Chapter 2

REVIEW
OF
LITERATURE
2.1: Distribution of Blood Pressure amongst Children and Adolescents

This chapter refers to the distribution of blood pressure in children and adolescents according to the standard textbooks and various studies of sample populations worldwide. In most studies where the blood pressure distribution is studied in children and or adolescents, the correlation of the blood pressure with certain factors like age, height, weight and gender etc has also been studied. Some studies also included the correlation of blood pressure with body surface area, body mass and adiposity. So, findings regarding correlation of blood pressure to these factors will also be reviewed under the heading of ‘Distribution’. However, the universally accepted factors influencing blood pressure levels and concepts about pathogenesis of essential hypertension are dealt with in the later chapters.

The blood pressure in children and adolescents is less than that in adults \(^{(118)}\). It has a direct relation with height of the individual \(^{(22,118,135)}\). This fact is depicted by studies with various sample populations in different parts of the world.

The distribution of blood pressure amongst the children has been studied worldwide.

The National Heart Lung and Blood Institute; US Department of Health Services \(^{(118)}\) in its Fourth report on the Diagnosis, Evaluation, and
Treatment of High Blood Pressure in Children and Adolescents gave guidelines for child hypertension by publishing a table depicting 50th, 90th, 95th and 99th percentiles of the blood pressures for the 5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles of height. 50th percentile of blood pressure was considered as normal average BP, a blood pressure below 90th percentile was considered normal and a blood pressure more than 90th percentile and less than 95th percentile as pre-hypertensive. A blood pressure more than 95th percentile was considered as hypertension. This report gives the blood pressure ranges for children and adolescents of United States of America.

This standard of blood pressure categorization in normal, prehypertension and hypertension has been followed in many international as well as Indian publications.

A. Distribution of Blood Pressure among the Children and Adolescents in the Populations other than Indians

Many studies other than those in Indian population have been conducted to get independent data of blood pressure. Some of such studies compared their data obtained with Bogalusa and Montreal studies (58).
Brotons et al (1989) reviewed the distribution of blood pressure in multiple populations worldwide of 6-18 years of age.\(^{(21)}\) They reviewed blood pressure values according to age groups, gender and the 4\(^{th}\) and 5\(^{th}\) phases of Korotkov sounds for measuring diastolic blood pressure (DBP4 and DBP5) in various populations. There was a constant increase in blood pressure with advancement of age till 17 years in boys and 16 years in girls. The blood pressure in boys was constant between 17-18 years while that in girls was even slightly lower after the age of 16. In their review, the data on DBP4 and DBP5 gave rather different pictures of blood pressure change with the age than data on SBP. The increases are modest by comparison, the differences between populations are somewhat greater, and time separation between the patterns by sex is later (DBP4) or earlier but much less striking (for DBP5).

While studying Blood Pressure Levels in Urban School-Age Population in Chile, in Norero et al (1981) found systolic hypertension (SH) in 9.5%; 10.2% was males and 8.9% females. 8.1% were obese; among them the incidence of SH increased to 28.8%. In the entire sample, diastolic hypertension (DH) was 4.3%; males, 2.7%, and females, 5.5%. Among obese students, DH increased to 8.3%, and showed prevalence figures of 5.8% for obese males and 10.3% for obese females. After a second measurement, DH for the sample decreased to 1.8%. Salt intake and familial antecedents of high BP showed differences between hypertensive and normal populations.\(^{(125)}\)
Handa et al (1985) studied blood pressure distribution in students of junior and senior high schools aged 12-18 in Saint John, NB, Canada. Values of SBP obtained in their study were different from those of US task force norms.

While studying arterial blood pressure of the children and adolescents Bourquia et al (1991) found that the blood pressure values were found to increase gradually with age, with sex-specific variations. Values were higher in post-pubertal girls. A linear positive correlation between arterial blood pressure and stature was found. This correlation was stronger than the blood pressure-age correlation.

In another study, blood pressure nomograms were prepared for children and adolescents of 1 to 17 years by height, sex, and age, in the United States (Rosner et al 1993). Height percentiles were computed on the basis of standard National Center for Health Statistics growth charts. When height is taken into account, more short children (10th age-sex-specific height percentile) and fewer tall children (90th age-sex-specific height percentile) are likely to be classified as hypertensive than when the current age-sex-specific percentiles of BP alone are used. Tables are provided for boys and girls separately, by single year of age (1 to 17 years) and by the 90th and 95th percentiles of systolic blood pressure and diastolic blood pressure (fifth phase of Korotkoff sounds) for selected age-sex-specific height percentiles based on standard U.S. growth charts.
Irgil et al 1998 studied prevalence of Hypertension among
schoolchildren aged 13-18 Years in Turkey (71). An elevated BP was
defined according to the Report of the Second Task Force on Blood
Pressure Control in Children. They found 7.2% had elevated systolic
and/or diastolic BP, 4.4% students had significant hypertension and
2.8% students had severe hypertension. They found that systolic and
diastolic BP increased with age, height and weight. BP measurements
should be included in physical examinations as part of the continuing
care of the child.

Paulus et al in 1999 studied blood pressure during adolescence in an
age range of 12-17 years among Belgian adolescents selected from a
high cardiovascular risk population from the city of Luxemburg (130).
They found high BP and body fatness indices in adolescents from a
high CV risk population. The model under study showed a moderate
relationship between body fatness and BP.

In Quebec, Canada, Paradis et al (2004) studied population-wide blood
pressure and adiposity in children and adolescents. They identified
important elevations of SBP distributions compared with North
American reference populations and a high prevalence of borderline or
elevated SBP in children and adolescents in Quebec. SBP was
associated with excess body weight. They felt the need for public
health programs and policies, as well as clinical and community based
education, to increase physical activity and decrease caloric intake in
children and adolescents. (129)
Prevalence of high blood pressure in children and adolescents from the city of Maceió, Brazil was studied by Moura et al in 2004. They found that the prevalence of elevated blood pressure (percentage of blood pressure above 95th percentiles of Mean blood pressure) was 9.4% in their study; no statistically significant differences were noted between the prevalences of elevated blood pressure between genders; the difference between the prevalences of elevated blood pressure was significant when the groups of children and preadolescents were compared with the group of adolescents, and extremely significant when the normal weight and overweight groups were compared.

Muntner et al (2004) studied trends in blood pressure among children and adolescents of United States. They had two serially conducted cross-sectional studies using nationally representative samples of children and adolescents, aged 8 to 17 years, from the third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988-1994 and NHANES 1999-2000. They found that the blood pressure had increased over the past decade among children and adolescents. This increase was partially attributable to an increased prevalence of overweight.

Ashrafi et al (2005) studied blood pressure distribution among healthy Iranian schoolchildren aged 6–13 years in Tehran. Mean systolic and diastolic blood pressure showed incremental increases with age, weight and height in both sexes. Mean increases in systolic blood pressure for boys and girls were 1.7 and 0.8 mm Hg per year respectively and for diastolic blood pressure were 0.7 and 0.9 mmHg
respectively. According to Second Task Force (STF) criteria, 4.9% of boys and 3.5% of girls had significant systolic hypertension and 10.1% of boys and 3.3% of girls had significant diastolic hypertension. Mean systolic and diastolic blood pressures were higher than STF reports, especially among boys.

Nichols S et al (2006) studied the age, height, gender specific blood pressure distribution in the Tobagonian adolescent population and compared with those established for the adolescents of U.S. A., U. K. and Jamaica (123). They found that growth and maturational factors were important determinants of blood pressure levels in that population. Overweight emerged as the strongest predictor of elevated blood pressure in that population and reiterated the central role of obesity as a major contributor to elevated blood pressure in children. There was a positive association between family history and elevated systolic blood pressure was consistent with other studies and suggested the need to continue interventions that target persons with a positive family history of hypertension.


For the Polish children and adolescents Krzyżaniak et al (2009) derived blood pressure references (85). They used percentiles of blood pressure to determine high normal blood pressure (the mean blood pressure between 90th and 95th percentiles for age and gender) and
hypertension (the mean blood pressure equals or exceeds the 95th percentiles on at least three occasions).

**B. Distribution blood pressure in India**

A study on a sample population of school children in 1991 in the northwest India by Sharma et al (1991) in the age group of 7-16 gave a significant correlation of body surface area with the blood pressure \(^{(158)}\). There was no difference in the systolic and diastolic pressures of boys compared with girls of corresponding age in their study. Their study also determined the upper limits of normal, the lower limits of hypertension, values indicative of severe hypertension of children and adolescents of 7-16 years for systolic/diastolic pressure.

In a study of blood pressure levels in South Indian Adolescents, Lakshmanudu et al (1992) found that the mean SBP and DBP levels were elevated in rural children as compared to that in urban children of respective sexes during 10 and 15 years age. The mean BP levels were higher in both the rural and urban girls as compared to their male counterparts till the age of fifteen, after which the trend was reversed. While the mean SBP and DBP levels for the rural children of either sex were stable over the age range considered, those for urban children exhibited consistent increase with age. In urban boys, the yearly mean increment in SBP and DBP were 2.5 mm Hg and 2.0 mm Hg and that in urban girls 2.4mm Hg and 1.7mm Hg, respectively. It was suggested that perhaps stress factors are responsible for the elevated mean BP
levels among the rural adolescents as they are generally engaged in activities that exert considerable physical and psychological stress.\(^\text{(88)}\)

Verma et al (1995) studied biophysical profile of blood pressure in schoolchildren of systolic as well as diastolic BP increased with age in both sexes, correlation coefficients being 0.59 and 0.6, respectively. A statistically significant linear relationship between BP and weight and height was noted. Children with BMI of >2.26 had a significantly higher BP (P<0.01). The mean BP did not vary among different religions. The BP of vegetarians and non-vegetarians also did not differ. A family history of hypertension was associated significantly with elevated BP (P <0.01).\(^\text{(186)}\)

Anand et al (1996) studied the prevalence of hypertension in school going children of Amritsar city in the Panjab state of India.\(^\text{(2)}\) The blood pressure increased with increase in age with a spurt in systolic blood pressure at the age of 12 years in both the sexes. There were no significant differences in the blood pressure of two sexes at various age groups except for systolic blood pressure at 5, 6 and 16 years and for diastolic blood pressure at 9 and 13 years. Only 0.46% children were hypertensive. Children with obesity (n=342) and family history of hypertension (n=271) had hypertension in 3.5% (n=12) and 5.9% (n=16) cases, respectively as compared to other children in which the prevalence was only 0.23% and 0.14%, respectively. They concluded that the norms for determining hypertension in this population were established and its prevalence was 0.46%. Significant risk factors were obesity and family history of hypertension.
An epidemiological Study of Blood Pressure in School Children (5-14 Years) In Delhi was done by Chadha et al (1999). They found that the mean values of systolic and diastolic blood pressure (SBP and DBP) increased with age in both sexes. The cut-off points for high blood pressure were based on average SBP and/or DBP values of 95th percentile or greater for each age. The values for SBP ranged from 70 mm Hg to 140 mm Hg and for DBP from 36 mm Hg to 100 mm Hg for the age group 5-9 years. In the age group 10-14 years, the values for SBP and DBP ranged from 72 mm Hg to 160 mm Hg and from 46 mm Hg to 120 mm Hg, respectively. There was no significant difference in the prevalence of hypertension (systolic, diastolic or both) on the basis of gender (11.9% in boys and 11.4% in girls). Anthropometric variables like height, weight and body mass index showed positive correlation with systolic as well as diastolic blood pressure but the waist-hip ratio showed negative correlation coefficient with blood pressure. Family history of hypertension in one or both the parents was present in 20.4 percent children with high blood pressure compared to 6.8 percent in normotensives. Family history of diabetes was also significantly higher in hypertensive children (5.4%) than in normotensives (3.1%). Chadha et al (1999) in another study found that age and height, but not gender, emerged as principal determinants of systolic and diastolic blood pressure in multivariable linear regression analyses. Age- and height-specific 90th and 95th percentile values of systolic and diastolic blood pressure were estimated, which enabled us to categorize children into normal, high normal, and high blood pressure groups.
They age- and height- specific reference values for blood pressure of Indian children based on a large study sample have been presented by this study. The use of these standards should aid the identification of children with high blood pressure. \(^{(28)}\)

Anjana et al (2005) Variation in Blood Pressure among School Children of Amritsar (Punjab) age group 6 to 14 years of Amritsar district of Punjab were studied cross-sectionally \(^{(4)}\). Three readings of blood pressure were recorded for each subject. The mean values of systolic blood pressure and diastolic blood pressure increase with age in both sexes. There was no significant difference in blood pressure of the two sexes at all age groups except for systolic blood pressure at age group 7+. The study has also revealed that hypertension is prevalent in 7.5% healthy children of Amritsar. It is, therefore recommended that the children must be screened regularly for blood pressure to detect the prevalence of blood pressure.

Soudarssanane (2006) emphasized on prevention of High Blood Pressure and Hypertension among Adolescents by investigating key Predictors of high blood pressure. Their study found significant rise in both SBP and DBP with increasing weight in both genders. This was compared with the findings from adolescents aged 17 years in Jerusalem whereas another study 14 reported weight dependent rise in blood pressure only among males with respect to SBP alone. Studies on population of 4-18 years and 7-16 years also identified weight to be a major determinant of blood pressure which is important as the childhood weight gain was positively associated with adult blood
pressure. With reference to height, association of blood pressure reported in the present study agrees well with other study. It is evident from this community based epidemiological survey that increase in BMI predisposes the adolescent individual to higher blood pressure and subsequently hypertension. This study results, strengthen the independent association of BMI with blood pressure. Finally, it can be concluded from both the multivariate analysis and the case control study that even in the adolescent population, pathogenesis of higher blood pressure is a process influenced by life style factors like higher BMI and higher salt intake. The case control study however identifies parental history of hypertension also as a risk factor. \(^{(168)}\)

While preparing Blood Pressure Reference Tables for Children and Adolescents of Karnataka, Krishna et al (2006) found that the blood pressure (both systolic and diastolic) tends to increase with age. The stepwise regression analysis revealed that the age and height but not gender, are important determinants of blood pressure. Age and height specific, 50th, 90th and 95th and 99th percentiles of systolic and diastolic blood pressure were derived and are presented in tabular form. Conclusion: The blood pressure of children and adolescents can be evaluated using the reference table according to body size. The table provided helps to classify blood pressure as ‘normal’ or ‘pre hypertension’ and to define different stages of ‘hypertension’. \(^{(84)}\)

Taksande (2008) studied distribution of blood pressure in school going children in rural area of Wardha district, Maharashtra, India. In boys, SBP and DBP increased with age except a marginal decline in SBP at
the age of 17 years (-0.09) and decrease in DBP (-1.29) at 16 years of age. In girls, SBP and DBP also increased with age except at 11 years, wherein there was a mild decrease in SBP (-0.09) as well as the DBP (-0.24). Correlation coefficient analysis showed highly significant positive correlation of height with SBP and DBP. There was a significant correlation of SBP and DBP with weight, and body mass index (BMI). The prevalence of HTN was 5.75% (i.e. 3.25% for systolic HTN and 2.49% for diastolic HTN). \(^{(178)}\)

Raj et al (2010) while studying blood pressure distribution in Indian Children found that the study population had higher diastolic pressures for both sexes than international standard across all age groups. For systolic blood pressure, girls showed higher values than the international standard while for boys, the difference appears to be minimal. They concluded that the higher blood pressure values in the study population were of considerable public health significance. \(^{(137)}\)

**2.2: Factors Influencing Blood Pressure Levels**

Factors influencing blood pressure or predisposing factors to essential hypertension can be divided in two categories viz. non-modifiable and modifiable and factors. \(^{(18, 8)}\)

(i) **Non-modifiable risk factors**

a) Ethnicity
b) Genetic influences  
c) Age  
d) Gender  
e) Seasonal Variation

(ii) Modifiable risk factors

1. Life style
   a) Diet  
   b) Inadequacy of Sleep and Sleep Disorders  
   c) Physical Inactivity:  
   d) Smoking/Tobacco Chewing  
   e) Excessive Alcohol Intake  
   f) Obesity  
   g) Intrauterine growth retardation  
   h) Environmental Factors

Some other factors which influence blood pressure are  

a) Height  

b) Weight  

c) Body mass  

d) Somatic growth and sexual maturation  

e) Sodium and other nutrient intakes  

f) Sympathetic nervous system reactivity  

g) Stress
Non-modifiable risk factors

(A) Ethnicity

In one study it has been found that at lower levels of BMI Blacks have higher blood pressure and more hypertension than do Whites, but that at the highest levels of BMI, Whites have more hypertension (systolic or diastolic pressure) than do Blacks (146). Another study showed significant BMI-adjusted differences in rates of BP elevation were found between Hispanic boys versus white boys (147).

Jaber et al in the year 2000 inferred that the Israeli Arab children and adolescents have higher blood pressure levels than their Israeli Jewish counterparts. (73)

Jafar et al (2003) studied a population of 15 years and above for ethnic subgroup differences in hypertension in Pakistan. The age-standardized prevalence of hypertension was highest among Baluchis (25.3% in men and 41.4% in women), then Pashtuns (23.7% in men and 28.4% in women), Muhajirs (24.1% in men and 24.6% in women), and lowest among Punjabis (17.3% in men and 16.4% in women) and Sindhis (19.0% in men and 9.9% in women) (P 0.001). While hypertension was more prevalent in urban (22.7%) versus rural dwellers (18.1%), this difference was no longer significant after adjusting for body mass and waist circumference. However, ethnic
differences persisted after adjusting for major socio-demographic, dietary and clinical risk factors.\textsuperscript{(74)}

\textbf{(B) Genetic influences}

In a study published in 1998, a blood pressure gene at the angiotensin I–converting enzyme locus was identified though other studies suggest there are multiple genes responsible for developing hypertension\textsuperscript{(164)}. Bochud et al\textsuperscript{(15)} derived the heritability estimates (± SE) for ambulatory SBP, DBP, and PP. The heritability estimates for SBP varied markedly according to whether participants were treated for hypertension at baseline. Their data showed that ambulatory BP and PP have a high heritability in families of African descent. They also demonstrated that antihypertensive treatment and the number of BP measurements have a major influence on the heritability estimates.

Fava et al (2004) found significantly high Heritability values for nighttime systolic (37%), diastolic (32%) and mean (32%) ambulatory blood pressure (P < 0.05 for all)\textsuperscript{(46)}. During daytime, systolic ambulatory blood pressure was significantly heritable (33%, P < 0.05). Twenty-four-hour systolic (30%) and diastolic (29%) ambulatory blood pressure also had significant values of heritability (P < 0.05). Pulse pressure ambulatory blood pressure was significantly heritable over 24 h (63%, P < 0.01), during daytime (53%, P < 0.01) and at night (34%, P < 0.05). None of the office blood pressure phenotypes had a significant heritability.
Left ventricular hypertrophy has been established as an independent risk factor for the development of cardiovascular morbidity and mortality.\(^{(34)}\) Palatini et al (2001) reported that heredity can explain a small, but definite proportion of the variance in LVM. Higher blood pressure favors the phenotypic expression of the genes that regulate LVM growth.\(^{(127)}\)

**(C) Age**

Isolated systolic hypertension, an elevation in systolic but not diastolic pressure, is the most prevalent type of hypertension in those aged 50 or over, occurring either de novo or as a development after a long period of systolic-diastolic hypertension with or without treatment\(^{(133)}\).

***(D) Gender**

Factors known to predispose hypertension cause more prevalence of hypertension in males than in females (Janghori et al 2008)\(^{(75)}\). In their study, the prevalence of HTN was 25.2\% in men and 24.8\% in women; and 50.1\% of men and 39.1\% of women were prehypertensives. WC and BMI were strongly associated with BP in both genders. Multivariate analysis revealed that both WC (waist circumference) and BMI had the stronger association with HTN and Pre-HTN in men than women. Compared to men and women with normal weight, the multivariate-adjusted odds ratio (OR) (95\% confidence interval) of HTN was 5.75 (5.13, 6.44) for men and 4.29 (3.95, 4.66) for women with BMI ≥ 30. The multivariate OR of
prevalence HTN in men with abdominal obesity compared with men without was 3.76 (3.41, 4.22) and in women, 2.92 (2.73, 3.13).

Danon (35) reported a higher prevalence of hypertension in mature men than the women of the same age.

The gender based differences in the blood pressure values of the same age groups of children and adolescent have been found to be much varied when we review various studies viz. in one study, boys had higher systolic blood pressures after the age of 14 and higher diastolic blood pressures after the age of 16 (9), while in an Indian study by Raj et al (2010), done in the schools in Ernakulam district, Kerala, India, in 5-16 years age group of children and adolescents, or systolic blood pressure, girls showed higher values than the international standard while for boys, the difference appeared to be minimal. Another study (Nawrot et al 2004) found that in older adolescents the systolic and diastolic blood pressure was higher in males than females. (119)

(E) Seasonal Variation

In 2010, Radke et al published their study on seasonal Variation in hemodynamics and blood pressure-regulating hormones. Cardiac output and stroke volume were significantly decreased 10 and 15%, respectively, from summer to winter, whereas heart rate and systemic vascular resistance significantly increased 5 and 11%, respectively. Plasma aldosterone (PA) significantly increased 59% from summer to
winter, whereas plasma norepinephrine (PNE), plasma epinephrine, and plasma renin activity (PRA) increased 19, 2, and 17%, respectively (PNS for each). Across the four seasons, mean arterial pressure significantly correlated with PRA and PA, whereas systemic vascular resistance significantly correlated with PNE and PRA. There are dramatic counter-regulatory hemodynamic and hormonal adaptations to maintain a relatively constant BP. Norepinephrine, PRA, and aldosterone have a function in mediating the changes in hemodynamics. (136)

**Modifiable risk factors**

1. **Life style**

   a) **Diet:** vegetarian diet has been found to significantly reduce systolic blood pressure (148). Appel et al (1997) reported that a diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat could substantially lower blood pressure. This diet offered an additional nutritional approach to preventing and treating hypertension (5).

   Armstrong et al (1979) could not find any correlation between dietary sodium and the blood pressure differences between vegetarians and non-vegetarians (6).

   Falkner et al (2000), while studying dietary nutrients and blood pressure in urban minority adolescents at risk for hypertension, reported a significantly higher mean blood pressure in the low folate versus the high folate group (boys: 72 versus 67 mm Hg; girls: 76 versus 73 mm Hg; P=.008). The
difference in systolic blood pressure was not significant. There was no
difference in body mass index between the diet groups.\(^{(44)}\)

In a randomized crossover trial 58 subjects aged 30-64 with mild untreated
hypertension were allocated either to a control group eating a typical
omnivorous diet or to one of two groups eating an ovolactovegetarian diet
for one of two six week periods (Margetts et al 1986). A fall in systolic
blood pressure of the order of 5 mmHg occurred during the vegetarian diet
periods, with a corresponding rise on resuming a meat diet. The main
nutrient changes with the vegetarian diet included an increase in the ratio
of polyunsaturated to saturated fats and intake of fibre, calcium, and
magnesium and a decrease in the intake of protein and vitamin B12. There
were no consistent changes in urinary sodium or potassium excretion or
body weight. This study inferred that in untreated subjects with mild
hypertension, changing to a vegetarian diet may bring about a worthwhile
fall in systolic blood pressure.\(^{(103)}\)

Rouse in 1983 did a randomized control trial in the normotensives subjects
to see the effect of diet change from omnivorous to vegetarian diet and
then again changing the diet to omnivorous diet. He found that the mean
systolic and diastolic blood pressures did not change in the control group
but fell significantly in both experimental groups during the vegetarian diet
and rose significantly in the experimental group which reverted to the
omnivorous diet\(^{(148)}\).

b) **Inadequacy of Sleep and Sleep Disorders:** Inadequate sleep and sleep
disorders can cause an increase in blood pressure in long term. Marcus et
al (1998) studied the blood pressure of children with and without OSAS
they concluded that childhood OSAS (obstructive sleep apnea syndrome) is associated with systemic diastolic hypertension \(^{(102)}\).

Tochikubo et al (1996) in Japan reported that lack of sleep may increase sympathetic nervous system activity on the following day, leading to increased blood pressure \(^{(183)}\). The PMB (Portable multibiomedical) recorder was used in the study for precisely evaluating the relationship between blood pressure and environmental factors.

c) **Physical Inactivity:** Lack of physical activity predisposes to hypertension. The basis of this fact lies in the role of physical inactivity in causing obesity, atherosclerosis and insulin resistance.

   While studying coronary risk factors in school children, Boreham et al (1993) counted poor cardio-respiratory fitness and a low physical activity in the school children as major coronary risk factors. \(^{(16)}\)

   Butte (2007) et al. studied energy imbalance underlying the development of childhood obesity. They discussed that halting the development or progression of childhood obesity, as observed in Hispanic children and adolescents of the studied population, by counteracting its total energy costs would require a sizable decrease in energy intake and/or reciprocal increase in physical activity. \(^{(23)}\)

   Daniels (2008) et al. studied Lipid Screening and Cardiovascular Health in Childhood. They recommended that the individual approach for children and adolescents at higher risk for CVD and with a high concentration of LDL includes recommended changes in diet with
nutritional counseling and other lifestyle interventions such as increased physical activity. \(^{(33)}\)

Lee (2010) et al observed the effects of an exercise program on anthropometric, metabolic, and cardiovascular parameters in obese children \(^{(93)}\). They inferred that a short-term exercise program can play an important role in decreasing BMI, blood pressure, waist circumference, LDL-Cholesterol and in improving physical fitness.

While reviewing the highlights of AMA Expert Committee Recommendations regarding Childhood Obesity, Rao et al (2008), recommended a four-stage approach to treatment of childhood obesity is recommended. Many of these recommendations can be carried out by family physicians for treatment and prevention \(^{(139)}\). These include advising families to limit consumption of sweetened beverages and fast food, limit screen time, engage in physical activity for at least 60 minutes per day, and encourage family meals on most, and preferably all, days of the week.

Studying Overweight and obesity in children and adolescents: relationship with blood pressure, and physical activity, Ribeiro et al (2003) suggested that higher BMI is associated with higher values of SBP and DBP. Children and adolescents in the upper quartile of BMI are 1.5 times as likely to have at least one risk factor. Also their data confirmed that higher levels of BMI are associated with an unfavourable risk profile for CVD risk factors. \(^{(142)}\)
Ribeiro (2004) et al studied physical activity and biological risk factors clustering in pediatric population. Their results of their study suggested that children and adolescents with higher PAI (Physical Activity Index) have a lower number of biological risk factors for CVD. (143)

In a study on evidence based physical activity for school-age youth, Strong 2005 et al concluded that the school-age youth should participate daily in 60 minutes or more of moderate to vigorous physical activity that is developmentally appropriate, enjoyable, and involves a variety of activities.

Ulf et al (2006) did a cross-sectional study in 9- to 10-y-old and 15- to 16-y-old boys and girls from three regions in Europe to see association of TV viewing and physical activity with metabolic risk in children. They found TV viewing and physical activity are independently associated with metabolic risk in children. (184)

d) **Smoking/Tobacco Chewing:** Nicotine raises blood pressure through stimulating adrenaline secretion (16,50,119).

e) **Excessive Alcohol Intake:** increases the blood pressure and also causes portal hypertension due to fatty liver and cirrhosis. In a study by Xue et al in 2001, it was found that the alcohol reduction was associated with a significant reduction in mean (95% confidence interval) systolic and diastolic blood pressures of -3.31 mm Hg (-2.52 to -4.10 mm Hg) and -2.04 mm Hg (-1.49 to -2.58 mm Hg), respectively. A dose-response relationship was observed between mean percentage of alcohol reduction and mean blood pressure reduction. Effects of
intervention were enhanced in those with higher baseline blood pressure. Our study suggests that alcohol reduction should be recommended as an important component of lifestyle modification for the prevention and treatment of hypertension.\(^{(204)}\)

f) **Obesity:** Adiposity has a positive correlation with the SBP and DBP in children and adolescents.\(^{(16,23,40,57,64)}\)

**Duarte et al (2008):** BMI, not BF or waist, is consistently and independently related to BP levels in children; overweight and obesity considerably increase the risk of hypertension.\(^{(40)}\)

An article by Hans, Sattar and Lean (2006) in British Medical Journal analyses various methods of assessment of obesity and its clinical implications.\(^{(60)}\) They emphasize on identifying people who are overweight, and particularly with accumulation of excessive visceral fat, are essential for directing future intervention.

Studying a sample population of children of age range 0.1 to 7.0 years, in mainland China, He et al (2000) found that the blood pressure is associated with body mass index in both normal and obese children. They took the BMI as a measure of obesity.\(^{(64)}\)

In Tehran, Janghorbani et al (2008) studied Gender Differential in the Association of Body Mass Index and Abdominal Obesity with Prehypertension and Hypertension in Iranian Adults.\(^{(75)}\)

While investigating the role of obesity in home and office blood pressure levels in children and adolescents Karatzi (2009) et al recruited a total of 778 healthy subjects aged 6-18 years in the study. OBP (office blood pressure) and HBP (home blood pressure) were
measured using electronic devices validated in children. The prevalence of systolic hypertension was higher than that of diastolic hypertension. This difference was significant only in office readings and independent from obesity. These data implied that in children and adolescents the z-score of BMI is the most appropriate index of the association between BP and obesity. It also suggested that obesity is probably more closely associated with home than office BP. Finally, although obesity appears to affect SBP more than DBP, these results suggest that the predominance of systolic hypertension in children and adolescents might not be only related to obesity but also to the measurement setting (office). \(^{(79)}\)

From the Korean National Health and Nutrition Examination Survey, 1998 and 2001, Kim et al (2006) while studying obesity and cardiovascular risk factors in children and adolescents aged 10–18 Years, defined Obesity by body mass index cutoff points provided by the US Centers for Disease Control and Prevention. The prevalence of obesity increased significantly from 5.4% in 1998 to 11.3% in 2001 (p < 0.0001). Korean obese children and adolescents in 1998 and 2001 had 4.6-and 4.9-fold risks for systolic hypertension, 4.2-and 2.8-fold risks for high levels of total cholesterol, 9.4-and 2.7-fold risks for high levels of low density lipoprotein cholesterol, 4.1-and 3.7-fold risks for low levels of high density lipoprotein cholesterol, and 5.3-and 2.8-fold risks for high levels of triglycerides, compared with their normal-weight counterparts (p < 0.05 in all). Approximately 60% of Korean obese
children and adolescents had at least one CVD risk factor. These findings suggest that Korean obese children and adolescents have an increased risk of CVD. \(^{(82)}\).

Another study regarding association of obesity with high blood pressure in children and adolescents Koulouridis et al (2008) reported that suggest that anthropometric indexes, particularly central obesity and body weight play the most important role in BP control among children and adolescents. Girls exhibit greater frequency of high BP than boys, as well as greater frequency of other metabolic syndrome risk factors. Insulin levels and insulin sensitivity are important factors influencing BP control. Insulin, per se, plays a pivotal role in BP control, normoinsulinemia produce a positive effect upon BP, but high insulin levels exert a hypotensive action. \(^{(83)}\)

Kunz et al (2000): Resting Metabolic Rate and Substrate Use in Obesity Hypertension. \(^{(86)}\) They examined resting metabolic rate (RMR) and basal substrate oxidation in subjects with obesity and obesity-related hypertension. A total of 166 subjects were characterized for RMR and basal substrate use through indirect calorimetry. Blood pressure was measured at rest and with 24-hour ambulatory monitoring. Blood samples were collected for the measurement of plasma catecholamines, leptin, and the insulin response to an oral glucose load. In our study population, 116 subjects were defined as hypertensive and 91 were defined as obese. Hypertensive patients under b-adrenergic blockade \((n=542)\) had a significantly lower RMR than did patients without b-blockade \((P<0.05)\) and were therefore
excluded from further analyses. Univariate regression analysis revealed a significant relationship between RMR and body fat mass, as well as body fat–free mass, in both groups. Compared with obese normotensive control subjects (n=527), obese hypertensives (n=543) had a 9% higher RMR (P<0.05), higher plasma catecholamine (P<0.05) and leptin (P<0.05) levels, and an increased insulin response to oral glucose (P<0.01). Together, these findings are compatible with the idea that chronic neurogenic and metabolic adaptations related to obesity may play a role in the development of obesity hypertension in susceptible individuals.

Studies (Lee et al 2010) have reported the reduced BMI and the obesity markers due to a short-term exercise program can improve the cardiovascular health 92.

Mohan et al (2004) reported a higher prevalence of sustained hypertension and obesity in urban school going children than their rural counterparts in Ludhiana. Prevalence of sustained hypertension was on the rise in urban area even in younger age groups. Blood pressure was frequently elevated in obese children as compared to lean subjects. This is possibly related to their sedentary lifestyle, altered eating habits, increased fat content of diet and decreased physical activities. 111.

Nawrot et al (2004) used BMI and serum lipid levels as a measure of overweight and obesity in older Belgian adolescents and they found that there is definite positive relationship with increase in BMI and serum cholesterol with increase in blood pressure. 119.
Ruiz et al (2007) As Estonian and Swedish part of the European Youth Heart Study, Ruiz et al (2007) studied school aged children of 9-10 years age. The results of this study showed a positive influence of simple anthropometric measurements of total and central adiposity on blood pressure, and suggested that higher cardiorespiratory fitness may attenuate the association between body fat and blood pressure in school-aged children especially in girls. (151)

According to the latest definition of metabolic syndrome (MetS), there are five criteria of the MetS. The patient who has three of the five criteria that include hypertriglyceridaemia, low HDL-cholesterol, high glucose level, central obesity and hypertension is considered as MetS. In this context Sevgi et al (2007) investigated obese hypertensive children and adolescents (10 boys and 10 girls of 7-20 years age). In 20 patients who were all obese and hypertensive, existence of a third metabolic syndrome component such as glucose intolerance or dyslipidaemia, was 47% and 35% respectively, whereas existence of both was 55%. Only three of the patients carry all of the five criteria of metabolic syndrome. (157)

Obesity is associated with alterations in the autonomic nervous system that may contribute to the increase in blood pressure and resting energy expenditure present in this condition. To test this hypothesis, Shibao et al (2006) induced autonomic withdrawal with the ganglionic blocker trimethaphan in 10 lean (32±3 years) and 10 obese (35±3 years) subjects. Systolic blood pressure fell more in obese compared with lean subjects. They confirmed that the autonomic contribution to
blood pressure was greater in obesity after including additional subjects with a wider range of blood pressures. Sympathetic activation induced by obesity is an important determinant to the blood pressure elevation associated with this condition but is not effective in increasing resting energy expenditure. This suggested that the sympathetic nervous system could be targeted in the treatment of obesity-associated hypertension.\(^{(160)}\)

Considering obesity hypertension in children as a problem of epidemic proportions, Sorof and Daniels (2002), in their brief review inferred that the obese children are at approximately a 3-fold higher risk for hypertension than nonobese children. They stated that the risk of hypertension in children increases across the entire range of body mass index (BMI) values and is not defined by a simple threshold effect. As in adults, a combination of factors including overactivity of the sympathetic nervous system (SNS), insulin resistance, and abnormalities in vascular structure and function may contribute to obesity-related hypertension in children. They emphasized that obesity in childhood should be considered a chronic medical condition that is likely to require long-term management.\(^{(166)}\)

In an American Heart Association (AHA) Scientific Statement Steinberger and Daniels (2003) discussed the correlation of obesity, insulin resistance, diabetes, with cardiovascular risk in children. The cardiovascular risk from obesity and insulin resistance (Type-2 DM) is hypertension and atherosclerotic cardiovascular disease. They
emphasized on early recognition and treatment of these cardiovascular risk factors. (171)

Based on the fact that the sympathetic overactivity and decreased cardiovascular β-adrenergic responsiveness have been described in hypertension, Stevo J et al (2000) worked on the hypothesis that the persons of equal weight who had higher initial blood pressures gain more weight in the future. They also propose a plausible hypothesis to explain this reverse relationship. Both the blood pressure elevation and the gain of weight may reflect a primary increase in sympathetic tone. It is well known that in a milieu of increased sympathetic tone, the β-adrenergic responsiveness decreases. Sympathetic overactivity and decreased cardiovascular β-adrenergic responsiveness have been described in hypertension. We also propose a plausible hypothesis to explain this reverse relationship. Both the blood pressure elevation and the gain of weight may reflect a primary increase in sympathetic tone. It is well known that in a milieu of increased sympathetic tone, the β-adrenergic responsiveness decreases. Sympathetic overactivity and decreased cardiovascular β-adrenergic responsiveness have been described in hypertension. (174)

Wilks et al (1999) investigated blood pressure in Jamaican children in relation to body size and composition. they found (199)

Williams 2002 Cardiovascular Health in Childhood: A Statement for Health Professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. (200)
Steinberger (2009) et al in an AHA (American Heart Association) document regarding progress and challenges in metabolic syndrome in children and adolescents”, has highlighted many aspects of the metabolic syndrome. They aimed to set of fundamental questions about what the metabolic syndrome meant in a clinical or research setting. It called attention to the fact that the stability of the metabolic syndrome, especially for adolescents, is low, which raises questions about the utility of the metabolic syndrome in a clinical context. For these reasons, they have focused on cardiometabolic risk factors and have called for the types of research that would hopefully provide much needed answers in this area. This statement aims to represent a balanced and critical appraisal of the strengths and weaknesses of the metabolic syndrome concept in pediatric patients.

It focuses on the pediatric issues related to cardio metabolic risk factors, primarily on the progress that has been made in recognizing the components of the metabolic syndrome in children, their interrelations, and their importance as predictors of longitudinal risk for ASCVD (atherosclerotic cardiovascular disease) and T2DM (Type-2 Diabetes mellitus), based on evidence accumulated over recent years and on the consensus of experts in the field. It also addresses the need for early detection and preventive measures regarding cardiometabolic risk factors in children and adolescents, with a strong focus on obesity, inflammation, insulin resistance, dyslipidemia, and hypertension, which emerge as core elements of morbidity.
This document is a review of various researches correlating metabolic syndrome (especially correlating obesity and insulin resistance with childhood hypertension)

g) Environmental Factors:

(i) Breast feeding: Is associated with a lowering of later blood pressure in children born at term \(^{(104)}\).

(ii) Birth weight and neonatal weight gain: Faster weight gain after birth may be associated with higher blood pressure in later life. Low birth-weight and low head circumference children have lower blood pressure till preadolescent period but, their post-adolescent blood pressure may not be different from normal birth-weight individuals. \(^{(22, 70, 163, 164)}\). A study finding associations between low birth weight and elevated triglyceride concentrations in later childhood was done by Donker et al in 1997. \(^{(39)}\)

(iii) Socioeconomic status (SES): SES may be one of the factors influencing adiposity through diet etc. thereby influencing blood pressure \(^{(36)}\).

(iv) Pulse rate: Zhou et al (2000) found that a higher pulse rate in early life was associated with a higher blood pressure in later life \(^{(205)}\).
Some more factors which influence blood pressure individually as well as in combination with other factors are as follows:

a) **Height, Weight and Body Mass:**

   (i) **Height:** There is a positive correlation of blood pressure with height i.e. as the height grows the blood pressure increases in children and adolescents. This fact is observed in all standard blood pressure tables and the literature related to blood pressure distribution in children and adolescents. Some investigators have excluded the overweight children and adolescents from the list to create reference tables of blood pressure with height percentiles $^{(137)}$.

   **Weight:** Blood pressure is found to be higher in high body weight individuals. The weight normally increases with age in children and adolescents. Thus, there is a positive correlation of the blood pressure with the body weight. Overweight and obesity in children causes an additional impact on blood pressure predisposing to hypertension $^{(129)}$.

   (ii) **Body mass:** the body mass index involves weight and height both. But, the height is the denominator so body mass index is largely indicating presence or absence of overweight and obesity. More is the body mass more is the blood pressure $^{(9)}$.

b) **Body surface area:** A study on a sample population of school children in the northwest India in the age group of 7-16 gave a significant correlation of body surface area with the blood pressure $^{(158)}$. There was
no difference in the systolic and diastolic pressures of boys compared with girls of corresponding age in their study. Their study also determined the upper limits of normal, the lower limits of hypertension, values indicative of severe hypertension of children and adolescents of 7-16 years for systolic/diastolic pressure.

c) **Somatic growth and sexual maturation:** Due to different patterns of somatic growth and sexual maturation, the adolescent period gives different picture of rise in blood pressure in different ethnic groups (32).

d) **Sodium and other nutrient intakes:** High salt intake in diet as well higher sensitivity to sodium in certain groups causes a rise in blood pressure (44).

e) **Sympathetic nervous system reactivity:** If the reactivity of the sympathetic nervous system is more, then there will be a higher blood pressure than that in the less sensitive individuals (24).

f) **Stress:** Stress causes increased blood pressure and individuals with raised blood pressure due to stress are having more strong cardiovascular reactivity than normotensives (152).

g) **Plasma uric acid levels:** Nagahama et al in 2004 examined the correlation between serum uric acid level and obesity, hypertension, dyslipidemia, and diabetes mellitus (DM) in both men and women of a screened cohort in Okinawa, Japan. They found that that the hyperuricemic individuals had higher rates of coexistence of two or more cardiovascular risk factors such as obesity, hypertension, hypercholesterolemia, hypertriglyceridemia, and hypo-HDL.
cholesterolemia than those of non-hyperuricemic individuals in men and women.

2.3: Pathogenesis of Essential Hypertension

Essential hypertension is one of the major causes of hypertension after the age of 6 years. (76, 98)

Table 2.1:

<table>
<thead>
<tr>
<th>Causes of Childhood Hypertension According to Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>--------------</td>
</tr>
</tbody>
</table>
| One to six years | Renal parenchymal disease  
|               | Renal vascular disease  
|               | Endocrine causes  
|               | Coarctation of the aorta  
|               | Essential hypertension |
| Six to 12 years | Renal parenchymal disease  
|               | Essential hypertension  
|               | Renal vascular disease  
|               | Endocrine causes  
|               | Coarctation of the aorta  
|               | Iatrogenic illness |
| 12 to 18 years | Essential hypertension  
|               | Iatrogenic illness  
|               | Renal parenchymal disease  
|               | Renal vascular disease  
|               | Endocrine causes  
|               | Coarctation of the aorta |
Factors responsible for development of hypertension are same in children and adolescents as those in adults.

Increased peripheral resistance is the hallmark of essential hypertension (98).

Various mechanisms in the Pathogenesis of Essential Hypertension

Neural Mechanism (105)

This is the mechanism that is considered to be responsible for hypertension in younger age group. According to this mechanism, hypertension occurs as a result of an increase in sympathetic activity which is evident from the findings of an increased heart rate, cardiac output, plasma and urinary norepinephrine levels, regional norepinephrine spillover, peripheral post-ganglionic sympathetic nerve firing and alpha-adrenergic receptor-mediated vasoconstriction tone in the peripheral circulation. Sympathetic activation induced by obesity is an important determinant to the blood pressure elevation associated with this condition but is not effective in increasing resting energy expenditure i.e. the β-adrenergic activity is less in comparison to the extent of sympathetic stimulation where increased α-adrenergic activity is causing the sustained rise in blood pressure. (160)
Renal Mechanism \(^{(105)}\)

Studies reveal that in many forms of human hypertension the basic abnormality is an acquired or inherited defect in the kidney’s ability to excrete excessive sodium load imposed by a high sodium and chloride diet. The major cause of sodium retention by the kidneys is reported to be the resetting of the pressure-natriuresis with the shift of pressure-natriuresis curve towards the right. Renal sodium retention tends to increase the plasma volume leading to an increase in cardiac output and triggering autoregulatory responses that increase systemic vascular resistance. Salt retention also facilitates the smooth muscle contraction produced by all endogenous vascular substances.

Hormonal Mechanism

**Role of Renin-Angiotensin-Aldosterone System (RAAS)**

Overactivation of the Renin-Angiotensin-Aldosterone System (RAAS) is also postulated to be an important mechanism causing essential hypertension. Activation of RAAS is responsible for endothelial cell dysfunction and vascular remodeling. Angiotensin–II causes vasoconstriction, generation of reactive oxygen species, vascular inflammation, vascular and cardiac remodeling. Sympathetic overactivation and production of aldosterone leads to sodium retention, cardiac and renal fibrosis. Hypertension in diabetes is because of insulin induced hypertrophy of the arteries which in its turn increases the peripheral resistance. \(^{(105, 166)}\)
Role of Adipocytes

Angiotensinogen (precursor of the hormone Angiotensin-I) is also produced by adipocytes \(^{(26)}\) thus if the adipose tissue is greater in amount (obesity), the raw material for angiotensin–I production will also be greater which finally enhance the angiotensin–II formation and aldosterone secretion and all these will contribute to elevate the blood pressure. In addition, Angiotensin II has been shown to play a role in adipocyte growth and differentiation.

Major adipokines produced by the adipocytes are adiponectin, leptin and TNF-\(\alpha\).

Role of Adiponectin

Adipocytes secrete adiponectin, enhancing insulin sensitivity and preventing atherosclerosis. Blockade of the RAS with either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker results in a substantial increase in adiponectin levels and improved insulin sensitivity.\(^{(72,155)}\)

Role of Leptin

Another adipose tissue-derived hormone Leptin, by way of distinct neurochemical pathways stimulates sympathetic nerve activity in thermogenic and nonthermogenic tissue, affecting the metabolic and cardiovascular system respectively. Leptin, acutely, could have a dual influence on blood pressure control, in which the net effect would depend on the balance between the pressor action through activation of the sympathetic nervous system and a possible natriuretic and peripheral vasorelaxant effect of the hormone on the renal tubules and endothelium.
In contrast, chronic hyperleptinemia may lead to abnormal renal sodium retention and vasoconstriction associated with renal sympathetic activation and NO deficiency, both contributing to pressure elevation in obese individuals, who may develop resistance to the satiety effect of leptin with preservation of the cardiovascular effect. Treatment of these individuals might be focused in overcoming the hemodynamic alterations seen in obesity, such as antinatriuresis and overactivity of the sympathetic and renin–angiotensin systems.\(^{(19)}\)

**Role of Ghrelin**

The polypeptide ghrelin is secreted by the stomach and binds to the growth hormone secretagogue (GHS) receptor in the anterior pituitary. However, it is also found in the hypothalamus, and GHS receptors are found in various parts of the brain stem. Systemically administered and intraventricular ghrelin both increase body weight. Circulating ghrelin is decreased by eating and increased during fasting.\(^{(49)}\)

**Role of Insulin**

The role of insulin (insulin resistance and consequent hyperinsulinemia) in producing cardiovascular morbidity remains controversial. Increased serum insulin can contribute to urinary sodium retention, impairment of endothelial-dependent vasodilation, and increased sympathetic activity.\(^{(105)}\)

hyperinsulinemia, a marker of insulin resistance, is associated with atherosclerosis and cardiovascular morbidity. Several lines of evidence suggest insulin may directly promote cardiovascular pathology:

1) Insulin stimulates mitogen-activated protein kinase, mitogenesis, and plasminogen activator inhibitor-1 within vascular smooth muscle cells;
2) Insulin stimulates endothelin-1 production, with subsequent vascular smooth muscle growth;
3) insulin stimulates ras-p21 in vascular smooth muscle, which promotes increased effects of other growth factors, such as platelet-derived growth factor; and
4) The vascular endothelial cell insulin receptor knockout mouse has lower blood pressure and endothelin-1 levels than its wild-type counterpart.

Conversely, other lines of evidence suggest that insulin may be antiatherogenic:

1) Insulin inhibits the inflammatory transcription factor nuclear factor-kB;
2) Insulin decreases levels of early growth response gene-1 and tissue factor;
3) Insulin decreases tumor necrosis factor-α (TNF-α); and
4) Insulin stimulates nitric oxide to lower blood pressure. As with other hormone-receptor interactions, the duration and amplitude of insulin effects may play a role, because chronic hyperstimulation by
excessive ligand may lead to alternative cellular responses (eg, cortisol) or tachyphylaxis (eg, opioids), which would alter hormone action.

**Vascular mechanism**

The role of changes in the structure and function of small and large arteries in the pathogenesis and progression of hypertension is very important. Endothelial cell dysfunction is the major cause of alteration in vascular function with consequent vasoconstriction. Endothelial dysfunction along with neurohumoral activation and elevated blood pressure also causes remodelling of blood vessels (hypertrophic remodeling in place of eutrophic remodelling), which further aids the hypertension.\(^{(105)}\)

Although different mechanisms may be responsible for an increase in peripheral vascular resistance in different individuals or ethnic groups, it is probably complex interplay of various factors as shown in the following figure that causes a rise in peripheral resistance and thereby hypertension.
Figure 2.1: Some of the factors involved in the control of blood pressure

BLOOD PRESSURE = CARDIAC OUTPUT x PERIPHERAL RESISTANCE

Hypertension = Increased CO and/or Increased PR

Excess sodium intake → Reduced nephron number → Renal sodium retention

Stress → Sympathetic nervous overactivity

Genetic alteration → Renin-angiotensin excess → Cell membrane alteration

Obesity → Hyper-insulinemia

Fluid volume → Venous constriction → Preload

Contractility

Functional constriction → Structural hypertrophy

Endothelium derived factors

Autoregulation