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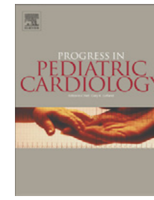

Review

Effects of systemic hypertension on the cardiovascular system

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ABSTRACT

Hypertension is a well-characterized risk factor for the development of cardiovascular disease in adults. More recently, data obtained from autopsy studies as well as epidemiological longitudinal studies have demonstrated that similar end organ changes occur in children and adolescents with even mild elevations in blood pressure. These changes in early life predict the development of adult end organ disease. Specifically, chronic elevations in blood pressure in pediatric patients lead to alteration in left atrial and ventricular structure. Hypertension is also associated with impaired ventricular relaxation and decreased compliance. These cardiac changes occur in parallel with alterations in the vascular system and development of atherosclerosis. For these reasons, children with elevated blood pressures must be identified and treated appropriately in order to improve their long-term outcomes.

1. Introduction

Hypertension is a significant public health challenge because of its high prevalence as well as its associated cardiovascular complications [1]. In fact, hypertension is the leading risk factor for cardiovascular mortality and ranked third as a cause of disability-adjusted life years in adults [1,2]. A recent study examining the economic burden of chronic cardiovascular disease suggested that medical expenditures attributable to hypertension are estimated at more than 73 billion dollars annually [3]. More disturbing is the fact that hypertension has its origins in childhood, and hypertension in children is a risk factor for the development of adult cardiovascular disease [4,5]. However, hypertension in children is often underdiagnosed, and the alterations in end-organ structure and function noted in adult hypertensive patients likely also have their origins in childhood [6,7]. Since treatment of hypertension has been shown to improve cardiovascular outcomes and to reduce the risk for the development of these complications in the adult population, we hypothesize that prompt recognition of these alterations in children and adolescents may also prevent future morbidity and mortality in these pediatric patients [8]. The structural and functional consequences of pediatric hypertension on cardiovascular structure and function are outlined in Table 1).

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2. Cardiac Structure

2.1. Pathophysiology

In the classical paradigm for the pathogenesis of hypertensive heart disease, the development of left ventricular failure is preceded by alterations in both left atrial and ventricular geometry [9–11]. The changes in ventricular geometry occur in two different patterns [11]. In concentric left ventricular hypertrophy, parallel addition of sarcomeres causes an increase in the cross-sectional area and diameter of the cardiac myocytes [12]. These alterations lead to a significant increase in left ventricular wall thickness out of proportion to an increase in size of the left ventricular cavity [12]. In contrast, a symmetric increase in wall thickness as well as left ventricular cavity size results in eccentric left ventricular hypertrophy as a result of sarcomere addition in series. Hypertension is generally associated with the development of concentric hypertrophy as increased blood pressure and pulse pressure oppose left ventricular ejection inducing increased left ventricular wall stress [13]. In addition to left ventricular stress, numerous nonhemodynamic factors are thought to influence the development of altered left ventricular geometry including neurohormonal activation, biomarkers of inflammation, and hemostatic factors (Fig. 1) [14–18]. A central role for the renin–angiotensin–aldosterone system was proposed based on a cross-sectional study examining the contribution of several biomarkers including C-reactive protein, plasminogen activator inhibitor-1, B-type natriuretic peptide, renin, and aldosterone (Fig. 1) [19]. The investigators found that the aldosterone–renin ratio alone was significantly associated with the development of both concentric and eccentric remodeling [19]. Regardless of the mechanism, these

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Table 1
Cardiovascular consequences of primary hypertension in children and adolescents.

Cardiac structure
Increased left atrial size
Left ventricular hypertrophy
Cardiac function
Decreased left ventricular relaxation
Decreased left ventricular compliance
Vascular structure
Atheromatous changes
Arterial stiffening
Endothelial dysfunction
Increased carotid intimal medial thickness
Decreased cerebrovascular reactivity

alterations are thought to provide for normalization of afterload and preservation of systolic performance early in the development of hypertension (Fig. 1) [14]. However, as myocardial oxygen demand increases due to increased cardiac mass and persistently elevated wall stress, a decrease in coronary artery oxygen reserve is noted leading to increased apoptosis and cardiac cell death (Fig. 1) [14]. Furthermore, abnormalities in myocardial electrical conduction in the hypertrophied muscle also trigger the development of arrhythmias.

2.2. Left Atrial Enlargement

In terms of atrial structure, left atrial enlargement is associated with the duration of elevated blood pressure, the severity of systolic blood pressure, and pulse pressure in the general adult population [20]. However, only age, race, and obesity were significant predictors of left atrial size in hypertensive adults [21]. Although not consistently associated with hypertension, the presence of left atrial enlargement is significant because it is associated with the development of cardiac arrhythmias, cerebrovascular events, and death in hypertensive adults [22]. Although data are limited in the pediatric population, Daniels et al. [23] studied a cohort of 112 pediatric patients with hypertension and found that 51% of patients had left atrial dimensions above the 95% upper confidence limit. In statistical analysis, height, body mass index, and systolic blood pressure were independent predictors for left atrial enlargement [23]. Interestingly, left ventricular geometry was also an independent predictor of left atrial size, and children with eccentric left ventricular hypertrophy demonstrated increased left atrial size compared to patients with other forms of left ventricular geometry [23]. Although the cross-sectional nature of this study prevented elucidation of cause and effect, the authors speculated that the hypertrophied left ventricle may demonstrate impaired diastolic filling necessitating increased left atrial volume [23]. The prognostic value of these findings in pediatric patients remains to be determined.

2.3. Left Ventricular Hypertrophy

Several studies have suggested that the prevalence of left ventricular hypertrophy in hypertensive adults ranges from 33 to 81% [24,25]. Left ventricular hypertrophy has been noted to be a risk factor for cardiovascular disease, cardiovascular morbidity, ventricular arrhythmias, and cardiovascular death in adults [26,27]. Similar changes are noted in childhood and adolescence (Table 2). However, one of the complicating factors in the assessment of left ventricular mass in children is that there is not a consensus on the method of defining left ventricular hypertrophy in this population. Some cardiologists utilize the wall-thickness z-score of the posterior wall to determine left ventricular hypertrophy. The American Academy of Pediatrics recommends the use of the left ventricular mass indexed to 2.7 with a value equal to or above 51 $g/m^{2.7}$ indicative of left ventricular hypertrophy [28]. Age-specific values for left ventricular mass index equal to or above the 95th percentile have also been developed [28]. A recent study by Mirchandani et al. found that there was 79% agreement between the two methods [28]. The authors highlighted the importance of establishing a consensus for diagnosing left ventricular hypertrophy [28].

Alterations in left ventricular structure are present in up to 40% of children and adolescents with pre-hypertension and hypertension [29–40]. These studies are summarized in Table 1. Although controversial, some evidence suggests that these cardiac alterations occur even in pediatric patients with "white coat hypertension" [33]. A recent study by Urbina et al. [35] measured several cardiovascular parameters including left ventricular mass and carotid intimal medial thickness in normotensive, pre-hypertensive, and hypertensive adolescents. The authors noted a gradual increase in left ventricular mass index in normotensive patients compared to both pre-hypertensive and hypertensive subjects [35]. Multivariate regression demonstrated that the presence of both pre-hypertension as well as hypertension independently predicted changes in end organs as assessed by carotid intimal medial thickness and left ventricular mass [35]. Richey et al. [36] detected associations between development of left ventricular hypertrophy and systolic blood pressure as well as 24-h systolic blood pressure load [36]. In a follow-up study of children aged 7–18 years, subjects with left ventricular hypertrophy had higher ambulatory systolic blood pressures, diastolic blood pressures, and body mass index [37]. Patients with eccentric left ventricular hypertrophy demonstrated higher

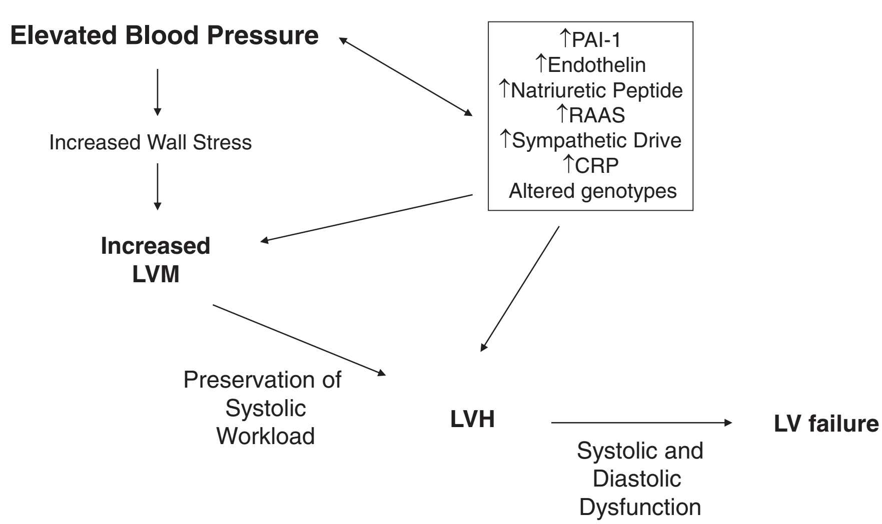

Fig. 1. Development of left ventricular hypertrophy.