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EDITORIAL COMMENTARY

Ambulatory blood pressure monitoring in children: imperfect yet essential

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Abstract There has been increasing emphasis on hypertension and early cardiovascular disease in the pediatric age group over the past decade as a result of various factors, including the obesity epidemic and publication of new clinical guidelines. A key component of identifying children and adolescents with definite or potential hypertension is proper blood pressure (BP) measurement. While ambulatory blood pressure monitoring (ABPM) offers the potential for improved detection of youths at increased cardiovascular risk, it has not been widely adopted. This commentary highlights the crucial role of ABPM in the context of current trends, while at the same time identifying the current barriers to more widespread application of this technique. Chief among these is the lack of a robust, universally applicable database of pediatric ABPM normative values. Even in the absence of ideal normative data, ABPM can and should be widely applied, and a potential algorithm for such an approach is presented.

Keywords Ambulatory blood pressure · Children · Adolescents · Race · Ethnicity · Practice guidelines

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Ambulatory blood pressure monitoring (ABPM) is not as widely used in the evaluation of pediatric patients with suspected or known hypertension as it is in adults. Why is this the case, and what is the rationale for increased application of ABPM in pediatrics? This commentary will review these issues in detail and offer a proposal for more widespread pediatric application of ABPM.

Cardiovascular risk is on the rise in children and adolescents

The epidemiology of elevated blood pressure (BP) in children and adolescents is changing. A 2004 analysis [1] of National Health and Nutrition Examination Survey (NHANES) data in the United Sates (US) demonstrated that overall BP levels in US children and adolescents have increased over the past decade: systolic BP was found to be 1.4 mmHg higher in 1999–2000 compared to 1988–1994, and diastolic BP was 3.3 mmHg higher. This increase was more pronounced in non-Hispanic black and Mexican-American children, suggesting that racial differences in BP between different racial/ethnic groups [2] have their origins in childhood.

A more recent review of BP data in 8 to 17-year-old children from the NHANES and other related population-based studies conducted in the US from 1963 to 2002 also demonstrates an increase in the prevalence of high BP in children [3]. As illustrated in Fig. 1, the prevalence of pre-hypertension among all US children has now reached 10%, and the prevalence of hypertension nearly 4%. Consistent with the earlier analysis by Muntner [1], Din-Dzietham demonstrated that the recent trends in high BP have had a much greater effect on non-Hispanic blacks and Mexican-Americans than on whites [3], mirroring the increased risk of hypertension and cardiovascular disease seen among minority adults [2, 4].

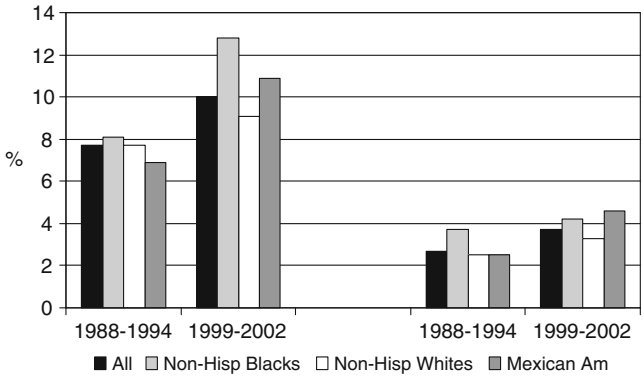

Fig. 1 Prevalence of pre-hypertension (*left-hand bars*) and hypertension (*right-hand bars*) among U.S. children in 1999–2002 compared to 1988–1994 [3]

Underlying this shift in the epidemiology of childhood BP is the childhood obesity epidemic. The prevalence of obesity among American children has more than tripled over the past 30 years, now approaching 17% in adolescents and 19% in younger children [5]. Similar trends have been seen in many other countries across the globe [6]. Hypertension is a well-known consequence of obesity in both adults and children; indeed, among adolescents, obesity-related hypertension has become one of the commonest forms of hypertension seen clinically [7]. Obesity also has other significant adverse cardiovascular implications in addition to elevated BP, including increased inflammation, dyslipidemia, and microalbuminuria (itself associated with kidney damage). In a recent study, it was projected that the increase in childhood obesity in the United States will result in a significant increase in obesity among 35-year-olds by 2020, which could then translate into a significant increase in adult cardiovascular disease [8].

Diabetes and chronic kidney disease (CKD) are two other increasingly common chronic childhood diseases associated with elevated cardiovascular risk. Both type 1 and type 2 diabetes mellitus (DM) appear to be increasing in incidence among US children, with an estimated 154,000 children affected with either type 1 or type 2 DM as of 2006 [9]. While type 2 DM is still relatively infrequent, incidence rates are greater in minority adolescents, especially among Native Americans. Cardiovascular disease is the leading cause of death in adults with diabetes, and similar risk factors for cardiovascular disease (elevated BP, dyslipidemia, elevated C-reactive protein, microalbuminuria) have been demonstrated in adolescents with DM as in adults with DM, especially adolescents with type 2 DM. Abnormal ambulatory BP profiles, especially blunted nocturnal dipping, are commonly seen in patients with types 1 and 2 DM, and have been associated even in adolescents with the development of microalbuminuria [10], an early marker of nephropathy. Casual BP (cBP) measurements, on the other hand, have not been correlated to outcomes in diabetes [11].

It is well established that there is an emerging epidemic of CKD in the US; how many children are affected with CKD is impossible to determine due to less frequent laboratory testing in children than adults and the lack of automatic estimated GFR (glomerular filtration rate) reporting in patients aged <18 years. However, many studies have documented that significantly elevated cardiovascular risk is present in patients with childhood-onset CKD, and it is now clear that cardiovascular disease is the leading cause of morbidity and mortality in young adults with childhood-onset CKD [12]. Recent data from the CKiD study demonstrating a remarkably high prevalence of uncontrolled and even undiagnosed hypertension among children with CKD [13] further reinforces this conclusion. Significant associations have also been demonstrated between 24-h BP patterns and left ventricular hypertrophy and CKD progression [14, 15] that were not apparent using cBP measurements. Unfortunately, as will be discussed below, the strength of these findings are somewhat uncertain due to the weaknesses in the currently available pediatric ABPM norms.

The emerging epidemic of cardiovascular disease in the young calls for innovative strategies to detect at-risk populations and institute appropriate preventative measures. Yet one of the most important cardiovascular risk factors, elevated BP, remains one of the most difficult to accurately detect in children and adolescents. Current consensus recommendations from the National High Blood Pressure Education Program (NHBPEP) state that children should have resting BP measured "…at least once during every health care episode" [16] in order to screen for elevated BP. Unfortunately, accurate BP measurement in children is complex, calling for specialized training, equipment that may not be readily available, and familiarity with cumbersome tables of normative BP values [17]. Numerous studies have documented problems with cBP measurement, including observer bias, digit preference, the white coat effect, and regression to the mean, among others [11, 18–20]. Current normative data for cBP are based on values obtained by auscultation, yet many practitioners are now using automated devices for routine BP measurement [21]. Furthermore, and perhaps most significantly, there are no outcome data in pediatrics that tie cBP values in childhood or adolescence with either hypertensive target-organ damage or long-term cardiovascular risk. Thus, reliance on cBP measurement will be inadequate to detect those children and adolescents at risk for future cardiovascular disease, which in turn will make institution of appropriate preventative measures difficult if not impossible.

The potential importance of ambulatory BP monitoring

ABPM offers a number of advantages that can overcome the shortcomings of cBP measurements [11, 18–20]. With

ABPM, BP is measured in the patient's usual environment, eliminating the white coat effect and allowing assessment of circadian variability (i.e., awake vs. sleep BP) neither of which are possible with cBP measurements. ABPM is the only technique that can detect masked hypertension (normal office BP but elevated out-of-office BP), which is associated with increased cardiovascular risk and development of target-organ damage [15, 22, 23]. Additionally, ABPM allows estimation of the mean BP, BP load (percentage of elevated readings) and BP variability, all of which have been shown to have important prognostic implications.

Abnormalities of ambulatory BP predict adverse cardiovascular events in adults such as myocardial infarction, stroke, and death [20], and also predict the development of hypertensive target-organ damage (e.g., left ventricular hypertrophy) in both adults [20] and children [11, 15, 22, 23]. Given this, ABPM is superior to cBP for detecting the elevated cardiovascular risk associated with conditions such as obesity, diabetes, and CKD, and therefore would enable earlier implementation of interventions designed to reduce future cardiovascular disease.

Several distinct sub-populations of children and adolescents could benefit from more widespread use of ABPM, including obese children and minority children. Routine incorporation of ABPM into the evaluation of such children would permit accurate detection of those with either persistent ambulatory hypertension, masked hypertension, or blunted nocturnal dipping, thereby identifying those who might need earlier institution of pharmacologic antihypertensive treatment. Children with diabetes and chronic kidney disease would clearly benefit from routine screening by ABPM given the extensive documentation of abnormal ambulatory BP profiles in these conditions.

In the clinical trial setting, ABPM has been applied extensively to studies of antihypertensive medications, where it has a number of distinct advantages over cBP measurements, including elimination of inter-center variability, reduction of required sample size, and calculation of trough-to-peak ratio, an important tool for assessment of 24-h BP control [24]. Diagnostically, not only can ABPM identify patients with white coat hypertension but it can also help differentiate between secondary and primary hypertension [25, 26], thus facilitating the identification of children who require a more thorough work-up. Finally, ABPM can be used to guide treatment [27] and also is crucial in the management of patients with resistant hypertension [28]. These advantages of ABPM have led to enthusiastic clinical and research use of ABPM among pediatric hypertension specialists [11, 29], and also to recommendations for more widespread pediatric use of ABPM by consensus organizations such as the NHBPEP [16] and American Heart Association (AHA) (Table 1) [19].

Table 1 Recommended indications for ABPM in pediatrics [19]

- Confirmation of the diagnosis of hypertension (HTN): true HTN vs. white coat HTN; masked HTN
- Assessment of the severity and persistence of BP elevation
- Determination of dipping status in patients at high risk for end-organ damage
- Evaluation of the effectiveness of antihypertensive drug therapy
- Accurate evaluation of BP levels in chronic pediatric diseases associated with hypertension
- Prediction of the development of hypertension related target-organ damage.

Robust normative ABPM data are lacking in children and adolescents

In the clinic, however, routine application of ABPM in children and adolescents remains limited. Why is this? Certainly issues of equipment cost and reimbursement are significant in many settings, although there are ample data proving the economic value of ABPM in children [30], as well as recommendations for insurance coverage by health authorities [31]. However, a more likely explanation is uncertainty as to how to analyze ABPM studies in the young, a topic highlighted in another article in this issue of *Pediatric Nephrology* [32].

Routine application of ABPM as described above and as advocated long ago [29] requires valid normative data that can easily be utilized clinically. In adults, the widespread use of ABPM for both clinical care and research has produced well-established normal values for ABPM that have been tied to clinical outcomes [33]. Unfortunately, currently there are limited normative pediatric ABPM data available to pediatric clinicians and researchers. Whereas the currently used tables of normal cBP in children and adolescents published by the NHBPEP [16] are based on BP measurements obtained in over 83,000 healthy American children, the most widely used normative values for pediatric ABPM, in contrast, are based upon ABPM studies conducted in approximately 1,100 Central European Caucasian children [19, 34, 35]. Although this dataset has been adopted out of necessity, it lacks racial and ethnic diversity, contains a limited number of subjects <140 cm in height, and demonstrates a striking lack of variability of diastolic ambulatory BP (Fig. 2). Due to these deficiencies, it is frankly unknown whether this dataset is applicable to ABPM conducted in populations of children different from those studied by the German Working Group. As noted in a recent scientific statement on pediatric ABPM issued by the AHA, "…there is a need for larger data sets, including normative data in healthy nonwhite populations." [19]

An example of the problem created by the lack of ethnic diversity in the Central European pediatric ABPM dataset can be seen in studies conducted in the multi-ethnic CKiD cohort, which contains approximately 30% minority subjects.

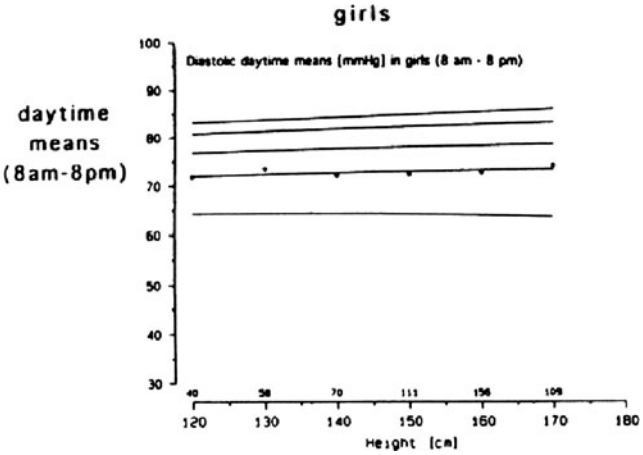

Fig. 2 Graph of mean daytime diastolic ambulatory BP for girls according to height in the Central European pediatric ABPM database (reprinted with permission from [33])

Other pediatric researchers studying primarily minority populations have also struggled with this issue [31, 36]. It is well known from both cross-sectional and longitudinal studies that African Americans, for example, have higher nocturnal BP and reduced nocturnal BP dipping compared to Caucasians [37–39]. In one small pediatric study of ABPM in healthy children, differences in both systolic and diastolic ambulatory BP were seen between African American and Caucasian subjects [40]. Use of the Central European pediatric ABPM dataset could therefore lead to misclassification of ambulatory BP when applied to studies conducted in populations of multi-ethnic children, or when interpreting clinical ABPM studies conducted in minority children.

The second issue related to use of the Central European pediatric ABPM data concerns the limited height distribution in that population, which may limit its application to children with health conditions such as chronic kidney disease. Here again the studies conducted by the CKiD investigators are instructive. With a median GFR of ~40 ml/min/1.73 m [2], the CKiD cohort contains a disproportionate number of children with short stature. Despite this, the NHBPEP normative data for resting childhood BP were easily used to classify cBP in that population [13]. However, the lack of valid normative values for shorter children made the analysis of ambulatory BP in the CKiD population more problematic. Specifically, while 42% of the ABPM studies conducted in CKiD have been in participants <140 cm in height, the Central European pediatric ABPM normative data were generated from a population in which only 16.9% were <140 cm [34, 35]. This has led to the decision by the CKiD investigators to rely upon the older publication from the German Working Group [34] instead of the more recent reanalyzed dataset [19, 35], simply because the older publication included some indication of 'normal' ABPM values in children <140 cm in height.

A more perplexing issue with the Central European pediatric ABPM dataset [34, 35] is that diastolic ambulatory BP values show essentially no variation by age or by height (Fig. 2), a feature that stands in sharp contrast to the well-known increases in resting diastolic BP by age and height seen in the NHBPEP database [16]. Systolic ambulatory BP does show the expected increases by age and height, however, which is consistent with resting BP data. While the fact that a similar lack of diastolic ambulatory BP variation was not seen in another large study that utilized an auscultatory ambulatory BP device [41] suggests that perhaps this issue is device-related, at least one small pediatric study that utilized an oscillometric device did demonstrate an increase in diastolic ambulatory BP with age [40]. Two other potential explanations are either the relatively small sample size used to generate the Central European dataset, or perhaps the fact that the Central European investigators utilized only 18 h of data from the 24-h ABPM studies [34, 35]. To date, however, no other large-scale study of

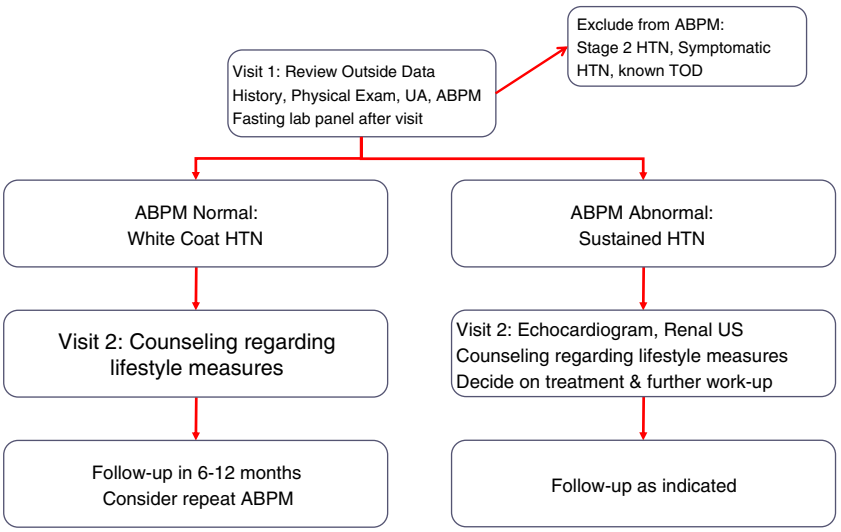

Fig. 3 Proposed routine application of ABPM in the evaluation of children with suspected hypertension. Children with confirmed cBP elevation are scheduled for an initial screening visit. At the conclusion of the visit, ABPM is performed (with a few exceptions), and the results of the ABPM study are then utilized to guide further evaluation and management

pediatric ABPM has been conducted to either confirm or disprove the lack of diastolic ambulatory BP variation.

The implications of this issue, particularly for younger or shorter children, are significant: if ambulatory diastolic BP actually does increase with age and height, use of the current dataset results in an underestimation of ambulatory hypertension in younger/shorter children. Further, given the high percentage of young and/or short children with CKD who may undergo ABPM, it is possible that diastolic BP elevation in such children will be under-diagnosed, which would then lead to under-treatment of hypertension and possibly more rapid progression of CKD [42].

With respect to research, expansion of ABPM to pediatric antihypertensive trials, a major use of ABPM in adult cardiovascular clinical research, is simply not possible without appropriate normative data, especially in the United States, given the requirements from the Food and Drug Administration for enhanced enrollment of minority children into such studies. This is especially problematic given the increasing prevalence of pediatric hypertension, especially among minorities (see above), and the recently reported increased use of antihypertensive medications in children and adolescents [43].

The final practical issue with the currently utilized pediatric normative dataset is highlighted in the report of Bell et al. [32]: that being which version of the Central European data should be used? In 2002, Wühl and coworkers [35] published LMS-corrected analysis of the original ABPM data published by Soergel [34] because of significant skewing of ambulatory BP in the original publication. Use of this updated analysis was actually recommended in the recent AHA consensus statement [19], which also included new tabular versions of the Wühl data not available in their 2002 publication. There is the potential for confusion among clinicians given the different versions of the data available. Fortunately, this does not appear to result in significant differences in analysis, but clearly it is important—for both clinicians and researchers—to consistently utilize the same version of the normative data over time [32].

In summary, while more widespread use of ABPM in children and adolescents offers enormous advantages over cBP measurement in detecting those at increased risk of cardiovascular disease, currently available normative pediatric ABPM data have significant limitations, particularly as applied to non-Caucasian children. The result is that efforts to expand routine clinical usage of ABPM and to advance research in pediatric cardiovascular disease utilizing ABPM have been hampered to some extent, and will continue to be hampered until better normative data are available.

Despite the problems, how should ABPM be used?

The case for wider application of ABPM in children and adolescents was made with the first publication of the German Working Group data [29], and has been reinforced by consensus organizations on numerous occasions since then [16, 19, 44]. Given this, it seems that ABPM should indeed be applied when evaluating children and adolescents with elevated BP.

At our center, we have decided that the enormous advantages of ABPM discussed herein, most notably the ability to screen out children with white coat hypertension, identify those with potential secondary hypertension, and guide the therapy of those with hypertensive CKD, outweigh the limitations of currently available normative data. We have developed a strategy for evaluating children and adolescents with elevated BP in which ABPM plays a central role (Fig. 3). While this approach does require consistency in performance and evaluation of ABPM studies, and meticulous follow-up by a team of providers, we believe that it represents the state-of-the-art in clinical application of ABPM in pediatrics. We do await the development of improved normative data that would reduce the uncertainties discussed herein that currently limit true routine application of ABPM in children and adolescents.

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