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NARRATIVE REVIEW

A Review of Blood Pressure Associated Changes in Arterial Characteristics in Children

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Abstract

Atherosclerosis, the gradual thickening and stiffening of the vasculature, is the cause of 50% of deaths in the westernized world. Several risk factors such as hyperlipidemia, obesity, gender, age and blood pressure are known to influence the progressive decline in arterial health. This process is thought to initiate in childhood and progress into adulthood, suggesting the most beneficial time for intervention may be early in life. The advent of non-invasive techniques to evaluate arterial health has allowed clinical paediatric investigations to become more commonplace. Several studies have investigated the impact various risk factors have on arterial health in children. However, the independent impact of blood pressure is especially difficult to investigate because of its close association with other cardiovascular risk factors. A well designed study with relevant and valid measurement of confounding factors is needed to clearly demonstrate the independent relationship between blood pressure and arterial health in children. **Health & Fitness Journal of Canada 2009;2(2):8-17.**

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Introduction

The cardiovascular system is comprised of the heart and blood vessels, which are jointly responsible for circulating blood throughout the body. The arterial system is responsible for carrying blood after ejection from the heart, and transporting it to the capillaries where oxygen is delivered to the working tissue. The arterial wall is composed of three layers: the intima, media, and adventitia. The intima is the innermost layer that lines the lumen of the artery (Ge et al., 1992; Juonala et al., 2005) and is highly involved in regulation of arterial diameter and elasticity (Mietus-Snyder and Malloy, 1998). The thick intermediate arterial layer, known as the media, is comprised of smooth muscle, extracellular matrix, and elastic fibres (Thyberg, 1996). The media responds to incoming signals originating from various sources including the arterial intima layer, liver and autonomic nervous system, in turn modulating arterial tone (Joyner et al., 2008). The adventitia is the outermost layer and primarily consists of connective collagen and elastin. Overall, arteries are highly elastic in order to cushion pulsatile flow and pressure following contractions of the ventricles, allowing for efficient diffusion at the capillaries (Chen, 2003).

Atherosclerosis refers to the gradual accumulation of fibrous tissue, cholesterol and calcium within the arterial walls (Chen, 2003). Severe atherosclerosis often leads to arterial occlusion, causing ischemia to occur in tissue downstream. The occlusion of cerebral arteries frequently leads to a stroke, while occlusion of the coronary arteries commonly leads to cardiac myopathy, and in severe cases myocardial infarction. A reduction in arterial elasticity is recognized as one of the earliest measureable changes to occur in the progression of atherosclerosis (Sanz and Fayad, 2008). This decrement in arterial health has been linked to cardiac morbidity and mortality (Berenson, 2002; Gan et al., 2007), along with a number of cardiovascular disease (CVD) risk factors such as obesity (Danias et al., 2003), hyperlipidemia (Mizuguchi et al., 2008) and hypertension (Blacher et al., 1999) in adults. Nevertheless, research has shown that changes in arterial health do not necessarily occur only in adults, but can even seen in infants (Stary, 1989). Therefore, the effects of several CVD risk factors on arterial health in children have begun to be investigated including obesity (Aggoun et al., 2008), lipid abnormalities (Mietus-Snyder and Malloy, 1998) and hypertension (Litwin et al., 2006).

Elevated blood pressure (BP) is thought to be a major factor influencing paediatric arterial health, but often occurs in concert with other CVD risk factors (Y. S. Lee, 2009; Machnica et al., 2008), making estimation of the independent effect of elevated BP difficult to evaluate. Taking into account that the current estimated prevalence of paediatric hypertension (1-5%) (Sorof et al., 2004) is thought to be higher (Hansen., 2007), as well as the fact that hypertensive children are likely to become hypertensive adults(Berenson, 2002), determining the effect of BP on arterial health in children is very important. What is also alarming is that children with hypertension are more likely to be overweight (Wang et al., 2004). This is of particular concern considering the recent drastic increase in childhood obesity (Lee, 2007), and the fact that obesity has been linked to poor arterial health in children (Tounian et al., 2001). In addition, hypertension has been linked to several physiological heart measures that have been found to be related to cardiovascular morbidity, such as left ventricular hypertrophy (Laird and Fixler, 1981) and diastolic dysfunction (Johnson et al., 1999). Similarly, surrogate markers of atherosclerotic burden, including both arterial stiffness and thickness have also been shown to correlate with CVD risk factors and predict CV events in adults (Hodis et al., 1998; Mackenzie et al., 2002). Unfortunately, because of the clustering of risk factors in children (Johnson et al., 2009), and the limited number of studies, the relative role of elevated BP on arterial health has yet to be clearly defined. Following is a review of research discussing the role BP plays influencing arterial health in children.

Blood Pressure and Cardiovascular Disease

Blood pressure generally refers to the pressure exerted on the arterial walls. Systolic blood pressure (SBP), which is the numerator when recording BP, is the arterial pressure (mmHg) created during ventricular contraction, while the denominator is diastolic blood pressure (DBP) and refers to the arterial pressure created during ventricular relaxation. SBP and DBP pulsate around a mean arterial pressure (MAP); commonly considered the steady component of BP (Chen, 2003).

Diagnosis of hypertension requires consistent results on three separate days ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004). For individuals over 18 years of age, hypertension is defined as BP above 140/90 mmHg, while pre-hypertension is having a BP between 139/89 and 120/80 mmHg. On the other hand, hypertension in children is defined as an average SBP and/or DBP that is ≥95th percentile for gender, age and height, while pre-hypertension is defined as an average SBP and/or DBP that is ≥90th percentile but <95th percentile for gender, age and height according to the National Health and Nutrition Examination Survey (NHANES) guidelines (Falkner and Daniels, 2004).

Systolic blood pressure and DBP have been investigated independently in order to further identify risk factors associated with CVD. Historically, elevated DBP has been implicated as the dominant predictor of CVD ("Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study," 1977). However, over the years SBP has proven to be more useful in CVD prediction (Dzielinska et al., 2009; Sagie et al., 1993). An additional variable which can be calculated from the measurement of BP is pulse pressure (PP), which is simply DBP subtracted from SBP (Madhavan et al., 1994) and has also been shown to be a powerful predictor of CVD risk (Chen, 2003; Darne et al., 1989; Must et al., 1992; Santucci et al., 1989).

In general, elevated BP is related to increased risk of CVD morbidity and mortality (Sesso et al., 2000). A relationship between increasing BP and coronary heart disease (CHD) was first illustrated conclusively through epidemiological evidence obtained from the Framingham studies. A major Framingham publication by Kannel and colleagues (1969) showed that over a 14 year follow-up, increasing casual SBP and DBP were related to an increasing risk of CHD (Kannel et al., 1969). Further supporting this relationship, Kannel and colleagues (1975) again showed that after 18 years, 73% of men and 81% of women who had died from CHD had a BP >140/90mmHg (Kannel, 1975).

Elevated BP is widely thought to exacerbate and accelerate atherosclerotic progression (Chen, 2003; Nichols and O'Rourke, 2005). The development of sub-endothelial plaque within the arterial wall is a major component of atherosclerosis (Barenbrock et al., 1995). It is hypothesized that elevated cyclical stress on the arterial vasculature leads to the enlargement of naturally occurring gaps in the intima (Chen, 2003). The enlargement of these openings between endothelial cells allows circulating low density lipoproteins (LDL) to migrate into the sub-endothelial space. Within this region LDL is more susceptible to oxidation. When oxidized, modified LDL (mLDL) has an inflammatory response, releasing cytokines which enhance macrophage migration towards the intimal damage. In turn, macrophages act to engulf mLDL. However, due to the lack of a proper negative feedback system, accumulation of mLDL occurs within the macrophages. As a result, these engorged macrophages, now known as foam cells for their fluffy appearance, cannot escape back into the circulation for metabolization. Eventually, the accumulation of these foam cells will result in a fatty streak; a yellow smear on the arterial surface and the first stage where the development of atherosclerosis becomes visible (Chen, 2003).

Arterial Properties

Traditionally, invasive techniques requiring catheterization such as angiography and angioscopy (fibre optic imaging of the inner vessel wall) were employed for the investigation of arterial wall adaptations (MacNeill et al., 2003). Recently however, non-invasive Echo-Doppler ultrasound techniques have emerged as useful estimators of arterial structure and function (MacNeill et al., 2003). This has allowed for more widespread arterial investigations in populations which would have been originally difficult to perform, for example children.

Arterial Stiffness

Through modern technological advances, Echo-Doppler ultrasound is now a common tool for measuring arterial properties such as arterial stiffness and wall thickness. Altered arterial stiffness is one of the earliest changes to occur in the sequele of atherosclerosis (Sanz and Fayad, 2008) and has been shown to be associated with elevated BP, obesity, insulin resistance, and cardiovascular morbidity (Mackenzie et al., 2002). Two major indices of arterial stiffness are arterial distensibility and pulse wave velocity (PWV).

Arterial distensibility is given by the formula:

$$\mathbf{Dist = [(sCSA - dCSA)/dCSA] / (Ps - Pd)}$$

Where Dist represents distensibility ($mmHg^{-1}$), sCSA and dSCA represent systolic and diastolic arterial cross-sectional area (cm^2) respectively, and (Ps–Pd) represents the pulse pressure (mmHg) within the same or comparable vessel.

Distensibility estimates arterial elasticity and is defined as a relative change in arterial CSA for a given change in pressure. In adults, distensibility is associated with several CVD risk factors such as hypertension, obesity, and age (Mackenzie et al., 2002). It is important to note that arterial stiffness can vary within the same artery, and between different arteries depending on proximity to vessel branches, vessel diameter and other factors (O'Rourke and Mancia, 1999).

Pulse Wave Velocity (PWV) velocity is given by the formula:

$$\mathbf{V = D/T}$$

Where V denotes velocity (cm/s), D equals the estimated distance the blood travels between two points of measurement (cm), and T equals the duration of time required for the pulse wave to travel between the two points of measurement.

Therefore, PWV is the speed of blood propagation through a chosen arterial segment (Qureshi et al., 2009). A healthy and relaxed arterial system propagates the wave relatively slowly, whereas a stiff system propagates waves quickly (Nichols et al., 2008). A study investigating PWV in adults showed that increasing wave velocity was positively related to BP, obesity, insulin insensitivity, and advancing age (Blacher et al., 1999).

Arterial Wall Thickness

In addition to arterial stiffening, atherosclerosis also results in thickening of the vasculature (Sanz & Fayad, 2008). A common technique to estimate arterial wall thickness is using arterial ultrasound images to measure intima-media thickness (IMT) (Burke et al., 1995). IMT is measured by taking the distance between the lumen-intima border and the media-adventitia border. IMT has been found to be correlated with a number of CVD risk factors such as diabetes (Park et al., 2009), hypercholesterolemia (Reinehr et al., 2006), and hypertension (Lim et al., 2009). As well, IMT is also a strong predictor of CVD morbidity and mortality (Aminbakhsh and Mancini, 1999).

Arterial Measures in Adults: Influencing Factors

Studies done in adults have shown arterial structure and function to be influenced by a number of CVD risk factors such as obesity (Danias et al., 2003), advancing age and gender (Stensland-Bugge et al., 2001), lipids (Shimetani, 2008), as well as BP (Kovaite et al., 2007). A study performed by Stensland-Bugge and colleagues. (2001) measured IMT in 6408 men and women between the ages of 25-84 years and found IMT to positively correlate with advancing age (Stensland-Bugge et al., 2001). However, the increase in IMT with age was not the same for males and females. In fact, men demonstrated a larger increase in IMT with age compared to women. A possible explanation for this finding appears in work by Medelsohn and others (1999) that showed that the feminizing hormone, estrogen, improves HDL/LDL ratio (Mendelsohn and Karas, 1999), which in turn would reduce sub-endothelial tissue accumulation (Burke et al., 1995).

The influence of obesity on arterial stiffness has been studied by Danias et al. (2003). These investigators used magnetic resonance imaging (MRI) to measure aortic elasticity in male participants aged 20-40 years. They found decreased abdominal aortic elasticity in their obese population compared to normal weight controls (Danias et al., 2003). Comparable findings were also found in women by Mizia-Stec et al. (2008). Similarly, PWV and common carotid artery stiffness were shown to be elevated in obese participants after matching for SBP and DBP, which was also found to have an independent affect on the arterial measures (Mizia-Stec et al., 2008). Indeed a comprehensive investigation performed by Kovaite and others (2007) found that after quantification of metabolic syndrome risk factors in 186 healthy asymptomatic adults, BP was the most important determinant of arterial structure and function as estimated by IMT and PWV (Kovaite et al., 2007). It is clear that age, obesity, gender and BP influence arterial thickness and stiffness in the adult population.

Arterial Measures in Children: Influencing Factors

Several factors are known to influence arterial measures in children including age (Cheung et al., 2002), gender (W. W. Nichols and Epstein, 2009), and body composition (Iannuzzi et al., 2008). Ishizu and colleagues (2004) measured IMT of the carotid artery in 60 healthy children aged 5-14 years and showed IMT to increase linearly with advancing age, even after controlling for gender, obesity, blood lipid profile, parental smoking history and BP (Ishizu et al., 2004). These authors suggested that the increase in IMT was the result of normal arterial development and not pathological consequences. Gender has also been shown to influence arterial measures, especially in relation to the role gender plays in puberty, which is a period of rapid hormonal change (Marshall and Tanner, 1968). Gender specific sex hormones are thought to have differing effects on arterial properties and function (Emi et al., , 2008). Ahimastos et al. (2003) compared arterial central and peripheral PWV between four groups; pre-pubescent and post pubescent males and females. Before puberty, females had significantly higher PWV than males indicating stiffer arteries. However, post-pubertal females showed significantly lower arterial stiffness than their pre-pubescent counterparts, while the opposite was true for males. The opposing adaptations resulted in an amelioration of the pre-pubescent difference between gender post puberty, which clearly illustrates pubertal maturation influencing arterial properties (Ahimastos at al., 2003). Further, demonstrating the relationship between increasing adiposity and arterial properties, a study measuring arterial wall thickness in 96 obese and 25 non-obese children aged 9-13 years found common carotid artery IMT to be significantly elevated in the obese participants (Reinehr et al., 2006). As well, common carotid artery distensibility has been shown to be lower in obese compared to non-obese children (Tounian et al., 2001). Physical activity and cardiovascular fitness have also been shown to influence arterial structure and function in children. Sakuragi et al. (2009) showed in 573 children (mean age: 10.1+/-0.3 years) that cardiorespiratory fitness was inversely related to arterial stiffening (Sakuragi et al., 2009). Also, Reed and colleagues (2005) showed that arterial compliance was positively related to aerobic fitness in 99 children 9-11 years of age (Reed et al., 2005). Hopkins et al. (2009) illustrated that vascular function as measured by flow mediated dilatation (FMD), is significantly correlated with the amount of moderate to high intensity physical activity measured by accelerometry. Furthermore, according to Hopkins' regression model, the amount of high-intensity physical activity was the only FMD predictor (Hopkins et al., 2009). Overall, these studies suggest that gender, age, obesity, and physical activity all play a role influencing arterial measures in children however the clustering of major risk factors has made identifying the independent influence of any one factor difficult in this population.

The Effects of Childhood Blood Pressure

Although the negative impact of CVD risk factors is well established in adults (Chen, 2003), there is much to learn regarding the arterial health of children and the early role of CVD risk factors such as high BP. Litwin and colleagues have completed several investigations looking at the impact of elevated BP on arterial health in children (Litwin et al., 2006; Litwin et al., 2004). In a2004 study , Litwin et al. found that common carotid artery IMT was larger and distensibility lower in their hypertensive children (Litwin et al., 2004). In a follow up study, Litwin and colleagues (2006) reported a positive correlation between IMT and BP; specifically SBP and PP (Litwin et al., 2006). Although these studies have added to the literature, extrapolating results is difficult as the age range of their child population was large, ranging between 6-20years and 5-18years respectively. Also, in the 2006 investigation by Litwin et al. the examining ultrasonographer was not blinded to the BP status of the children, possibly invalidating the results as visualization of Echo-Doppler arterial images is somewhat subjective, making results more valid when performed blinded (Baldassarre et al., 1994).

Nevertheless, when using a more narrow age range of peri-pubescent children, the relationship between childhood BP and arterial health is even less clear. Lande et al. (2006) investigated arterial parameters of children (mean age 14.9 years) and showed a significantly elevated common carotid artery IMT in their hypertensive population versus normotensive controls (Lande et al., 2006). In another study however, Sorof and colleagues (2003) failed to show a relationship between BP and common carotid artery IMT in similar aged children (mean age 13.9 years), but did show a significant correlation between BMI and IMT (Sorof et al., 2003). It is also notable that the above studies (Lande et al., 2006; Litwin et al., 2006; Litwin et al., 2004) used 24- hour ambulatory BP monitoring. This technique, although gaining popularity, is not often used in a clinical setting, so there is limited relevance of these results to physician guidelines for risk stratification according to their routine casual BP measurements ("Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A Cooperative Study" 1977).

Likewise, PWV is widely used in clinical research and may shed additional light on the effect that BP has on arterial health. A study by Blacher and colleagues (1999) revealed that at a given age, PWV was a more powerful atherosclerotic predictor than left ventricular hypertrophy, hypertension, plasma lipids and glucose, and smoking duration (Blacher et al., 1999). Nakamura et al. (2003) showed PWV to be significantly correlated with abdominal aortic calcification in older adults (Nakamura et al., 2003). Li et al. (2004) looked at how risk factors measured in asymptomatic healthy children related to PWV measured in young adulthood. They concluded that SBP in childhood significantly correlated with PWV measured 25 years later (Li et al., 2004). However, no investigators have studied the simultaneous relationship between PWV and BP status in a paediatric population.

Conclusion

Elevated BP is known to exacerbate and accelerate atherosclerotic progression (Nichols and O'Rourke 2005, Chen 2003). This process is thought to initiate in childhood and progress into adulthood, suggesting the most beneficial time for intervention may be early in life. As well, due to the prevalence of childhood hypertension, and the apparent voids in the literature and shortcomings of prior investigations, future studies should investigate the relationship between arterial health and BP in children. These investigations need to consider the effects of age, gender physical activity and several CVD specific risk factors, in particular obesity, in order to get a firm understanding of how these factors, along with elevated BP, interact to impact arterial health in children. By gaining some insight into the role of elevated BP on arterial health in children, we may be able to prevent the future onset of adult CVD.

Qualifications

The author qualifications are as follows: Aaron. A. Phillips MSc; Deborah D. O'Leary MSc, PhD.

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