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ENDOTHELIAL DYSFUNCTION, OBESITY, AND BLOOD PRESSURE IN CHILDREN

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In this issue of *Current Concepts* we are pleased to present an outstanding and informative discussion of endothelial dysfunction in hypertension and how it can be improved with antihypertensive drugs of the angiotensin converting enzyme, angiotensin receptor blocker and calcium channel entry blocker classes by Dr. Ernesto Schiffrin. In addition, the much-neglected area of blood pressure in the pediatric age group is addressed by 2 articles. One discusses ambulatory blood pressure monitoring in children to establish appropriate blood pressure criteria by Dr. Joseph Flynn and the other deals with the common problem of obesity in childhood by Dr. Albert Rocchini. The latter article briefly reviews the evidence connecting obesity to blood pressure and other risk factors for cardiovascular disease in childhood as well as suggesting a multiple-pronged therapeutic approach.

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EFFECT OF ANTIHYPERTENSIVE DRUGS ON ENDOTHELIAL DYSFUNCTION IN HYPERTENSION

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The endothelium plays an important role in regulation of vascular wall homeostasis. It also exerts a critical influence on the blood stream, particularly formed elements such as leukocytes and platelets, and on substances involved in blood coagulation. The control of blood vessel wall homeostasis is accomplished via production of vasorelaxants and vasoconstrictors. Among the vasorelaxants are nitric oxide (NO), prostacyclin (PGI_2), and various endothelium-derived hyperpolarizing factors (EDHFs) such as cytochrome P-450 products like epoxyeicosatrienoic acids.[1] Among the vasoconstrictors are endothelin-1 (ET-1) and endothelium-derived contracting factors (EDCFs) that are cyclooxygenase products like endoperoxides and thromboxanes. The regulation of secretion of these products is complex and includes mechanical stimuli like shear stress that stimulate release of NO, or pressure, which stimulates production of ET-1. As we age, under the influence of cardiovascular risk factors like hypertension (HTN), hyperlipidemia, atherosclerosis, diabetes mellitus, or as a result of the nefarious effects of smoking, the endothelium may become dysfunctional. Endothelial dysfunction in HTN may contribute to target organ damage and complications, although the exact mechanism for this remains unclear. Increased oxidative stress in the vascular wall is one of the mechanisms leading to endothelial dysfunction. It results in increased breakdown of NO[2] and in enhanced production of ET-1 and EDCF, leading to vasospasm. ET-1 also contributes to stimulate smooth muscle migration and, together with exaggerated oxidation of low density lipoportein (LDL) cholesterol, MCP-1 upregulation, and increased inflammation in the vascular wall, leads to progression of atherosclerosis.

Endothelial dysfunction in human HTN is associated with increased oxidative stress in the vascular wall.[3] The mechanism responsible for the increased generation of superoxide free radical anions is unclear, although angiotensin II acting via the AT_1 receptor and through stimulation of the NADH/NADPH oxidase system may be one of the major contributors.[4] Importantly, increased oxidant stress in the arterial wall accelerates breakdown of NO.[2] Decreased NO and enhanced production of endothelin-1, as a result of both endothelial damage by elevated blood pressure (BP) and the relative NO deficiency, induces a condition in which vasoconstriction predominates over vasodilatation. Increased vasoconstriction leads to capillary rarefaction, decreased tissue oxygen and nutrient exchange, and target organ damage (myocardial fibrosis and ischemia, nephroangiosclerosis, and renal dysfunction). Endothelial dysfunction is associated with increased coronary risk, but the role of dysfunction of the endothelium in this increased rate of events remains undefined. Endothelial dysfunction may affect the progression of atherosclerosis in proximal coronary arteries. Increased oxidative stress is associated with an inflammatory response; upregulation of adhesion molecules, cytokines, and chemoattractants (MCP-1); production of PAI-1; activation of matrix metalloproteinases and other molecular events leading to enlargement of atherosclerotic plaques; thinning of the fibrous cap; increased inflammation at the shoulder; and increased instability of the plaque. Together with enhanced platelet adhesiveness and activation of procoagulant factors on the damaged endothelial surface, this leads to triggering of plaque rupture, intramural hemorrhage, thrombosis, and coronary artery occlusion, along with distal embolization into a microcirculation with reduced reserve, and triggering of acute coronary syndrome. In hypertensive subjects these events may have more serious consequences in the myocardium because of the limited microcirculatory reserve.[5]

Although a causal relationship between endothelial dysfunction and atherosclerosis and events has not been definitively established, there has been great interest in determining whether it is possible to improve endothelial function with drugs. In particular, in hypertensive patients, which are the antihypertensive agents that not only lower BP but also correct or do not correct endothelial function?

Antihypertensive Drugs and Endothelial Function

β-adrenoceptor Blockers

We investigated in repeated clinical trials the effect of atenolol treatment for 1 and 2 years.[6,7] We found that in essential hypertensive patients small resistance size subcutaneous arteries, which have altered endothelium-dependent responses to acetylcholine, do not exhibit any improvement of response even though BP was very well controlled. However, β-blockers like carvedilol, which has antioxidant properties, may improve endothelium-dependent responses to acetylcholine in small arteries in spontaneously hypertensive rats.[8] Carvedilol has also been shown to induce increased brachial artery dilatation in response to reactive hyperemia, an endothelium-dependent effect.[9] Nebivolol, a selective β1-adrenoceptor blocker with vasodilating properties, may stimulate release of NO.[10]

Angiotensin Converting Enzyme (ACE) Inhibitors

Inhibition of angiotensin II generation may result in improved endothelial function by several mechanisms. Angiotensin II stimulates production of oxygen free radicals, as already mentioned, that decrease bioavailability of NO. Inhibition of angiotensin II generation may thus contribute to improved endothelial function. ACE inhibitor-induced accumulation of bradykinin may stimulate NO generation. Thus, ACE inhibitors have a potential to improve endothelium-dependent relaxation. Indeed, in both experimental animals[11] and human HTN,[6,7,12] acetylcholine-induced relaxation of large and small arteries has improved with treatment using ACE inhibitors such as enalapril, cilazapril, lisinopril, and quinapril, in different vascular beds, including coronary arteries.[13] Interestingly, impaired forearm blood flow response to methacholine or acetylcholine did not improve after short-term treatment with captopril, enalapril, or cilazapril[14-16] but 1-year treatment with lisinopril increased vasodilatation to bradykinin.[17] The latter effect has been attributed to improved generation of endothelium-dependent hyperpolarizing factor rather than to increased generation of NO.

Angiotensin Receptor Antagonists

For the reasons cited above regarding the actions of angiotensin II, it would be expected that angiotensin II type 1 (AT-1) receptor antagonists would improve endothelial dysfunction. Angiotensin II blockade may improve endothelial function not only by blocking the AT-1 receptor, but also by inducing increases in angiotensin II in plasma that impact on unblocked AT-2 receptors. AT-2 receptors stimulate NO synthesis by endothelial cells. Indeed, treatment for 1 year of essential hypertensive patients with the AT-1 antagonist losartan normalized acetylcholine-induced relaxation of gluteal subcutaneous resistance arteries.[18] In contrast, the AT-1 antagonist candesartan (8 to 16 mg daily) did not improve the response to acetylcholine or the lack of inhibition by NG-monomethyl-L-arginine (L-NMMA) on vasodilatation induced by acetylcholine.[19] Nonetheless, candesartan increased the vasoconstrictor effect of L-NMMA, indicating an increase in the release of NO after treatment of hypertensive patients with this angiotensin AT-1 antagonist.

Calcium Entry Blockers

In both experimental animals and human HTN calcium entry blockers increase endothelium-dependent relaxation.[11,20] One-year treatment with nifedipine gastrointestinal therapeutic system (GITS) improved relaxation to acetylcholine in gluteal subcutaneous resistance arteries in essential hypertensive patients.[20] Nifedipine[3] and lacidipine[21] improved flow-mediated dilatation of the brachial artery in essential hypertensive patients. Underlining the significance of treatment results obtained in hypertensive patients at the level of peripheral vessels,[3,20,21] nicardipine and diltiazem improved endothelium-dependent coronary vasomotion in essential hypertensive patients.[22]

Conclusion

Endothelial dysfunction occurs in essential hypertension and involves decreased availability of NO resulting from enhanced breakdown by oxidative stress as well as increased release of EDCFs such as endoperoxides and thromboxanes, oxygen free radicals, and ET-1. Endothelial dysfunction may accelerate atherosclerosis in HTN. Antihypertensive treatment may reverse endothelial dysfunction. ACE inhibitors, AT-1 antagonists, and calcium channel blockers can restore endothelium-dependent vasodilatation, probably by increasing NO availability by reducing oxidant stress in the vascular wall. ACE inhibitors can also improve endothelium-dependent vasodilatation to bradykinin, probably via a hyperpolarizing factor rather than effects on NO availability.

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APPLICATION OF AMBULATORY BLOOD PRESSURE MONITORING TO THE EVALUATION OF HYPERTENSIVE CHILDREN

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Accurate blood pressure (BP) measurement is essential if hypertension (HTN) in children is not to be over-diagnosed or under-treated. Both the First and Second Task Force reports,[1,2] as well as the recent Working Group report,[3] have focused on this problem, and have addressed in detail various methods of BP measurement in children. Such methods produce so-called "casual" BP readings, which may be obtained either manually or by automated devices in either the clinic or home setting. However, casual BP readings obtained by these methods may not accurately reflect a child's true BP because of operator error,[4] inaccurate reporting of results,[5] device inaccuracies,[4,6] white-coat HTN,[7,8] or simply because of the known lability of children's BP.[9] Therefore, even if pediatricians and other health care providers follow the recommendations of the previously mentioned consensus bodies, a significant potential exists for inaccurate diagnosis or management of HTN in children.

Ambulatory BP monitoring (ABPM) is a relatively new technique in which a subject's BP can be measured at regular intervals over 24 hours.[4,8] Although several methods of determining ambulatory BP have been developed, the most widely used devices employ oscillometry to determine BP. Such devices are usually tolerated well by patients and produce reliable, reproducible results. ABPM offers numerous advantages that could potentially address the difficulties in BP measurement mentioned above. Chief among these is the ability to objectively record an entire day's worth of BP readings, avoiding the potential problems of operator error and inaccurate result reporting. Since the BP readings are being obtained out of the office setting, the white-coat effect is avoided. Because the monitors record BP over an entire 24-hour period, the impact of BP lability is lessened.

In hypertensive adults, ABPM has gained widespread acceptance as a diagnostic and monitoring technique.[4] It has been used to predict the development of end-organ damage and other HTN-associated morbidity and to assess the efficacy of antihypertensive medications.[8,10,11] Several studies have demonstrated that routine application of ABPM to the management of hypertensive patients can lead to changes in medical decision-making.[12,13] Because of its demonstrated utility, clear indications for the use of ABPM in adults have been developed by consensus bodies.[14]

ABPM in children, however, is still in its infancy. Although appropriate equipment for pediatric ABPM is available (including lightweight monitors and a wide range of cuff sizes), and even though numerous studies have demonstrated that ABPM is a feasible, accurate, and reproducible technique in children,[8,9,15-17] consensus bodies have not yet endorsed its routine use in the evaluation and management of hypertensive children.[3,15]

The major barriers hindering more widespread application of ABPM to the practice of pediatric HTN are twofold: first is the lack of accepted standards for analyzing ABPM studies in children and second is the relative lack of data demonstrating that ABPM results in children correlate to end-organ damage and other outcome measures. While there are reasonably widely accepted normal values for daytime and nocturnal BP and BP "load" (usually defined as the percentage of readings greater than a preset threshold value) in adults, similar standards have not been established for children. This creates the potential for over-diagnosis of HTN, particularly if diagnostic criteria are too lenient. One potential solution to this problem is to use the Second Task Force recommendations[2] as modified in the working group report[3] to set the threshold BPs for interpretation of ABPM studies. Consideration could also be given to choosing a somewhat higher BP load than that used for interpreting ABPM studies in adults. However, at least 1 recent large-scale study of ambulatory BP in children has demonstrated that normotensive children (as defined by casual BP) may have higher ambulatory BPs than previously believed.[18] Therefore, it may be even more appropriate to use these newer normative data in interpreting pediatric ABPM studies. Hopefully, collaborative efforts such as the ABPM database of the International Pediatric Hypertension Association will answer this important question.

With respect to correlating ABPM results with end-organ damage in children, some useful data are beginning to emerge. Several groups of investigators have recently begun to examine whether left ventricular (LV) mass in hypertensive children can be correlated with the results of ABPM studies. Preliminary data appear to confirm that such a relationship exists, with higher LV mass seen in children with sustained BP elevation as measured by ABPM.[19,20] Correlation between ABPM results and other markers of hypertensive end-organ damage, such as the development of retinopathy and microalbuminuria, still need to be studied in children.[16,19] Given the relatively short duration of HTN in most children compared to adults, studies examining these issues will need to be carefully designed and carried out at multiple centers if meaningful data are to be obtained.

What, then, is the potential role of ABPM in evaluating hypertensive children given the current status of this technique in children? Preliminary data from two recent studies indicate ABPM may be a useful tool for identifying children at risk of complications of HTN or children with potentially serious secondary causes of HTN. Sorof and colleagues have demonstrated that children with an elevated load on ABPM have a 60% chance of also having LV hypertrophy, thus suggesting that ABPM can be used as a screening test prior to the performance of echocardiography.[20] We have demonstrated that children with secondary forms of HTN are more likely to have diastolic and/or nocturnal HTN as measured by ABPM than children with essential HTN, suggesting ABPM has a potential role in identifying children who require more extensive evaluation for underlying renal disease or other secondary causes of HTN.[21] In addition, ABPM is also

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clearly useful for identifying children with white-coat HTN.[7,9] Furthermore, although data are still lacking, it is likely that ABPM will eventually also find a role in the management of children who require antihypertensive drug therapy.

In conclusion, ABPM is a useful technique that can potentially overcome many of the shortcomings of using casual BP data in evaluating and managing hypertensive children. Although further study is needed with respect to pediatric ABPM standards and correlation to outcome, widespread adoption of this technique should be encouraged.

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ADOLESCENT OBESITY AND HYPERTENSION

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Obesity is a difficult clinical problem. It is the most serious and prevalent nutritional disease in the United States. Childhood obesity is known to exert a major impact on cardiovascular risk. Becque and coworkers documented that 80% of obese adolescents have elevated systolic and/or diastolic blood pressures (BPs).[1] Becque also demonstrated that 97% of obese adolescents had 4 or more of the following cardiovascular disease risk factors: elevated serum triglyceride levels, decreased high-density lipoprotein (HDL) cholesterol levels, increased total cholesterol level, elevated systolic and/or diastolic BP, a diminished maximum work capacity, and a strong family history of coronary heart disease. The following article will summarize how obesity might lead to the development of hypertension (HTN), how obesity alters cardiovascular risk, and how to treat the obese child.

What is Obesity?

Before describing how obesity may cause hypertension and be associated with increased cardiovascular risk it is important to give a brief definition of obesity. Weight for height standards are also useful in defining childhood obesity. A commonly accepted definition for child-hood obesity is the combination of triceps and subscapular skinfolds and being greater than the 80th percentile and weight for height being greater than the 75th percentile for age and sex. Obesity defined by these criteria is currently present in 15% to 20% of school age children.

How Does Obesity Lead to the Development of Hypertension?

HTN has been known to be associated with obesity for over 70 years. Figure 1 depicts the BP distribution for systolic and diastolic blood pressure of 72 obese adolescents studied by us.[2] As can be seen in this figure, the obese adolescent has a BP distribution that is skewed to the right. The mean BP for the group is >1 standard deviation greater than the mean blood pressure for the general population. We have also demonstrated that, although obese adolescents had a BP distribution skewed 1 standard deviation to the right of normal following weight loss, this distribution no longer differed from that of the general population.[2]

Based on available data in the literature, the most reasonable hypothesis to explain the pathogenesis of obesity HTN is that the HTN is related to a complex interaction between sodium retention, activation of the sympathetic nervous system, and selective insulin resistance.

Adolescent Obesity and Cardiovascular Risk

In addition to HTN, the other major cardiovascular risk factor associated with obesity is an abnormal plasma lipid profile. When children and adults are stratified for fatness, there is a direct and significant relationship between lipid levels and obesity. The pri-

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mary cause of hypertriglyceridemia in children who are free from other diseases causing secondary hypertriglyceridemia is obesity. Obesity is also frequently associated with a significant depression in plasma HDL-cholesterol. Sternberger and co-workers demonstrated that the lipid abnormalities observed in obese adolescents are directly associated with insulin resistance.[3] Insulin resistance was assessed in 82 obese adolescents. Using a step-wise multiple regression analysis, Steinberger demonstrated that whole body glucose uptake was the only factor that entered into the relationship for triglycerides and low-density lipoprotein (LDL) cholesterol and that both whole body glucose uptake and fasting insulin were the only two variables that entered into the relationship for HDL-cholesterol. Therefore, in obese adolescents, the degree of insulin resistance (not adiposity [percent fat]) appears to explain the largest portion of the variance in the levels of triglycerides, LDL cholesterol, and HDL cholesterol. The mechanism whereby insulin resistance leads to these lipid abnormalities has not been completely characterized. There is good evidence to suggest that two of the ways by which hyperinsulinemia elevates triglycerides are through enhanced hepatic very low density lipoprotein (VLDL) synthesis and through a defect in VLDL removal. An increased rate of degradation of the apoprotein A-I (the major lipoprotein in HDL cholesterol) is believed to be a cause for the reduced level of HDL-cholesterol observed in many insulin resistant patients.

How Do You Treat Childhood Obesity?

Treatment modalities employed in obese children and adolescents can be categorized into one of a combination of six basic approaches: calorie restriction, anorectic drugs, increased physical activity, therapeutic starvation, bypass surgery and habit pattern changes based on social learning therapy. Certainly drugs, starvation, and surgery are unacceptable treatment strategies for the majority of children.

The weight loss program we have used consists of three components: diet, behavior change, and exercise. The caloric requirements necessary for a child to lose 1 to 2 pounds per week are determined by reducing the current level of calories by 500 to 1000 calories per day. An exchange type diet is used, since it teaches the child the essentials of good nutrition and gets the child actively involved in determining his or her own diet. The behavior change component of the program includes a weekly class for 20 weeks, then every other week until the child has maintained his or her goal weight for at least 1 month. The classes should center around: 1) nutrition education, 2) record keeping, 3) obtaining control over the external cues that set the occasion for eating, and 4) reinforcement of altered behavior. All children are also encouraged to exercise for 30 to 60 minutes per day at least 3 days a week. The weight loss program should have a built-in reinforcement system to help the child establish and maintain new habits. Finally, in addition to the child's structured portion of the program, family support is critical. The child's family needs to be taught how to give the child positive support without nagging or taking over the child's weight loss program. Using this type of program we have been able to achieve adequate weight loss in adolescents who are motivated to lose weight. It is important to remember that if the child does not want to lose weight no weight loss program, regardless of its approach, organization, or cost will be successful.

Summary

There is ample data, with the obese child, to suggest that selective insulin resistance, hyperlipidemia, and essential HTN are directly related. In addition, childhood obesity is the single best marker for predicting who will develop cardiovascular disease later in life.

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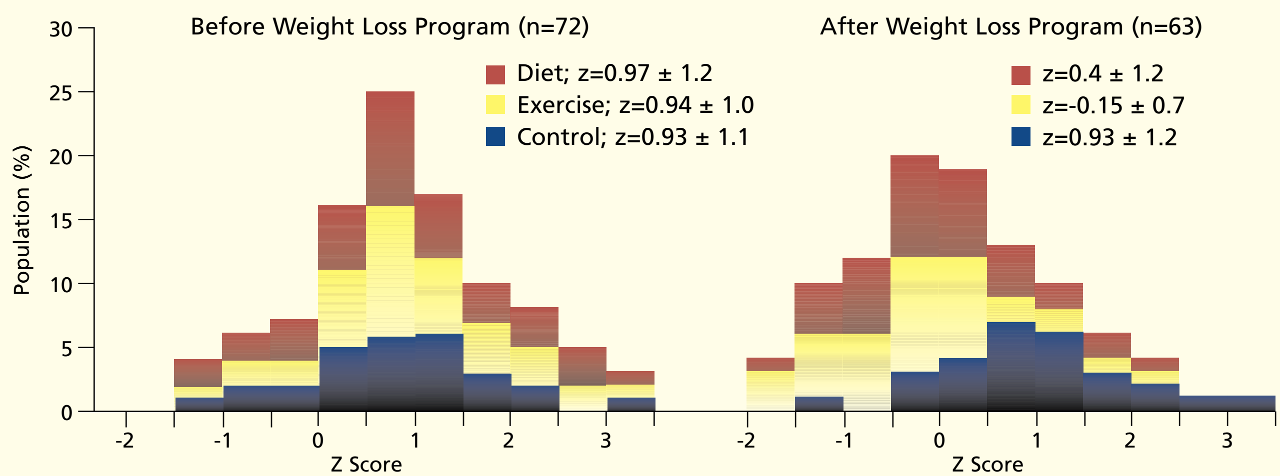
Figure 1 Distribution of Diastolic BP in Obese Adolescents Compared With Those Rates in the Second National Health and Nutrition Examination Survey Before and After a 20-week Weight Loss Program[2]



All values presented are means ± SD. Diet (diet and behavior change group); exercise (diet, exercise, and behavior change group); control (obese control group). Adapted from Pediatrics 1988;82:16-23.