Supplement to: Update of 2008 Scientific Statement on Ambulatory Blood Pressure Monitoring in Children and Adolescents

From the Atherosclerosis, Hypertension & Obesity in Youth Committee of the Cardiovascular Disease in the Young Council of the American Heart Association

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Conditions in which ABPM has proven useful

The most common application of ABPM in pediatric patients is likely confirmation of suspected HTN in patient with elevated office BP readings. This application of ABPM is discussed extensively in the main paper. However, HTN experts have applied ABPM to the evaluation and management of other types of patients. Some of the most pertinent literature is summarized in this supplement. The interested reader is also referred to the comprehensive review by Flynn and Urbina,¹ and to pertinent chapters in the recently updated <u>Pediatric Hypertension.²</u>

Renal diseases: ABPM may be especially useful in evaluation for secondary HTN, since elevated BP load,³ increased BP variability,^{4, 5} and reduced nocturnal dipping⁶⁻⁸ often signal a renal cause for the BP elevation. For this reason, ABPM has been extensively used in children with CKD. Many studies have looked at the association of abnormal ABPM parameters with end-organ damage such as increased LVM,^{9, 10} increased cIMT¹¹ or even abnormal biopsy findings as seen in children with IgA nephropathy, where higher nocturnal BP was associated with adverse histopathology.¹² Other studies in children with CKD have focused on defining the prevalence of HTN using ABPM, which was found to have greater reproducibility than casual BP.¹³

Recent data from the Chronic Kidney Disease in Children (CKiD) study, a large multicenter observational cohort study of children with mild-to-moderate CKD in the United States and Canada, confirmed a high prevalence of ambulatory HTN in this population.¹⁴ Given the increased risk of CV disease in patients with CKD^{15, 16} ambulatory BP in this study was considered abnormal when either ambulatory mean or load was elevated. Thus, subjects with 2008 AHA classified pre-HTN (high casual BP, normal mean ambulatory BP and high ambulatory BP load) were classified as hypertensive (i.e., abnormal ABPM) by these investigators. Additionally, those with unclassified AHA BP parameters (normal casual, normal mean ABP, high load) were classified as having MH. Of 332 children in the CKiD study who had ABPM, only 138 (42%) subjects had both normal BP by casual and ambulatory measurements. WCH was diagnosed in only 13 (4%) subjects, while 116 (35%) were classified as having MH. There were 48 (14%) subjects with confirmed HTN, of whom 21 had "severe" ambulatory HTN

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(loads > 50%). Ambulatory HTN was more common in African Americans and slightly more common among those with glomerular disease as a primary cause of CKD.

The CKiD investigators have also described the association between renal damage (proteinuria) and the presence of abnormal ABPM. Specifically, a one standard deviation increase in urine protein to creatinine ratio in this population (e.g., 2.25-fold increase) was associated with a 31% higher odds of having an abnormal ABPM (OR: 1.31, 95%CI: 1.04, 1.67; p= 0.024) when controlling for confounders. CKiD subjects on ACEi/ARB were less likely to have abnormal ABPM when compared to those taking other classes of antihypertensive medications. ¹⁴ These data are complementary to the results of the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial, which has shown that intensified, ABPM-guided control of HTN led to decreased CKD progression.¹⁷

Another report from the CKiD study analyzed the association of ambulatory BP with LVH.¹⁸ LVH was more frequent in children with confirmed (34%, p<0.0005) and masked (20%, p=0.039) HTN than in children with normal casual and ambulatory BP (8%) (Figure 1). More importantly, the likelihood of having LVH was four times higher in those children identified as having MH compared to children with normal clinic and ambulatory BP. This is worrisome, since MH is associated with increased CV risk and progression of CKD in adults.¹⁹

The long-term effect of ABPM-guided treatment on the development of end-organ damage in children with renal transplant has recently been reported.²⁰ In this study, 22 children had baseline carotid scan and echocardiography and underwent two additional evaluations for a follow-up of 9.1 ± 0.9 years. Antihypertensive therapy was determined according to the recipient's ABPM results, which were performed at yearly intervals. At the last examination, 14 of 17 children with treated HTN had excellent BP control, with an overall prevalence of LVH of just 4.5%, and no progression of cIMT. The authors concluded that the lack of progression of cIMT over time and the low prevalence of LVH might reflect the effect of strict BP control over time.

Diabetes: Many studies have confirmed the usefulness of ABPM in evaluating CV risk related to HTN in youth with diabetes mellitus. As seen in children with CKD, children with T1DM were often found to have masked or nocturnal HTN, conditions that can be diagnosed only with ABPM.²¹ Poor diabetic control may be a contributing factor, as glycated hemoglobin is related to abnormal mean ambulatory SBP²² and reduced BP dipping.²³ ABPM was also found to be more highly correlated with albuminuria than home BP in youth with T1DM.²⁴ Monitoring and control of nocturnal BP might actually prevent the development of microalbuminuria, a marker of early kidney injury, as illustrated in the study by Lurbe et al.²⁵ In this study, 75 adolescents and young adults with T1DM with normal urinary albumin excretion and BP were monitored for more than 5 years. At the end of follow up, nocturnal SBP increased in subjects who ultimately developed microalbuminuria. Moreover, the risk of developing microalbuminuria was 70% lower in subjects with normal nocturnal SBP. Even if normotensive, patients with T1DM who had a non-dipper pattern had greater end systolic LV diameter, end diastolic LV diameter and higher LVM than dippers and they had reduced mean 24-HR, suggesting a degree of autonomic dysfunction.²⁶ Another study of children with T1DM showed that nocturnal HTN has been associated with higher carotid IMT.²⁷

Obesity and ABPM: Several studies have consistently reported positive correlations between ABPM parameters and adiposity (e.g., BMI, waist-hip ratio, waist circumference, subcutaneous and abdominal body fat).^{28, 29} The positive associations with BMI could be found in children with both severe ambulatory HTN and with WCH.³⁰ Many studies have classified more obese children as non-dippers comparing to lean children^{29, 31} suggesting a high rate of MH in obese children. A recent multi-ethnic study of obese children and adolescents found that 33% had elevated night time systolic BP.³² In obese children and adolescents, ambulatory systolic BP and ambulatory pulse pressure correlated positively and significantly with carotid artery IMT and with the presence of LVH, suggesting the potential of ABPM to better identify early target-organ damage.³³

Obstructive sleep apnea (OSA), which is more prevalent in obese insulin-resistant children, is also linked to higher mean ABPM³⁴, greater daytime BP variability, and reduced nocturnal dipping.³⁵ The

degree of ABPM abnormality is directly correlated with severity of OSA. Children with an apneichypopneic index >5 have significantly higher nocturnal BP levels than less severely affected patients.³⁶ Children with OSA are also more likely to have a pronounced early morning BP surge.³⁷ This ABPM pattern is associated with increased risk for adverse CV outcomes in adults.³⁸ Fortunately, there is some evidence that improvement in OSA after adenotonsillectomy may improve ABPM levels.³⁹

ABPM might also be useful in obesity-related conditions such type 2 diabetes and metabolic syndrome. Marcovecchio et al⁴⁰ evaluated the correlation between insulin resistance and ABPM parameters in a population of obese pre-pubertal children and found significant correlations among insulin resistance indexes (e.g., HOMA-IR) and 24-hr diastolic BP and non-dipping status. ABPM measures (day and night time systolic BP) and left ventricular mass index (LVMI) are higher in children and adolescents with metabolic syndrome compared with controls.⁴¹

Genetics of hypertension. ABPM is also useful in evaluating the genetic risk for HTN. Children with hypertensive parents have higher ABPM, but not casual BP.^{42, 43} Twin studies have demonstrated the high heritability of ABPM patterns.^{44, 45} In a large study of youth with type 1 diabetes, parental ABPM was associated with offspring's BP and maternal DBP was closely related to urinary albumin creatinine ratio in the offspring.⁴⁶

It is not surprising that ABPM is useful in other genetic syndromes at high risk for HTN such as neurofibromatosis⁴⁷ where one study found ½ of children with renovascular lesions on invasive radiology had normal resting BP but all had abnormal ABPM.⁴⁸ Similarly, ABPM is more sensitive in identifying occult HTN in patients with residual coarctation of the aorta,⁴⁹ Williams^{50, 51} and Turner's syndromes.⁵¹

Management of hypertension: ABPM may be a valuable tool for measuring changes in BP associated with interventions in children and adolescents, such as diet, exercise and anti-hypertensive drugs. When compared to traditional office BP measurement, ABPM offers a better appreciation of the temporal effects of drugs, a larger amount of data per reading, greater reproducibility and a more accurate reflection of BP during the relevant, free-living ambulatory state.⁵² Still, only a limited number of clinical trials to-date have been performed using ABPM as an outcome measure.^{53, 54} due to current limitations in

its applicability in research.⁵⁵ In existing clinical studies, ambulatory systolic and diastolic BP were shown to decrease with diet and exercise intervention, specifically increases in habitual physical activity and reduced dietary salt and sugar intake.⁵⁶ However, in salt-sensitive subjects, day-time but not night-time ABPM was reduced on low salt diet.⁵⁷ Exercise alone has also been shown to reduce 24-hour systolic BP measured by ABPM in obese patients, independent of body weight or fat reduction.⁵⁸ Breathing awareness meditation was found to be superior in decreasing ABPM as compared to life skills training and health education in school age children.⁵⁹

Pediatric studies have also been conducted measuring ambulatory BP in response to pharmacological anti-hypertensive treatment. Pharmacotherapy with ACE inhibitors (enalapril) and angiotensin receptor type I blockers (losartan) have been shown to reduce ambulatory systolic and diastolic BP. The anti-hypertensive effect of pharmacotherapy administered concurrent to lifestyle interventions has been shown to be greater than that achieved with lifestyle modification alone.⁵⁶ ABPM is also useful in determining 24-hour effect of other drugs known to affect BP, such as hydrocortisone⁶⁰ and immunosuppressants used after heart transplantation.⁶¹

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Figure 1



*Normotensive < Masked HTN P=0.039; †Masked HTN = Confirmed HTN P=0.097. N = 194; adapted from Mitsnefes JASN 2010;21:137-144.

Figure 1. Prevalence of LVH for 9-15 year olds with CKD by BP category from the CKiD study. Normotensive < Masked HTN; *P=0.039; Masked HTN = Confirmed HTN; †P=0.097. Modified from Mitsnefes et al¹⁸ with permission of American Society of Nephrology in the format Republish in a journal/magazine via Copyright Clearance Center.