Overweight, physical activity and high blood pressure in children: a review of the literature

Brian Torrance[1]
K Ashlee McGuire[2]
Richard Lewanczuk[1]
Jonathan McGavock[2]

[1]Division of Endocrinology, Faculty of Medicine, University of Alberta, Canada; [2]Manitoba Institute of Child Health, Department of Pediatrics and Child Health, Faculty of Medicine, University of Manitoba, Canada

Abstract: Obesity is a growing problem in developed countries and is likely a major cause of the increased prevalence of high blood pressure in children. The aim of this review is to provide clinicians and clinical scientists with an overview of the current state of the literature describing the negative influence of obesity on blood pressure and it's determinants in children. In short, we discuss the array of vascular abnormalities seen in overweight children and adolescents, including endothelial dysfunction, arterial stiffening and insulin resistance. We also discuss the potential role of an increased activation of the sympathetic nervous system in the development of high blood pressure and vascular dysfunction associated with obesity. As there is little consensus regarding the methods to prevent or treat high blood pressure in children, we also provide a summary of the evidence supporting relationship between physical activity and blood pressure in children and adolescents. After reviewing a number of physical activity intervention studies performed in children, it appears as though 40 minutes of moderate to vigorous aerobic-based physical activity 3–5 days/week is required to improve vascular function and reduce blood pressure in obese children. Future studies should focus on describing the influence of physical activity on blood pressure control in overweight children.

Keywords: arterial compliance, insulin sensitivity, aerobic exercise, sympathetic nervous system

Obesity is an emerging problem in children and adolescents

The appearance of pediatric forms of chronic diseases such as type 2 diabetes and hypertension, underscores the enormous burden the childhood obesity epidemic is imposing on developed countries worldwide (Sorof and Daniels 2002; Hannon et al 2005). Currently, nearly 1/3 of all children in Canada and the United States are considered overweight, placing millions of children at risk for chronic illness, notably hypertension (Strauss and Pollack 2001; Willms et al 2003). In adults, the development of hypertension in obese individuals is chronic and progressive, taking years to develop (Mikhail et al 1999). In children and adolescents, high blood pressure appears to develop more rapidly and persists into adulthood suggesting that the mechanisms for the disease may be unique (Sorof and Daniels 2005). Regardless of the pathology, the appearance of obesity-related high blood pressure in children forecasts a major health care burden and a need for early intervention strategies.

A suspected cause for the growing prevalence of obesity and its associated diseases is a reduction in daily physical activity performed by children over the past two decades (Tremblay and Willms 2003). It is possible that disproportionately low physical activity patterns also predispose overweight children and adolescents to a premature progression to high blood pressure. Studies in adults provide overwhelming evidence that low physical activity patterns or fitness are associated with an exaggerated risk

Correspondence: Jonathan McGavock
510A JBRC, Manitoba Institute of Child Health, University of Manitoba, 715 McDermott Ave, Winnipeg, MB, Canada, R3E 3P4
Tel +1 204 480 1359
Fax +1 204 789 3915
Email jmcgavock@mich.ca

for chronic diseases, including hypertension (Carnethon et al 2003). Conversely, increased daily physical activity and high cardiorespiratory fitness reduce the risk for a large number of chronic diseases, including, hypertension (Paffenbarger et al 1983; Hayashi et al 1999; Hu et al 2004). Impressively, increased physical activity patterns and/or high cardiorespiratory fitness confer protection from chronic illness in individuals with underlying risk factors, including obesity (Myers et al 2002; Tanescu et al 2003). Unfortunately, there is currently little evidence describing the potential for increased physical activity to attenuate cardiovascular risk in children. More importantly, it is unclear if increased physical activity can protect overweight youth from progressing to high blood pressure, the most prevalent chronic illness associated with childhood obesity (Jago et al 2006). The purpose of this review is to provide a summary of the current literature describing the influence of overweight on blood pressure and its determinants in children and adolescents. Furthermore, we would like to explore the potential role of physical activity as a countermeasure against the development of high blood pressure in the overweight pediatric population.

Qualification of terms

A major limitation for clinicians interested in this area is the inconsistent use of definitions for obesity in children (Table 1). In the US, the terms "at risk for overweight" and "overweight" are used to refer to children with body mass index values above the 85th and 95th percentile for their age and gender respectively. These percentiles are provided by the Centers for Disease Control CDC (2000) and were derived by averaging five national surveys performed on children 18–73 months of age between 1963 and 1994. There are another set of definitions which were established by Cole and Colleagues (2000), sometimes referred to as "International Cut Off Points" for the classification of obesity in children. These standards were derived from survey data collected in over 60 000 children and adolescents 6–18 years from six countries and include the US national surveys between 1963 and 1980. The standards were derived by converting the Z-score of 25 and 30 kg/m^2 at age 18 for boys and girls into corresponding body mass index values for all ages from 6–17 years. We will use the term overweight to refer to children with a body mass index considered above the 85th percentile or above the international "overweight" cut-off for age and gender.

The relationship between overweight and elevated systolic blood pressure in children

A number of community based studies have demonstrated that there is a strong positive relationship between body mass index (BMI) and blood pressure in children (Voors et al 1977; Aristimuno et al 1984; Clarke et al 1986; Jiang et al 1995; Munter et al 2004; Weiss et al 2004; Falkner et al 2006). The original and most compelling evidence emerged from the Bogalusa Heart Study, a school-based longitudinal tracking study of cardiovascular disease risk factors in multiple samples of school-aged children that began in 1973 (Voors et al 1977; Aristimuno et al 1984; Jiang et al 1995). In a series of studies, they have conclusively demonstrated that systolic blood pressure is significantly elevated in children within the upper percentiles of BMI or ponderosity relative to their leaner peers. Furthermore, longitudinal tracking of children included in the original cohort revealed that those who remained within the upper percentiles of BMI displayed a disproportionate rise in systolic blood pressure over time, relative to children who remained within the lower percentiles for body habitus (Aristimuno et al 1984).

Cross sectional comparisons between obese children admitted to pediatric weight loss clinics and their lean peers have also demonstrated that overweight and obese children

Table 1 Definitions of overweight and high blood pressure in children

Term	Definition	Source	Adult Equivalent
At risk for overweight	85th–94th percentile for age and gender	CDC	25–29.9 kg/m^2
Overweight	> 95th percentile for age and gender	CDC	>30 kg/m^2
Overweight (International Standard)	Age and gender specific values	International Obesity Task Force	25–29.9 kg/m^2
Obese (International Standard)	Age and gender specific values	International Obesity Task Force	>30 kg/m^2
High blood pressure	SBP or DBP > 95th percentile for height	NHLBI	>140 mmHg

Abbreviations: CDC, Centers for Disease Control; NHLBI, National Heart, Lung, and Blood Institute.

display significantly higher blood pressure than their lean peers, in a dose-response manner (Munter et al 2004; Weiss et al 2004). The positive relationship between BMI and systolic blood pressure has been reproduced in several other large population-based studies including NHANES III (Munter et al 2004). Interestingly, national survey data indicate a trend towards an overall rise in the average blood pressure values in children in the US, which the authors attribute to the increasing prevalence of overweight in youth (Munter et al 2004).

Despite the large number of population-based studies reporting a positive relationship between body habitus and systolic blood pressure, few reports have attempted to describe the prevalence of high blood pressure (ie, hypertension) within these populations. This is for good reason, as the criteria for high blood pressure in children is not as clear-cut as it is adults, and is dependent on many variables including age, relative height, and gender (www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm) (Table 2). Two recent community-based surveys have attempted to address this limitation (Sorof et al 2004; Paradis et al 2004). In a study of 5100 children, aged 10–19 years, Sorof and colleagues (2004) recently reported that the prevalence of high blood pressure was higher in children within the upper quintiles of BMI and that 38% of overweight children (BMI > 95th percentile) displayed high-normal blood pressure for their height when initially screened. More recently, the Quebec Family Study revealed a similar 30% prevalence of high-normal systolic blood pressure in a cohort of Canadian adolescents (Paradis et al 2004). Multiple linear regression analysis revealed that within the cohort of children aged 9, 13, and 16 years, BMI was a primary determinant of systolic blood pressure ($\beta = 0.9–1.1$, $p < 0.001$). Taken together, these data strongly suggest that overweight is a key determinant of elevated systolic blood pressure in children and adolescents and is a major contributing factor to the rising prevalence of high blood pressure in children and adolescents.

Table 2 An example of the criteria for high systolic blood pressure in boys

Age (years)	Systolic blood pressure (mmHg)			
Percentile of height	**25th**	**50th**	**75th**	**90th**
4	109	111	112	114
6	112	114	115	117
8	114	116	118	119
10	117	119	121	122
12	122	123	125	127
14	127	128	130	132
16	132	134	135	137

Note: Blood pressure values represent the 95th percentile for age. Actual table includes values for the 90th and 99th percentile. To use this table to diagnose high blood pressure in children, a clinician would measure a patient's height, weight, and blood pressure. Using CDC growth charts to determine the patient's age and gender-specific percentile rank for their height, they would than determine if the blood pressure exceeds the 95th percentile for the child's age, gender and percentile rank for height. Using the abbreviated table presented here as an example, high blood pressure for a 4-year-old boy would be a systolic blood pressure > 109 mmHg if they were in the 25th percentile for their height; > 111 mmHg if they were above the 50th percentile for their height; and 114 mmHg if they were > 90th percentile for their height. CDC growth charts can be found at: http://www.cdc.gov/nchs/data/ad/ad314.pdf.

Mechanisms underlying the development of elevated systolic blood pressure in children

The mechanism(s) that contribute to elevated systolic blood pressure in obese individuals is a controversial topic. Conventional wisdom suggests that the root cause of high blood pressure in obese individuals is due primarily to a combination of factors that raise systemic vascular resistance (Hall and Davy 2004; Rahmouni et al 2005). Several factors are believed to contribute to the increased vascular tone in obese individuals, including but not limited to: (1) activation of the sympathetic nervous system; (2) insulin resistance and (3) vascular dysfunction (Figure 1).

Data accumulated over the past decade strongly suggest that activation of the sympathetic nervous system appears to be a leading candidate to explain the relationship between obesity and hypertension (Landberg et al 1991; Scherrer et al 1994; Reaven et al 1996). Studies in animals placed on a high fat diet reveal a near dose-response increase in sympathetic outflow which is believed to be a centrally-mediated counter-response to restore the expanded adipose tissue mass to normal levels (Hall et al 1993). Although overfeeding studies are unlikely to be performed in humans, measurements of muscle sympathetic nerve activity from the peroneal nerve, reveal that obese individuals are characterized by an increased burst frequency, indicating increased sympathetic activity, relative to lean individuals (Grassi et al 1995; Abate et al 2001; Alvarez et al 2002). Impressively, the increased sympathetic activity is reduced substantially with weight loss, which coincides with a drop a blood pressure (Grassi et al 1998; Trombetta et al 2003). Furthermore, obese individuals with normal blood pressure display low muscle sympathetic nerve activity relative to obese peers with high blood pressure (Spraul et al 1993). Finally, treatment of obese individuals with sympatholytic agents effectively reduces systolic blood pressure and muscle sympathetic nerve activity (Wofford et al 2001) providing evidence that the sympathetic nervous system is a key determinant of obesity-related hypertension.

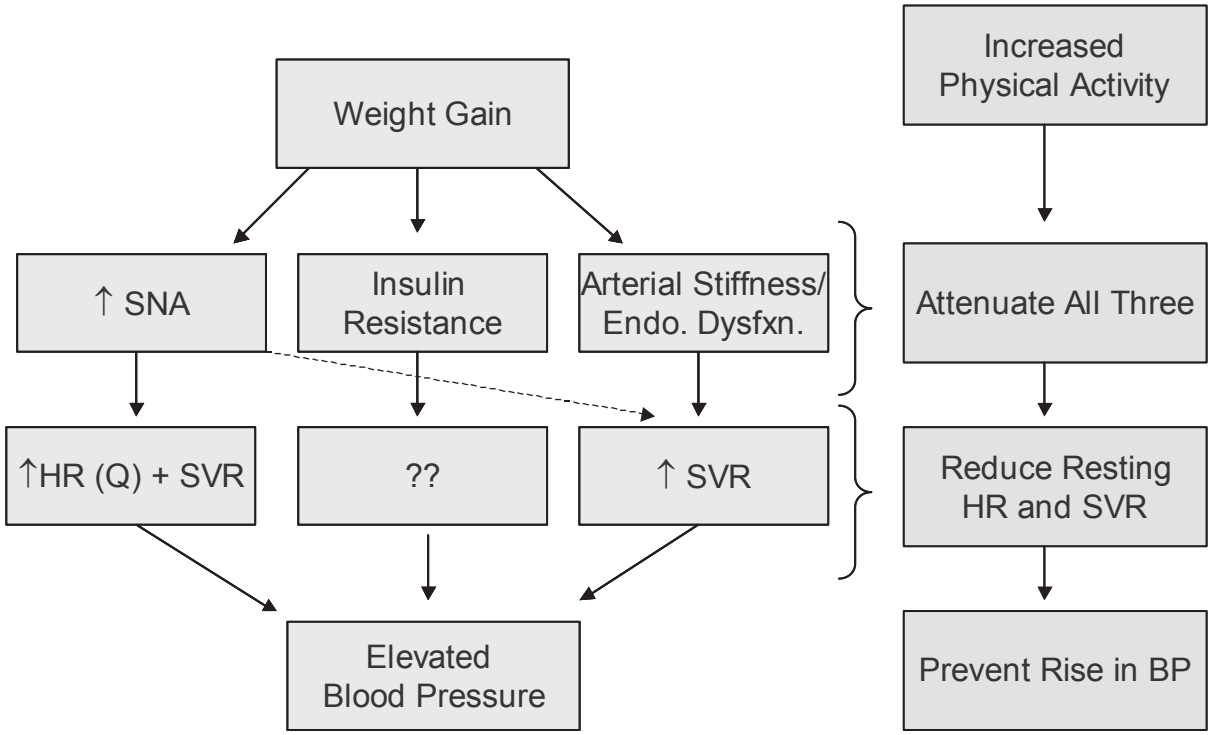

Figure 1 Mechanisms through which obesity lead to high blood pressure and sites of action for physical activity. Three main mechanisms have been proposed to explain elevated blood pressure in overweight youth: (1) activation of the sympathetic nervous system, (2) insulin resistance and (3) vascular dysfunction. Each of these maladaptations to weight gain can lead to an elevated blood pressure by increasing cardiac output or systemic vascular resistance. Previous authors have suggested that increased sympathetic activation increases resting heart rate and therefore cardiac output; however, activation of sympathetic nerve traffic may also increase systemic vascular resistance through vasoconstriction of resistance arteries in the periphery (dotted arrow). Insulin resistance and elevated systolic blood pressure frequently co-exist in youth; however, the mechanisms are as yet undefined (question marks). Finally, vascular dysfunction in the form of arterial stiffening or impaired endothelial-dependent dilatation are believed to lead to elevated systolic blood pressure through a rise in systemic vascular resistance.
Abbreviations: Q, cardiac output; Endo. Dys., endothelial dysfunction; HR, heart rate; SVR, systemic vascular resistance.

Insulin resistance is a very common and long appreciated corollary of obesity (Rabinowitz et al 1962; Reaven et al 1996). The coordinated appearance of insulin resistance and high blood pressure in obese individuals and the observation that lean hypertensive individuals exhibit some degree of insulin resistance, led several authors to hypothesize that insulin resistance or hyperinsulinemia is a major determinant of increased systemic vascular resistance in obese individuals (Modan et al 1985; Tuck 1991; Rocchini 1991; Landsberg 1992). In support of this theory, several large epidemiological studies have noted a relationship between fasting insulin and systolic blood pressure within a broad sample of adults including those with hypertension (Ferannini et al 1991; Saad et al 1991, 2004). Furthermore, high insulin sensitivity (measured directly with a frequently sampled glucose tolerance test) is associated with a lower 5-year incidence of hypertension in individuals without type 2 diabetes (Goff et al 2003). Observational studies also reveal that obese individuals with hypertension are more insulin resistant than BMI-matched peers with normal blood pressure (Manicardi et al 1986). Conversely, Ferannani and colleagues (1987) revealed that insulin-mediated glucose disposal is reduced 30%–40% in lean hypertensive individuals relative to normotensive peers.

Although these relationships appear to be robust, they are not universal, as Hispanic Americans and the Pima Indian population have a disproportionately high prevalence of obesity-related insulin resistance and type 2 diabetes however the development of hypertension is infrequent (Ferannini et al 1991; Saad et al 2004). Similarly, studies in which hemodynamic variables are quantified during short-term administration of insulin in lean healthy controls to levels seen in obese individuals, does not elicit a rise in blood pressure (Laakso et al 1990; Vollenweider et al 1994; Scherrer et al 1997). In fact, short (hours) or long (days)-term hyperinsulinemia causes a peripheral vasodilatation and a slight reduction in systemic vascular resistance, with little change in blood pressure (Hall et al 1990; Brands et al 1991; Scherrer et al 1997). These studies have been performed in both lean and obese animals and humans, revealing that

hyperinsulinemia alone has little effect on blood pressure acutely (Davy and Hall 2004). Finally, transgenic manipulation of systems involved in both the regulation of blood pressure and insulin-mediated glucose disposal (ie, central control centers for leptin signaling) reveal that it is possible to uncouple these two consequences of obesity, suggesting that hyperinsulinemia is not a primary cause of hypertension associated with obesity (Mark et al 2004; Tallam et al 2005). It is entirely possible that the two conditions share a similar cellular defect/pathway that is exacerbated with weight gain, which would explain why the two conditions frequently appear simultaneously (Sowers 2004).

In addition to these traditional views, several studies have demonstrated that obese individuals are characterized by unfavorable reductions in subclinical measures of vascular health (Laakso et al 1990; Steinberg et al 1996; Caballero 2003; Gordano et al 2003; Wildman et al 2003; Freedman et al 2005; Zebekakis et al 2005). For example, non-invasive measurements of central and peripheral arterial stiffness are elevated ~15 and 25% in young and middle aged obese men and women (Widlman et al 2003; Zebekakis et al 2005). Similarly, obese individuals are characterized by reduced endothelial-dependent dilatation (Laakso et al 1990; Steinberg et al 1996) and carotid artery wall thickening (Freedman et al 2004). These adverse changes in vascular function are believed to contribute to the propensity towards hypertension in overweight and obese adults.

Unfortunately a similar body of knowledge is not currently available describing the mechanisms responsible for high blood pressure in children. A limited number of studies have measured the determinants of blood pressure in lean and obese children using non-invasive measures, such as acetylene re-breathing and echocardiography (Voors et al 1982; Rocchini et al 1989; Daniels et al 1996). In contrast to commonly held beliefs, these studies reveal that overweight children are characterized by an increased resting cardiac output mediated in large part by an expanded stroke volume and not an elevated systemic vascular resistance (Rocchini et al 1989; Daniels et al 1996). Seminal work in this area was performed by Rocchini and colleagues (1989) in which cardiac output and plasma volume were determined in obese adolescents in response to a salt-loading diet before and after weight loss. In 60 obese adolescents, aged 10–16 years, elevated blood pressure was directly associated with a volume-dependent increased stroke volume, which could be reduced with a low sodium diet. Weight loss not only normalized blood pressure but desensitized adolescents to the sodium-dependent high blood pressure. It was therefore concluded that increased sodium sensitivity mediated a plasma volume-dependent increase of stroke volume and cardiac output, thereby increasing blood pressure (Rocchini et al 1989). Interestingly, weight loss also reduced serum norepinephrine concentrations, suggesting that the changes in sympathetic tone may also have contributed to the blood pressure lowering effects of weight loss.

Although reports of muscle sympathetic nerve activity in children and adolescents have yet to be published, evidence from several large population based studies suggest that autonomic activation is a common feature of high blood pressure and in particular obesity-related high blood pressure in children (Rocchini et al 1987; Sorof et al 2002; Gutin et al 2000). Using serum measurements of norepinephrine, resting heart rate and heart rate variability as surrogates of autonomic tone, several population-based studies in children have revealed that overweight in children is associated with an activation of the sympathetic nervous system (Berenson et al 1979; Rabbia et al 2003; Nagai and Moratini 2004). In support of these observations, smaller randomized interventional studies have shown that heart rate and norepinephrine levels decline significantly with weight loss in children, implicating autonomic tone in the development of high blood pressure in overweight children (Daniels et al 1996; Rabbia et al 2003).

Large population-based studies in children have also demonstrated a relationship between serum insulin concentration and blood pressure (Kanai et al 1990; Tounian et al 2001; Lambert et al 2004; Pankow et al 2004). For this reason, several authors have hypothesized that insulin resistance may play a role in the development of high blood pressure in children and adolescents (Rocchini 1991; Sorof and Daniels 2002). A modified oral glucose tolerance test was performed on a subset of participants studied in the early cohorts in the Bogalusa Heart Study. Stratification of the children into categories according to the glucose and insulin response to this challenge revealed that those with a hyperinsulinemic or hyperglycemic response displayed significantly elevated systolic blood pressure, relative to the more insulin sensitive controls (Kanai et al 1990). Similar to adults however, the relationship between insulin sensitivity and blood pressure seems to be dependent upon race, being less robust in African American and Hispanic children (Berenson et al 1979; Kanai et al 1990). It is likely, that, similar to adults, the relationship between these two conditions is coordinated but not causal.

Similar to adults, obese children also appear to be characterized by adverse changes in vascular health, which

may also contribute to the propensity for high blood pressure seen in this population (Watts et al 2004; Woo et al 2004a, 2004b; Ribeiro et al 2005; Whincup et al 2005). For example, ultrasound imaging of the carotid artery revealed that severely obese (BMI ~34 kg/m^2) children display arterial stiffness and increased diastolic wall stress, compared with age and gender matched lean (BMI ~16 kg/m^2) peers (Woo et al 2004a). These same children also displayed significantly attenuated endothelial dilatation in response to forearm ischemia demonstrating that the endothelium is sensitive to the negative effects of weight gain independent of age. More recent studies in a larger sample of children who exhibited a broader range of BMI values support this concept as they revealed that endothelial dependent dilatation in response to forearm ischemia was negatively associated with BMI (r –0.47; = $p <$ 0.01) in children aged 9–12 years old (Whincup et al 2005). Furthermore, carotid artery stiffness and carotid intima media thickness are both significantly elevated in overweight children and negatively correlated with several measures of adiposity (Tounian et al 2001). The pattern of vascular dysfunction in overweight children is strikingly similar to that observed in obese adults, suggesting that children are not immune to the cardiovascular complications of obesity.

Physical activity as a countermeasure for high blood pressure in children

The benefits of physical activity in the prevention and treatment of high blood pressure in adults have been very well described (Hagberg et al 2000; Whelton et al 2002). Individuals who perform regular physical activity have a lower risk for the development of hypertension (Blair et al 1984), and acute and chronic physical activity lowers blood pressure in individuals with hypertension, including those who are obese (Hagberg et al 2000). Conversely, low fitness, defined as the lowest quintile of fitness measured on a treadmill test, is associated with a 2.6- and 1.3-fold increased risk for hypertension in lean and overweight young adults, respectively (Carnethon et al 2003). Taken together these data suggest that increased physical activity provides some degree of protection from high blood pressure in overweight adults.

Unfortunately there is little evidence that increased physical activity can prevent the development of high blood pressure in overweight children. However, a large number of studies have emerged recently describing the influence of lifestyle interventions on various risk factors associated with high blood pressure in overweight and obese children and have been reviewed elsewhere (Bautista-Castano et al 2004; Watts et al 2005; Cruz et al 2005). We will restrict the focus of this section specifically on the effects of activity-based interventions on blood pressure and its determinants in overweight children. At the time of this review, there are a very limited number of studies designed to specifically assess the influence of physical activity on elevated systolic blood pressure in overweight children or adolescents, however most suggest that physical activity can effectively reduce blood pressure in children (Table 3). The majority of randomized controlled trials in overweight children were designed to assess the influence of combined lifestyle changes including both diet and exercise on multiple cardiovascular risk factors in overweight adolescents, therefore it is difficult to interpret the influence of exercise alone on blood pressure.

Longitudinal studies support the findings from cross sectional studies as they demonstrate that baseline fitness and improved fitness after one year follow-up are both associated with lower blood pressure in youth (Gutin et al 1990; Shea et al 1994). Specifically, relative to children who experienced no change in fitness, the age related rise in systolic blood pressure was nearly 40% lower (2.94 vs 5.10 mmHg) in children who experienced the largest improvements in fitness after one-year of follow-up (Shea et al 1994). More recent data from 1998–2002 NHANES sample, reveal a significant negative relationship between fitness and systolic blood pressure in adolescents (Carnethon et al 2005) while low fitness was associated with a 35% increased odds of being diagnosed with hypertension. Unfortunately, these studies were performed in otherwise healthy children, therefore it is unclear if overweight children who are physically active display lower blood pressure than their overweight sedentary peers.

Intervention studies provide more information regarding the causal relationship between activity and blood pressure in children. Early studies by Hagberg and colleagues (1983, 1984) focused on the role of physical activity interventions on systolic blood pressure in hypertensive adolescents, some of whom would be considered obese by current standards. Aerobic exercise training at an intensity of 70%–80% of maximal fitness for 30–40 minutes per day, 5 days per week was associated with a significant 6–10 mmHg reduction in systolic blood pressure of hypertensive adolescents (Hagberg et al 1984). Unfortunately, blood pressure returned to pre-training values within 9 months following cessation of exercise, suggesting that the exercise stimulus needs to be maintained for sustained blood pressure control. A similar response to aerobic training was observed in obese adolescents (13–16 years), randomized to 8 months of "high-intensity" physical activity and lifestyle education (Rocchini et al 1988; Gutin et al 2000). In the study by Rocchini et al (1988) activity was offered 5 days/week

Table 3 Studies that have assessed the influence of physical activity[a] on blood pressure in overweight children

Study (sample size)	Age (yrs)	BMI (kg/m^2)	Intervention				Change in outcome	Weight change	Conclusions
			Duration	Intensity	Frequency	Type			
Hagberg (1983) n = 25	16±1	NR	6 ± 1 mos 30–40 min	70–80% of VO_2max	5x/week	Aerobic: Walking/ jogging	SBP: ↓ 8 mmHg	None	Returned to baseline following cessation
Becque et al (1988) n = 36	~13	~29	20 wks 50 min	60–80% of age pred. max	3x/wk	Aerobic, walk, jog, activities	SBP: ↓ 1.4 Z-score	None	Combined with diet was effective in reducing BP and CHD risk factors
Rocchini et al 1988 n = 25	10–17 ~12	>75th %	20 wks 40 min	70–75% max HR	3x/wk	Aerobic walk, jog activities	SBP: ↓ 16 mmHg	↓ 2 kg	Combined with Diet exercise lowered BP an improved forearm reactivity
Ewart et al (1998) n = 88	NR	NR	18 wks 50 min	NR	5x/wk	Aerobic during PE class	SBP: ↓ 6 mmHg	None	Aerobic activity in PE class reduces BP in adolescent girls
Gutin et al (2002) n = 20 LI / 21 HI	13–16		8 mo 29 min/ 43 min	LI=55–60% HI=75–80%	5x/wk	Activities	SBP: LI: ↓ 2.1 HI: ↓ 6.1 mmHg	↓ VAT	High-intensity activity was associated with favorable changes in markers of insulin resistance syndrome
McMurray et al (2002) n = 1140	11–14	21–22	8 wks 30 min	NR	3x/wk	Activities	SBP: ↓ ~3 mmHg	None	Exercise reduced systolic blood pressure to a greater degree than education alone
Watts et al (2004) n = 19	14 ± 2	34 ± 1	8 wks cross over 60 min	65–85% of HR max	3x/wk	Circuit weight training	↔ SBP	None	Aerobic activity restored endothelial reactivity to levels seen in lean controls
Woo et al (2004) n = 82	9-12	25 ± 3	6 wks–1 yr 75 min	60–70% of pred. HR max	2x/wk–1x-wk	Aerobic + resistance + activities	NR	None	Compared with diet, exercise improved endothelial reactivity whichreturned to baseline after cessation
Ribiero et al (2005) n= 21	10 ± 1	28 ± 1	16 weeks 60 min	10% below VT	3x/wk	Walking/ jogging + activity	MAP: ↓ 6 mmHg	↓ 5kg	Compared with diet alone; improved BP response to mental and physical stress

Note: [a]Activity (ies) refers to play or unstructured physical activity.
Abbreviations: BMI, body mass index; HR, heart rate; LI/HI, high intensity/low intensity; NR, not reported; PE, physical education class; SBP, systolic blood Pressure; VAT, visceral adipose tissue; VT, ventilatory threshold; x/wk, number of training session per week.

at an intensity of 75%–80% of maximal fitness. This intervention significantly reduced systolic blood pressure by ~6 mmHg over the 8-month period, which was associated with a significant improvement in fitness. Unfortunately, the change in BMI was not reported in this investigation therefore, it is unclear if the blood pressure reducing effects of high intensity activity were related to weight loss or activity. Interestingly, the magnitude of blood pressure reduction was significantly less (~2 mmHg) in a third arm of the trial that performed low intensity (55%–60%) aerobic exercise during the 8-month intervention (Rocchini et al 1988).

Other studies have compared the influence of diet and exercise to diet alone on blood pressure or components of the insulin resistance syndrome, including blood pressure (Becque et al 1988; Rocchini et al 1988; Watts et al 2004; Ribeiro et al 2005). Early studies by Becque and colleagues (1988) randomized 63 obese children, 13 ± 3 years, to a dietary intervention or dietary intervention plus exercise for a period of 20 weeks. Systolic blood pressure dropped from 129 ± 9 to 113 ± 6 mmHg, in children involved in the exercise and diet group, while children in the diet-only group observed a significant ~10 mmHg decline. Systolic blood

pressure was unchanged in the control group. Children in both intervention groups lost a similar amount of weight (~2 kg) suggesting that aerobic activity elicits blood pressure lowering effects over and above those observed with weight loss alone (Becque et al 1988). Finally, in a more recent investigation, obese (BMI: 28 ± 1 kg/m^2) children (10 ± 0.2 years) were randomized to a dietary or dietary plus aerobic activity intervention for a period of four months (Ribeiro et al 2005). The exercise component of the trial was administered for 60 minutes, three-times per week, at an intensity of 10% below ventilatory threshold. Both interventions effectively reduced mean arterial blood pressure by ~3–5 mmHg at rest however children who undertook the exercise arm also observed a significant ~10% reduction mean arterial pressure coupled with a 25%–30% increase in forearm blood flow during mechanical and mental stress, which was not noted in the diet-only group. Impressively forearm vascular conductance was normalized (ie, values were similar to age-matched lean children) in obese children within the exercise and diet intervention group, but remained lower in the diet-only intervention (Ribeiro et al 2005). Taken together these data suggest that a chronic aerobic exercise intervention lasting 4–8 months, at high to moderate intensities, effectively reduces blood pressure in overweight children and adolescents. Unfortunately, because weight loss was not uniformly reported in these investigations, it is unclear if the benefits of aerobic exercise on systolic blood pressure in children are independent of weight loss.

The mechanisms through which physical activity reduces blood pressure in overweight children and adolescents are currently unclear. Hagberg and colleagues (1984) measured cardiac output and systemic vascular resistance in the study described above and revealed that the only change in resting hemodynamics associated with increased physical activity was a reduction in heart rate which paralleled the reduction in systolic blood pressure. More recent investigations have demonstrated that prolonged aerobic exercise alone or in combination with a hypocaloric diet is sufficient to improve vascular function in obese children and adolescents (Watts et al 2004; Woo et al 2004; Ribeiro et al 2005). Interestingly however, the investigators have consistently selected adolescents with normal blood pressure and noted that blood pressure was not reduced any further with aerobic exercise, despite improved endothelial-dependent dilatation.

For example, Watts et al (2004) measured brachial artery reactivity before and after an 8-week randomized, controled cross over study in obese adolescents. They revealed that exercise training normalized endothelial-dependent dilatation to levels seen in lean controls. Again, arterial reactivity returned to pre-training levels within eight weeks following cessation from exercise, suggesting that the vascular adaptations to exercise training are transient and will remain sensitive to the negative effects of obesity if children return to sedentary habits. The beneficial effects of physical activity on endothelial-dependent dilatation were replicated in two other studies of overweight children with abnormal vascular function, implicating a role for physical activity in the prevention of vascular dysfunction in children (Woo et al 2004; Ribeiro et al 2005). Unfortunately the mechanisms underlying the beneficial effects of exercise on vascular health in overweight children remain unresolved.

Currently, we are unaware of any studies designed specifically to evaluate the influence of physical activity on arterial stiffness in overweight children. Using a cross sectional design in 100 children aged 10–12 years we have recently demonstrated that high fitness is associated with lower arterial stiffness determined non-invasively with pulse wave analysis, relative to BMI-matched children with lower fitness scores (Reed et al 2005). Taken together, these data suggest that positive adaptations in the peripheral vasculature may also contribute to the blood pressure reducing effects of physical activity in children. Further studies are required to determine the influence of structured aerobic physical activity alone on systolic blood pressure and its determinants (cardiac output and systemic vascular resistance) in obese children and adolescents with elevated systolic blood pressure.

Conclusions

Although the definition of hypertension in children and adolescents is variable and dependent upon height and gender, excess fat mass is associated with elevated systolic blood pressure, regardless of age. The degree of elevation in blood pressure with weight gain in children is similar to that in adults; however, this seems to be a function of an increased heart rate and cardiac output rather than a rise in systemic vascular resistance. Impressively, endothelial-dependent dilatation and arterial compliance are also reduced in obese adolescents in a pattern similar to that observed in adults, suggesting that the atherogenic process is accelerated at an early age when exposed to excessive adiposity. These observations carry significant clinical implications as both blood pressure and body mass index track heavily from adolescence to adulthood.

Physical activity is a proven countermeasure for the development of various chronic diseases in adults, including hypertension. Preliminary evidence suggests that increased

aerobic-based physical activity can reduce systolic blood pressure and significantly restore endothelial function in overweight children and adolescents. Based on these studies, a minimum of 40 minutes of moderate intensity (70%–80% of maximal fitness) aerobic physical activity should be performed on at least five days of the week to prevent vascular dysfunction in overweight children. It is important recognize that the Institute of Medicine recommends a minimum of 60 minutes daily to maintain a healthy body weight and 90 minutes daily for weight loss in children. With the growing prevalence of overweight and obesity in children in developed countries, there is a substantial need for more research describing the influence and efficacy of lifestyle programs designed to prevent the development of high blood pressure in overweight children.

References

Abate NI, Mansour YH, Tuncel M, et al. 2001. Overweight and sympathetic overactivity in black Americans. *Hypertension*, 38:379–83.

Alvarez GE, Beske SD, Ballard TP, et al. 2002. Sympathetic neural activation in visceral obesity. *Circulation*, 106:2533–6.

Aristimuno GG, Foster TA, Voors AW, et al. 1984. Influence of persistent obesity in children on cardiovascular risk factors: the Bogalusa Heart Study. *Circulation*, 69:895–904.

Bautista-Castano I, Doreste J, Serra-Majem L. 2004. Effectiveness of interventions in the prevention of childhood obesity. *Eur J Epidemiol*, 19:617–22.

Becque MD, Katch VL, Rocchini AP, et al. 1988. Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. *Pediatrics*, 81:605–12.

Berenson GS, Voors AW, Webber LS, et al. 1979. Racial differences of parameters associated with blood pressure levels in children–the Bogalusa heart study. *Metabolism*, 28:1218–28.

Blair SN, Goodyear NN, Gibbons LW, et al. 1984. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA*, 252: 487–90.

Brands MW, Mizelle HL, Gaillard CA, et al. 1991. The hemodynamic response to chronic hyperinsulinemia in conscious dogs. *Am J Hypertens*, 4:164–8.

Caballero AE. 2003. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. *Obes Res*, 11:1278–89.

Carnethon MR, Gidding SS, Nehgme R, et al. 2003. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA*, 290:3092–100.

Carnethon MR, Gulati M, Greenland P. 2005. Prevalence and cardiovascular disease correlates of low cardiorespiratory fitness in adolescents and adults. *JAMA*, 294:2981–8.

Centers for Disease Control and Prevention. 2000. CDC growth charts: United States [online]. *Advance Data*, 314:1–28. http://www.cdc.gov/nchs/data/ad/ad314.pdf.

Clarke WR, Woolson RF, Lauer RM. 1986. Changes in ponderosity and blood pressure in childhood: the Muscatine Study. *Am J Epidemiol*, 124:195–206.

Cole TJ, Bellizzi MC, Flegal KM, et al. 2000. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*, 320:1240–3.

Cruz ML, Shaibi GQ, Weigensberg MJ, et al. 2005. Pediatric obesity and insulin resistance: chronic disease risk and implications for treatment and prevention beyond body weight modification. *Annu Rev Nutr*, 25:435–68.

Daniels SR, Kimball TR, Khoury P, et al. 1996. Correlates of the hemodynamic determinants of blood pressure. *Hypertension*, 28:37–41.

Davy KP, Hall JE. 2004. Obesity and hypertension: two epidemics or one? *Am J Physiol Regul Integr Comp Physiol*, 286:R803–13.

Falkner B, Gidding SS, Ramirez-Garnica G, et al. 2006. The relationship of body mass index and blood pressure in primary care pediatric patients. *J Pediatr*, 148:195–200.

Ferrannini E, Buzzigoli G, Bonadonna R, et al. 1987. Insulin resistance in essential hypertension. *N Engl J Med*, 317:350–7.

Ferrannini E, Haffner SM, Stern MP, et al. 1991. High blood pressure and insulin resistance: influence of ethnic background. *Eur J Clin Invest*, 21:280–7.

Freedman DS, Dietz WH, Tang R, et al. 2004. The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord*, 28:159–66.

Giordano U, Ciampalini P, Turchetta A, et al. 2003. Cardiovascular hemodynamics: relationships with insulin resistance in obese children. *Pediatr Cardiol*, 24:548–52.

Goff DC Jr, Zaccaro DJ, Haffner SM, et al. 2003. Insulin Resistance Atherosclerosis Study. Insulin sensitivity and the risk of incident hypertension: insights from the Insulin Resistance Atherosclerosis Study. *Diabetes Care*, 26:805–9.

Grassi G, Seravalle G, Cattaneo BM, et al. 1995. Sympathetic activation in obese normotensive subjects. *Hypertension*, 25:560–3.

Grassi G, Seravalle G, Colombo M, et al. 1998. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation*, 97:2037–42.

Gutin B, Barbeau P, Litaker MS, et al. 2000. Heart rate variability in obese children: relations to total body and visceral adiposity, and changes with physical training and detraining. *Obes Res*, 8:12–9.

Gutin B, Basch C, Shea S, et al. 1990. Blood pressure, fitness, and fatness in 5- and 6-year-old children. *JAMA*, 264:1123–7.

Hagberg JM, Goldring D, Ehsani AA, et al. 1983. Effect of exercise training on the blood pressure and hemodynamic features of hypertensive adolescents. *Am J Cardiol*, 52:763–8.

Hagberg JM, Ehsani AA, Goldring D. 1984. Effect of weight training on blood pressure and hemodynamics in hypertensive adolescents. *J Pediatr*, 104:147–51.

Hagberg JM, Park JJ, Brown MD. 2000. The role of exercise training in the treatment of hypertension: an update. *Sports Med*, 30:193–206.

Hall JE, Brands MW, Dixon WN, et al. 1993. Obesity-induced hypertension: renal function and systemic hemodynamics. *Hypertension*, 22:292–99.

Hall JE, Coleman TG, Mizelle HL, et al. 1990. Chronic hyperinsulinemia and blood pressure regulation. *Am J Physiol*, 258:F722–31.

Hannon TS, Rao G, Arslanian SA. 2005. Childhood obesity and type 2 diabetes mellitus. *Pediatrics*, 116:473–80.

Hayashi T, Tsumura K, Suematsu C, et al. 1999. Walking to work and the risk for hypertension in men: The Osaka Health Survey. *Ann Intern Med*, 131:21–6.

Hu G, Lindstrom J, Valle TT, et al. 2004. Physical activity, body mass index, and risk of type 2 diabetes in patients with normal or impaired glucose regulation. *Arch Intern Med*, 164:892–6.

Jago R, Harrell JS, McMurray RG, et al. 2006. Prevalence of abnormal lipid and blood pressure values among an ethnically diverse population of eighth-grade adolescents and screening implications. *Pediatrics*, 117:2065–73.

Jiang X, Srinivasan SR, Urbina E, et al. 1995. Hyperdynamic circulation and cardiovascular risk in children and adolescents. The Bogalusa Heart Study. *Circulation*, 91:1101–06.

Kanai H, Matsuzawa Y, Tokunaga K, et al. 1990. Hypertension in obese children: fasting serum insulin levels are closely correlated with blood pressure. *Int J Obes*, 14:1047–56.

Kang HS, Gutin B, Barbeau P, et al. 2002. Physical training improves insulin resistance syndrome markers in obese adolescents. *Med Sci Sports Exerc*, 34:1920–7.

Laakso M, Edelman SV, Brechtel G, et al. 1990. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. A novel mechanism for insulin resistance. *J Clin Invest*, 85:1844–52.

Lambert M, Paradis G, O'Loughlin J, et al. 2004. Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada. *Int J Obes Relat Metab Disord*, 28:833–41.

Landsberg L, Troisi R, Parker D, et al. 1991. Obesity, blood pressure, and the sympathetic nervous system. *Ann Epidemiol*, 1:295–303.

Landsberg L.1992. Hyperinsulinemia: possible role in obesity-induced hypertension. *Hypertension*, 19:I61–6.

Manicardi V, Camellini L, Bellodi G, et al. 1986. Evidence for an association of high blood pressure and hyperinsulinemia in obese man. *J Clin Endocrinol Metab*, 62:1302–4.

Mark AL, Shaffer RA, Correia ML, et al. 1999. Contrasting blood pressure effects of obesity in leptin-deficient ob/ob mice and agouti yellow obese mice. *J Hypertens*, 17:1949–53.

Mcmurray RG, Harrell JS, Bangdiwala SI, et al. 2002. A school-based intervention can reduce body fat and blood pressure in young. *J Adolesc Health*, 31:125–32.

Meyer AA, Kundt G, Steiner M, Schuff-Werner P, et al. 2006. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. *Pediatrics*, 117:1560–7.

Mikhail N, Golub MS, Tuck ML. 1999. Obesity and hypertension. *Prog Cardiovasc Dis*, 42:39–58.

Modan M, Halkin H, Almog S, et al. 1985. Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. *J Clin Invest*, 75:809–17.

Muntner P, He J, Cutler JA, et al. 2004. Trends in blood pressure among children and adolescents. *JAMA*, 291:2107–13.

Myers J, Prakash M, Froelicher V, et al. 2002. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*, 346:793–801.

Nagai N, Moritani T. 2004. Effect of physical activity on autonomic nervous system function in lean and obese children. *Int J Obes Relat Metab Disord*, 28:27–33.

Paffenbarger RS Jr, Wing AL, Hyde RT, et al. 1983. Physical activity and incidence of hypertension in college alumni. *Am J Epidemiol*, 117:245–57.

Pankow JS, Jacobs DR Jr, Steinberger J, et al. 2004. Insulin resistance and cardiovascular disease risk factors in children of parents with the insulin resistance (metabolic) syndrome. *Diabetes Care*, 27:775–80.

Paradis G, Lambert M, O'Loughlin J, et al. 2004. Blood pressure and adiposity in children and adolescents. *Circulation*, 110:1832–8.

Rabbia F, Silke B, Conterno A, et al. 2003. Assessment of cardiac autonomic modulation during adolescent obesity. *Obes Res*, 11:541–8.

Rabinowitz D, Zierkler KL. 1962. Forearm metabolism in obesity and its response to intra-arterial insulin. Characterization of insulin resistance and evidence for adaptive hyperinsulinism. *J Clin Invest*, 41:2173–81.

Rahmouni K, Correia ML, Haynes WG, et al. 2005. Obesity-associated hypertension: new insights into mechanisms. *Hypertension*, 45:9–14.

Reaven GM, Lithell H, Landsberg L. 1996. Hypertension and associated metabolic abnormalities–the role of insulin resistance and the sympathoadrenal system. *N Engl J Med*, 334:374–81.

Reed KE, Warburton DE, Lewanczuk RZ, et al. 2005. Arterial compliance in young children: the role of aerobic fitness. *Eur J Cardiovasc Prev Rehabil*, 12:492–7.

Ribeiro MM, Silva AG, Santos NS, et al. 2005. Diet and exercise training restore blood pressure and vasodilatory responses during physiological maneuvers in obese children. *Circulation*, 111:1915–23.

Rocchini AP, Katch V, Schork A, et al. 1987. Insulin and blood pressure during weight loss in obese adolescents. *Hypertension*, 10: 267–273.

Rocchini AP, Katch V, Anderson J, et al. 1988. Blood pressure in obese adolescents: effect of weight loss. *Pediatrics*, 82:16–23.

Rocchini AP, Key J, Bondie D, et al. 1989. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med*, 321:580–5.

Rocchini AP, 1991. Insulin resistance and blood pressure regulation in obese and nonobese subjects. *Hypertension*, 17:837–42.

Saad MF, Lillioja S, Nyomba BL, et al. 1991. Racial differences in the relation between blood pressure and insulin resistance. *N Engl J Med*, 324:733–9.

Saad MF, Rewers M, Selby J, et al. 2004. Insulin resistance and hypertension: the Insulin Resistance Atherosclerosis study. *Hypertension*, 43:1324–31.

Sawada SS, Lee IM, Muto T, et al. Cardiorespiratory fitness and the incidence of type 2 diabetes: prospective study of Japanese men. *Diabetes Care*, 26:2918–22.

Scherrer U, Randin D, Tappy L, et al. 1994. Body fat and sympathetic nerve activity in healthy subjects. *Circulation*, 89:2634–40.

Scherrer U, Sartori C. 1997. Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. *Circulation*, 96:4104–13.

Shea S, Basch CE, Gutin B, et al. 1994. The rate of increase in blood pressure in children 5 years of age is related to changes in aerobic fitness and body mass index. *Pediatrics*, 94:465–70.

Sorof J, Daniels S. 2002. Obesity hypertension in children: a problem of epidemic proportions. *Hypertension*, 40:441–7.

Sorof JM, Lai D, Turner J, et al. 2004. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics*, 113:475–82.

Sorof JM, Poffenbarger T, Franco K, et al. 2002. Isolated systolic hypertension, obesity, and hyperkinetic hemodynamic states in children. *J Pediatr*, 140:660–6.

Sowers JR. 2004. Insulin resistance and hypertension. *Am J Physiol Heart Circ Physiol*, 286:H1597–602.

Spraul M, Ravussin E, Fontvieille AM, et al. 1993. Reduced sympathetic nervous activity. A potential mechanism predisposing to body weight gain. *J Clin Invest*, 92:1730–5.

Steinberg HO, Chaker H, Leaming R, et al. 1996. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest*, 97:2601–10.

Strauss RS, Pollack HA. 2001. Epidemic increase in childhood overweight, 1986-1998. *JAMA*, 286:2845–8.

Tallam LS, Stec DE, Willis MA, et al. 2005. Melanocortin-4 receptor-deficient mice are not hypertensive or salt-sensitive despite obesity, hyperinsulinemia, and hyperleptinemia. *Hypertension*, 46:326–32.

Tanasescu M, Leitzmann MF, Rimm EB, et al. 2003. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation*, 107:2435–9.

Tounian P, Aggoun Y, Dubern B, et al. 2001. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*, 358:1400–4.

Tremblay MS, Willms JD. 2003. Is the Canadian childhood obesity epidemic related to physical inactivity? *Int J Obes Relat Metab Disord*, 27:1100–5.

Trombetta IC, Batalha LT, Rondon MU, et al. 2003. Weight loss improves neurovascular and muscle metaboreflex control in obesity. *Am J Physiol Heart Circ Physiol*, 285:H974–82.

Tuck M. 1991. Glucose, insulin, and insulin resistance as biochemical predictors of hypertension. *Am J Hypertens*, 4:638S–41S.

Vollenweider P, Randin D, Tappy L, et al. 1994. Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle in obese humans. *J Clin Invest*, 93:2365–71.

Voors AW, Webber LS, Frerichs RR, et al. 1977. Body height and body mass as determinants of basal blood pressure in children--The Bogalusa Heart Study. *Am J Epidemiol*, 106:101–8.

Voors AW, Webber LS, Berenson GS. 1982. Resting heart rate and pressure-rate product of children in a total biracial community. The Bogalusa Heart Study. *Am J Epidemiol*, 116: 276–86.

Watts K, Beye P, Siafarikas A, Davis EA, et al. 2004. Exercise training normalizes vascular dysfunction and improves central adiposity in obese adolescents. *J Am Coll Cardiol*, 43:1823–7.

Watts K, Jones TW, Davis EA, et al. 2005. Exercise training in obese children and adolescents: current concepts. *Sports Med*, 35:375–92.

Wei M, Kampert JB, Barlow CE, et al. 1999. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA*, 282:1547–53.

Weiss R, Dziura J, Burgert TS, et al. 2004. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*, 350:2362–74.

Whelton SP, Chin A, Xin X, et al. 2002. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*, 136:493–503.

Whincup PH, Gilg JA, Donald AE, et al. 2005. Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. *Circulation*, 112:1789–97.

Wildman RP, Mackey RH, Bostom A, et al. 2003. Measures of obesity are associated with vascular stiffness in young and older adults. Hypertension, 42:468–73.

Willms JD, Tremblay MS, Katzmarzyk PT. 2003. Geographic and demographic variation in the prevalence of overweight Canadian children. *Obes Res*, 11:668–73.

Wofford MR, Anderson DC Jr, Brown CA, et al. 2001. Antihypertensive effect of alpha- and beta-adrenergic blockade in obese and lean hypertensive subjects. *Am J Hypertens*, 14:694–8.

Woo KS, Chook P, Yu CW, et al. 2004. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation*, 109:1981–6.

Woo KS, Chook P, Yu CW, et al. 2004. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obes Relat Metab Disord*, 28:852–7.

Zebekakis PE, Nawrot T, Thijs L, et al. 2005. Obesity is associated with increased arterial stiffness from adolescence until old age. *J Hypertens*, 23:1839–46.