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# Pulse Wave Reflection in Children: Amplification through the Lifecourse

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**Keywords**

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In this issue, Murakami and colleagues detail the presence of wave reflection in the aortic system of well children.[1] Identifying the components of early life blood pressure(BP) are of critical importance as evidence builds on the role of BP in predicting future atherosclerotic cardiovascular disease (ASCVD). Classic literature has demonstrated the ability for historical BP to predict presence of atherosclerotic plaque in younger persons victim to unfortunate mortality like accident and war.[2–5] Recent data shows a continuous relation between adolescent male BP separated into various indices including systolic, diastolic, pulse(PP), or mean(MAP) and eventual adult ASCVD events.[6] Similar data from Native American populations show physician diagnosed hypertension in childhood as a risk factor for early mortality.[7] One study of adolescent males suggests adolescent BP predicts future ASCVD even after adjustment for middle aged BP, underscoring the additive utility of early life blood pressure.[8] Mounting evidence further demonstrates the specific role of elevated BP in preclinical atherosclerotic changes including left ventricular hypertrophy and vascular change.[9, 10] Intriguing longitudinal data even suggests normalization of elevated BP from childhood into adulthood ameliorates these preclinical atherosclerotic change.[11] There are now multiple threads of evidence linking early life BP to preclinical in vivo atherosclerosis, pathological evidence of atherosclerotic plaque, actual ASCVD events and mortality, and even reversal of atherosclerotic change with attenuation in blood pressure.

Turning to physiologic classification, BP may be classified using traditional systolic and diastolic BP per sphygmomanometer. An alternate description classifies BP by PP, an index of large artery properties, and MAP, an index of small artery function. Both combinations predict future ASCVD.[12, 13] But PP and MAP lend themselves to more mechanistic study of BP. For example, recent trends show that population systolic BP in adults is declining throughout the world despite rising obesity.[14, 15] These contradictory trends could be explained by percolation of antihypertensive therapy in various parts of the globe. But similar BP trends are seen in children and children are not being treated.[16–18] When the

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trend is disambiguated into PP and MAP, PP is demonstrated to rise in lockstep with obesity trends, but MAP has fallen.[18] While the exact determinants for these trends are not clear, PP and MAP classification allows for more focused hypotheses. PP itself is determined by the dynamics of the ventricular ejection, aortic size, aortic stiffness, height, sex, age, heart rate, mean arterial pressure, and wave reflection.[13, 19–21] Mechanistically, the ejection occurs in a time varying fashion, engaging the distensible aorta in time-varying ways. Aortic input impedance is an index of the interaction between time-varying pulsatile flow and pressure. Different parts of the arterial tree, for example at branch points or thicker muscular arteries, have different properties and consequent ability to accommodate the pulsatile flow which summates into a different impedance parameter value than the proximal aorta. At points where mismatch in impedance occurs, some of the pulsatile energy is reflected back in a direction opposite to the initial ventricular ejection. Pulsatile energy thus oscillates back and forth leading to higher pulse pressure due to the convergence of waves adding to each other. The magnitude of the reflected wave is determined by factors such as the ejection pulse dynamics, the degree of impedance mismatch, and the aortic length between the ventricular outlet and the impedance mismatch locations. In adults, the role of the wave reflection is believed to be a major driver of PP in the peripheral arteries exceeding PP in the proximal aorta, in a phenomenon called PP amplification.

Against this backdrop, Murakami et al. detail aortic hemodynamic data collected in 62 children. The children were under 15 years old, both sexes, had no chronic medication use, were normal weight, and were undergoing arterial catheterization for minor left-to-right shunting. All children were sedated with midazolam, femoral arterial access was obtained and pressure sensor mounted catheter was used to obtain aortic pressure tracings at the level of the diaphragm to index descending aorta and near the aortic valve to represent proximal aorta. With this invasive measurement, the investigators found that descending aortic PP was higher than proximal aortic PP, suggesting PP amplification as hypothesized. The degree PP amplification appeared to be related to age or height and MAP, while sex, heart rate and BMI (within this normal weight group) were not related. The investigators conclude that PP amplification occurs in children and increases with age.

The investigators findings contrast with previous descriptions of PP amplification varying inversely with age.[22] Purported arguments for this phenomenon center around increasing aortic stiffness across adulthood with peripheral artery impedance and arterial lengths staying the same. As aortic impedance rises it will better match peripheral artery impedance and there by diminish the mismatch and resultant reflection. Therefore PP amplification would decline as a function of the diminished reflected wave. More contemporary studies offer an alternate paradigm. In a sample of the Framingham Study where pressure and flow were disambiguated, PP fell in young adults until about age 50 and then rose thereafter.[23] A distinction was drawn between true PP amplification as the convergence of measured reflected and forward pressure waves in the proximal aorta, versus apparent PP amplification as the difference in PP between central and peripheral sites. Higher reflection actually corresponded to lower apparent PP amplification in adults younger than 50, while after 50 apparent PP amplification was lower and reflection also declined. Combined with data on forward wave dynamics, the inference drawn highlights the forward wave and aortic impedance as the prime driver of PP throughout the lifecourse.

In the case of children, mechanistic evidence is sparse. The authors of the current study are saddled with a thorny problem: how to reconcile an increase in PP amplification with increasing age. Based on previous studies in children showing reflected waves being smaller, Murakami et al. infer that the distance traveled to reflecting sites must be the dominant driver of PP amplification in children who naturally have lower arterial stiffness.[24, 25] As the slow reflected wave travels backward along the arterial tree that lengthens with age, it is likely to converge on the forward wave in the distal aorta, but in older children may arrive 'too late' to converge, leaving it out of phase with the forward wave. Countering this narrative is data suggesting a generally increasing trend in arterial stiffness with older age in children.[24] To their credit the authors acknowledge the possibility that if aortic stiffness is truly increasing with age in children, the velocity of the reflected wave cannot be assumed to underbalance the lengthening of the arterial tree. As alternate explanations, Murakami et al do consider the interaction between aortic properties and flow. If cardiac output is scaled to body size as widely maintained, and aortic properties like size or stiffness does not accommodate the increased flow in lockstep, it is possible that an imbalance between flow and accommodation can lead to increased forward pulse wave, which could be consistent with the previous observation on the dominant role of forward wave on PP amplification. Likewise, the role of MAP in younger adult PP amplification is also consistent with the observations in children as MAP is documented to be higher with age or height.[18] Unfortunately, the authors did not create a regression model to adjust for the measured MAP, probably due to sample size. Murakami et al are to be commended on a noble attempt at defining PP amplification in children to extend observations across the lifecourse. Future work should help disentangle the complex relations between age, growth, flow, arterial properties, and resulting pressure.

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