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The Effect of "Unclassified" Blood Pressure Phenotypes on Left Ventricular Hypertrophy

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What is already known on this topic?

- *Whether blood pressure load has a significant effect on left ventricular hypertrophy is contradictory.*
- *It also causes a large group of patients to be unclassified in the classification of blood pressure phenotypes.*

What this study adds on this topic?

- *Blood pressure load should not be used for the classification of blood pressure phenotypes.*
- *For this reason, the new 2022 American Heart Association classification of blood pressure phenotypes will be more inclusive and useful in predicting target organ damage.*

ABSTRACT

Objective: We aimed to evaluate the clinical significance of the "unclassified" blood pressure phenotypes on left ventricular hypertrophy in children.

Materials and Methods: All children evaluated with ambulatory blood pressure monitoring in the pediatric nephrology department between October 2018 and January 2021 were included in the study. Prehypertension, normotensive, white coat hypertension, masked hypertension, ambulatory hypertension groups and 2 other groups including increased blood pressure load, normal ambulatory blood pressure measurements, but normal (unclassified group 1) or high (unclassified group 2) office blood pressure measurements were defined according to the American Heart Association 2014 statement. Left ventricular mass index, left ventricular mass index/95 percentile values, and left ventricular hypertrophy ratios were compared between the groups separately to establish the influence of the unclassified cases.

Results: A total of 497 children were included. There were 52 cases in normotensive, 47 cases in unclassified group 1, 50 cases in masked hypertension, 79 cases in white coat hypertension, 104 cases in unclassified group 2, and 165 cases in the ambulatory hypertension group. Left ventricular mass index/95 percentile and left ventricular hypertrophy in masked hypertension were significantly higher than normotensive but similar between normotensive and unclassified group 1 groups. Left ventricular hypertrophy was significantly higher in the ambulatory hypertension group compared to white coat hypertension, and similar between white coat hypertension and unclassified group 2 groups.

Conclusion: Independent of age, we have found that interpretation of blood pressure load not only has a limited predictable effect on left ventricular hypertrophy but also causes a large group of patients to be unclassified.

Keywords: Unclassified, children, left ventricular hypertrophy, ambulatory blood pressure monitoring

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INTRODUCTION

Childhood-onset hypertension is a growing worldwide problem that can cause adverse changes in left ventricle, carotid intima–media thickness, pulse wave velocity, and cognitive functions.[1] Early detection and treatment of childhood hypertension are important to prevent the development of cardiovascular diseases in adulthood.[2,3]

The first step in detecting hypertension is routine office blood pressure measurement and evaluation of the measurement result. The most current guideline for evaluating office

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blood pressure measurement in children is the American Academy of Pediatrics Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents (AAP-2017) published in 2017.[4] This guideline has been revised to reflect normative data of healthy-weight children with a body mass index <85 percentile (P) because overweight and obesity affect blood pressure values. In addition, it recommends the use of adult static cutoff points for adolescents aged ≥13 years, in line with the American Heart Association (AHA) and American College of Cardiology (ACC) guidelines published in 2017.[5]

In addition to all these, 24-hour ambulatory blood pressure monitoring (ABPM) can detect actual blood pressure status and target organ damage better than office blood pressure.[6] The AAP-2017 recommends confirming the diagnosis of hypertension with ABPM in children with high office blood pressure measurements. For the interpretation of ABPM normative values published by Wuhl et al[7] are usually used.

An important issue of debate in the evaluation of hypertension is whether to include blood pressure load in the classification of blood pressure phenotypes. The definition of blood pressure phenotypes resulting from the joint evaluation of both office and ambulatory blood pressure has changed over time, especially in parallel with the increase in studies evaluating ABPM in children. In 2014, Flynn et al[1] identified 2 more groups, which they defined as "unclassified groups" that did not fit into any of the previously defined categories. These are the groups with office blood pressure measurements <90 P and normal ABPM despite elevated blood pressure loads (which will be grouped as "unclassified 1" throughout the study), and the group with normal ABPM and office blood pressure ≥95 P despite elevated blood pressure loads (which will be grouped as "unclassified 2").

In our study, we aimed to evaluate the effect of unclassified phenotypes on left ventricular hypertrophy and whether these groups should be included in the classification.

MATERIALS AND METHODS

This study is a single-center retrospective cross-sectional study. The study protocol was approved by the Ethics Committee of the İzmir Tepecik Training and Research Hospital Ethics Committee (July 14, 2021/2021/7-10). No informed consent was needed because of the retrospective non-interventional study design. All patients evaluated with APBM between October 2018 and January 2021 in our pediatric nephrology department were included in the study.

Body weight, height, age, and gender data of all children were recorded from patient files. Calibrated scales and stadiometers were used for height and weight measurements. Body mass index was determined by calculating the ratio of body weight (kg) to height (m^2) squared for each child. The body mass index standard deviation scores (SDSs) were calculated using the reference values developed by Neyzi et al[8] using the child metrics program.[9]

Office Blood Pressure Measurements

Blood pressure measurements in the pediatric nephrology department were measured by an experienced nurse with an aneroid sphygmomanometer, which was regularly calibrated after a 5-minute rest period, by the auscultation method on the right arm. The width of the cuffs used for blood pressure measurement was at least 40% of the arm circumference and 80%-100% of the length at the midpoint between the olecranon and acromion.[4] The average of the measurements determined at 3 different visits 1 week apart was taken as the blood pressure value.

The evaluation of systolic and diastolic office blood pressure measurements of all patients was performed according to the AAP-2017 threshold values. Accordingly, blood pressure values below 90 P for children under the age of 13 and <120/<80 mm Hg for those over the age of 13 were accepted as normotensive. For high blood pressure, values between 90-95 P or 120/80-95 P are accepted under 13 years of age, and 120-129/<80 mm Hg above 13 years of age. Hypertension was defined as measurements of ≥95 P or ≥130/80 mm Hg for children under 13 years of age and ≥130/80 mmHg for adolescents over 13 years of age.[4]

Ambulatory Blood Pressure Monitoring Measurements

A standard device for ABPM (Mobil-O-Graph IEM GmbH, Germany) with a child's age-appropriate cuff was used for the measurements. Measurements were taken on the nondominant arm at 30-minute intervals during the day and at 15-minute intervals at night. During the measurement, the children continued their daily activities. They were told to write down their sleeping and waking times in a notebook. Blood pressure measurements were converted to SDSs with the help of the LMS method using skewness (L), median (M), and coefficient of variation (S) to normalize the data.[7] "Blood pressure load" was defined as the ratio of the number of measurements above the 95 P to the total number of measurements over 24 hours. Age, height, and gender-specific normative value tables for boys and girls published by Wuhl et al[7] were used for ABPM assessment.

Blood Pressure Phenotypes

Blood pressure phenotypes formed by evaluating office blood pressure and ABPM together were collected as follows (Table 1):

1. Office blood pressure measurements ≥90 P or >120/80 mm Hg and <95 P with mean day and night systolic and diastolic blood pressure measurements <95 P and systolic or diastolic blood pressure load ≥25% were grouped as prehypertension.

Table 1. Classification of Ambulatory Blood Pressure Phenotypes, Modified from Flynn et al[1]

Classification	OBP	Mean Ambulatory SBP or DBP	SBP or DBP Load
PHT	90-95 P	<95 P	≥25%
NT	<90 P	<95 P	<25%
UC1	<90 P	<95 P	≥25%
MHT	<95 P	≥95 P	≥25%
WCHT	≥95 P	<95 P	<25%
UC2	≥95 P	<95 P	≥25%
AHT	≥95 P	≥95 P	≥25%

AHT, ambulatory hypertension; DBP, diastolic blood pressure; MHT, masked hypertension; NT, normotensive; OBP, office blood pressure; P, percentile; PHT, prehypertension; SBP, systolic blood pressure; UC1, unclassified group 1; UC2, unclassified group 2; WCHT, white coat hypertension.

2. Office blood pressure measurement values <90 P according to gender, age, and height; day and night systolic and diastolic ABPM measurement averages <95 P with a systolic or diastolic blood pressure load <25% in ABPM were considered normotensive.
3. The group with an office blood pressure measurement <90 P and day and night systolic and diastolic ABPM measurement averages <95 P despite an elevated blood pressure load was defined as unclassified group 1.
4. Office blood pressure measurement values <95 P for gender, age, and height, and those with day and night systolic and diastolic blood pressure measurement averages ≥95 P and systolic or diastolic blood pressure load ≥25% in ABPM were grouped as masked hypertension.
5. Office blood pressure measurement values ≥95 P according to gender, age, and height, with day and night systolic and diastolic ABPM measurement averages <95 P in ABPM with systolic or diastolic blood pressure load <25% were evaluated as white coat hypertension.
6. The group with office blood pressure ≥95 P despite systolic and diastolic ABPM measurement averages <95 P in ABPM and elevated blood pressure load was defined as unclassified group 2.
7. Both office blood pressure and ABPM measurement values of ≥95 P and those with a systolic or diastolic blood pressure load of ≥25% are considered ambulatory hypertension.

Echocardiographic Assessment

Echocardiographic examination, performed using the same device by the same pediatric cardiologist working in our institution, was performed within 3 months after the date of ABPM. Left ventricular mass was calculated with the Devereux formula: Left ventricular mass: 0.8×1.04 [(LVEDD+IVST+PWT)^3 − (LVEDD)^3]+0.6 [LVEDD: left ventricular end-diastolic diameter, IVST: interventricular septum thickness, PWT: rear wall thickness]. The left ventricular mass index was calculated by dividing the left ventricular mass by the body surface area.[10] Left ventricular mass index values exceeding 95 P for age and gender were defined as left ventricular hypertrophy.[11]

Statistical Analysis

For descriptive analysis, categorical variables were presented as percentages. Continuous variables were given as mean ± standard deviation or median (interquartile range) according to the data distribution. The Kolmogorov–Smirnov test was used to evaluate whether continuous variables were normally distributed between groups. The ANOVA test and Kruskal–Wallis test were used to compare data between the 3 groups according to the data distribution. Categorical variables were compared with the Pearson chi-square test and Bonferroni correction. A *P*-value of <.05 was considered statistically significant. Statistical Package for the Social Sciences Statistics 26.0 (IBM Inc., Armonk, NY USA) program was used for statistical analyses.

RESULTS

A total of 524 cases were included. Children with prehypertension (n = 27) were not included in the statistical analysis. When we classify the remaining 497 cases according to blood pressure phenotypes, we had 52 (10.4%) cases in the normotensive group, 47 (9.5%) cases in the unclassified group 1, 50 (10.1%) cases in the masked hypertension group, 79 (15.9%) cases in the white coat hypertension group, 104 (20.9%) cases in the unclassified group 2, and 165 (33.2%) cases in the ambulatory hypertension group. Unclassified group 1 represents normotensive cases with a high load or masked hypertension cases with lower mean ambulatory blood pressure. Similarly, unclassified group 2 represents white coat hypertension cases with a high load or ambulatory hypertension cases with lower mean ambulatory blood pressure. Thus, data were compared separately between the normotensive, unclassified group 1, and masked hypertension classes and between white coat hypertension, unclassified group 2 and ambulatory hypertension groups to detect the effect of unclassified cases.

Office and 24-hour systolic and diastolic blood pressure averages of all groups are given in Table 2.

Age, gender, body mass index, body mass index SDS, and left ventricular mass index values were similar between the subjects in the normotensive, unclassified group 1 and masked hypertension groups and the subjects in the white coat hypertension, unclassified group 2, and ambulatory hypertension groups. Left ventricular mass index/95 P and left ventricular hypertrophy in masked hypertension were significantly higher than normotensive, but similar between normotensive and unclassified group 1 groups. Left ventricular hypertrophy was significantly higher in the ambulatory hypertension group compared to the cases in the white coat hypertension group and was similar between the cases in the white coat hypertension and unclassified 2 groups (Table 3 and Table 4).

The LVH ratio and LVMI/95th P of all ABPM phenotypes are shown in Figure 1.

DISCUSSION

In our study evaluating the clinical importance of unclassified groups, we have shown that being in unclassified group 1 or unclassified group 2 does not pose any additional risk for left

Table 2. Office and 24-Hour Blood Pressure Averages of All Groups

	NT (n = 52)	UC1 (n = 47)	MHT (n = 50)	WCHT (n = 79)	UC2 (n = 104)	AHT (n = 165)
Office SBP	107.24 ± 5.94	106.91 ± 8.32	114.72 ± 8.83	129.03 ± 11.59	131.44 ± 12.66	134.33 ± 12.39
Office DBP	68.42 ± 5.61	66.76 ± 6.24	71.64 ± 5.22	80.89 ± 8.25	80.98 ± 8.75	82.73 ± 10.21
24-hour SBP	104.70 ± 6.50	108.87 ± 4.66	117.90 ± 9.24	110.65 ± 6.23	114.51 ± 6.77	129.85 ± 7.96
24-hour DBP	60.78 ± 4.97	64.29 ± 4.84	70.98 ± 6.31	62.97 ± 3.50	66.25 ± 4.96	72.00 ± 8.58

AHT, ambulatory hypertension; DBP, diastolic blood pressure; MHT, masked hypertension; NT, normotensive; SBP, systolic blood pressure; UC1, unclassified group 1; UC2, unclassified group 2; WCHT, white coat hypertension.

Table 3. Comparison of Demographic and Left Ventricular Parameters between Normotensive, Unclassified Group 1, and Masked Hypertension Groups

	NT (n = 52)	UC1 (n = 47)	MHT (n = 50)	*P*
Age (year)	12 (9-14)	13 (10-16)	15 (11-16)	.058
Gender (male)**	26 (50.0%)	26 (55.3%)	33 (66.0%)	.253
BMI***	20.90 (17.63-27.63)	21.30 (19.30-25.80)	24.55 (20.28-27.88)	.065
BMI SDS***	0.70 ± 1.63 (−3.00-3.70)	0.83 ± 1.30 (−1.72-0.39)	0.96 ± 1.64 (−3.08-3.91)	.707
LVMI***	28.85 (24.53-34.80)	33.50 (26.60-34.50)	32.85 (26.30-39.25)	.131
LVMI/95 P***	0.75 ± 0.14 (0.47-1.02)	0.79 ± 1.17 (0.44-1.26)	0.85 ± 0.21 (0.49-1.29)	.014*
LVH**	2%	8.5%	24%	.002*

BMI, body mass index; LVH, left ventricular hypertrophy; LVMI, left ventricle mass index; MHT, masked hypertension; NT, normotensive; P, percentile; SDS, standard deviation scores; UC1, unclassified group 1.
*Significantly higher in MHT vs. NT group and similar between NT and UC1 groups.
**Categorical variables are presented as percentages.
***Continuous variables are given as mean ± standard deviation or median (interquartile range) according to data distribution.

Table 4. Comparison of Demographic and Left Ventricular Parameters between White Coat Hypertension, Unclassified Group 2, and Ambulatory Hypertension.

	WCHT (n = 79)	UC2 (n = 104)	AHT (n = 165)	*P*
Age (year)	14 (11-16)	13 (10-15)	14 (12-15)	.201
Gender (male)**	33 (41.7%)	46 (44.2%)	83 (50.3%)	.390
BMI***	23.40 (20.80-27.40)	25.15 (20.03-29)	25.1 (21.35-30.35)	.113
BMI SDS***	1.25 (0.06-2.10)	1.55 (0.40-2.40)	1.47 (0.42-2.50)	.097
LVMI***	31.52 ± 7.95 (6.50-1.10)	32.75 ± 9.58 (11.40-63.80)	33.62 ± 9.54 (16.90-71.70)	.250
LVMI/95 P***	0.80 ± 0.20 (0.16-1.23)	0.83 ± 0.24 (0.28-1.75)	0.86 ± 0.24 (0.42-1.74)	.168
LVH**	15.2%	19.2%	29.1%	.030*

AHT, ambulatory hypertension; BMI, body mass index; LVH, left ventricular hypertrophy; LVMI, left ventricle mass index; p, percentile; SDS, standard deviation scores; UC2, unclassified group 2; WCHT, white coat hypertension.
*Significantly higher in AHT vs. WCHT group and similar between WCHT and UC2 groups.
**Categorical variables are presented as percentages.
***Continuous variables are given as mean ± standard deviation or median (interquartile range) according to data distribution.

ventricular hypertrophy. Since the difference between normotensive and unclassified group 1 and white coat hypertension and unclassified group 2 groups is due to blood pressure load, we can conclude that a blood pressure load of >25% in children or adolescents does not contribute to left ventricular hypertrophy.

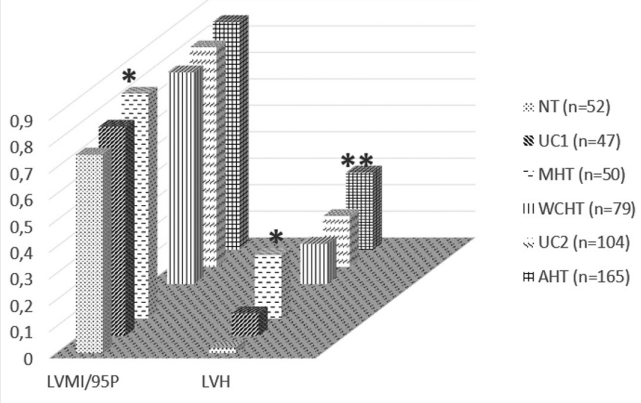

Figure 1. The LVH ratio and LVMI/95th percentile of all ABPM phenotypes. *Significantly higher in MHT vs. NT group and similar between NT and UC1 groups. **Significantly higher in AHT vs. WCHT group and similar between WCHT and UC2 groups. ABPM, ambulatory blood pressure monitoring; AHT, ambulatory hypertension; LVH, left ventricular hypertrophy; LVMI, Left Ventricle Mass Index; MHT, masked hypertension; NT, normotensive; UC1, unclassified group 1; UC2, unclassified group 2; WCHT, white coat hypertension.

Blood pressure load reflects the ratio of measurements above 95 P to all measurements in ABPM. European adult and pediatric hypertension guidelines define blood pressure phenotypes in 4 main groups as normotensive, masked hypertension, white coat hypertension, and ambulatory hypertension, without addressing the concept of blood pressure load. However, the 2014 AHA guidelines for pediatric blood pressure classification are different and include 2 more groups: prehypertension and severe ambulatory hypertension. In addition, the use of the AHA categories results in the unclassification of some patients with high blood pressure loads and normal mean ambulatory blood pressure but with normal (<90 P) (unclassified group 1) or hypertensive (≥95 P) (unclassified group 2) office blood pressure.[1,5,12] In a multicenter study involving children undergoing kidney transplantation, Hamdani et al[13] found that close to 30% of children could not be classified using current AHA recommendations. In the retrospective analysis of 500 children evaluated for hypertension in Italy, it was shown that 14% of the children could not be classified.[14] Campbell et al[15] reported the highest number and rate of unclassified patients, which was 145 of 495 patients (29%). Very similarly, we have found that 151 of our 524 patients (29%) were in the unclassified group (47 of them in the unclassified group 1 and 104 of them in the unclassified group 2 group). As seen, the number of unclassified cases is too high to be underestimated.

The only difference between unclassified group 1 and normotensive; and between unclassified group 2 and white coat

hypertension is the blood pressure load. Although some studies have concluded that blood pressure load in 24-hour ABPM is an indicator of target organ damage, some studies have shown that it has no effect on left ventricular hypertrophy.[16,17] Hamdani et al[18] concluded in their study that blood pressure load did not provide an additional benefit in determining left ventricular hypertrophy in adolescents. Lee et al[19] found that blood pressure load did not provide an additional value for predicting left ventricular hypertrophy or chronic kidney disease (CKD) progression in 553 children with CKD stages 2-4 (CKiD study).[19] The Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth found no additional benefit of blood pressure load in the assessment of hypertension in children. However, they did not consider unclassified groups.[20] In our previous study comparing pediatric hypertension guidelines, we similarly found that addressing blood pressure load has no additional effect on left ventricular hypertrophy.[21]

In the study by Campbell et al,[15] the ABPM measurements of 495 patients were screened retrospectively, and the importance of blood pressure load and its relationship with left ventricular hypertrophy in the unclassified group were examined. The unclassified group was reclassified according to the 2017 ACC/AHA adult thresholds. The hypertensive and normotensive cases were found to have similar left ventricular mass index levels and rates of left ventricular hypertrophy. This study also showed no difference in the prevalence of left ventricular hypertrophy between unclassified and normotensive cases. As a result, it was recommended to exclude blood pressure load from the definition of ABPM and to use the adult ACC/AHA 2017 standards for children ≥13 years old.[15] In our current study addressing directly unclassified groups, we have also shown that the rate of left ventricular hypertrophy is the same between the normotensive and unclassified 1 groups and, additionally, between the white coat hypertension and unclassified 2 groups as well. The difference between the rates of left ventricular hypertrophy was lower in the unclassified 1 and unclassified 2 groups compared to masked hypertension and ambulatory hypertension groups, respectively. However, we could not show that this difference was statistically significant. Our results justify the discussion regarding the exclusion of blood pressure load in the interpretation of blood pressure phenotypes. This would eliminate unclassified groups.

The AAP-2017 guideline uses adult thresholds for office blood pressure measurements in children over 13 years of age. Current pediatric ABPM guidelines use mean blood pressure ≥95 P and blood pressure load ≥25 for gender, age, and height for the definition of hypertension without considering adult thresholds. In the assessment of adult ABPM, load is not taken into account, and only a fixed blood pressure threshold is used. Therefore, when evaluating older and taller children, the threshold values accepted for children may exceed adult values. In their study, Merchant et al[22] found a higher left ventricular hypertrophy ratio in adolescents using the ACC/AHA adult blood pressure threshold. Finally, in the 2022 update of the AHA guideline, Flynn et al[23] suggested that there is no additional value of the blood pressure load over mean blood pressure in predicting left ventricular hypertrophy and defined new fixed cutoff points in adolescents consistent with adult guidelines.

Although it has been a long time since the AHA recommendations were established for blood pressure phenotypes in 2014, the number of studies on unclassified patients is very limited, and this is the strength of our study. The weak points are its cross-sectional nature and the limited number of cases.

In conclusion, we have found that adding blood pressure load to the assessment of ABPM not only has a limited predictive effect on left ventricular hypertrophy regardless of age but also causes a large group of patients to be unclassified. Therefore, with the disappearance of the concept of blood pressure load, groups that cannot be classified also disappear. The new 2022 AHA classification of blood pressure phenotypes created in this context will be more comprehensive than the 2014 AHA statements that were used to form the framework of this study and useful in predicting target organ damage, which warrants further investigations.

Ethics Committee Approval: The study protocol of this single-center, cross-sectional study was approved by the Ethics Committee of the İzmir Tepecik Training and Research Hospital Ethics Committee (July 14, 2021/2021/7-10).

Informed Consent: No informed consent was needed because of the retrospective non-interventional study design.

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