described the significance of MH in children and adolescents.

In the current study, we demonstrated that the median age was significantly higher in the MH group as compared with the normal morning BP group. The median serum level of uric acid was higher in MH group, but which did not reach a statistical significance. However, the proportion of the patients with hyperuricemia was significantly higher in the MH group as compared with the normal morning BP group. Animal experimental studies have provided evidence that supports the role of serum levels of uric acid in patients with hypertension. Raising uric acid levels in rats resulted in increased BP and development of microvascular disease in the kidneys[20]. Elevated fasting blood glucose may be a prerequisite for hyperuricemia in susceptible children who develop abdominal fatness. In the current study, however, there was no significant correlation between hyperuricemia and elevated fasting blood glucose levels.

The LV geometry as well as the increased LVM is a key indicator for the cardiovascular risk stratification. Our results showed that the E/A ratio was an independent factor that is associated with the MH, thus suggesting that the abnormal relaxation may be an early consequence of cardiac overload due to a morning rise in BP. This is also in agreement with previous reports that the morning rise in systolic BP has a significant correlation with the E/A ratio, but does not with the LV fractional shortening[21]. In addition, the LV diastolic function is a significant predictor for the cardiovascular events, irrespective of the LV mass, in initially untreated hypertensive patients[22].

LVH has been shown to increase the risk to hypertensive adults[23]. It can be easily measured in children and adolescents and has become a surrogate marker for hypertensive end-organ damage in children. However, LVH is not specific to hypertensive disease. This is because it is also associated with a number of other conditions unrelated to the BP (e.g., obesity)[24]. In our study, there was no significant difference of the BMI in both groups (25.2 kg/m^2 vs. 23.2 kg/m^2, P=0.233).

At the present, it is up to clinical practitioners to make a choice of antihypertensive treatments in children and adolescents. Pharmacologic treatments should be started for patients with

stage 2 hypertension, those with stage 1 or symptomatic hypertension who had a persistent presence of LVH and those with stage 1 hypertension whose BP is unresponsive to the lifestyle change[25]. In our study, the number of patients with stage 2 hypertension was fourteen in the MH group and zero in the normal morning BP group. There were three patients with stage 1 and symptomatic hypertension in each group. It has been reported that β-blockers are less effective in decreasing the LVMI as compared with renin-angiotensin system inhibitors or Ca antagonists; this is also seen even after the adjustment of the differences in the BP among the treatment groups[26]. In the current study, ACE inhibitors were the most commonly used agents. It has been reported that both ACE inhibitors and angiotensin receptor antagonists are greatly effective in reducing the LVH[27].

Hyperuricemia reduction may play a role in BP control. In the current study, there was a 17-year-old male patient who received allopurinol at a dose of 200 mg/day added on ACE inhibitors for four weeks. In this patient, the initial uric acid levels were 8.3 mg/dL and the morning BP was 142/86 mmHg. The patient showed decreased uric acid and BP level after treatment with no adverse effects of allopurinol. To date, only one clinical trial has been conducted to assess the effects of allopurinol in lowering the BP in children; it is a randomized, double-blind, placebo-controlled, crossover trial conducted in 30 adolescents with newly diagnosed primary hypertension (serum uric acid levels≥6 mg/dL) who were treated with either allopurinol 400 mg/day or placebo for 4 weeks[28]. The antihypertensive effects of allopurinol are based on the significant decrease in both the systemic vascular resistance and serum renin levels after the treatment.

In the current study, there was no significant difference of LVMI between the two groups. This can be explained by relatively early age of diagnosis of hypertension in our study. In contrast, the degree of LVH was higher due to high BP variability in the morning hypertensive adults[29]. The vascular hypertrophy induced by exaggerated and steep BP variations may thus lead to an impaired distensibility of the large arteries, resulting in the increased cardiac overload and favoring LVH[30]. The severity of sleep apnea is also associated with LVH. Of note, our results showed that the casual systolic BP measurements also had a predictive value for the LVH. However, casual BP measurements alone continue to be a less specific indicator for hypertensive end-organ damage; this is the case with patients with milder disease[31].

Once-daily antihypertensive regimens are now widely used to treat patients with hypertension, particularly including those whose clinic BP is well-controlled. In these patients, the morning BP is frequently maintained high before the medication. Shibuya et al.[32] suggested that the morning BP rise is a key factor that may affect the occurrence of LVH in hypertensive patients on antihypertensive medication.

There are two limitations of the current study as following: first,

the current study was conducted under retrospective design. Therefore, we failed to determine whether the current antihypertensive treatment regimens are also effective in promoting the LVH regression. At a follow-up, seven patients underwent repeated ABPM and echocardiography; second, we enrolled a small number of patients with a male predilection. We could not determine whether our results are also applicable to different geographic populations.

In conclusion, MH is more likely to seen among patients who are older and is related to hyperuricemia. Further randomized prospective study is necessary to clarify the usefulness of antihypertensive drugs in children with morning rise of BP and LVH.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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