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Hypertension in the elderly

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Hypertension is a major and frequent problem that affects the adult population. In the United States the prevalence of hypertension in adults before age 60 is 20 percent; between the ages of 60 to 65 it is 30 percent and over age 65 it may be as high as 40 percent [1]. It has long been recognized that hypertension results in an increased cardiovascular morbidity and mortality. Stroke, congestive heart failure, angina pectoris, myocardial infarction and renal failure are frequent complications of hypertension. The risk of cardiovascular disease increases with age in hypertensive subjects [2]. Over 50 percent of the mortality after age 65 is caused by cardiac and cerebrovascular diseases. In addition, chronic disability which impairs quality of life may result from these cardiovascular diseases.

A recent decline in cardiovascular morbidity and mortality has been achieved by judicious and rational antihypertensive treatment. Nevertheless, several misconceptions about the treatment of hypertension in the elderly patient have resulted in considerable neglect of the management of hypertension in these individuals. In this review we present some epidemiological and pathophysiological characteristics of the aging process as related to hypertension. Based on this background, we will propose a safe and effective therapeutic program for the management of hypertension in the elderly.

Epidemiology

The World Health Organization has defined a normal blood pressure in an adult as one that is less than 140 mmHg systolic and less than 90 mmHg diastolic. In sustained hypertension the values are clearly over 160/95 mmHg: values in between normal and sustained hypertension have been classified as borderline hypertension. Blood pressure increases with age, but after 60 years there is a steep rise in systolic and a decline in diastolic pressure. Systolic blood pressure in women rises from 133 mmHg at age 50 to 165 mmHg at age 85, while men increase from 128 mmHg to 154 mmHg during the same period [3]. In some primitive societies a rise in blood pressure with age does not occur [4].

For many years it was thought that gradual elevation of blood pressure with age was necessary to adequately perfuse vital organs. This concept was proved to be erroneous by the Framingham study [5]. This epidemiologic survey of 5,209 men and women assessed a number of risk factors in the development of cardiovascular disease. Increased systolic and/or diastolic hypertension were both associated with increased cardiovascular morbidity and mortality. Indeed, in the older age group, hypertension is one of the major risk factors of cardiovascular mortality. The annual incidence of cardiovascular disease was three to four times greater in those patients between 65 and 74 years old who had blood pressures over 160/95 mmHg [6]. This study revealed that compared to diastolic blood pressure, systolic blood pressure is the most potent contributor to cardiovascular complications [7]. Other risk factors such as hypercholesterolemia and smoking are less important in this age group.

Among the cardiovascular complications, stroke is the major cause of mortality and a leading cause of disability in young as well as in elderly hypertensives. The Framingham study [8] reported an overall incidence of atherothrombotic infarction seven times greater in hypertensive individuals. The risk increased to 30 per cent for each 10 mmHg rise in blood pressure recorded in those persons over age 65. Likewise, the Hisayama study reported an increased incidence of stroke with age in 1,621 individuals evaluated over a period of 13 years [9]. In addition, Ostfeld et al. [10] demonstrated an incidence rate of stroke twice as high in blacks as compared to whites. It seems clear that older, black, hypertensive individuals are more vulnerable to stroke and require particularly careful attention and appropriate treatment

Coronary events such as angina pectoris, myocardial infarction and sudden death are commonly observed in the hypertensive elderly patient. Men between the ages of 60 and 64 years, who have a diastolic blood pressure of 95 mmHg or above have an annual risk of a major coronary event that is 3.7 times greater than those age-matched individuals with less than 80 mmHg [11]. Similarly, in men and women between 65 and 74 years of age the presence of left ventricular hypertrophy predicted a tenfold increase in the risk of congestive heart failure

as compared with subjects without evidence of left ventricular hypertrophy [12]. The level of systolic pressure correlated best with the development of left ventricular hypertrophy. Indeed, isolated systolic hypertension has been associated with an increased incidence of myocardial infarction or ischemia. A systolic blood pressure greater than 180 mmHg predicted an increased risk with electrocardiographic signs of myocardial infarction or ischemia [13]. In view of the demonstration that isolated systolic pressure elevation and systolic-diastolic hypertension are detrimental to the cardiovascular system, it remains important to prove that treatment will decrease the risks associated with hypertension. Several long term therapeutic studies that have included elderly patients have looked into this question.

The first controlled trial to examine the effects of therapy on cardiovascular morbidity and mortality was the Chelmsford study reported by Hamilton, Thompson and Wisniewski [14]. Sixty one patients with moderate to severe hypertension (diastolic blood pressure over 110 mmHg) clearly demonstrated a distinct benefit from therapy. Similar results were obtained in 143 male veterans by the first Veterans Administration Cooperative Study [15] published in 1967. A more detailed study of 380 patients, 81 of them over the age of 60, with diastolic pressure between 90 and 114 mmHg was published in 1970 by the Veterans Administration [16]. This study showed an unquestionable decrease in the incidence of morbid cardiovascular events in patients with diastolic pressures ranging from 105 through 114 mmHg who were successfully treated. In those with diastolic pressure in the 90 to 104 mmHg range there was a protective trend but this was not statistically significant. In particular, no benefits from coronary events were noted in the group with mild hypertension.

These results created much speculation as to whether mild hypertension should be treated or not. In view of this, several studies in patients with mild hypertension were initiated.

The studies on mild hypertension were conducted by the Public Health Services in the United States [17] and one performed in Chelmsford, England [18]. They included a small number of patients which made analysis of data less reliable. Recently, two large scale trials have been published in Australia and the United States. The Australian trial (Australian National Blood Pressure Study Management Group) [19, 20] examined 3,427 patients aged 30 to 69 years for an average study duration of 4 years. All cases had diastolic blood pressure between 95 and 109 mmHg and were treated with placebo or diuretics followed by beta blockers. There was a significant reduction of strokes and deaths from all causes; there was also a reduction in fatal ischemic heart disease which did not attain statistical significance. This study demonstrated that therapeutic blood pressure reduction was much more important in preventing complications than the initial value of the blood pressure. Also, a 39 percent reduction in complications was observed in those patients over 60 years of age at entry.

The Hypertension Detection and Follow up Program [21, 22] included 11,000 hypertensive patients in 14 centers followed for 5 years. Patients were randomized to either stepped care (SC) or referred care (RC) groups. The SC patients attended special clinics where tey received special therapeutic intervention and counselling; the RC patients were referred to their private physicians for usual care. The findings indicated that the five year mortality rates from all cardiovascular causes were significantly lower in the SC group, and this was largely due to reduction in stroke and noncardiovascular deaths.

Table 1. Alterations and consecuences of Hypertension at Rest and During Exercise in the Elderly

	Anatomic and Functional Alterations		Hemodynamic consequences	
Rest	Myocardial contractility	↓	Left ventricular stoke volume	↓
	Left ventricular stiffness	↑	Cardiac output	↓
	Afterload	↑	Systolic blood pressure	↑
			Total peripheral resistance	↑
			Ejection time	↑
Exercise	Myocardial contractility	↓	Maximal cardiac output	↓ ↓
	Heart rate	↓	Left ventricle end diastolic pressure	↓
	Left ventricular stiffness	↑	Systolic blood pressure	↑ ↑
	Afterload	↑	Systemic vascular resistance	↑
	Adrenergic receptors	↓	Maximal O_2 consumption	↓
	↑ - increased			
	↓ - decreased			
	↓ ↓ - greatly decreased			
	↑ ↑ - greatly increased			

The incidence of myocardial infarction was less in patients with mild hypertension than in those with higher levels of blood pressure. A subgroup of 2,376 patients aged 60 to 69 also benefited greatly from therapy. The overall mortality in the elderly SC group was 16.4 lower than the RC group, with marked reduction in both fatal and non-fatal stroke. A recent report of this program shows that left ventricular hypertrophy, a predictor of poor prognosis, can be prevented and reversed by systematic antihypertensive treatment [23].

Whereas no doubts may exist as to the treatment of diastolic hypertension, serious questions have been raised about the benefit of the treatment of isolated systolic hypertension in the elderly. As mentioned earlier, systolic hypertension correlates best with increased cardiovascular morbidity and mortality. Data from several epidemiological surveys are consistent with this observation [24, 25, 26]. In addition, a recent Framingham report of 1,254 untreated persons surviving after age 65 supports the univariate relationship of several measures of systolic blood pressure over time with increased risk of cardiovascular disease [27]. On the other hand, if systolic hypertension indicates rigidity of large arteries, reduction of systolic blood pressure may not decrease the risk of cardiovascular events since therapy could lead to an unacceptable decrease in diastolic blood pressure and the side effects of treatment would mitigate against the use of antihypertensive agents. Nonetheless, it is generally believed that systolic hypertension exceeding 180 mmHg should be treated [28]. In an attempt to answer these questions better the European Working Party on High Blood Pressure in the Elderly has established a double blind, multicenter trial in patients over the age of 60 years [29]. Patients are receiving either thiazide diuretics or placebo. Final results of this large scale study are eagerly awaited to clarify any doubts about the treatment of purely systolic and systolic-diastolic hypertension in the elderly.

Pathophysiological characteristics

Advancing age affects the anatomy and physiology of the cardiovascular system. Structural and functional changes are observed in the arteries and cerebro-cardio-renal parenchymas. Arterial intimal thickening is a common finding [30, 31]. The endothelial surface may appear irregular with an increased number and accumulation of subendothelial cells which mat be derived from the vessel wall and blood [32]. In the arterial media, collagen content increases and elastin is replaced by lipid infiltration followed by thickening and atheromatous formation with calcification of the wall. There is loss of elasticity and compliance with elongation, tortuosity and obstruction of arteries. As wall to lumen ratio increases with the aging process, the resistance of vessels increase. Regardless of age, similar changes occur with hypertension. These observations have led to the hypothesis that these vascular changes may be accelerated by a hypertensive process. The aortic wall distends during systole and recoils during diastole maintaining a small difference between systolic and diastolic pressures. The aging process diminises aortic wall compliance, widening the pulse pressure and producing a rise in pressure for a given change in volume. Loss of the aortic capacity of maintaining a small pressure difference may result in isolated hypertension, particularly in the aged. In addition, arterial wall rigidity blunts the responsiveness of the aortic and carotid sinus baroreceptors to changes in blood pressure. The insensitivity of baroreceptors impairs cardiac acceleration during hypotension and cardiac slowing in response to acute increases in blood pressure [33, 34]

Regional hemodynamics

Cardiac

The influence of advancing age on left ventricular function and cardiac hemodynamics has been extensively investigated. The function of the left ventricle as a pump is determined by 1) the filling or preload measured as the end diastolic volume, 2) the afterload or impedance of ejection of blood and 3) the inotropic or contractile state of the ventricular muscle. At rest invasive studies have shown a decline of cardiac output an stroke volume [35, 36] with no variations in heart rate [37]. Brandfronbrener, Landowne and Schock [38] observed a 50 percent decrease in cardiac index as age increased from 20 to 80 years of age. However, the population studied was afflicted with disease or other medical conditions which may affect cardiac performance. Participants of the Baltimore Longitudinal Study of Aging [39] who were free of organic heart disease, had mild hypertrophy as noted by increasing thickness of systolic and diastolic left ventricular wall by echocardiography. However, cardiac output measured by radionuclide scanning did not vary over an age range of 30 to 80 years. Similarly, Proper and Wall [40] reported no age associated changes in cardiac output and stroke volume. Preload does not change significantly with age in healthy individuals; afterload is modestly increased at rest, mostly due to a higher systolic pressure [41]. As a consequence, a mild left ventricular hypertrophy occurs probably as an adaptive mechanism to maintain normal all stress.

There is a general agreement that the cardiovascular response to exercise is seriously affected by advancing age. As early as Master and Oppenheimer [42] described a limitation in exercise tolerance in elderly inividuals. At maximal workload, heart rate, stroke volume, cardiac output and oxygen uptake were lower. Left and right ventricular end diastolic and pulmonary artery pressures are elevated [43, 44] and the peripheral vascular resistance is higher during exercise. The end result is an inability to increase the left ventricular ejection fraction [45].

The mechanisms which have been implicated to explain the abnormal response to exercise in the elderly are: 1) a diminished action of the Frank-Starling mechanism; 2) a decreased contractility of the myocardium, and 3) an increased afterload.

Echocardiographic studies have shown that the Frank-Starling mechanism is not altered in the older individual [46]. In addition, isometric contraction of the myocardium remains intact but its contractile response to catecholamines markedly diminished [47]. The latter abnormality is attributed to a generalized deficiency of the sympathetic system in the elderly (vide infra). Anatomic and functional changes may occur in the conduction system, muscle fibers and valves and in the peripheral arteries. Metabolic changes can also occur in the cardiac musculature. Of great interest is the decline in myofibillar ATPase [48]. However, the physiologic significance of these changes is unknown.

Most investigators agree that the main factor which limits the increase in the left ventricular ejection fraction during exercise is the vascular impedance or afterload which is determined by the size and compliance of the aorta, and the pressure waves reflected by the peripheral resistance vessels. Several indexes have been used to determine aortic compliance in the elderly. Tarazi [49] has found a close correlation between the ratio of pulse pressure to stroke volume (PP/SV, mmHg rise in pressure per ml of ejected blood) and the index derived from pulse pressure tracings. With exercise, systolic pressure increases in teh presence of a poorly compliant aortic wall and a greater vasodilatory response and as result afterload increases [50]. The increase in cardiac work which ensues is almost proportional to the elevation of systolic pressure. Myocardial oxygen supply is therefore impaired and symptoms of cardiac anoxia may develop. Table 1 summarizes the main changes that occur at rest and exercise in the elderly individual.

During the early phase of essential hypertension cardiac output is high and total peripheral resistance is normal or low. The young and the older patients with sustained essential hypertension exhibit an increase in total peripheral resistance. Cardiac output remains normal or is reduced in the older hypertensive patients. A small group of elderly patients may present with a hyperkinetic circulation and increased cardiac output [51]. Topol, Traill & Fortuin [52] a subgroup of elderly patients with hypertension who demonstrated severe concentric cardiac hypertrophy by echocardiography, a small left ventricular cavity and supernormal indexes of systolic function. These patients are best treated with beta blockers. It is clear then that subgroups of elderly hypertensive patients may be identified using echocardiographic techniques. The importance of classifying them may help to delineate a more rational therapeutic approach.

Renal

Senescense also affects the renal anatomy and function. Total and cortical renal mass, the number and surface area of glomeruli, and the proximal tubule length and volume decrease with age [53]. These changes are primarily a consequence of vascular abnormalities in the kidneys. The cortex is principally affected, there is relative sparing of the renal medulla [54]. The great majority of arterioles and glomeruli in the juxtamedullary region show no alterations but glomeruli in the cortical area may become sclerosed [55].

As a consequence of these anatomical changes effective renal plasma flow is reduced; the most dramatic decrease observed is after the age of 50 years [56]. As renal blood flow decreases the renal vascular resistance progressively increases [57] and glomerular filtration rate falls. This reduction in glomerular filtration has important clinical implications in the aged. For example, drugs that are excreted by the kidneys must be used with extreme caution in elderly patients.

Cerebral

The cerebral vessels also suffer major changes with aging. Narrowing of the lumen of cerebral arteries by the process of sclerosis is commonly observed. Hypertension accelerates the formation of atheromatous plaques that damage the integrity of vessels. Thrombotic occlusions and cerebral infarction are their sequelae. In addition, hypertension results in the formation of microaneurysms in small cerebral arteries. These are located principally in basal ganglia, internal capsule, pons and subcortical white matter [58]. These lesions have been reported in 15 percent of elderly normotensive sujects and in 71 per cent of elderly

hypertensives [59]. Rupture of these aneurysms may result in extensive destruction of brain tissue.

The anatomical changes that occur with age in the brain may reduce cerebral blood flow and increase cerebral vascular resistance. However, cerebral blood flow is under an autoregulatory mechanism which maintains a constant flow despite wide fluctuations in blood pressure. In elderly individuals the range of autoregulation narrows and shifts to a higher level of mean pressure. A similar change occurs in hypertensive patients regardless of age. As a result, a sudden fall of blood pressure in aged hypertensives may bring profound changes in cerebral blood flow and the development of a stroke. It is recommendable that blood pressure reduction in this group of patients be carried out slowly and with extreme caution.

Neurohumoral alterations

Renin - Angiotensin - Aldosterone System

Advancing age displays major changes in the endocrine and neurogenic functions. Systems which control blood pressure such as the renin-angiotensin-aldosterone system and the sympathoadrenal medullary systems are clearly affected. It is possible that other vasoactive systems such as the prostaglandin and the Kallikrein-Kinin systems may also be affected but have not been studied in depth with aging.

The renin-angiotensin-aldosterone system shows marked variations through the lifetime of an individual. Plasma renin and aldosterone levels are high during infancy and decrease rapidly as adult age is reached. A persistent decline in plasma renin activity, angiotensin II and aldosterone is observed with age in normotensive subjects [60]. However, racial differences in renin secretion have been reported; at all ages black people have substantially lower levels of renin activity.

Several theories have been advanced to explain the low renin state in elderly subjects. Among them are: 1) thinning of renal cortex and renal atrophy; 2) hyposensitivity to circulating catecholamines possibly related to a decrease in the number or a reduced sensitivity of beta adrenergic receptors, and 3) a physiologic response to the gradual increase in systemic blood pressure.

In addition to a low renin state, the capacity to increase renin and aldosterone secretion following sodium restriction or furosemide administration is markedly impaired in the elderly subject [61]. This abnormal response to volume contraction makes them more vulnerable to hypovolemia and hypotension.

Sympathetic system

The sympathetic system is also affected with age. Circulating catecholamines can arise from the adrenal medulla or from the peripheral nerves. A qualitative or quantitative difference in the degree of dysfunction of these two systems has not been described. Nevertheless, most studies have focused on the influence of age on the sympathetic nervous system rather than in the function of the adrenal medulla. Several investigators have shown that plasma norepinephrine concentrations increase with age; no change in plasma epinephrine was observed [62, 63]. The higher norepinephrine levels may indicate a heightened sympathetic tone. This possibility is strengthened by the demonstration that the number of adrenergic receptors and their binding affinity and sensitivity are decreased [64, 65]. Nevertheless, recent studies on the kinetics of norepinephrine have shown a reduced clearance from the circulation in older subjects [66] indicating that higher norepinephrine levels can not be ascribed solely to increased sympathetic tone.

As mentioned before, baroreceptor sensitivity is reduced with aging. This perturbation is largely due to rigidity of the arterial wall and/or intrinsic alteration of the receptors. The capacity to produce bradycardia and peripheral vasodilatation is impaired when acute increases in pressure occur. During hypotension, the reflex vasoconstrictor response and tachycardia is blunted to a greater extent in the elderly as compared to the young [67]. These abnormalities make the elderly subject much more sensitive to changes in posture and hypotensive drugs.

It has been proposed that there is a causal relationship between plasma norepinephrine levels, baroreceptor sensitivity and blood pressure elevation. In fact, a recent study supports the hypothesis that in aged individuals an impairment of baroreflex sensitivity may cause a sympathetic activation with an associated increase in plasma norepinephrine levels resulting in elevation of blood pressure [68].

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