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PEDIATRIC HYPERTENSION (JT FLYNN, SECTION EDITOR)

Progression of Prehypertension to Hypertension in Adolescents

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Abstract In the 2004 report from the National High Blood Pressure (BP) Education Program Working Group on BP in Children and Adolescents, the term "high normal BP" was replaced with the designation "prehypertension". It was proposed that BP levels that were higher than normal but did not reach the level of hypertension posed an increased risk for progression to hypertension. The overall intent of this description was to help identify children who were at the greatest risk for the development of hypertension. These are children and adolescents for whom targeted prevention programs are expected to be most beneficial. Following the 2004 report, the prehypertension condition has been examined and described in adolescents as well as adults. This review summarizes the knowledge that has been gained on prehypertension including clinical characteristics, rates of progression to hypertension, and evidence of cardiovascular pathology.

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Introduction

The theory that primary (or essential) hypertension has its origins in the young was proposed in the first report from the National Heart Lung and Blood Institute (NHLBI) on high blood pressure (BP) in children, published in 1977 [1]. Over subsequent years the theory on childhood origins of hypertension has been supported by a substantial body of epidemiologic data that link higher BP levels in childhood with early onset hypertension in adulthood [2]. Cohort studies that obtained repeated measures of BP from childhood into young adulthood describe tracking of BP, with higher BP levels in childhood corresponding with higher BP levels in young adulthood. The BP tracking phenomenon was confirmed by Chen and Wang [3] in their meta-analysis on 50 published cohort studies, representing diverse populations. Their analysis demonstrated an overall average tracking coefficient of 0.38 for systolic BP, thus confirming the observation that higher BP levels in childhood are associated with higher BP levels in young adulthood.

Both epidemiologic and clinical data in adults link a BP level above 140/90 mm Hg with a marked increase in risk for morbid events. However, no such data are available to link a BP level in childhood with an event such as heart failure, kidney failure, stroke, or death in adulthood some decades later. In the absence of outcome data on events that relate back to BP levels in childhood, the definition of hypertension in children and adolescents has been a statistical definition that is based on a body of normative data in children and adolescents. The upper 5 % of the normal BP distribution continues to be the basis on which hypertension

in children and adolescents is defined [4]. This definition becomes more complicated due to the normal progressive rise in BP throughout childhood that is concurrent with growth and development. Therefore, the definition of hypertension in childhood is systolic and/or diastolic BP that is ≥95th percentile according to sex, age, and height. Because of consistent observations of variability in BP measurements in children, along with concerns about over-diagnosis of hypertension in children, a further requirement for defining hypertension in children is that the average BP must be ≥95th percentile over at least three separate measurement periods.

Previously, children who had a BP measurement above the 95th percentile but, with repeated measurements, had an average BP that was just below the 95th percentile were considered to have "high normal BP". The 2004 National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (Fourth Report) [5], in parallel with recent updated recommendations for the evaluation of elevated BP in adults [6], created a new designation of "prehypertension" to identify children at greatest risk for developing future hypertension. The definition for prehypertension replaced the term "high normal BP". The criteria defining prehypertension were also statistically based and reflected expert opinion. The BP category of prehypertension in both adults and children was designed to identify a group of individuals for whom targeted preventive efforts could be most beneficial. This review discusses the reports on prehypertension that have been published since the 2004 Working Group report with consideration on the evolution of hypertensive disease beginning in the young.

Definition of Prehypertension

The clinical evaluation of high BP is usually based on BP measurements obtained in an office or clinic setting where the preferred method of measurement is by auscultation. Based on office, or "casual" BP measurement, the definition for prehypertension in adults is systolic BP that is 120-139 mmHg and/or a diastolic BP between 80-89 mmHg [6]. In children, prehypertension is defined as systolic and/or diastolic BP≥90th percentile but <95th percentile for age, sex, and height according to normative tables published in the Fourth Report [5]. However, during adolescence, the 90th percentile often exceeds the adult threshold of 120/80 mmHg. Therefore, in adolescence, beginning at age 12 years, the BP range that defines prehypertension is ≥120/80 mmHg but<95th percentile.

The diagnosis of hypertension in children requires an average systolic or diastolic BP ≥95th percentile from measurements taken on three separate occasions. However, no recommendations were made in the Fourth Report on the necessity for repeated BP measurements for classification of prehypertension. Recommended interventions for children with a BP measurement in the prehypertension range were lifestyle counseling that included an age appropriate optimal diet, increased physical activity and weight control for overweight and obese children. It was also recommended that the child's BP be monitored every 6 months in order to determine if there is improvement in BP level or progression to sustained hypertension.

More recently, a definition of prehypertension that is based on ambulatory blood pressure monitoring (ABPM) has also been proposed for children [7]. ABPM captures multiple BP measurements throughout a 24-hour time period, and thus provides a more complete assessment of an individual's BP pattern. In hypertensive adults, ABPM values correlate better than casual BP values with morbidity and mortality [8]. Recent reports also provide evidence that in hypertensive children ABPM values correlate better than casual BP values with measures of target organ damage [9–14]. It has not yet been determined if certain ABPM profiles identify children with greater risk for progression to hypertension. However, a recent scientific statement from the American Heart Association proposed that children with a mean 24-hour BP<95th percentile but a BP load (percentage of readings and/or time≥95th percentile) between 25 – 50 % should be considered prehypertensive [7]. Further observations are needed to determine if an increase in BP load, as ascertained by ABPM, is indicative of greater risk for progression to hypertension.

Prevalence of Prehypertension in Children and Adolescents

At the time that prehypertension was defined in the Fourth Report, the current prevalence of hypertension in childhood was estimated to be about 1 - 3 %, and the prevalence of prehypertension in childhood was not known. A concurrent publication by Muntner et al [15] reported on an analysis of data from the National Health and Nutrition Examination Surveys (NHANES) that demonstrated childhood BP levels were increasing. The authors found that the increase in childhood BP levels were largely, but not entirely, due to the childhood obesity epidemic. Subsequently, another analysis of childhood data in NHANES and earlier surveys by Din-Dzietham et al [16], confirmed that in recent decades there has been an increase in prevalence of hypertension in children. According to current reports the prevalence of childhood hypertension ranges from 3 - 5 % in US children with higher rates among minority adolescents [17, 18•, 19•, 20–23]. These reports consistently describe a strong association of obesity with high BP in both children and adolescents. Hansen et al [24•] applied the criteria for hypertension

to electronic medical record data on well-child care visits of over 14,000 primary care visits. In children with a recorded BP measurement above the 95th percentile, the average of three separate BP measurements was computed. These investigators determined the prevalence of hypertension to be 3.6 % in children and adolescents between the ages of 3 and 18 years. In a study, limited to adolescents and based on in-school BP screening, the prevalence of hypertension in a cohort of 6790 adolescents was reported at 3.2 % [18•].

Prehypertension, as currently defined in the 2004 Fourth Report [5], is based on a single BP measurement from the 90th to <95th percentile (or 120/80 mm Hg to <95th percentile in adolescents). Based on BP measurements at a single time point, the reported prevalence of prehypertension among adolescents ranges from 12 % to 17 % [18•, 25–28]. These estimates come primarily from US populations with the exception of a single report including 6th grade students from Switzerland [25]. As expected, based on the epidemiology of hypertension, prehypertension in this population is more common among the overweight [18•, 27, 28] and in adolescent males [18•, 26, 28]. Differences by race and ethnic groups are less well understood. McNiece et al [18•] reported a higher prevalence of prehypertension among both African American and Hispanic adolescents when compared to their non-Hispanic White counterparts, but this association has not been confirmed in other studies [27, 28].

A limitation of the prehypertension definition is that it is based on a single BP measurement and does not account for the inherent variability of BP. The definition of hypertension in childhood is more rigorous in that multiple elevated BP measurements are required for diagnosis, largely to account for the BP variability. Hansen et al [24•] also utilized electronic medical data in the primary pediatric care setting to determine the prevalence of prehypertension based on the average of three separate BP measurements. They reported that, among children between the ages 3 and 18 years with primary care visits over a 7-year time period, prehypertension was present in 3.4 %. However, a recent report by Acosta et al [19•] highlights the complexity of trying to create a viable, categorical definition for pre-hypertension given the variability of BP measurements in childhood. As part of a high school screening program in the Houston area, BP was measured in 1020 students on up to three separate occasions if BP remained in the pre-hypertensive or hypertensive range. Almost 30 % of the population had an elevated BP on at least one occasion and over 75 % of them crossed BP categories between sessions (either normalizing or alternating between hypertension and pre-hypertension. Appropriately accounting for this variability within definitions for abnormal BP represents a challenge in both diagnosis and assessing risk for subsequent hypertension. Moreover, the significance of BP variability and its impact on long-term outcomes remains unknown.

Another issue that is built into the challenge of delineating at-risk BP and determining the prevalence of prehypertension is the manner in which prehypertension is defined. The definition of prehypertension as BP from the 90th to <95th percentile reflects a relatively narrow BP range. At a given sex, age, and height, the range from the 90th to 95th percentile for systolic BP is only 4 to 5 mm Hg. However, because the 90th percentile for BP in adolescents generally exceeds the adult threshold of 120/80 mm Hg, the prehypertension definition in adolescents is a mixture of fixed level (≥120/80 mm Hg) for the lower limit and percentile (<95th) for the upper limit. This adolescent definition for prehypertension creates a variable range for prehypertension, as shown in Table 1. The table depicts the systolic BP percentiles for boys from age 13 to 17 years at the 50th height percentile. With increasing age, the systolic BP level for the 90th and 95th percentile increase. When 120 mm Hg is used as the threshold for prehypertension, the BP range for prehypertension increases from 6 mm Hg at age 13 years to 16 mm Hg at age 17 years. Thus, the definition of prehypertension in adolescents inherently decreases the BP percentile threshold for prehypertension as adolescents age. By age 16 to 17 years the prehypertension threshold approximates the 80th percentile. The combination of a mixed definition along with BP variability may explain, to some extent, the higher rates of prehypertension reported in adolescents.

The original intent of the prehypertension designation was to identify children with some degree of risk who could benefit from attention to lifestyle counseling and weight control. What is not clearly resolved are the BP levels, either percentile or measured BP levels, that represent heightened risk. It is possible that repeatedly elevated but "sub-hypertensive" BP levels may represent a higher risk status for subsequent hypertension or hypertension related vascular disease. Further studies on the prehypertensive phenotype and determinants of progression from prehypertension to hypertension will be needed to resolve the best, or most useful, definition of prehypertension.

Table 1 Blood pressure levels for adolescent boys with height at the 50th percentile

SBP	13 yr	14 yr	15 yr	16 yr	17 yr
mm Hg	120	120	120	120	120
90th%	122	125	127	130	132
95th%	126	128	131	134	136
PreHt Range mm Hg	6	8	11	14	16

SBP=Systolic BP

PreHt=Prehypertension

Risk for Progression to Hypertension

A meta-analysis of longitudinal studies on BP levels from childhood to adulthood verifies the consistent phenomenon of BP tracking wherein childhood BP levels are associated with BP levels in later life [3]. Additionally, as demonstrated by the Bogalusa Heart Study, children with elevated BP are 2 - 3 times more likely to develop essential hypertension in young adulthood [29]. The impact of the current designation of prehypertension on a more immediate progression of BP during adolescence is less well understood. Falkner et al [26], identified a sub-group of adolescents in the National Childhood Blood Pressure database with repeated BP measurements at intervals of 2 and 4 years. Among adolescents with initial BP in the prehypertensive range, the estimated rate of progression from prehypertension to hypertension was approximately 7 % per year. This study was limited as both the initial the final designation of hypertension or prehypertension were based on a single measurement session rather than on average BP across three different measurement sessions, as required for diagnosis of hypertension.

The rate for progression from prehypertension to confirmed hypertension based on BP measurements at three separate visits is significantly lower as recently described by Redwine et al [30••]. In a retrospective review of their Houston-based school screening program, hypertension developed among 1006 adolescent participants at a rate of 0.7 % per year with a mean follow-up time of 2.1 years. Adolescents who were normotensive at initial screening developed hypertension at a rate of 0.3 % per year while the incidence rate among those with prehypertension was 1.1 % per year. Interestingly, a group designated as "at-risk for hypertension" which included subjects who were either prehypertensive at baseline or who had an elevated BP that normalized prior to completing baseline screening had an even higher rate of progression to hypertension at 1.4 % per year. These numbers suggest that adolescents with a high BP measurement and subsequent normal BP measurement may not be "normotensive" as the current guidelines indicate. However, the largest risk group for progression to hypertension in the Houston cohort was adolescents with elevated BP at all three visits. These students developed hypertension at a rate of 6.6 % per year. While these adolescents had BP readings in both the hypertensive and prehypertensive ranges during the baseline screening process, this observation supports the notion that persistent prehypertension may be a more useful definition for a greater and more immediate risk for progression to hypertension in this age group.

Although rates of progression from prehypertension to hypertension described by Redwine et al may seem small, from a clinical and public health perspective, these numbers are quite substantial for a population. Assuming an annual incidence rate of 0.7 % among the current US adolescent population of 17,000,000 (www.census.gov), approximately 119,000 adolescents will develop hypertension over the next year and more than half a million adolescents and young adults will be diagnosed with hypertension within 5 years [31]. It is also notable that hypertension serves as an easily measured biomarker for an underlying progressive vascular disease process which is highly associated with aging. The incidence rate for hypertension among adults participating in the Framingham Heart Study aged 35 - 64 years with optimal BP (<120/80 mmHg) was reported to be 1.3 % per year [32]. The similar incidence rates of 1.1 - 1.4 % per year observed among youth with prehypertension by Redwine et al. suggests that these prehypertensive adolescents may already have vascular abnormalities similar to those found in adults. Studies that compare cardiac and vascular structure, as well as other biomarkers of injury, in adults and adolescents are necessary to determine if prehypertension in adolescence contributes to an acceleration of cardiovascular disease.

Cardiovascular Risks Associated With Prehypertension

There is now some evidence that prehypertension may not just present a risk for future hypertension but is also associated with the presence of active disease. Some adolescents with prehypertension already demonstrate evidence of target organ damage (TOD). Left ventricular hypertrophy (LVH) is the most widely recognized abnormality attributed to high BP in children. Left ventricular mass index (LVMI) is a height adjusted index of LVM. The odds of having an elevated LVMI increases by 54 % for each incremental increase of 1 in the 24-hour systolic BP standard deviation score [33]. Stabouli et al [34] report similar findings in a group of 5 - 18 year olds referred for evaluation of suspected hypertension of which 89 were ultimately normotensive, 10 were prehypertensive, and 25 were hypertensive based on daytime ABPM readings. LVMI increased sequentially across BP groups and the prevalence of LVH was higher among children and adolescents with prehypertension and hypertension (20 % each) than children with normal BP (6.7 %). While the number of children with prehypertension in these studies is small, their findings are supported by larger studies involving both older adolescents and young adults. Individuals with both hypertension and prehypertension in the Strong Heart Study were found to have a three- and two- fold higher prevalence of LVH respectively than their normotensive counterparts [35].

Obesity in childhood has been consistently shown to be associated with both hypertension and prehypertension. Tu et al [36] reported that being overweight raises risk for high BP. Data reported by these investigators demonstrate

that as BMI exceeds the 85th percentile (for age and sex) there is a four-fold increase in prevalence of combined prehypertension and hypertension. The combination of high BP and obesity in adolescents appears to amplify the risk for cardiac pathology. In a study that focused on African Americans, the prevalence of LVH among non-obese adolescents with prehypertension was 19 % and among obese adolescents with prehypertension the prevalence of LVH increased to 57 % [37].

Abnormal pathology associated with prehypertension is not limited to LVH. Urbina et al [38] conducted a study on adolescents and young adults participating in a large cross-sectional study designed to evaluate the independent effects of obesity and diabetes on cardiovascular abnormalities. The investigators detected an independent association between BP and LVMI along with diastolic cardiac dysfunction among prehypertensive participants. The prehypertension participants in this study were also noted to have increased carotid artery intima-media thickness and arterial stiffness. Vascular abnormalities have also been reported in other prehypertensive populations [35] and may vary by ethnic group as demonstrated in the Georgia Cardiovascular Twin Study [28].

There are no longitudinal data that are sufficiently long term to permit defining a level of child or adolescent BP that is associated with an increase in risk for hypertension related events in later life. However, as described above, intermediate markers of cardiovascular disease that are associated with high BP such as increased cardiac mass, vascular stiffness, and metabolic risk factors are being reported in adolescents with prehypertension as well as hypertension. Despite the relatively small study samples in the reports to date, the detection of underlying cardiac and vascular alterations raises a significant concern.

Although the evidence for underlying cardiovascular disease associated with prehypertension in the young remains sparse, it is becoming apparent that the line between those at-risk for hypertensive disease and those who already have hypertensive disease is not distinct. The working definitions of hypertension and prehypertension are statistically based and have relied heavily on the hypothesis that evidence of target organ injury occurs more commonly in children with hypertension than those with normal BP. Some but not all children with hypertension develop target organ injury. Moreover, there is now evidence that some children with prehypertension have findings consistent with target organ injury. These observations suggest that using the 95th percentile as a BP threshold to define hypertension in children and adolescents may underestimate the risk for hypertensive disease.

Also to be considered are other risk factors associated with cardiovascular and metabolic disease. The most prominent of these is the overwhelming impact of childhood obesity and obesity associated abnormalities including diabetes, dyslipidemia, and inflammation. Developing insights on the interactions among these factors on target organ injury will contribute to a more accurate estimate of underlying cardiovascular pathology among adolescents with both hypertension and prehypertension.

Despite the progress that has been made in understanding the childhood phase of primary hypertension, there are major fundamental challenges to address. Evidence to date indicates that characterizing BP beyond a single measurement is necessary to appropriately identify children and adolescents with future risk for hypertension. It is also a challenge to define the BP threshold for injury, or the BP-risk factor profile for injury. It is likely that overcoming these challenges will lead to a better informed and more accurate definition of both hypertension and prehypertension in childhood. Improving the effectiveness of childhood prevention strategies will be critical in reversing current trends for hypertension and cardiovascular disease in both adults and adolescents. Multiple interventions, including weight loss, increased physical activity and a low sodium diet, have been shown to reduce BP and prevent the development of hypertension [6, 39]. Despite this knowledge, our ability to translate this knowledge to long-term successful interventions for both individuals at-risk and in public health programs is limited, as indicated by the continued rise in obesity and hypertension related illnesses. Additionally, the role that pharmacologic therapy may play in conjunction with lifestyle changes in preventing the development of hypertension in adolescents with prehypertension should be explored. The Treatment of Prehypertension Study (TROPHY) study suggests that among adults with prehypertension there may be some benefit from early treatment with certain anti-hypertensive agents [40]. Finally, it should be noted that current evidence regarding prehypertension in children and adolescents is based almost entirely on studies in adolescents and there is very limited information about this condition derived from younger children.

Conclusion

Prehypertension is common among adolescents and presents a clear risk for subsequent hypertension and cardiovascular disease. Prehypertension may also be associated with underlying cardiac and vascular changes. Implementing the lifestyle changes recommended in the Fourth Report [5] is likely to be beneficial for the long-term cardiovascular health of these young patients. Future efforts in this area should focus on refining our definitions for both prehypertension and hypertension, identifying risks associated with prehypertension in younger children, and improving our

prevention strategies at both the individual and population levels.

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