Review

Pulsatile and Steady-State Pressure Trends in Children: A Window into the Future?

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Key Words

Pediatric obesity · Cardiovascular risk factors · Blood pressure · Arterial stiffness · Atherosclerosis

Abstract

The aorta has limited ability to accommodate increasing body size by remodeling. The dramatic rise in pediatric obesity threatens to overwhelm this intrinsic remodeling program and lead to abnormal aortic function. As hypothesized, pulse pressure, as an index of aortic function, has indeed risen dramatically in parallel with the rise of pediatric obesity, while at the same time mean arterial pressure, as an index of small resistance artery function, has fallen. These divergent large-artery-versus-small-artery indices may combine to explain the counterintuitive decrease in systolic blood pressure in children and adults during the global obesity pandemic. The pathophysiologic mechanisms underpinning these contrasting trends are not yet known.

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Across the globe, pediatric obesity rates are climbing. A concurrent rise in the prevalence of diabetes mellitus, cholesterol disorder, and hypertension can also be observed, effectively increasing childhood risk of overweight and obesity-related cardiovascular disease (CVD). In the United States, more than one third of children carry excess weight, close to 20% present with abnormal lipid levels, and almost 5% have abnormal blood pressure (BP) [1–3]. Furthermore, it has been shown that a large proportion of children carry their CVD risk factors into adulthood; ≥70% of overweight children will be overweight or will become obese as adults [4, 5]. Pediatric excess weight threatens to disturb the decreasing trend of adult coronary heart disease mortality seen over the past 30 years [6], which, if realized, would be followed by a consequent decrease in the quality of life, shorter life spans, and heavy utili-

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zation of medical resources. Furthermore, excess weight substantially increases the likelihood of high BP, the combination of which has the potential to threaten a child's cardiac health far into the future [2, 5, 7–11].

The effects of abnormal adolescent BP on future cardiac health have been demonstrated in recent longitudinal studies. For example, systolic (SBP) and diastolic BP (DBP) were measured in Swedish adolescent male military conscripts and were found to predict future CVD mortality in a continuous fashion [12]. Furthermore, an inverse-graded relationship between BP category and freedom from CVD events was seen in predominantly Caucasian male college matriculates [13]. Thus, adolescent BP adds additional information and could play a role in CVD prevention. However, the association between childhood elevated BP and adult mortality has not been thoroughly investigated. One study by Franks et al. [14] reported a positive association between physician-reported hypertension and early mortality in children of Native American origin (mean age 11.3 years). Importantly, it was found that CVD was not the primary mechanism that led to early mortality in this population despite an inordinately high prevalence of CVD risk factors. Secondly, a recent temporal study drawn from administrative databases revealed that the incidence of stroke decreased in all groups with the exception of adolescents and young adults, where it increased dramatically. In these children, the prevalence of CVD risk factors was greater [15]. Therefore, early-life BP does appear to predict life-threatening events both in the short and long term, although its role in younger children is unclear.

The challenges inherent in demonstrating the association between childhood BP and cardiac events are multifarious and complex. First, longitudinal tracking is logistically challenging. Extensive resources, dedicated funding, and institutional memory all determine an institution's success in collecting statistically and clinically significant data on CVD events over a time span of 30–50 years. Based on the current scientific funding climate, it is debatable whether or not long-term studies can be carried out.

The second challenge involves the ever-changing nature of kids. If children are constantly changing, how do we distinguish between natural variation and accumulated CVD insults? Among adults, data suggests that subclinical atherosclerosis can predict CVD events. The role of carotid intima-media thickness (CIMT) among clinical and subclinical atherosclerosis patients is intriguing. Studies have shown that common CIMT does not offer more information than CVD risk factors alone, but that internal carotid plaque adds to discrimination in comparison to classic CVD risk factors [16]. While adult physicians may not find common CIMT valuable in its predictive power, CIMT may prove to be an advantageous tool for pediatric-focused investigators searching for a summary index of accumulated and fluctuating CVD risk factors. More data is needed in order to fully understand the effect of early-life CIMT on future CVD events.

A third challenge is regarding what constitutes gold-standard data. Leaning on principles outlined by Hill's criteria on causation and supported by research that shows how intuitively satisfying cardiac interventions can actually be misleading or dangerous, the scientific community is beginning to recognize that the 'right' answer is sometimes irrational [17, 18]. In an effort to avoid such miscalculations, randomized blinded placebo-controlled trials (RCT) have been developed in order to determine the 'truth'. The RCT undoubtedly bolsters scientific findings, but does a lack of RCT then condone inaction or prevent and dissuade alternative action? For example, does one need an RCT to determine whether children should eat vegetables? These types of questions exemplify the difficulties in testing primordial and primary CVD prevention strategies.

In the absence of an RCT conducted over several decades, several recent observational studies provide useful data. Long-term observational studies have revealed that single point-in-time measurements of CVD risk factors in youth can predict subclinical atherosclerotic

changes, including CIMT and arterial stiffness, especially among the adolescent population. For example, 41% of children with normal BP presented with elevated BP as adults, while 59% of children with elevated BP maintained their elevated status in adulthood [19, 20]. In another study [21], researchers investigated the association between childhood BP and left ventricular (LV) hypertrophy, a precursor to congestive heart failure. Just as middle-aged BP predicts later LV mass and early adult BP predicts middle-aged LV mass, recent studies have demonstrated that elevated childhood BP and BMI independently determine early-adult LV mass [21, 22]. Moreover, a recent observational study [20] has demonstrated that children who improved their BP upon entering adulthood had healthier CIMT compared to those with persistently elevated BP. The physiology of the improvement in this study may relate to a decreasing BMI in the resolution group.

In order to mitigate CVD risk factors in patients, providers and researchers are tempted to simply recommend weight loss. However, the answer is not that simple. While nearly 1 in 20 children has elevated BP and excess weight doubles or triples the risk of abnormal BP, it turns out that population data from the US reveals approximately 50% of children with abnormal BP are of normal weight [23]. This counterintuitive outcome can be derived from a simple calculation: a small proportion of a large number still amounts to a relatively larger number. Applied here, a relatively smaller proportion of a larger normal-weight cohort, in comparison to a large proportion of the smaller obese population, still amounts to a significant number of normal-weight youth with abnormal BP.

Trends in population BP over the past three decades are also counterintuitive. Reliable data illustrates a pronounced increase in adult and pediatric obesity around the globe, while also showing that excess weight markedly increases the risk of hypertension in youth and adult populations [24–26]. Since pediatric excess weight and hypertension track into adulthood, it follows that we should be able to classify pediatric hypertension and excess weight as risk factors for adult hypertension and CVD [4, 27]. However, high-quality data reports a stable or decreasing SBP temporal trend in child and adult populations despite increasing obesity [28–30].

We investigated this contrary set of trends by focusing on mechanistic decomposition. Instead of analyzing BP through SBP and DBP values, it has been shown that decomposition into pulse pressure (PP; $SBP - DBP$) as well as mean arterial pressure (MAP; $DBP + PP/3$) can offer further insight into the pathophysiology of high BP, and can also equally predict incident CVD events [31, 32]. Large artery stiffness and flow pulsatility are determinants of PP, and high PP is known to predict incident CVD and is also a precursor of isolated systolic hypertension [32–36]. Key drivers of MAP include small resistance artery function and cardiac output [32]. Sorof et al. [37] found that isolated systolic elevation presented as the most common form of elevated BP in children and was more characteristic in obese children. Additional weight in children may cause incongruity between cardiac output and peripheral resistance as well as between pulsatile blood flow and aortic size. For this reason, we hypothesized that a temporal increase in PP and MAP would accompany the observed rise in pediatric excess weight. We examined the US national population-representative National Health and Nutrition Examination Surveys (NHANES) to interrogate this hypothesis.

In accordance with our postulate that excess weight may alter aortic function during childhood, data from the past three decades reveals that PP values have notably increased alongside the growing prevalence of childhood obesity. More obesity accounts for a substantial proportion of the increasing temporal trend in PP. These observations suggest either that common mechanisms are responsible for a parallel increase in both obesity and PP, or that the national increase in excess weight contributed to the increase in PP. We found that PP was related to age and height. Obesity further augmented the relation between height and PP. Obesity also amplified the relation among PP and age in males, yet not in females. Recent

studies have shown that high PP in normotensive individuals is predictive of future hypertension, and thus the parallel increase in obesity and PP we observed foreshadows the mechanism by which the pediatric obesity epidemic may burden systolic hypertension rates through higher PP in the future [38].

Pathophysiological mechanisms that lead to high PP are exacerbated by excess weight. After the first years of life, the aorta is known to remodel in order to accommodate somatic growth. For example, large arteries increase their diameter to accommodate for higher flow [39–41]. A wider diameter decreases impedance to pulsatile flow and can actually help keep PP in a physiologic range; however, a large diameter can also increase pulsatile and mean tension on the aortic wall. Once active elastic fiber production ceases and is essentially fixed in the first couple of years of life, continuing aortic dilation increases load on elastin and hence requires extracellular matrix remodeling to transfer load from elastin to much stiffer collagen [39, 42, 43]. An increase in wall tension can lead to elastin fragmentation and deposition of stiffer matrix elements, the effects of which can accumulate and lead to increased wall stiffness [39]. In addition, children who are obese exhibit large stroke volume, increased blood volume, and higher pulsatile and steady flow, which, when paired with increased wall stiffness, can contribute to the development of high PP [44]. Thus, higher PP in obese children likely represents the interaction between greater aortic wall stiffness and higher flow, which together exceed the capacity for outward aortic remodeling [45–47]. Repeated cycles of high PP lead to more arterial stiffness with central adiposity as a key driver [35, 36].

Furthermore, the fact that the relationship between PP and height is being amplified by obesity suggests that a prominent increase in pulsatile flow in conjunction with rapid somatic growth and excess weight could overwhelm the aorta's remodeling capacity, resulting in increased PP. Alternatively, matching the aortic diameter and flow could be complicated by obesity, either due to increased aortic wall stiffness or an adverse effect on the endothelial function that inhibits adaptive remodeling through limited transduction of the flow stimulus.

The trends in MAP are complex. Although associations between higher BMI and higher MAP are expected and were found in our investigation, the average MAP decreased throughout the study period. For this reason, obesity cannot be responsible for the decreasing MAP trend. In both sexes, obesity diminished the relationship between MAP and a child's age or height. In theory, it is plausible that countervailing trends in small artery resistance versus pressure pulsatility could occur, given the fact that developing children are able to dissipate excess pulsatile energy while in a physiologic growth period through an increase in the cross-sectional arterial area. For example in adults, angiogenic growth factors relate to pulsatile and steady-state parameters [48]. According to our analysis, population temporal trends in smoking do not explain the downward trend in MAP [49, 50]. The root of the MAP decrement is unclear.

Based on our analyses of pediatric PP trends today, we can predict that a rise in pediatric PP trends today may translate into an increased risk of hypertension and exacerbated CVD endpoints in the future, especially in light of the fact that higher PP correlates with excess risk at any given SBP in adulthood. The cohorts of children examined in previous NHANES studies may reflect this prediction, as they are already starting to experience adverse consequences of elevated PP. For example, a 19% prevalence of elevated BP has been reported in recent studies of 25- to 34-year-old subjects [51]. More troubling, given that the incident stroke risk in adults is greater in individuals with elevated PP [33, 34, 52], studies report a temporal increase in stroke hospitalization for persons between the age of 15 and 34 years, more of whom suffer from hypertension [15]. It is important to note that previous publications, which reported a minimized association between PP and CVD risk, may not be relevant to children and adolescents today, since the effects of perpetual exposure to increased obesity-related PP throughout somatic growth have not yet been studied [32, 52].

Between 1976 and 2008, PP increased synchronously with rising rates of obesity. Therefore, it is critical that population-wide obesity is reconciled, and that mechanistic links between obesity and aortic function are elucidated. Understanding these mechanisms is the only way through which potentially severe adverse sequelae that stem from elevated pressure pulsatility, such as hypertension and consequent CVD, can be prevented.

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