Prehypertension in Adolescents: Risk and Progression

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The presence of hypertensive disease among children and adolescents is rising, with a prevalence ranging from 3% to 5% now reported in some populations.1,2,4–7 This rise in hypertension has been largely attributed to the obesity epidemic also being observed in developed countries and places a growing number of children at risk for the early development of hypertensive sequelae, including myocardial infarction, stroke, and renal failure. Recognizing that the precursors for cardiovascular (CV) disease begin in childhood and that the risk for CV disease begins at relatively low levels of blood pressure (BP), the 2004 National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (Working Group)8 in parallel with recent updated recommendations for the evaluation of elevated BP in adults9 created a new designation of “prehypertension” to identify children at greatest risk for developing future hypertensive disease. This definition for prehypertension was based primarily on epidemiologic normal values and expert opinions and was designed to identify a group of children for whom targeted preventive efforts would be most beneficial. This review examines the knowledge that has been gained regarding the epidemiology and risk associated with prehypertension in adolescents since its inception and highlights future challenges in understanding and preventing the development of hypertensive disease in this population.

DEFINITIONS OF PREHYPERTENSION

Traditional evaluation for hypertension has relied on measuring BP in an office setting preferably with auscultatory methods (Table). Using these casual BP methods, the definition for prehypertension in adults as presented in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) is having a systolic BP in the range of 120 mm Hg to 139 mm Hg and/or a diastolic BP between 80 mm Hg and 89 mm Hg.9 In children and adolescents, prehypertension is defined by a systolic and/or diastolic BP ≥90th percentile but <95th percentile for age, sex, and height according to normative tables published in the Working Group report.8 However, during adolescence, the 90th percentile often exceeds the adult threshold of 120/80 mm Hg and in these cases prehypertension should be considered as BP ≥120/80 mm Hg but <95th percentile. It is also important to note that while recommendations for the diagnosis of hypertension in children require that BP remain elevated on three separate occasions, repeated measures are not necessary to classify an adolescent as prehypertensive. Rather, the Working Group report recommends instituting lifestyle changes as appropriate and continuing to monitor BP every 6 months to evaluate for improvement or progression to sustained hypertension.

More recently, a definition of prehypertension based on ambulatory BP monitoring (ABPM) has also been proposed for children.10 ABPM captures multiple BP measurements throughout a 24-hour period, and thus provides a more complete assessment of an individual’s BP. ABPM values correlate better with morbidity and mortality in hypertensive adults11 and with measures of target organ damage in hypertensive children12–17 than traditional office measurements. Its superiority in identifying adolescents with increased risk for progression to persistent hypertension remains unknown; 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% and 50% be considered prehypertensive.10

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The reported prevalence of prehypertension based on BP measurements at a single point in time as currently defined in the Working Group report ranges from 12% to 17%.2,18–21 These estimates come primarily from US populations with the exception of a single report that included 6th-grade students from Switzerland.18 As expected based on the epidemiology of hypertension, prehypertension in this population is more common among overweight2,20,21 and adolescent boys.2,19,21 Differences by race and ethnic groups are less well understood. McNiece and colleagues2 reported a higher prevalence of prehypertension among both African American and Hispanic adolescents when compared with their non-Hispanic white counterparts, but this association has not been confirmed in other studies.20,21

One early critique of the Working Group report’s definition of prehypertension was that it did not account for the inherent variability of BP as the more rigorous definition of hypertension attempts to do. While this “omission” was in part intentional, reflecting an effort to capture a larger population of individuals at risk for hypertension for whom to specifically target lifestyle interventions, it has been suggested that having an elevated BP on repeated measures may be more representative of true risk for future hypertension. Predictably, the prevalence of prehypertension decreases with this type of definition as demonstrated by Hansen and colleagues,22 who reported that 3.4% of children and adolescents seen by their primary care provider during a 7-year time span were prehypertensive during at least three visits. However, a recent report by Acosta and colleagues3 highlights the complexity of trying to create a viable, mutually exclusive working definition for prehypertension given the fluidity of BP measurements in adolescents. As part of a school screening program in the Houston area, BP was measured in 1020 students on up to three occasions if BP remained in the prehypertensive or hypertensive range. Almost 30% of the population had an elevated BP on at least one occasion and more than 75% of them crossed BP categories between sessions (either normalizing or alternating between hypertension and prehypertension) (Figure 1). Appropriately accounting for this variability within definitions for abnormal BP represents a future challenge although the significance of this variability and its impact on long-term CV outcomes remains unknown.

These results suggest that prehypertension as presently defined may not be a homogeneous entity and that this definition may require further refinement. One approach might be to define low-, moderate-, and high-risk prehypertension, depending on the level of BP, persistence of elevation over time, and perhaps other factors determined to be predictive of progression to hypertension.

### PREVALENCE OF PREHYPERTENSION IN CHILDREN AND ADOLESCENTS

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### RISK FOR PROGRESSION TO HYPERTENSION

Multiple longitudinal studies have established that BP levels track with age such that childhood BP levels are...
associated with BP levels in later life.\textsuperscript{23} Additionally, as demonstrated by the Bogalusa Heart Study, children with elevated BP are 2 to 3 times more likely to develop essential hypertension as a young adult.\textsuperscript{24} The impact of the current designation of prehypertension on the more immediate progression of BP during adolescence, however, is less well understood. Falkner and colleagues\textsuperscript{25} initially described a rate of progression from prehypertension to hypertension of approximately 7% per year among adolescents included in the National Childhood Blood Pressure Database for whom single serial BP measurements were obtained at 2-year intervals. This study was limited as the final diagnosis of hypertension was based on a single measurement session rather than on persistence of elevation across three different points as defined in the Working Group report. The rate for progression to confirmed hypertension based on BP measurements at three separate visits is significantly lower, as recently described by Redwine and colleagues.\textsuperscript{25} In a retrospective review of their Houston-based hypertension school screening program, hypertension developed among 1006 adolescent participants at a rate of 0.7% per year with a mean follow-up 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 patients 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. This suggests that adolescents whose BP is initially high but is normal later may not be “normotensive” as the current guidelines would suggest. However, the largest risk for progression to hypertension in this cohort of adolescents were those whose BP was elevated at all three visits of their baseline screening. These students developed hypertension at a rate of 6.6% per year. While these children had BP readings in both the hypertensive and prehypertensive ranges during the baseline screening process, this does provide some support for the suggestion that persistent prehypertension may be a more useful definition for immediate risk in this age group.

While the rates of progression described by Redwine and colleagues may seem small, from a clinical and public health perspective these numbers are quite substantial. Assuming an annual incidence rate of 0.7% among the current US adolescent population of 17,000,000 (http://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.\textsuperscript{26} Additionally, it should be noted that hypertension serves as an easily measured biomarker for an underlying progressive vascular disease process that is highly associated with aging. The incidence rate for hypertension among adults participating in the Framingham Heart Study aged 35 to 64 years with optimal BP (120/80 mm Hg) was reported to be 1.3% per year.\textsuperscript{27} The similar incidence rates of 1.1% to 1.4% per year observed among youth with prehypertension by Redwine and colleagues suggests that these prehypertensive children may already have vascular abnormalities similar to those found in adults. Studies comparing cardiac and vascular function in these populations are necessary to confirm this hypothesis.

**CARDIOVASCULAR RISKS ASSOCIATED WITH PREHYPERTENSION**

Emerging evidence suggests 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 (Figure 2). Increased left ventricular mass index (LVMl) has been shown to be strongly associated with systolic BP in children referred for evaluation of possible hypertension. The odds of having an elevated LVMl increases by 54% for each incremental increase of one in the 24-hour systolic BP standard deviation score.\textsuperscript{28} Stabouli and colleagues\textsuperscript{29} report similar findings in a group of 5- to 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. LVMl increased sequentially across BP groups and the ultimate 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 3- and 2-fold higher prevalence of LVH, respectively, than their normotensive counterparts.\textsuperscript{30}

Abnormal pathology is associated with prehypertension; however, it is not limited to LVH. Urbina and colleagues\textsuperscript{31} report an independent association between BP and elevated LVMl along with diastolic cardiac dysfunction among prehypertensive adolescents and young adults participating in a large cross-sectional study designed to evaluate the independent effects of obesity and diabetes on CV abnormalities. Patients in this study with prehypertension were also noted to have increased carotid artery intimal-media thickness and arterial stiffness. Vascular abnormalities have also been reported in other prehypertensive populations\textsuperscript{30} and may vary by ethnic group as demonstrated in the Georgia Cardiovascular Twin Study.\textsuperscript{21} Finally, it should be noted that decreased cognitive
function has been reported in children with elevated BP, although differences between hypertensive and prehypertensive children have not been independently evaluated.32

AREAS FOR FUTURE RESEARCH
While the evidence for the true risks associated with prehypertension in children and adolescents remains sparse, it is becoming apparent that the line between those at-risk for hypertensive disease and those already developing it is not as clear cut as current definitions would suggest. Efforts to validate current epidemiologically based definitions have relied heavily on the hypothesis that TOD (early precursors of CV disease in adults) occurs more commonly in children with hypertension than those with normal BP. These efforts have demonstrated that some but not all children with hypertension develop TOD. Additionally, some children with prehypertension already appear to have evidence of CV damage. Thus, current definitions may, in fact, be too high for identifying those with hypertensive disease. It’s important to remember, however, that BP does not act alone in producing TOD and CV disease. Factors such as obesity, diabetes, dyslipidemia, inflammation, and tobacco exposure have all been implicated in this process.9,33 Understanding the interactions among all of these factors on the development of TOD will be critical in developing precise definitions for both prehypertension and hypertension. Ultimately, a stratified approach to the definition of abnormal BP levels based on the presence of other underlying risk factors may prove more successful than considering BP levels alone.

Characterizing an individual’s BP beyond a single measurement would also likely improve our ability to appropriately identify hypertensive risk in this population. While ABPM is used widely to confirm the diagnosis of hypertension in pediatric patients, this technology may not be cost-effective for screening the general population. Capturing multiple BP readings across different settings is another approach to intensified BP screening. However, developing an understanding of the significance of the variability that occurs between readings and across settings will be essential to effectively identify children at-risk using this strategy. Ultimately, an approach to defining abnormal BP that combines both methods will likely yield the highest sensitivity and specificity particularly if more complex techniques for examining the profile generated by capturing BP at multiple points in time are developed. In the end, both current and any future definitions for prehypertension need to be evaluated by long-term prospective studies to truly understand the risks associated with this designation.

Improving our effectiveness with prevention strategies will also be critical in reversing current trends for hypertension and CV disease. Multiple interventions have been shown to reduce BP and prevent the development of hypertension including weight loss, increased physical activity, and a low-sodium diet.9,33 Despite this knowledge, our ability to translate this knowledge to long-term successful interventions for individuals at-risk and in wide-scale public health programs is sorely limited as indicated by the continued rise in obesity- and hypertension-related illnesses in our country. 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 Trial of Preventing Hypertension (TROPHY) study suggests that for adults with prehypertension there may be some benefit from early treatment with certain antihypertensive agents.34 Ultimately, it should be noted that current evidence regarding prehypertension in children and adolescents is based almost entirely on studies from adolescent populations with

FIGURE 2. Left ventricular mass in youth by blood pressure (BP) classification. *P<.05 normotensive vs prehypertensive patients; P<.01 normotensive vs hypertensive patients. †P<.05 for normotensive patients †prehypertensive patients †hypertensive patients.
practically no information about this disease process derived from younger children.

CONCLUSIONS

Prehypertension is common among adolescents and presents a clear risk for future persistent hypertension and CV disease. Prehypertension may also be associated with ongoing CV changes. Thus, implementing the lifestyle changes recommended in the Working Group report is likely to be beneficial for the long-term CV health of these children. 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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