HHS Public Access

Author manuscript

*Curr Hypertens Rep*. Author manuscript; available in PMC 2016 May 18.

Published in final edited form as:

*Curr Hypertens Rep*. 2016 January ; 18(1): 3. doi:10.1007/s11906-015-0608-3.

# The Role of Obesity in the Development of Left Ventricular Hypertrophy Among Children and Adolescents

**Tammy M. Brady**[1]

[1]Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, 200 North Wolfe Street, #3062, Baltimore, MD 21287, USA

## Abstract

Both obesity and hypertension have increased substantially among children over the last several decades. At the same time, mounting evidence has pointed to the role of these and other cardiovascular disease risk factors on the development of end organ damage such as left ventricular hypertrophy in children. While traditionally thought to occur in response to an increased afterload as in systemic hypertension, evidence demonstrates that obesity is associated with left ventricular hypertrophy independent of blood pressure. Both hemodynamic and non-hemodynamic factors contribute to the pathogenesis of obesity-related left ventricular remodeling. However, more contemporary research suggests that adiposity and blood pressure have a greater effect on left ventricular geometry when present together than when present alone. Normalization of left ventricular mass in obese hypertensive individuals requires achievement of both normotension and weight loss. Additional strategies are needed to promote the cardiovascular health of children, with greater emphasis placed on obesity prevention.

### Keywords

Pediatrics; Bloodpressure; Overweight; Youth; End organ damage; Cardiovascular disease

## Introduction

Currently, there are more than 24 million overweight or obese children and adolescents in the USA [1]. Pediatric hypertension, reported to affect only 0.3–1.2 % of children in the 1970s and 1980s [2, 3], is now thought to be present in up to 5 % of all children [4, 5]. This secular increase has been attributed to the concurrent obesity epidemic. When considering that the prevalence of hypertension among overweight and obese children is more than four times that of all children [6], this hypothesis seems plausible.

The association between increased body weight and blood pressure (BP) is well established with many studies demonstrating the increased risk of sustained BP elevations among obese

Tammy M. Brady, tbrady8@jhmi.edu.

**Conflict of Interest** Dr. Brady declares no conflict of interest.

**Compliance with Ethics Guidelines**

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

youth. It is becoming more widely recognized that, in addition to this increased risk of hypertension, obese youth are at overall greater cardiovascular disease (CVD) risk. Recent meta-analysis data shows obese children to have higher lipid levels, fasting glucose values, greater homeostasis model assessments of insulin resistance, and higher fasting insulin values than children and adolescents of normal weight [7]. Obese children also have greater carotid intima media thickness, an ultrasound measurement associated with vascular disease, when compared to normal weight children. Indeed, autopsy studies support this finding. Atherosclerosis can be found among children as young as 2 years of age and is associated with known CVD risk factors such as body mass index (BMI), dyslipidemia, and systolic and diastolic BP [8].

In addition to being associated with atherosclerosis, these CVD risk factors are also associated with another form of end organ damage—left ventricular hypertrophy (LVH). LVH, a pathological remodeling of the heart, has been historically thought to occur primarily in response to an increased afterload as can be seen with systemic hypertension. Mounting evidence, however, points to a significant and independent role of adiposity on the development of LVH among children and adolescents [7]. While the mainstay of therapy of hypertensive children continues to be therapeutic lifestyle change, current guidelines emphasize the need for pharmacological therapy once LVH is present. Contemporary research suggests that a greater emphasis on weight loss may be needed to effectively treat those children with obesity, hypertension, and LVH.

## How Is Left Ventricular Hypertrophy Defined?

LVH is defined as an increase in left ventricular mass (LVM). LVM can be calculated using left ventricular (LV) wall thickness and LV cavity size measurements obtained during diastole from 2D M-mode echocardiography:

$$LVM = 0.81^{*}\left[1.04^{*}\left(\text{intraventricular septal thickness} + \text{posterior wall thickness} + LV \text{ end diastolic internal dimension}\right)^{3} - \left(LV \text{ end diastolic internal dimension}\right)^{3}\right] + 0.6 \text{ g} \quad [9]$$

Due to the known relationship of body size with LVM, the calculated LVM is then indexed to correct for these differences. There are a multitude of proposed indexing methods available, but the most commonly used method in pediatrics, and the one recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents [10••], is LVM(g)/(height in meters)$^{2.7}$. This indexing by allometric height is thought to best correct for the differences in body size while not "normalizing" LVM when increased fat mass is present. As body size changes dramatically throughout childhood, normal LVM changes as well. To determine if a measurement is elevated in the pediatric population, the indexed value of LVM is compared to normative data. LVH is diagnosed when the LVM index (LVMI g/m$^{2.7}$) is ≥95th percentile [11•].

Among individuals with LVH, there are two different forms of LV cardiac geometry: concentric hypertrophy, where the LVMI is elevated and the relative wall thickness is

elevated (RWT= [(2 × posterior wall thickness in diastole) / LV internal dimension in diastole]; elevated is ≥0.41), and eccentric hypertrophy where the LVMI is elevated but the relative wall thickness (RWT) is normal (<0.41) [12]. Among those with a normal LVMI, some individuals will have an elevated RWT. This category, referred to as concentric remodeling, is also associated with elevated CVD risk [13].

## LVH—Why Do We Care?

LVH is a form of end organ damage seen in hypertensive individuals. In children, as with other intermediate CVD outcomes, this form of abnormal cardiac geometry is usually asymptomatic. However, in adults, LVH is associated with ventricular arrhythmias and heart failure and confers a four-time increased risk of CVD morbidity and mortality [14]. These hard outcomes are fortunately not seen frequently in children, but prospective longitudinal studies have demonstrated that CVD risk factors present in childhood persist, or "track," into adulthood, leading to greater risk of CV events over time [15, 16, 17•]. As described above, the diagnosis of LVH in hypertensive children escalates the prescribed therapeutic interventions to ensure LVM regression and normalization of cardiac structure.

## Association of Obesity and LVH Among Children

All children with incident and prevalent hypertension should undergo echocardiography to assess for the presence of LVH and to follow the effectiveness of prescribed therapy which would be demonstrated by LVH regression [10••, 17•]. LVH is present among 34–41 % of hypertensive children at initial diagnosis of hypertension [18–20], can be present among children with presumably good BP control, and has been described in those without hypertension [21, 22]. These findings suggest that CVD risk factors other than BP may have an important role in the development of LVH in children.

We have previously shown that, among hypertensive children, degree of BP elevation is not associated with the presence of LVH. Instead, adiposity as measured by the BMI *z* score is strongly and independently associated with LVH [23, 24]. Other authors have shown that this association remains true among non-hypertensive children [25]. In a compelling retrospective chart review of healthy, normotensive children 2–19 years of age who underwent echocardiography in one of two time periods [26], the children evaluated in 2008 had significantly higher mean BMI and LVMI than those evaluated in the late 1980s, which was prior to the sudden rise in obesity seen in the USA. In fact, the prevalence of obesity increased fourfold between the eras while the prevalence of LVH doubled. Importantly, their analyses found the determinants of LVMI in both eras to be age, sex, race, and BMI *z* score.

This association between obesity and LVMI is not a new concept. In 1991, results from the Framingham Heart Study demonstrated that even after adjusting for age and BP, BMI was a strong independent predictor of LVM and LVH in adults [27]. Since then, both cross-sectional and prospective studies have shown this independent association in children and adults alike. Recently, Dusan et al. showed that LVH and diastolic dysfunction are present in obese normotensive children [28]. In fact, in this study the obese hypertensive children had the same LVMI as the obese normotensive children despite having significantly different

blood pressures. Newer evidence has also shown this association to track from childhood to adulthood and to strengthen over time [29, 30], supporting the notion that the antecedents of adult CVD are in childhood. In a longitudinal study of adolescents followed into young adulthood, BMI in both adolescence and adulthood was associated with current and future LVMI. Additionally, the greater the degree of weight gain from adolescence to young adulthood, the greater the increase in LVMI over time, regardless of starting weight [29]. Blood pressure was not independently associated with LVMI in this study.

## Mechanisms Contributing to Obesity-Related Cardiac Structure and Function

There are multiple physiologic pathways hypothesized to link increased body mass with increased LVM. These pathways can be categorized, as suggested by Abel et al., into hemodynamic factors and non-hemodynamic factors (further categorized as metabolic factors and direct/other factors) [31••].

### Hemodynamic Factors

It necessarily follows that with obesity there is an increase in adipose tissue. This results in greater metabolic requirements, vascularity, circulating blood volume, and cardiac output. Obesity can therefore be considered a mildly volume overloaded state [31••, 32]. Further exacerbating this increase in intravascular volume is the greater levels of sodium intake that accompanies increased caloric intake. With increased intravascular volume, stroke volume increases as does pre-load, resulting in a left shift of the Frank–Starling curve [33]. When these CValterations are sustained, cardiac remodeling results. This remodeling is at first adaptive and protective but over time becomes maladaptive and detrimental.

It is not just the characteristic increase in adipose mass seen with obesity that leads to the hemodynamic changes resulting in altered cardiac geometry. Metabolic dysfunction plays a prominent role in the pathogenesis of obesity-related LV remodeling. With increasing degrees of obesity and greater demands for fuel storage, adipocytes hypertrophy. Over time, classically activated macrophages and T-lymphocytes infiltrate the expanding adipose tissue leading to the secretion of a multitude of pro-inflammatory cytokines and loss of metabolic control. This phenotypic change from a metabolically normal state with acceptable vascular function to a metabolically abnormal state characterized by inflammation, adipocyte necrosis, and loss of vascular function contributes to end organ damage [34••].

Hemodynamic changes are also evident with obstructive sleep apnea. This form of sleep disordered breathing is highly prevalent among obese individuals and causes sympathetic nervous system activation and catecholamine release. This neurohumoral response leads to cardiac hypertrophy via direct cardiac effects and indirect effects related to the resultant increase in BP and cardiac contractility [31••].

Chronic hypoxemia and the significant alterations in intrathoracic pressure that typify obstructive sleep apnea present additional mechanisms by which LVH develops. Obstructive sleep apnea has long been recognized as an important cause of resistant hypertension, with successful treatment leading to a decrease in BP of up to 10 mmHg [35]. There is also

evidence that adherence to nightly CPAP for a period as short as 6 months can result in a reduction of LV wall thickness [36]. It should also be mentioned that the renin–angiotensin–aldosterone system is also activated with obesity, similarly leading to vasoconstriction, increased BP, and ultimately increased LV mass.

## Metabolic Factors

The most commonly understood role of the adipocyte is that of fat and fuel storage.

With progressive obesity, the ability of the adipocytes to store superfluous fuel becomes overwhelmed due to an impairment of adipogenesis. As a result, excess triglycerides are stored in ectopic tissue such as the pancreas, the liver, and the heart. When these organs are exposed to excessive free fatty acids, lipid droplets accumulate in the cystosol proximal to mitochondria. Organ dysfunction and occasional failure result, leading to the clinical comorbidities of diabetes mellitus, non-alcoholic steatohepatitis, and dilated cardiomyopathy [37••].

Insulin resistance and hyperinsulinemia, sequelae from beta-cell failure due to lipotoxicity, promotes LVH via several interconnected mechanisms. Glucotoxicity can directly and indirectly affect the cardiomyocyte. Abnormal insulin regulation increases hepatic angiotensin synthesis; angiotensin II, a cardiomyocyte growth factor, increases as a result, leading to myocardial hypertrophy, fibrosis, and apoptosis. Hyperinsulinemia also activates the sympathetic nervous system further leading to myocardial dysfunction. There may also be a role of advanced glycation end products in the heart; however, this is controversial.

When visceral fat deposition involves the heart, there is an increased amount of epicardial fat present. The amount of epicardial fat is correlated with the severity of LVH [38]. Just as described above, this adipose tissue is dysfunctional and the cardiomyocytes hypertrophy as a consequence of excessive free fatty acid accumulation and lipotoxicity. Inflammation, adipokine secretion, and vessel expansion then follow. Further, the invasion of fat tissue impairs cardiac contractility and limits the dilatory capacity of the left ventricle [38].

Beyond its role as a site for fat depot, the adipocyte is an active endocrinological cell. It secretes multiple pro-inflammatory cytokines which have a role in cardiac remodeling. These adipokines can directly influence hypertrophy, apoptosis, fibrosis, and contractility.

## Direct and Other Factors

Adipokines are cytokines, hormones, and inflammatory markers produced by adipose tissue. They are upregulated in obesity and have direct and indirect roles in the development of LVH. Adipokines contribute to myocyte extracellular matrix regulation and apoptosis, two major aspects of cardiac remodeling. Two adipokines deserve mention for their role in cardiac remodeling. Adiponectin, an adipokine almost exclusively synthesized by the adipocyte, has an important role in the regulation of lipid and glucose metabolism. In the obese state, adiponectin activity is diminished due to both decreased adiponectin secretion and decreased receptor expression. Diminished adiponectin activity not only contributes to LVH via the insulin resistance that results but also leads to cardiac disease via the loss of its

usual protective effects of decreasing inflammation, preventing endothelial cell adhesion and diminishing foam cell accumulation in the heart [31••, 34••, 39].

Another adipokine with a significant role in obesity is leptin. Leptin regulates feeding behavior and body weight. Interestingly, obese individuals have elevated leptin but remain resistant to its “obesity-preventative” properties [40]. As such, leptin resistance is thought to play a prominent role in obesity. As this pertains to the heart, hyperleptinemia leads to unfavorable cardiac sequelae such as increased reactive oxygen species in the heart, cardiomyocyte apoptosis, and direct inducement of cardiac hypertrophy [34••].

## What Happens with Weight Loss?

Weight loss ameliorates many of the comorbidities that are present in obesity: BP, diabetes/insulin resistance, obstructive sleep apnea, and dyslipidemia all improve. Sympathetic tone is also improved. Over time, these beneficial effects of weight loss lead to improvement in cardiac structure and function.

The most dramatic pediatric evidence we have for the favorable cardiac effects of weight loss comes from bariatric surgery studies. Ippisch et al. published pre–post results of 38 morbidly obese adolescents aged 13–19 years who underwent bariatric surgery [41]. After 10 months of follow-up, mean weight loss was 59 kg [standard deviation (SD) 15 kg], mean change in BMI was −20 $kg/m^2$ (SD 5 $kg/m^2$), mean change in heart rate was −18 beats per minute (SD 20 bpm), mean change in systolic BP was −12 mmHg (SD 15 mmHg), and mean change in diastolic BP was −3 mmHg (SD 16 mmHg). Even more striking was the mean change in LVMI, which was −12 $g/m^{2.7}$, with mean LVMI declining from 54 $g/m^{2.7}$ (SD 13 $g/m^{2.7}$) to 42 $g/m^{2.7}$ (SD 10 $g/m^{2.7}$), $p < 0.0001$.

This decrease in LVMI was independent of systolic and diastolic BP and was only predicted by degree of adiposity.

## Is Weight Loss More Important than Lowering BP When Aiming to Achieve LVH Regression?

Evidence in children and adults points to the beneficial effects of BP lowering on cardiac geometry [42, 43]. As such, the pediatric hypertension guidelines clearly recommend starting or intensifying pharmacological anti-hypertensive therapy in children when LVH is present. However, as both hypertension and overweight/obesity have become more prevalent in the USA, it has become increasingly evident that each of these CVD risk factors has a role in the development of LVH and therefore presents a treatment target when aiming to achieve regression.

Adult trial data has led some to conclude that persistent obesity may inhibit our ability to reduce LVM despite good BP control and that hypertensive LVH may be sustained when weight loss is not achieved. Gerdts et al. was able to show that despite comparable BP reduction, hypertensive obese individuals with LVH have a blunted response to therapy compared to normal weight patients [44]. Similarly, treated hypertensive adults who did not

experience the anticipated decrease in LVM over time in the Strong Heart Study had similar BPs to those who did have the anticipated regression, but had greater measures of adiposity (BMI, waist/hip ratio) as well as higher heart rate and albuminuria. Multivariable regression confirmed baseline BMI to be an independent predictor of lack of LVM regression [45].

Pediatric data demonstrate a similar lack of LVH regression when only BP control is achieved. A study conducted in hypertensive European children reported that successful treatment of hypertension was not associated with LVH regression; instead, a decrease in waist circumference was the biggest predictor of LVMI decline [46]. Among a more racially diverse population of treated hypertensive American children followed for a year, measures of adiposity, not BP, were independently associated with change in LVMI over time. Children who were overweight or obese throughout the study had a greater increase in LVMI over time than those who were of healthy weight despite good BP control [mean change LVMI 6.4 $g/m^{2.7}$ (9.6 SD) vs 0.95 $g/m^{2.7}$ (8.9 SD); $p = 0.056$] [47].

One common theme is that overweight and obesity often cluster with hypertension in children and treatment of each has beneficial cardiac effects. However, the simultaneous presence of both obesity and hypertension may result in an amplified response by the heart, greater than would be seen with the presence of either alone. This potential additive and/or interactive effects of obesity and BP on cardiac structure and function has been described for several decades [48••]. In adults, BP has been shown to have a differential effect on LVMI based on the presence or absence of obesity: hypertension increased LVMI among adults with increased waist circumference, but not among those with a normal waist circumference [49]. The degree to which body mass and BP contribute to LVMI may also be on different orders of magnitude. Palatini et al. followed middle-aged adults for 20 years and found that an increase in BMI of 1 $kg/m^2$ led to a similar odds of developing abnormal LV geometry as a 10-mmHg increase in systolic BP [odds ratio (OR) 1.07, $p < 0.0001$ and OR 1.22, $p < 0.0001$] [50]. When examined longitudinally in a large biracial sample of adults, BP and BMI in childhood and adulthood were both associated with LVH and LVMI in adulthood, but BMI had a greater association with the cardiac outcomes [51].

Children also have evidence for an interactive effect of overweight/obesity and BP on the heart. In a single-center, case–control study of children 9–18 years of age with untreated incident primary hypertension, only measures of adiposity were associated with the presence of LVH in multivariable adjusted analysis. However, when the children were stratified into groups based on obesity and LVH status, non-obese children with LVH had significantly higher 24-h ambulatory systolic BP than did the non-obese children without LVH. In the obese children, 24-h ambulatory systolic BP was no different between those with and without LVH [52].

So, naturally this leads to the question—where should treatment efforts be focused? Again, guidelines state that hypertensive children with LVH should have antihypertensive medications initiated or increased to promote LVH regression. As reviewed above, this may not be enough when treating overweight or obese patients with LVH. One must not forget that common to all children with hypertension is the need for prescribed therapeutic lifestyle change [10••, 17•]. This heart healthy lifestyle is similar to that prescribed to overweight and

obese children with essential tenets being weight loss when overweight, daily moderate to vigorous physical activity, avoidance of sugar-sweetened beverages, and a focus on dietary choices to include low-fat dairy, fruits and vegetables, and high-fiber foods. Recognizing how difficult it is for families to adhere to these recommendations and successfully achieve weight loss, either greater efforts need to be made to assist families with weight loss goals or lower BP targets should be sought for those with obesity, hypertension, and persistent LVH. More than anything, these findings speak to the need for a paradigm shift in how we approach childhood overweight and obesity, focusing on prevention rather than treatment [53]. Decreasing the prevalence of CVD risk factors in childhood and adolescence will allow us to prevent adult CVD and the devastating sequelae that result.

## Conclusions

Obesity remains highly prevalent among children and adolescents. Overweight and obese youth are at increased risk for hypertension, dyslipidemia, and insulin resistance/diabetes mellitus as well as end organ damage such as atherosclerosis and LVH. While traditionally thought to be a consequence of increased afterload in hypertensive individuals, LVH is now known to be independently associated with measures of adiposity. There are multiple hemodynamic and non-hemodynamic factors to explain the role of obesity on this pathological remodeling of the heart. Further, evidence suggests that the presence of both hypertension and obesity may have a greater effect on the heart than either CVD risk factor alone. With obesity a common cause of pediatric hypertension, particularly among adolescents, prevention of obesity and early treatment with weight loss remain of paramount importance as we work to decrease the CVD risk in children.

## Acknowledgments

None of the sponsors had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The first draft of this manuscript was written by Tammy M. Brady, and there was no honorarium, grant, or other form of payment given to anyone to produce the manuscript.

**Funding Source** TMB is funded by the NIH/NHLBI (1K23 HL119622-01).

## Abbreviations

| | |
|---|---|
| **BMI** | Body mass index |
| **BP** | Blood pressure |
| **CV** | Cardiovascular |
| **CVD** | Cardiovascular disease |
| **LV** | Left ventricular |
| **LVH** | Left ventricular hypertrophy |
| **LVM** | Left ventricular mass |
| **LVMI** | Left ventricular mass index |

| | |
|---|---|
| **RWT** | Relative wall thickness |
| **SD** | Standard deviation |

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