Session 13

Overview of Physiology in Senescence*

David T. Lowenthal, M.D.; Kwan E. Kim, M.D.; Melton B. Afframe, Pharm. D.; and Bonita Faulkner, M.D.

As one ages, blood pressure and hemodynamic changes become apparent. This is reflected in a fall in cardiac output and a gradual increase in total peripheral-vascular resistance. Systolic hypertension is one of the fundamental abnormalities of the cardiovascular system in the elderly. Baroreceptor function and cerebral blood flow likewise may be compromised and result in altered drug sensitivity. Renal function decreases with age and is manifested by a decrease in renal blood plasma flow and in glomerular filtration rate. There is a gradual blunting of sympathetic nervous system responsiveness demonstrated by a decrease in the activity of the renin-angiotensin-aldosterone system. Finally, pathways of drug biotransformation may be altered, resulting in adverse drug reactions.

The aging process produces anatomic and functional changes in the cardiovascular renal system and biochemical alterations of the sympathetic nervous system. These changes are of direct relevance to the pathophysiology and management of hypertension in the elderly.

Blood Pressure and Hemodynamic Changes

Blood pressure rises with advancing age in most populations.1,2 With the exception of some isolated tribes,3,4 the systolic pressure increases more than the diastolic pressure. Longitudinal cohort data of the Framingham Study5 showed an increase in systolic pressure between the ages of 36 and 74 years that was equal in men and women. In the same study, the diastolic pressure tended to fall in both men and women older than 80 years.

Aging is associated with a progressive increase in the rigidity of the aorta and peripheral arteries,5,6 which is produced by the loss of elastic fibers and an increase in the collagenous materials and calcium deposition in the media. As aortic rigidity increases with advancing age, the aorta becomes closer to an inelastic tube, the pulse generated during systole is transmitted to the arterial tree relatively unchanged. The wide pulse pressure in elderly is primarily caused by an increase in systolic pressure; therefore, systolic hypertension predominates in elderly hypertensive patients.

It has been reported that there is a gradual decrease of O2 consumption and cardiac output with advancing age.7,8 This decrease in cardiac output is due to a fall in stroke volume.9 Therefore, the calculated total peripheral resistance increases with age. These hemodynamic changes are more pronounced when hypertension coexists in the elderly. Cardiac output and stroke volume are lower in elderly hypertensive than in elderly normotensive subjects. Thus, the total peripheral resistance is much higher in elderly hypertensive than in elderly normotensive subjects.6

Baroreceptor Reflex Function

Baroreceptor sensitivity decreases with advancing age10 and hypertension.11 It has been reported that increasing age and arterial pressure act independently to reduce baroreflex sensitivity.12 Therefore, rapid adjustment of the circulation to changes in posture may be impaired so that postural hypotension occurs. Adrenergic-blocking agents should be carefully titrated, and blood pressure should be checked in the supine, the sitting, and the standing positions.

Cerebral Blood Flow

Although the adult human brain weighs 1,400 g or 2 percent of body weight, the average value for cerebral blood flow is 750 ml/min or 15 percent of the total resting cardiac output.13 There is no significant decline in cerebral blood flow in normal elderly subjects.14 However, when elderly subjects show objective evidence of minimal atherosclerosis, cerebral blood flow is significantly lower.15 This atherosclerotic change may predispose one to transient ischemic attacks or cerebral thrombosis. Consequently, the customary doses of those centrally acting antihypertensives when given to the elderly may be associated with exaggerated manifestations of drug effect and toxicity.

Renal Function

It has been reported that glomerular filtration rate (GFR) and renal plasma flow are well maintained up to the fourth decade. Thereafter, there is a progressive decrease of about 10 percent per decade.16 Recently, a linear decrease in GFR and renal plasma flow after the age of 20 years was reported, with a loss of 4 ml/min/decade in the GFR and 35 ml/min/decade in the renal plasma flow.17

The GFR and renal plasma flow of patients with mild hypertension may be normal during the early stage of the disease. As the disease progresses, the GFR and renal plasma flow decrease. The more severe the blood pressure elevation, the lower the GFR and renal plasma flow, indicating that high blood pressure causes renal damage.18 Uremia is the most common cause of death in untreated patients with malignant hypertension.19 Thus, the GFR and renal plasma flow in elderly hypertensive patients may decrease due to both high blood pressure and aging.

Table 1—Influence of Age on Plasma Elimination of Extensively Metabolized Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major Route of Metabolism</th>
<th>Plasma T1/2</th>
<th>Plasma Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipyrine</td>
<td>Hydroxylation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Glycine conjugation</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Demethylation</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Hydroxylation</td>
<td>NS</td>
<td>1</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Hydroxylation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*From the Likoff Cardiovascular Institute and Departments of Medicine and Pediatrics, Hahnemann University, Philadelphia. Reprint requests: Dr. Lowenthal, 230 North Broad Street, Philadelphia 19102.
Renal concentrating ability is reduced in the elderly. Renal conservation of sodium during the restriction of sodium intake also is sluggish in the elderly. This defect in renal concentration ability and sluggish renal conservation of sodium intake during the restriction of sodium intake can make elderly patients more liable to dehydration. Therefore, diuretics should be used cautiously.

Furthermore, a decline in renal tubular function results in defects in tubular transport not only of salt but also of glucose and acid loads; alterations in sympathetic nervous input to the juxtaglomerular apparatus result in an altered renin-aldosterone response; hyponatraemia and oversecretion of antidiuretic hormone in the elderly further compromise normal salt, water, and electrolyte homeostasis, which can be compounded by theoverzealous diuretic administration. The aging kidney conforms to the intact nephron hypothesis of Bricker et al. Davies and Shock have demonstrated that glomerular and tubular function fall in parallel at similar rates, thus implying an intact unit. Prior to functional deterioration, nephron hypertrophy compensates for nephron loss. The GFR falls maximally 10 to 20 years after age-induced glomerular loss ensues.

Renin-Angiotensin-Aldosterone System

Plasma renin activity and plasma aldosterone concentration decrease with advancing age in normotensive subjects. Plasma renin activity and plasma aldosterone concentration are lower in the elderly hypertensive subjects than in young hypertensive subjects. There is no significant difference in plasma renin activity and plasma aldosterone concentration in the elderly with and without hypertension. These findings suggest that the presence of low renin levels in elderly hypertensive subjects indicates a change attributable not to hypertension, but rather to advancing age. The mechanisms responsible for the decrease in plasma renin activity in the elderly have not yet clearly been explained.

Thus, the combined results of physiologic alterations and altered drug biotransformation in the elderly dictate the need for altered dosage of antihypertensive agents when treating the hypertension of senescence.

**References**